Use of controlled temperature chain and compact prefilled auto-disable devices to reach 2030 hepatitis B birth dose vaccination targets in LMICs: a modelling and cost-optimisation study

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Summary

Background **Hepatitis B causes more than 800 000 deaths globally each year. Perinatal infections are a major driver of this burden but can be prevented by vaccination within 24 h of birth. Currently, only 44% of newborn babies in low-income and middle-income countries (LMICs) receive a timely birth dose. We investigated the effects and cost-effectiveness of implementing ambient storage of hepatitis B vaccines under a controlled temperature chain (CTC) protocol and the use of compact prefilled auto-disable (CPAD) devices for community births.**

Methods **In this mathematical modelling study of perinatal hepatitis B transmission and disease progression, we estimated the coverage impact and cost-effectiveness of implementing CTC and CPAD interventions in the six Global Burden of Disease (GBD) regions containing LMICs. Combinations of four different scenarios of birth dose delivery strategies (cold chain, CTC) and interventions (needle and syringe, CPAD) were modelled across facility or community birth locations. We also estimated the minimum cost and most cost-effective strategy to achieve the WHO 90% hepatitis B birth dose coverage target in GBD regions and in 46 LMICs with a reported coverage of less than 90%.**

Findings **Current delivery protocols achieved a maximum coverage of 65% (IQR 64–65) across GBD regions. Reaching 90% hepatitis B birth dose coverage across all GBD regions was estimated to cost a minimum of US$687·5 million per annum ($494·0 million more than the estimated current expenditure), of which $516·5 million (75%) was required for CTC and CPAD interventions. Reaching 90% coverage in this way was estimated to be cost saving in five of the six regions (and in 40 of 46 LMICs individually assessed) due to the disease costs averted, with the cost per disability-adjusted life-years averted being less than $83·27 otherwise.**

Interpretation **Hepatitis B birth dose coverage of 90% is unlikely to be reached under current protocols. CTC and CPAD vaccine strategies present cost-effective solutions to overcome coverage barriers.**

Funding **The Burnet Institute.**

Introduction

Hepatitis B presents a substantial global health threat: an estimated 257 million people are chronically infected, causing about 35 million disability-adjusted life-years (DALYs) and more than 800 000 deaths annually.[1,2] Mother-to-child hepatitis B transmission is a major driver of this burden,[3] with perinatal infections carrying the highest risk of chronicity, progression to cirrhosis and hepatocellular carcinoma, and mortality.[4,5] Administration of hepatitis B vaccine within 24 h of birth can substantially decrease the risk of perinatal infection[1,6] and is key to achieving global hepatitis B elimination.[3]

The benefits of including or expanding coverage of hepatitis B birth dose in low-income and middle-incomes countries' (LMICs) immunisation programmes have been shown,[7] but current programme costs and logistical difficulties associated with reaching all births restrict the coverage to 44% of newborns.[8–11] The birth dose provides unique challenges to immunisation programmes: with optimal vaccine effectiveness limited to a 24-h post-partum window and uncertain birth timings, coverage relies upon maintaining a constant supply of vaccines and service delivery. Currently, birth dose protocols mandate vaccine storage in the standard cold-chain (2–8°C) at the delivery level and administration by a professional health worker (ie, a medical or nursing professional).[12] However, within many LMICs, cold chain capacity is heavily restricted and expensive to expand,[9,13] and many births occur beyond the reach of traditional health-care systems, unattended by professional health workers.[14] Therefore, to achieve 90% hepatitis B birth dose coverage by 2030, as targeted by WHO,[15] changes to current practice are required.[9,10]

Two approaches are of growing interest to facilitate the expansion of hepatitis B birth dose coverage in

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Research in context

Evidence before this study

Ambient storage of hepatitis B vaccines under a controlled temperature chain (CTC) protocol and the use of compact prefilled auto-disable (CPAD) devices to expand service provision, by enabling trained lay health workers to deliver community vaccinations, might provide viable means of overcoming coverage barriers and reaching 90% coverage of hepatitis B birth dose vaccination in low-income and middle-income countries (LMICs). Pilot studies of CTC and CPAD date back two decades, and evidence suggests that both might be successful at increasing coverage without having to expand existing infrastructure. Although data on impact and cost-effectiveness are required to inform their use within national immunisation programmes, a study assessing these could not be identified.

Added value of this study

Our modelling study found that current hepatitis B birth dose protocols are insufficient to meet the WHO birth dose coverage target across LMICs in all six Global Burden of Disease (GBD) regions, reaching an estimated maximum coverage level of 65%. In our model, the addition of a combination of CTC and CPAD interventions were needed to achieve 90% hepatitis B birth dose coverage in most modelled settings. Although the use of CTC and CPAD interventions to achieve the WHO coverage target was associated with substantially higher upfront costs (times 3·6 on average), averted disease management costs meant that over the cohort lifetime, use was cost saving or cost-effective in all modelled settings. Overall, we estimate that the use of CTC and CPAD to achieve 90% coverage across LMICs in all six GBD regions would cost a minimum of US$687·5 million per year ($494·0 million above the estimated current expenditure) and would avert 36·3 million (IQR 24·1–49·3) disability-adjusted life-years across each cohort lifetime.

Implications of all the available evidence

These findings provide an economic argument to support the development of new birth dose protocols that include CTC and CPAD interventions.

