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Cost-utility analysis of adding a fourth dose at birth to the hepatitis B vaccination schedule in Côte d'Ivoire

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Abstract

Background. Côte d'Ivoire is considering adding a birth dose of the Hepatitis B vaccine to the current vaccination schedule (at 6, 10, and 14 weeks) in order to decrease vertical transmissions. The study aims to perform a cost-utility analysis of adding the extra Hepatitis B dose at birth.

Methods: Using a Markov model which included economic and epidemiological data, the incremental cost-effectiveness ratio (ICER) per averted disability-adjusted life years (DALYs) of adding a birth dose was calculated using a 3% discount rate. Parameter values in the model were obtained from experts' interviews in Cote d'Ivoire, WHO Global Health Observatory data, international publications and hospital reports. Univariate sensitivity analyses were performed to account for uncertainty.

Results: In 2018, under the base case (no-vaccination) scenario, 3,940 out of the newborn cohort of 947,687 would become HBV carriers. Under the current three-dose vaccination regimen, only 947 are at risk. Adding a birth dose will reduce this by a further 104 transmissions to 843 cases. The birth dose costs $1.02 per fully immunized child, totaling $899,000 per annual birth cohort, these are exceeded by $1,627,000 savings in lifetime treatment costs. An estimated 823 DALYs will be averted due to decreased morbidity and mortality. Adopting a four-dose immunization schedule is cost-saving, cost-effective and very cost-effective when vaccine efficacy gains (relative to the current three dose-schedule) are above 1.56%, 0.35% and 0.72% respectively.

Conclusion: Since our model shows it is likely to be a cost-saving strategy, we recommend introducing the fourth dose of HBV immunization at birth in Cote d'Ivoire.

Keywords: Cost-Utility Analysis, Hepatitis B, Vaccinations

Background

Hepatitis (liver inflammation) caused by the Hepatitis B Virus (HBV) is a critical worldwide public health issue having several possible outcomes: acute, fulminant, or chronic Hepatitis, liver cirrhosis; and hepatocellular carcinoma (HCC) (1) (Figure 1). HBV, having vertical, perinatal, parenteral, sexual, and horizontal transmission patterns (2,3), is the main cause of human viral Hepatitis. Globally, viral Hepatitis is the tenth leading cause of death, with around 600,000 deaths annually (4), an annual incidence of 50 million diagnoses (5) and a chronic carrier prevalence of 350 million (6). In addition, infants infected at birth with viral Hepatitis have a 90% chance of developing Chronic Hepatitis B (CHB) illness (7). However, the HBV vaccine administered at birth, as recommended in the Expanded Program on Immunization (EPI) schedule (8), can reduce the risk of HBV infection from vertical transmissions considerably, hence reducing incidence and mortality from liver cancer (9).

Côte d'Ivoire is a highly endemic area, with prevalence rates between 8% and 13% (10). In the country, where the first newborn vaccination against HBV is currently given at six weeks, the reported mother-to-child transmission rate varies widely from 4% to 32.8% (8,11). Furthermore, liver cancer, a potential chronic sequela of HBV, is the third most common cancer in the country (12). More so, the financial burden of the disease leads to considerable health care costs for the country and catastrophic costs for medical care for some individuals (13).

Numerous researchers have addressed the question of the cost-effectiveness of vaccination of HBV at birth. However, very few studies have been conducted in high-endemic countries, especially those in Africa. Evidence in Gambia and Mozambique indicated that immunization against HBV is a cost-effective approach and could be used on a large scale in the high-endemic country, especially in most of Sub-Saharan Africa (14, 15). Another study in Mozambique found that the option of adding an additional birth dose in the current schedule was highly cost-effective with an incremental cost-effectiveness ratio (ICER) of 250.95 US$ per DALY averted considering the GDP per capita (15). Also, a study conducted by Ginsberg and Shouval (1992) in a cost-benefit analysis in Israel - a middle-endemic country, found that vaccination at birth was cost-saving (16). In Cote d'Ivoire, no studies to date addressed an economic evaluation of adding a fourth dose at birth to hepatitis B.