LMICs, although neither is new and pilot studies date back two decades:[16] the storage of hepatitis B vaccines at ambient temperatures under a controlled temperature chain (CTC) protocol, and the use of compact prefilled auto-disable (CPAD) devices by community-based professional or trained lay health workers.[17] Hepatitis B vaccines are heat tolerant, and a CTC protocol could allow on-label storage in ambient temperatures approaching 40°C for up to 4 weeks,[18] therefore bypassing the cold-chain, increasing storage capacity, and securing a constant vaccine supply. CPAD devices are single use, can be stored ambiently, and could expand service delivery coverage by allowing peripheral community-based staff, possibly including appropriately trained lay health workers, to deliver the birth dose. In many LMICs, most community births are attended by lay health workers,[14] and the use of CPADs by lay health workers to deliver vaccines has been demonstrated as acceptable in a variety of community settings.[19] Although pilot data has indicated that both ambient storage of vaccines and CPAD approaches can expand birth dose coverage,[20–23] a key barrier that is stalling uptake in national immunisation programmes is inadequate data on their cost-effectiveness and overall impact on coverage.[24]

Mathematical models can generate impact and cost-effectiveness estimates, and a previous model has shown that the implementation of a CTC protocol could be cost saving in most countries.[25] However, reaching 90% birth dose coverage within LMICs will probably require a combination approach.[9,10] We present an expanded birth dose model, integrating and contrasting multiple combinations of birth dose delivery strategies (cold-chain and CTC) and interventions (needle and syringe and CPAD) across different birth locations (health facility and community). Within six world regions, we aimed to estimate the potential coverage impact, health impact, and cost-effectiveness of implementing new vaccination strategies. We also use mathematical optimisation to estimate the most cost-effective intervention strategy to achieve 90% coverage in Global Burden of Disease (GBD) regions and in the subset of LMICs that provide a birth dose but are not currently achieving this target.

Methods

Model and settings

In this modelling study, we simulated perinatal hepatitis B transmission, disease progression, and mortality for 1000 births using a deterministic, compartmental model constructed in Python (version 3.6.10), building on previous work (figure 1).[25] We estimated mother-to-child hepatitis B transmission risk as a function of hepatitis B maternal surface antigen (HBsAg) and envelope antigen (HBeAg) prevalence, and assumed that the risk was equal for facility births (eg, hospital or birthing clinic) and community births (eg, home). Birth dose vaccination could occur across four post-partum time strata (day 1, day 2, days 3–7, or days 8–41), and vaccine effectiveness reduced with delays (table 1).[6]

Where mother-to-child transmission occurred, perinatal infections were initially classified as latent and progressed to acute infection after an average period of 3 weeks.[31] Acute infections lasted an average of 6 months and became chronic in 88·5% of infants.[4,31] Once chronically infected, individuals could remain with chronic infection, progress to cirrhosis (compensated or decompensated) or hepatocellular carcinoma, or achieve spontaneous viral clearance leading to immunity. The

model was run until the entire cohort had died either due to all-cause mortality or hepatitis-B-related mortality.

Modelling was completed for six of the seven GBD regions (ie, excluding high-income).[30] Model inputs for the GBD regions were calculated so that each GBD region reflects as well as possible an aggregate of all LMICs within the region. GBD region inputs were based on population-weighted averages of country-level data, with individual parameter inputs calculated using as many country-level estimates as were available for LMICs in the region (countries with missing data were excluded from calculations).

Additional analyses were done for 46 individual LMICs with birth dose coverage reported as less than 90%. Where these countries were missing demographic or epidemiological data, inputs were imputed from relevant population-weighted averages for GBD regions used in WHO-Choosing Interventions that are Cost-Effective analyses (appendix pp 2–3).[32] The model code and data have been uploaded onto GitHub.

Demographic and epidemiological inputs

We calculated the values, uncertainty, and proportions of different sources for demographic and epidemiological inputs for the GBD regions (table 2; individual countries in appendix pp 6–8). We assumed that all facility births had access to a professional health worker to potentially deliver the birth dose, whereas coverage from professional health workers for community births were estimated from a review.[14] Consistent with a global review, we assumed that prevalence of HBeAg among HBsAg positive mothers was 30% in all modelled settings and that HBeAg presence increased risk of mother-to-child transmission from 15·0% to 87·5%.[26]

Vaccine coverage at model baseline was reflective of 2017 levels, with 87 LMICs providing the hepatitis B birth dose and 155 LMICs providing complete three-dose hepatitis B series.[8] Within each setting, overall baseline birth dose coverage came from reported estimates but was distributed among facility and community births at a ratio of 2:1, with the relative likelihood of vaccination doubled and delivery more prompt in facilities than with community births (appendix p 4).[28] Annual age-specific, all-cause mortality probabilities were taken from the UN Population Division, reflective of 2015–20.[36] Population-weighted GBD region averages can be seen in the appendix (pp 3–4).

Cost and health utilities inputs

Total hepatitis-B-related DALYs per birth cohort during their lifetime was used as the health outcome measue.[30] Economic costs were calculated from a health-care provider's perspective and are presented in 2020 US dollars. Annual costs of disease management were taken from a modelling study by Nayagam and colleagues.[3] Vaccine costs were calculated per dose and included commodity, wastage, training, delivery, and outreach costs.

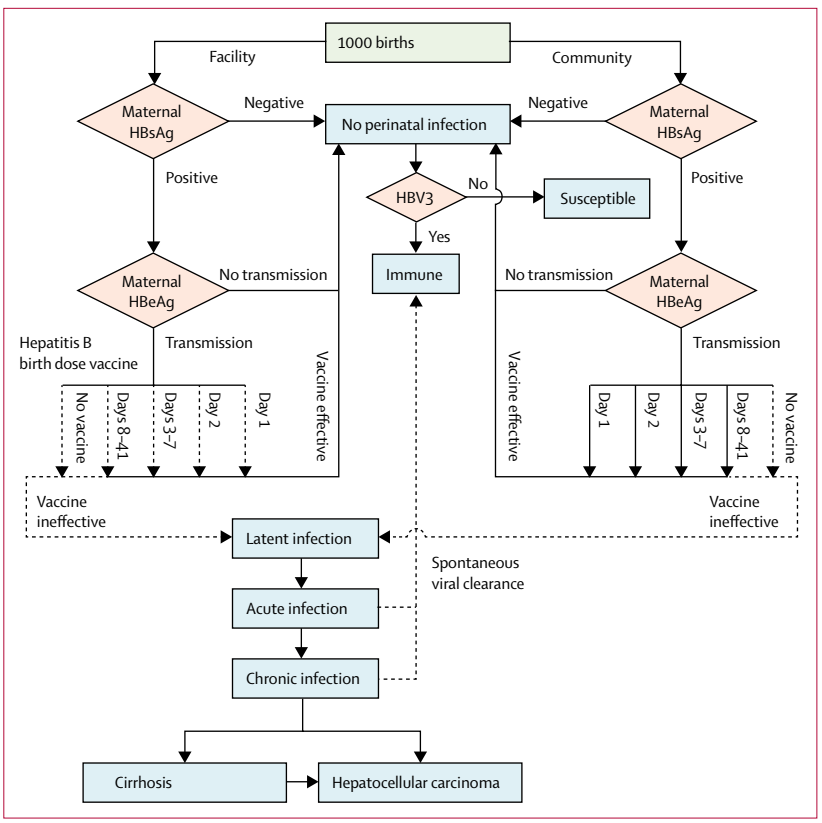


Figure 1: **Model diagram**
HBsAg=hepatitis B surface antigen. HBeAg=hepatitis B envelope antigen. HBV3=complete three-dose hepatitis B vaccine series.

For the commodity cost (ie, vaccine price), all vaccines administered by a professional health worker were assumed to come from a single dose vial, priced at US$0·55 per dose.[37] Additional manufacturer testing and development was estimated to double the price of CTC-licensed single dose vaccines ($1·10; tested in sensitivity analysis).[24] CPAD vaccines were priced at $1·63.[38] Regarding closed vial vaccine wastage, for both cold-chain and CTC-licensed vaccines, we assumed 5% closed vial wastage (due to breaking, freezing, or exceeding temperature limits) and 2% for CPAD vaccines.[20,39]

Concerning the training of delivery staff, as CTC vaccines were delivered by professional health workers, we assumed that training would be limited to understanding protocols and would cost less per dose than would training lay health workers to administer vaccines from CPADs. Hence, a training cost of $0·04 per dose was applied to CTC vaccines and $0·10 per dose to CPAD vaccines.[20,39] Delivery costs were applied to facility and community births, and included payment of the vaccine provider, necessary supplies such as syringes and disposal units, and storage of the vaccine (in either cold-chain or CTC).[3] Because of inadequate data, delivery costs were assumed to be equal for professional health workers and trained lay health workers in the community

For more on **WHO-Choosing Interventions that are Cost Effective** see https://www.who.int/choice/en/

See **Online** for appendix

For the **model code and data** see https://github.com/ChrisSeaman-Burnet/Seaman-et-al.-HBV-Birth-Dose-Model

	Value (95% uncertainty interval)
Hepatitis B envelope antigen[26,27]	
Prevalence	30·0% (20·0–40·0)
Positive transmission risk	87·5% (75·0–100·0)
Negative transmission risk	15·0% (5·0–25·0)
Vaccine effectiveness[6,25]	
Day 1	95·3%
Day 2	88·9% (83·0–92·8)
Days 3–7	82·5% (70·7–90·2)
Days 8–41	52·3% (22·3–80·7)
Odds of vaccination in facility versus community[28]	2
Annual probability of hepatitis B progression[4,29]	
Acute to chronic*	88·5% (84·0–93·0)
Chronic to compensated cirrhosis	1·9% (1·0–2·4)
Compensated cirrhosis to decompensated cirrhosis	3·9% (3·2–4·6)
Chronic to hepatocellular carcinoma	0·6% (0·3–1·0)
Compensated cirrhosis to hepatocellular carcinoma	4·8% (3·0–6·6)
Decompensated cirrhosis to hepatocellular carcinoma	7·1%
Annual probability of hepatitis B recovery[29]	
Chronic	1·1% (0·1–2·2)
Annual probability of hepatitis B mortality[29]	
Acute	0·7% (0·4–0·9)
Chronic	0·9% (0·3–1·5)
Compensated cirrhosis	4·6% (3·1–6·6)
Decompensated cirrhosis	16·2% (9·9–20·0)
Hepatocellular carcinoma	54·5% (8·1–60·5)
Annual hepatitis B disability weightings[30]†	
Acute	0·051 (0·032–0·074)
Chronic	0·051 (0·032–0·074)
Compensated cirrhosis	0·051 (0·032–0·074)
Decompensated cirrhosis	0·178 (0·123–0·250)
Hepatocellular cirrhosis	0·288 (0·193–0·399)

Annual parameters taken as an average over the lifetime. *Acute to chronic infection transition is time-dependent after 6 months; the tabulated value represents initial probability. †Disability weightings correspond with the following Global Burden of Disease study classifications: infectious disease, acute, moderate (acute, carrier, and compensated cirrhosis); decompensated cirrhosis of the liver (decompensated cirrhosis); and cancer, diagnosis, and primary therapy (hepatocellular carcinoma).

Table 1: **Global parameters**

(tested in sensitivity analysis). Outreach costs were only applied to community births and included the cost of travel for the vaccine provider to collect and deliver the vaccine.[3] Costs and health outcomes were discounted at 3% per annum.

Cost-coverage functions and cost-effectiveness modelling

For each intervention, cost-coverage functions were modelled linking expenditure on the intervention to total births reached, and vice versa. For facility birth interventions, as births were in a fixed location and professional health workers were available to provide all vaccines, functions were linear. For community birth interventions, cost-coverage functions were logistic to the approximate increasing marginal costs that were associated with reaching more difficult populations as coverage levels expanded.

For the six GBD regions and the 46 LMICs that currently report less than 90% hepatitis B birth dose coverage, a baseline scenario was modelled using estimated 2017 coverage of the hepatitis B birth dose, assuming that vaccines were delivered by professional health workers from vials stored within the cold-chain.

For the baseline and four model scenarios, total costs (vaccination and disease management) and DALYs per birth cohort during the lifetime were calculated, as well as incremental cost-effectiveness ratios (ICERs) in US$ per DALY averted compared with the baseline.

Scenario 1 was maximised current practice: within the community, coverage stayed at baseline levels because evidence has suggested that cold-chain use in the community has already reached capacity.[9,13,23] Within facilities, cold-chain capacity was either expanded to 80% of births, consistent with reports that 20% of facilities in LMICs do not have any cold-chain,[13] or it was maintained at baseline levels if they were already above 80%. All vaccinations were administered by professional health workers, from vials stored in the cold-chain.

In scenario 2, the conditions of scenario 1 were supplemented by CTC vial storage for facility births. Coverage in facilities could increase to the WHO target (90%) or by 5% beyond baseline cold-chain coverage, whichever was greater. Coverage in the community stayed at baseline levels.