This study, constructs a cost-utility analysis (calculating the net costs and the estimated DALYs averted) to aid Cote d'Ivoire health planners in deciding whether to add an extra vaccination at birth to the currently used 3-dose schedule of vaccinating at 6, 10 and 14 weeks (17,18).

Methods

Data sources

The economic data (vaccine, and treatment costs) were obtained from Cote d'Ivoire's Ministry of Economic Department, published data and expert opinions (19–27). Epidemiologic, demographic and health service data were extracted from national reports, and scientific and public literature (20, 28–33). Since not all the relevant data are available for the Cote d'Ivoire population, proxy data from published data has been used (20, 28–31). We developed a Microsoft Excel-based spreadsheet model incorporating vaccine efficacy, epidemiological, economic, health service

utilization, and demographic data (Appendix 1).

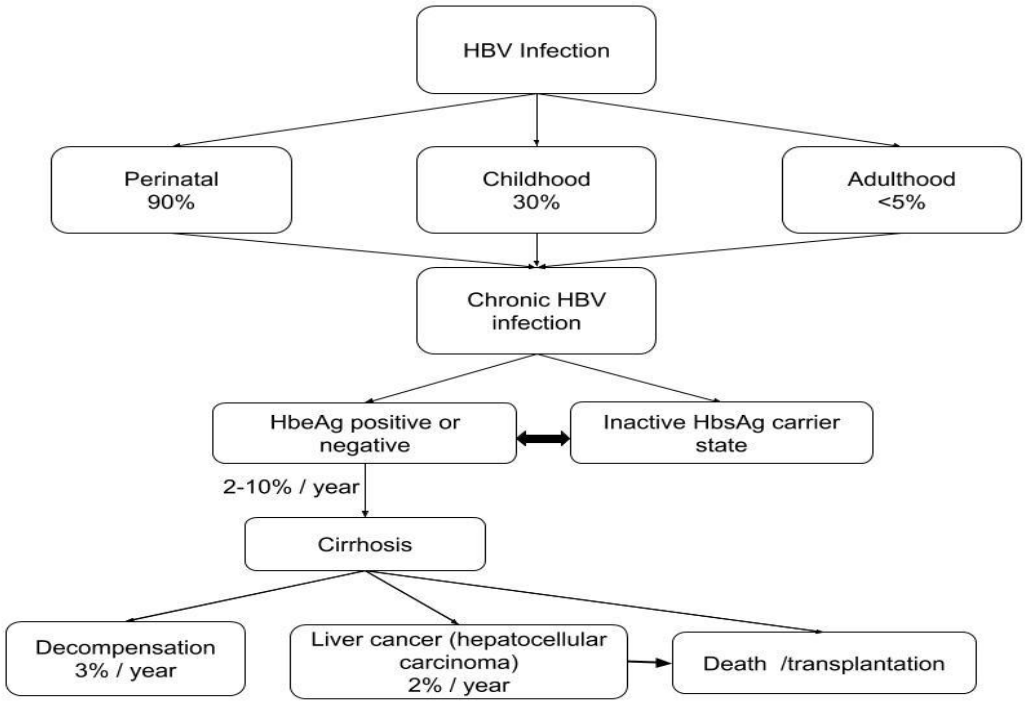

Fig 1: HBV and complications

Cost-Utility Ratio (CUR)

The CUR calculated the net costs per averted DALY as a result of adding a vaccination at birth (the intervention) to the current three-dose schedule - All costs are presented in US dollars ($) at mid-2020 price levels at the exchange rate of 528.304 Central African Francs to the US dollar; Future costs and DALYs were discounted using a 3% per annum rate and; A health service perspective was used, that excluded work-related income losses, caregiver transportation costs and production losses (since these were not available).

Vaccine Efficacy

Vaccine immunogenicity is significantly higher for a four-dose schedule starting at three months than for four or three doses starting at birth (32). However, delaying the first dose, would not prevent vertical transmissions during the first three months. Our model used an 81.7% baseline efficacy for three doses (derived from protective anti-HB levels) reported from a study in Cote d'Ivoire based on doses scheduled at age 6, 10, and 14 weeks (29).

Using the midpoint of the range (97.6%-100%), that is 98.8% reported from four-dose studies (albeit not including any 6, 10, 14-week schedules) (32,34), we estimated the efficacy of a 0, 6, 10, 14-week four-dose protocol in the Cote D'Ivoire to be 84.52% (98.8%/95.5% x 81.69%) (range 83.50% - 85.54%). The magnitude of this range was used to estimate a range of 80.7%-82.7% for the three-dose regimen.

The size of the birth cohort in 2018 was estimated to be 951,122 based on projections of 2014 census data (33). This was adjusted for the very early (under 30 hours old) neonatal mortality rate (33). Based on 7.7% of mothers being Hepatitis B positive (HB+) and a vertical transmission rate of 5.4% from Cote D'Ivoire (29), we estimate that 0.44% (or 3,940) newborns would be carriers.

Since no other vaccinations were given at birth in Cote d'Ivoire, we assumed a 93% coverage rate from the literature (35,36), when allied to the 81.7% efficacy of the current three-dose regimen, would reduce the number of surviving newborns who were HB+ by 74.5% (81.7% x 93%), from 3,940 to 947 (range 911-983) infected infants. Adding an initial dose at birth will further reduce the number of infants with HB+ to 843 cases (range 806-880). The effects of this reduction of 104 cases (caused by the addition of the birth dose), on the number of carriers developing the disease later in life (and attendant treatment costs), were modelled. The spreadsheet-based model traced for 100 years the progression through the following states: carrier state, chronic active state, cirrhosis, HCC, mortality related to CHB, and deaths from other causes. Since in Cote d'Ivoire, there is a lack of available data on CHB and its complications, especially acute Hepatitis incidence rates, or associated mortality, our model focused only on CHB infections and their sequelae (since these constitute the largest burden of disease) using transition probabilities from literature reviews (4,37,38).

Vaccination Costs

Based on EPI, WHO, and UNICEF data, the total costs of the vaccine were adjusted for freight costs and wastage rates (20). Wastage rates were based on the midpoint (15%) of the 5%-25% range reported in Vietnam, whose upper limit corresponded to the upper limit reported in sub-Saharan South Africa (15,39). Using a bottom-up approach, we also included the cost of syringes, transportation, storage, and safety boxes based on the ingredient approach described in the WHO guidelines on introducing a new vaccine into an existing immunization program (21,40,41). In order to estimate employment costs per hour: public holidays, vacation days, and sick leave (assuming an average of 5 days out of an allowable 15 annual days) were taken into account in addition to any staff positions that were distributed jointly with other hospital departments.

We assumed that the distribution system (transport and cold chain) will not be affected by the additional HB monovalent shot at birth (as it represents just 7.7% of current EPI shots) and, therefore, these marginal costs would be zero. Surveillance, social mobilization, and training costs were estimated from the introductory costs of the measles-rubella vaccine in Côte d'Ivoire (20). Since the adverse effects are of a mild nature, that are resolved without sequelae (or hospitalization), we included only the cost of mild fever, which is expected to occur in between 25%-50% of vaccinations, assuming that 10% of these fevers required an ambulatory visit (16,33,34,42,43).

Treatment Costs

A bottom-up approach was also used to determine treatment costs, which included outpatient visits and/or hospitalizations associated with the chronic form of HBV and its complications. Costs of treatment included hospital ward costs, "hotel costs,"

and overhead costs as well as patient-specific costs related to drugs, imaging, and laboratory tests. These were collected from a tertiary care hospital (CHU de Yopougon), that provides 113,174 bed days annually from a total annual budget of $18.4 million. Day surgery, outpatient, and emergency room visits were assumed to cost 100%, 25%, and 50% respectively of the cost of a full day's hospitalization. The total area of the hospital is 39,617 sq meters, of which 4% is devoted to the gastro-enterology ward, which supplies 2,986 bed days each year. Estimates for cost inputs were obtained through reviews of published and unpublished literature, program budgets, price catalogues, and consultation with experts using a predefined questionnaire collecting data on the drug, imaging, and laboratory costs, to the existing protocol. For patients with cirrhosis and HCC, transplantation is currently not available in Cote d'Ivoire (22).