Scenario 3 supplemented the conditions of scenario 2 by vial storage for community births. CTC increased vaccine access in the community, but vaccines still needed to be delivered by professional health workers. As the number of professional health workers was unchanged, the impact was mostly to timely vaccinations. We assumed that all community births that were attended by a professional health worker but not already covered by a cold-chain vaccine would receive a birth dose on the day of birth,[14] a 10% increase in non-timely coverage,[25] and total coverage constrained not to exceed 95%.

Finally, scenario 4 was the conditions of scenario 3 plus CPAD vaccines for community births. Trained lay health workers were able to deliver vaccines using ambiently stored CPAD devices in the community. CPAD use was restricted to community births, because we had assumed all facility births to have professional health workers providing vaccinations,[14] and all vaccinations administered by professional health workers could be from a vial. In all settings, we assumed that CPAD coverage could reach 95% of community births and would not be required if this coverage was already achieved under scenario 3.

	Central Europe, eastern Europe, and central Asia	Southeast Asia, east Asia, and Oceania	Latin America and Caribbean	North Africa and Middle East	South Asia	Sub-Saharan Africa	All GBD regions
Demographic parameters*							
Facility births[33]	94·8%	91·5%	93·5%	61·6%	73·1%	58·2%	74·1%
Professional health worker attendance at community births[34]	43·5%	43·6%	17·5%	20·6%	12·9%	6·0%	14·9%
Epidemiological parameters*							
HBsAg prevalence[34,35] (95% uncertainty interval)	2·7% (1·8–3·5)	6·1 (5·5–7·1)	0·5 (0·3–0·9)	2·5% (2·1–3·2)	2·9% (2·4–3·3)	7·8% (6·8–8·7)	4·4% (3·8–5·2)
Birth dose coverage[8]	63·5%	79·0%	72·5%	33·8%	45·5%	10·0%	44·2%
Complete three-dose hepatitis B vaccine series coverage[8]	92·0%	93·7%	89·2%	80·5%	89·1%	72·0%	84·3%
Costing parameters							
Birth dose vaccine							
Facility, cold chain ($)	6·42	1·34	1·51	1·50	0·96	0·97	1·44
Facility, CTC ($)	7·04	1·96	2·13	2·12	1·58	1·59	2·06
Community, cold chain ($)	10·48	1·97	1·54	1·98	33·03	5·80	10·67
Community, CTC ($)	11·10	2·59	2·15	2·60	33·65	6·41	11·29
Community, CPAD ($)	11·67	3·16	2·72	3·17	34·22	6·98	11·86
Hepatitis B management, per annum[3]							
Acute ($)	44·53	73·06	86·86	57·91	57·36	29·91	54·76
Chronic ($)	44·53	73·06	86·86	57·91	57·36	29·91	54·76
Compensated cirrhosis ($)	92·25	120·79	134·59	105·64	105·09	77·64	102·48
Decompensated cirrhosis ($)	92·25	120·79	134·59	105·64	105·09	77·64	102·48
Hepatocellular carcinoma ($)	92·25	120·79	134·59	105·64	105·09	77·64	102·48
Optimisation parameters: maximum coverage of interventions, by birth location							
Facility, cold chain	80·0%	80·2%	80·0%	80·0%	80·0%	80·0%	80·0%
Facility, CTC	90·0%	90·0%	90·0%	90·0%	90·0%	90·0%	90·0%
Community, cold chain	40·4%	66·1%	55·4%	19·9%	23·3%	6·1%	22·4%
Community, CTC	77·7%	93·3%	60·7%	42·6%	36·9%	19·6%	38·3%
Community, CPAD	95·0%	95·0%	95·0%	95·0%	95·0%	95·0%	95·0%

Data indicated as population-weighted averages are available for the 87 low-income and middle-income countries that provide the hepatitis B birth dose in the appendix (pp 6–8). All costs are in US$. GBD=Global Burden of Disease. HBsAg=hepatitis B surface antigen. CTC=controlled temperature chain. CPAD=compact prefilled auto-disable device. *Population-weighted average across countries where data was available.

Table 2: **Setting-specific model inputs, for GBD regions**

Each vaccination method was associated with a timing distribution across the vaccine effectiveness stratum (appendix pp 4–5). The effectiveness of CTC and CPAD interventions were assumed to be equal to cold-chain vaccinations.

Optimisations and uncertainty and sensitivity analysis

For the six GBD regions, we estimated baseline vaccine expenditure using the cost-coverage functions. All birth dose interventions were then made available (cold-chain in facility and community, CTC in facility and community, and CPAD in community), and an optimisation was used to reallocate estimated baseline vaccine expenditure across interventions to maximise coverage. For the six GBD regions and the 46 LMICs with reported birth dose coverage below 90%, optimisation was used to calculate the minimum total expenditure and allocation across vaccination interventions to reach the coverage target. DALYs and disease costs averted per birth cohort during the lifetime were calculated, as well as ICERs compared with baseline. Optimisations assumed that facility birth proportions, trained health-care worker attendance at community births, and vaccine costs were fixed. Sequential least squares programming within SciPy. Optimize.Minimize (version 1.3.2) was used for optimisations and was constrained such that each intervention could not exceed maximum coverage levels (table 2).

A multivariate probabilistic uncertainty analysis was done, in which 1000 model simulations were made with parameters drawn at random from their individual uncertainty bounds or a range of plus or minus 5% if unavailable (table 1, 2). The model outcomes presented represent the median and IQR of these 1000 simulations.