Disease Burden

Since current maternal HBV prevalence and perinatal transmission data were unavailable, we used, in our base case scenario, an approximation of 0.42% based on a 7.7% maternal prevalence and a 5.4% birth transmission rate (29).

Annual transition rates (Appendix 1) to Chronic, Cirrhosis, HCC status and death were applied to the birth cohort. These were adjusted by condition-specific death rates and all-cause death rates in order to calculate the number of persons in each state and their attendant treatment costs and DALY losses from morbidity (based on the Disability Weights shown in Appendix 1). The product of the number of persons in each stage, the stage-specific death rates and the age-specific HALEs (healthy adjusted life expectancies) at the time of death (44,45) provide the DALYs lost due to mortality.

Cost-Effectiveness Thresholds

In the absence of country-specific guidelines for cost-effectiveness thresholds, we used the WHO guidelines (46) define an intervention to be very cost-effective if the net cost per averted DALYs is less than the GNP per capita. If the net cost per DALYs lies between one- and three-times per capita GDP, then the intervention is said to be cost-effective. Based on the GNP per capita for Cote d'Ivoire in 2018 of $2,303 results in the thresholds being $2,303 - $6,909 for very cost-effectiveness or cost-effectiveness to be achieved (47).

Sensitivity Analyses

Univariate sensitivity analyses on the ICER were carried out on several variables identified in the literature on HBV viz: vaccine efficacy and price, schedule strategy, discount rate, coverage, and transmission rate at birth, based on the upper and lower limits of the ranges shown in Appendix I (15,40,46,48,49).

Results

Vaccination Costs

Assuming a coverage rate of 93%, vaccine wastage rate of 15% (39) and unit dose costs of $0.245 (26,27), the annual incremental cost of introducing the fourth dose of Hepatitis B vaccine at birth to the 947,970 newborns amounts to $899,477 or $1.02 per fully immunized newborn. Personnel costs accounted for 49% of these costs, vaccine (28%), social mobilization (9%), auto-disposable syringes (5%), side effects (4%), training (2%), safety boxes (0.7%) and surveillance (0.5%).

Treatment Costs

In Côte d'Ivoire, the cost per case (Table 1) for treating acute Hepatitis B was $2,271 based on an average length of stay of 15 days in a hospital. The discounted lifetime costs of chronic Hepatitis B ($54,991 per case) are similar to that of cirrhosis ($54,061) despite the latter requiring hospitalization. Treatment of liver cancer is purely palliative ($1,655).

Table 1: Lifetime treatment costs (USD at 2020 levels) per Hepatitis B case and sequelae (a)

Variable	**In-Hospital**				
	LBAH (b)	Individual (c)	Out-Patient Pharmaceuticals	Out-Patient Visits	Total Costs
Acute Hepatitis B	1,658	461	-	-	2,271
Chronic Hepatitis B	-	-	39,153	15,838	54,991
Cirrhosis	787	5,481	29,419	18,374	54,061
Liver Cancer (d)	774	806	-	-	1,655
(a) Excludes transport costs and lost productivity of patient and care-giver.					
(b) Labor, building, administration, and hotel (food & laundry) costs.					
(c) Includes in-hospital pharmaceuticals, imaging, and laboratory tests.					
(d) Just palliative care as chemotherapy, radiotherapy, and transplants are not available.					

Transmission Reductions

The addition of a fourth dose to the schedule reduces HB carrier transmissions by 104 (range 66 – 141) to 843 (range 806 – 880) infant carriers per annum. Multiplying these incidence reductions by the lifetime costs results in an estimated saving in discounted treatment costs of $1.63 million (range of $1.05 - $2.21 million). Thus, the additional vaccination intervention (which costs $0.9 million) will result in a net saving of around $0.73 million (range $0.15 - $ 1.31 million) in health service resources.