One-way sensitivity analysis used parameters averaged from all six GBD regions, and assumed maximum coverage using all modelled interventions (ie, scenario 4). It was used to test all model assumptions on costing and

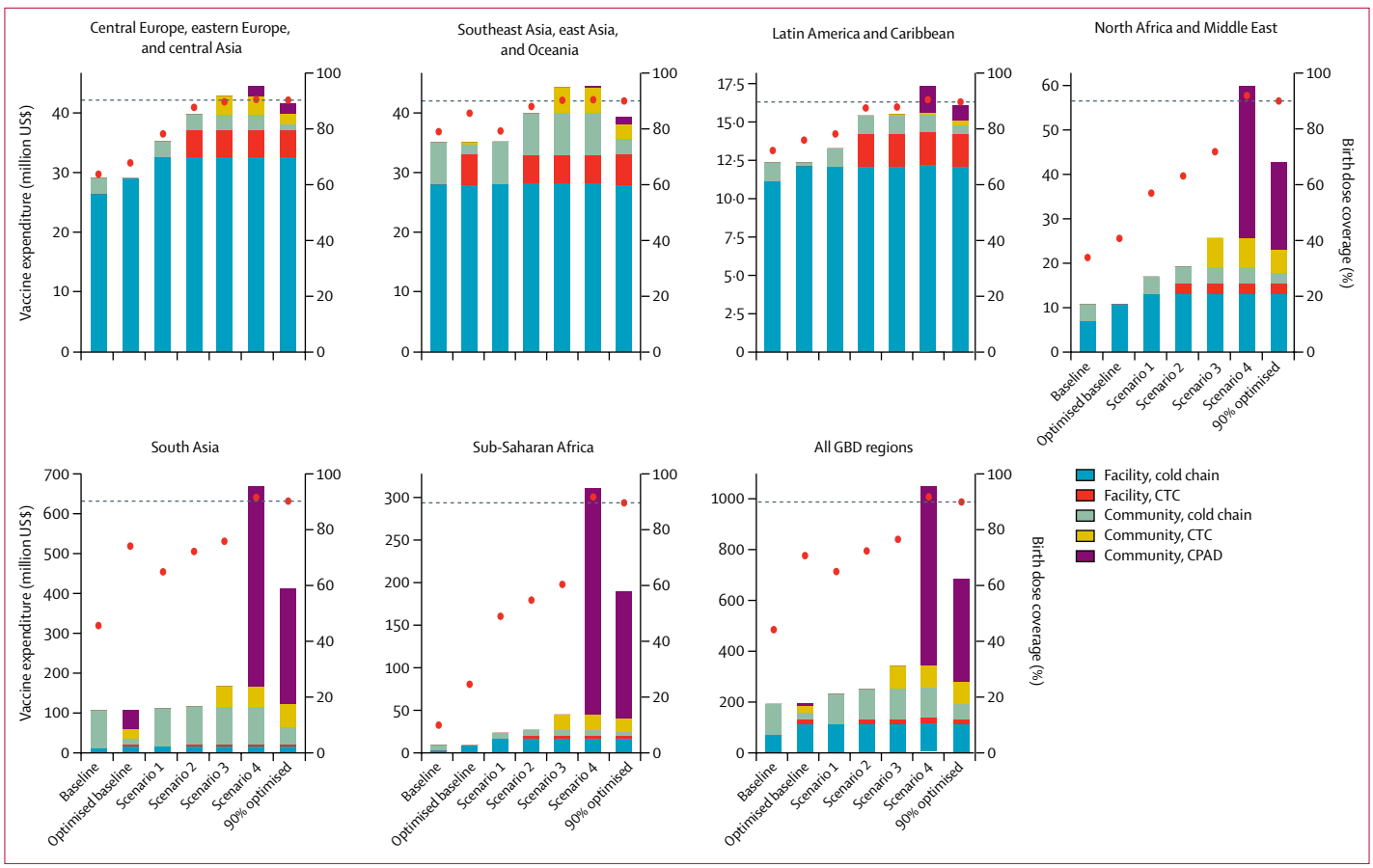


Figure 2: **Population-level cost and coverage estimates for current vaccine expenditure, optimised current expenditure, modelled scenarios, and 90% optimised coverage**
The dashed horizontal line represents 90% coverage and the red circles are median coverage of 1000 model runs for each bar. Inputs for each region are based on population-weighted averages from the relevant subset low-income and middle-income countries, with the total number of births scaled for the region. GBD=Globen Burden of Disease. CTC=controlled temperature chain. CPAD=compact prefilled auto-disable device.

epidemiological parameters, including the impact of maternal HBsAg prevalence, existing hepatitis B vaccination coverage, and the proportion of facility births on model outcomes.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In our baseline scenario, we estimated global hepatitis B birth dose coverage across the six GBD regions to be 44% (IQR 43–45). Per 1000 births globally, an estimated $1466 (IQR 1383–1566) is spent on vaccination, 389 DALYs (IQR 319–468) related to hepatitis B are accrued, and $11 681 (IQR 10 190–13 388) is spent on disease management over the cohort lifetime. Under current birth dose protocols, coverage across all GBD regions could expand to 65% (IQR 64–66), but in no region could coverage reach 90%; maximum coverage ranged from 49% in sub-Saharan Africa to 79% in the southeast Asia, east Asia, and Oceania region (scenario 1; figure 2).

In one region, southeast Asia, east Asia, and Oceania, 90% coverage became possible when a CTC protocol was implemented within facilities and the community (scenario 3; figure 2). Across the five other regions, achieving 90% coverage required both CTC and CPAD interventions. Overall, using CTC and CPAD vaccines to deliver the hepatitis B birth dose, we estimate that across all GBD regions coverage could reach 91% (scenario 4; figure 2).

Maximum coverage under model scenario 4 incurred incremental vaccine costs of between $339 per 1000 births in southeast Asia, east Asia, and Oceania, and $18 524 per 1000 births in south Asia (appendix pp 12–13). Expanded coverage was overall cost saving in four GBD regions due to disease costs averted, with the exceptions of central and eastern Europe and central Asia (ICER up to $4·79 per DALY averted) and south Asia (ICER up to $94·58 per DALY averted). Across all GBD regions, maximum

coverage under model scenario 4 averted 280 DALYs (IQR 227–330) and saved a net $1924 (IQR 628–3096) per 1000 births over the lifetime (scenario 4; figure 3).

In all GBD regions, when the estimated baseline expenditure was optimised, prioritising the vaccination of facility births—including the use of CTC vaccines to maximise coverage—was the most cost-effective means to increase coverage (figure 2).

Our optimisation estimated that to reach 90% hepatitis B birth dose coverage in all six GBD regions, an annual minimum of $687·5 million would be required, of which $516·5 million (75%) was allocated to CTC and CPAD interventions (figure 2). This value is $494·0 million per annum more than estimated current expenditure; however, over the cohort lifetime, 36·3 million DALYs (IQR 30·1–43·4) were averted and investment proved cost saving overall because of disease costs averted (figure 3; appendix pp 14–15).

Reaching 90% coverage in the optimal way was cost saving in five GBD regions; however, higher cost of delivery meant this was not the case in south Asia (ICER up to $37·49 per DALY averted; figure 2; appendix pp 14–15). Use of CPAD vaccines generally enhanced cost-effectiveness of coverage expansion, despite having the highest unit costs. Although 90% coverage was possible in southeast Asia, east Asia, and Oceania without CPAD (scenario 3), optimisation showed that it was more cost-effective to allocate $1·2 million per annum to CPAD in the region (figure 3). About 80% of the disease burden averted upon reaching 90% coverage across LMICs was in sub-Saharan Africa: 29·0 million DALYs (IQR 22·6–34·0) across a cohort lifetime (appendix pp 14–15).

We did additional analyses for 46 LMICs (figure 4). The annual costs of reaching 90% coverage were highest for south Asian countries, because of the high cost of community outreach, and ranged between $10 486 in Bhutan and $35 220 in Timor-Leste, per 1000 births. Outside south Asia, the highest annual costs were in Nigeria ($6501 per 1000 births), which was attributable to a low proportion of facility births (32·5%) and low baseline birth dose coverage levels (30%).

Within two LMICs (Suriname and Costa Rica), optimised 90% birth dose coverage did not require the use of CPAD vaccines. Across the remaining 44 LMICs, dependence upon CPAD ranged between 0·04% of annual vaccine expenditure in Lebanon and 84·7% in Myanmar. Reaching 90% birth dose coverage using CTC

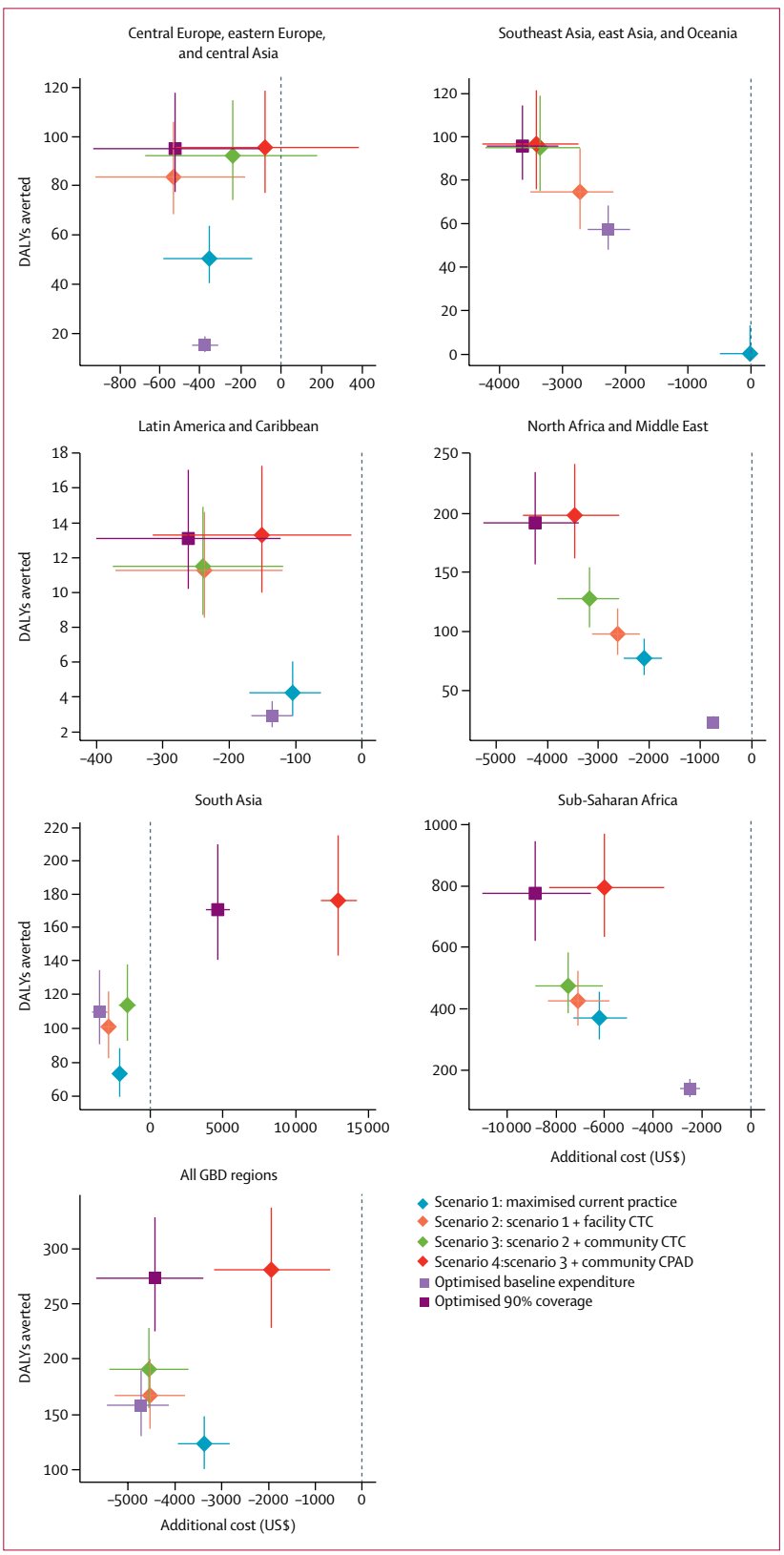
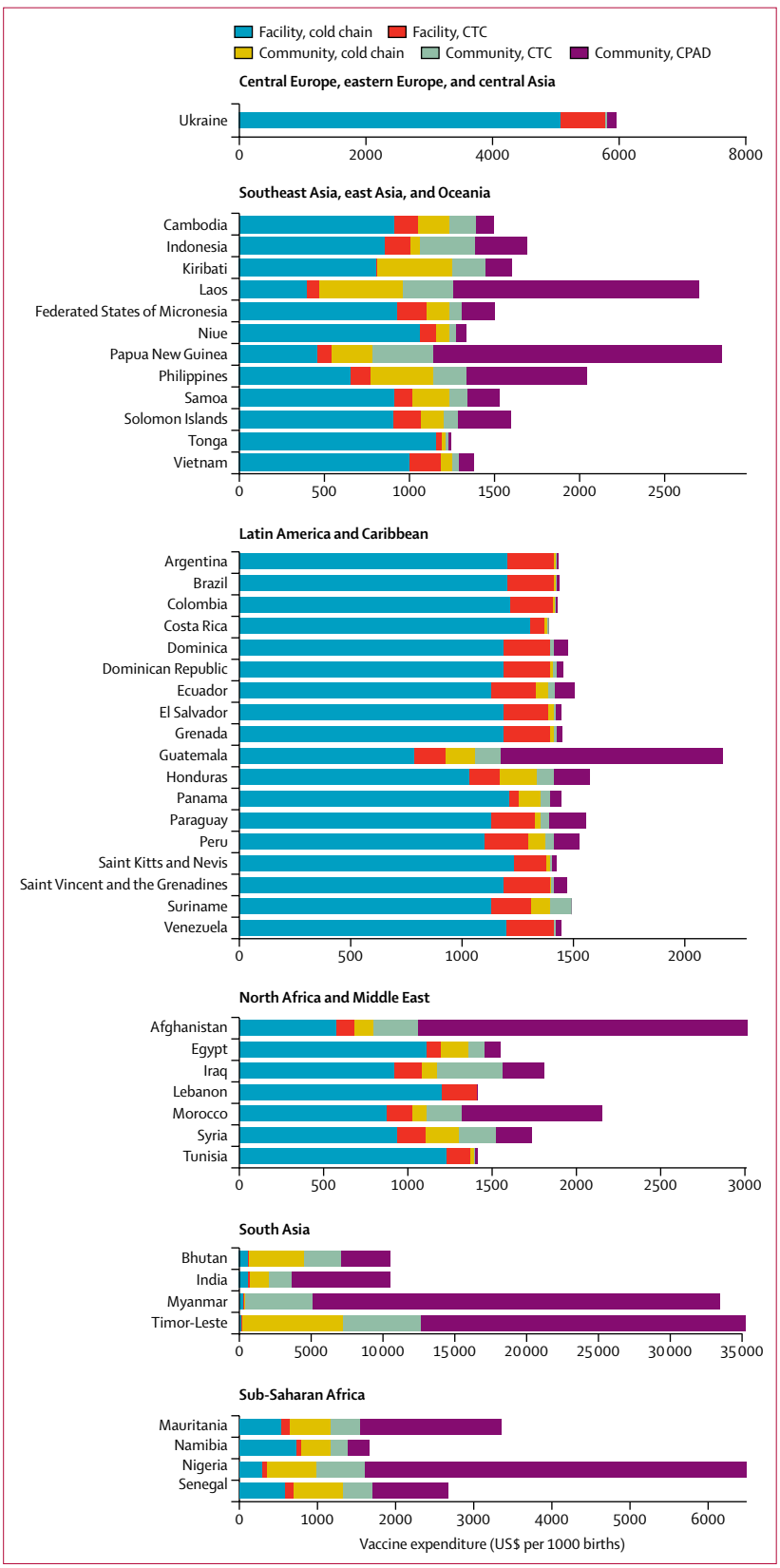


Figure 3: **Outcomes of cost-effectiveness and impact modelling within GBD regions, per 1000 births**

Uncertainty intervals presented as IQR of 1000 model simulations. Scatter points to the left of 0 (as indicated by dashed line) show cost savings, and a point higher on the plot represents greater disease aversion. Costs presented are sum of commodity (vaccine) costs, delivery costs, and health-care costs for each scenario. GBD=Global Burden of Disease. DALYs=disability-adjusted life-years. CTC=controlled temperature chain. CPAD=compact prefilled auto-disable device.



and CPAD was cost saving in 40 LMICs, with the additional costs ranging between $1·88 (IQR –1·91 to 7·80) per DALY averted in Myanmar and $64·50 (IQR 49·79 to 83·27) per DALY averted in Timor-Leste (appendix pp 16–20).

The full results of sensitivity analysis can be seen in the appendix (p 21). Briefly, the model outcomes were sensitive to HBsAg prevalence and facility birth proportions, and the findings were robust to changes in costing assumptions.

Discussion

Using a mathematical model, we estimated that to reach 90% hepatitis B birth dose coverage across all six LMIC GBD regions would cost a minimum of $687·5 million per annum ($494·0 million more than the estimated current expenditure), of which $516·5 million (75%) per annum would be required for CTC and CPAD interventions. Without making changes to current birth dose protocols such that vaccines must be stored in the cold-chain and administered by professional health workers, coverage could only increase from 44% to 65%; this clearly falls short of WHO coverage targets. Our modelling shows that reaching 90% birth dose coverage with the use of CTC and CPAD interventions in the six GBD regions could avert 36·3 million DALYs (IQR 30·1–43·4) during each birth cohort's lifetime and be cost saving overall. The importance of new approaches such as CTC and CPAD vaccines to increase birth dose coverage has been discussed,[9,10] and we now add a strong economic argument supporting their use in LMICs.

One key barrier currently prohibiting the uptake of CTC and CPAD interventions is the additional costs associated with vaccine procurement and training.[24] Although our findings show that the use of CTC and CPAD interventions to reach 90% birth dose coverage entailed an average expenditure increase of 3·6 times, within 40 LMICs this investment was returned through the savings made by avoiding chronic disease management costs during the cohort lifetime. Additionally, within the six eligible LMICs (Argentina, Costa Rica, India, Myanmar, Timor-Leste, and Ukraine) where additional costs were incurred—as a result of high vaccine delivery costs in the community or low maternal HBsAg prevalence—the calculated ICERs fell within reported willingness-to-pay-thresholds (estimated as the opportunity costs of existing health expenditure) and can still be considered as cost-effective.[40] The

Figure 4: **Optimised expenditure to reach 90% hepatitis B birth dose coverage in the 46 low-income and middle-income countries with reported coverage of less than 90%, per 1000 births to account for population size heterogeneity**

Population-level cost estimates and baseline expenditure estimates are available in the appendix (pp 16–20). CTC=controlled temperature chain. CPAD=compact prefilled auto-disable device.

cost-effectiveness of expanding hepatitis B birth dose provision has already been shown,[7,41] but the analyses rarely considered alternatives to standard cold chain practices or the greater reach of community-based lay health workers, or both. The use of CTC and CPAD could provide means to overcome the common barriers of human resources and cold chain limits, and we show that, when used in conjunction with existing infrastructure, CTC and CPAD maintain or enhance the cost-effectiveness of achieving birth dose coverage targets.

Currently, birth dose protocols prioritise vaccination of facility births because they provide the fewest logistical challenges,[12] and this recommendation is supported by our optimisation modelling. Using a CTC protocol to make facility-based vaccination more feasible was highly cost-effective in our model even though we were cautious in our assumptions. The role of CTC in facilities acknowledges that some 20% of facilities in LMICs might have no cold-chain capacity, that it might be unreliable in up to 65% of cases, and that not having a refrigerator in a delivery room or postnatal ward might be the crucial obstacle to neonatal vaccination.[13,42] The use of CTC to circumvent these barriers complements other good practices such as vaccine standing orders, integration of birth dose vaccination into neonatal care protocols and staff education, and the training to provide it.[12,43]

The maximum benefit of ambiently stored hepatitis B vaccines is likely to be for community births, in which the absence of cold-chain capacity is a leading constraint on birth dose vaccination.[9,43,44] Ambient storage of the hepatitis B vaccine is endorsed by WHO in settings where it might enhance coverage; however, as this is not a licensed use, the practice has not been adopted in many LMICs.[18] Licensure under a CTC protocol would enable widespread ambient vaccine storage for birth dose coverage expansion and is currently being pursued by global development partners.[17] Within this context, CTC has been shown to be highly cost-effective and when piloted has increased hepatitis B birth dose coverage by 27–40%,[22,23,25] both of which are consistent with our model's findings. In addition, our optimisations indicate that the cost-effectiveness of achieving 90% coverage was enhanced by switching a proportion of existing community cold-chain birth dose vaccinations to CTC. As coverage increases, the marginal costs of community vaccinations will also increase, reflecting the extra cost inherent in reaching increasingly remote births. Remote community births derive the greatest cost benefits where a CTC protocol allows vaccine storage nearer to the birth, reducing travel requirements and marginal costs.[23] Our results support the development of CTC licensed hepatitis B vaccines and indicate that a substantial market might exist.

Despite the modelled coverage gains from CTC licensure, birth attendance by professional health workers in the community remained insufficient in most LMICs to facilitate 90% birth dose coverage. Ambiently stored CPAD vaccines delivered by lay health workers were required in most settings to reach birth dose coverage targets, and use generally enhanced the cost-effectiveness of expansion. Furthermore, the costing of CPADs used the only current WHO-prequalified device (Uniject, Biofarma, Indonesia),[20] which is perceived as relatively expensive, and it assumed that delivery from a trained lay health worker would cost the same as from a professional health worker. Although our modelling still supports CPAD use as cost-effective, if newer CPAD devices were cheaper or if the cost of delivery was reduced, the economic argument for this approach reaching community births would become even more compelling.

Within each region, optimised expenditure to reach 90% birth dose coverage showed increased dependence upon CPAD, again illustrating the impact of marginal costs when considering implementation strategies. It has previously been shown that among the most remote births, ambiently stored vaccine vials have a minimal effect on birth dose coverage[23] and the use of trained lay health workers could provide an economically viable way to overcome this barrier. Although CPAD administration of vaccines by lay health workers has been shown to be safe and acceptable within the community,[19] further research into implementation is required.

Our study presents an investment case supporting the use of CTC and CPAD vaccines in LMICs to achieve 90% birth dose coverage, acknowledging that a combined annual sum of $687·5 million will require substantial additional funding to current levels. This amount is, however, considerably less than current spending on HIV, which receives an annual $19 billion towards elimination[45] and causes comparable levels of global mortality.[30] Furthermore, given the elevated risk of chronicity from perinatal infection with hepatitis B compared with transmission later in life, investment in birth dose vaccination could break the current transmission cycle and reduce required future investment.[3,5]

This study has several limitations. Most of the averted disease burden was in sub-Saharan Africa, where genotypes of circulating hepatitis B viruses are associated with lower rates of perinatal transmission,[9] but supplemental analyses indicated that cost savings would remain in sub-Saharan Africa and overall at lower transmission risks (appendix pp 22–23). We did not consider the effect of maternal antiviral drugs during pregnancy or immunoglobulin at birth, both of which are associated with additional reduced risk of perinatal transmission.[12] It is important to note that hepatitis immunoglobulin at birth is not compatible with a CTC protocol and its use is not feasible in many countries,[9,10] and that maternal antiviral use in mothers with hepatitis B is estimated at less than 1% in LMICs.[34] We did not consider the cost or impact of demand-side activities such as community awareness, and costing data were not

available for all programmatic aspects. However, pilot data have indicated that improved availability of the vaccine alone might increase birth dose coverage,[22] and our findings should encourage further study to ascertain programmatic costs. Finally, our study did not consider in-country heterogeneity, such as the difference in hepatitis B prevalence between rural and urban settings, and it was reliant upon historical data for many parameters. To counterbalance these uncertainties, sensitivity analysis was used to elucidate the impact of individual parameters and uncertainty analysis produced moderate intervals for model outputs.

CTC and CPAD interventions provide cost-effective means to overcome current barriers to timely hepatitis B birth dose coverage in LMICs. These data provide an economic argument to support their use in hepatitis B birth dose protocols in LMICs. Future cost-effectiveness studies in specific country contexts are warranted.

Contributors

CPS reviewed the literature to obtain model parameters, completed the modelling, and drafted the manuscript. NS gave critical analysis on model design and implementation. CM, MEH, and NS conceived the study and provided guidance on scenario design. JH, YX, CWS, MS, OL, and MIA all provided critical assessment and review of model outcomes. All authors revised and approved of the submitted manuscript

Declaration of interests

JH and MEH report grants from Gilead Sciences, AbbVie, Merck, and Bristol-Myers Squibb, outside of the submitted work. NS reports grants from Gilead Sciences, outside of the submitted work. All other authors declare no competing interests.

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