Averted DALY losses

In addition to these resource savings, there will be DALY savings resulting from decreased morbidity and mortality. In the base case, around 823 (Range 533-1,120) DALY losses will be averted from reduced morbidity and mortality. The average age of death from hepatitis-related conditions is around 44 years old.

The 4-dose regimen is cost-saving when its efficacy exceeds that of the current 3-dose schedule by a small factor of only 1.56%. For cost-effectiveness and very cost-effectiveness to be obtained, the 4-dose schedule need only have an efficacy advantage of 0.35% or 0.72% respectively.

Sensitivity Analysis

A univariate sensitivity analysis showed that in nearly every case the intervention was cost-saving (otherwise being very cost-effective) when using the parameters including the vaccine price, the schedule strategy, the discount rate, coverage rates, and the rate of transmission at birth.

Discussion

The present study was designed to estimate the cost-effectiveness of adding an extra

vaccination against Hepatitis B at birth to the existing immunization schedule in Cote d'Ivoire, a highly endemic country. The results conclude that a strategy to immunize children at birth should be implemented. Using the WHO guidelines (46), moving to the proposed four-dose immunization schedule is actually cost-saving when the vaccine efficacy gain (relative to the current three dose-schedule) is only above 1.56%. Threshold efficiencies for the intervention to be cost-effective or very cost-effective are only 0.35% or 0.72% respectively, which appear to be easily attainable.

Since the additional dose at birth is usually cost-saving, there is a win-win situation, in that the intervention provides both extra health (averting DALY losses) in addition to saving scarce resources. Hence, the only non-logistical constraint is an "affordability constraint" relating to Cote d'Ivoire's ability to obtain funding now in order to generate resource savings in the future that will arise as a result of the additional vaccination decreasing morbidity and mortality.

Our study's epidemiological-economic evaluation demonstrated that universal vaccination would gain around 823 DALYs respectively from decreases in morbidity and mortality. This is probably an underestimate as there is a secondary effect of reduced child mortality in that fewer children will lose parents to HBV and its sequelae and parentless since these children have higher mortality rates than children whose parents are alive (14).

Due to the paucity of HBV studies in Côte d'Ivoire, we were forced to rely on data available from expert opinions as well as data from the literature that was mostly from industrialized, developed countries. This problem is particularly pertinent with regards to vaccine efficacy—the Côte d'Ivoire (29) study (used in our sensitivity analysis) indicated an HBV vaccine efficacy of 81.7%, at least 10% inferior to other studies (33,50).

In Côte d'Ivoire, the proportion of the national health budget allocated to immunization programs has been on the decline, decreasing from 2.5% to 1.6% during the 2012-2015 period. [66] However, the absolute amount allocated for immunizations increased by around 23%. Bearing in mind that Gavi's financial support will withdraw soon, it is important for the country to consider alternative ways of funding the vaccination schedule, as was the recent consideration in Vietnam (15).

As the estimated incremental cost of vaccinations against HBV at birth is only $1.02 per child, it has been proposed the vaccination should be funded by out-of-pocket expenditures by Ivorian households. We reject this proposal not only on the grounds of equity but more importantly, it is likely to considerably reduce vaccine compliance levels, which will, in turn, reduce the program's effectiveness, especially via the mechanism of herd immunity.

Cost-benefit studies of Hepatitis B vaccinations tend to be carried out in high-income countries with low-endemicity. These studies generally indicated that selective vaccination was more cost-effective than universal vaccination, focusing on specific groups such as children at high risk of contracting the disease and recommending a three-dose schedule (16,51,52). In countries with intermediate endemicity, a Spanish study which compared three vaccination strategies (among adolescents, infants, and both combined), found mass vaccination of adolescents to be the most cost-effective option (53). In Israel, a cost-benefit analysis

reported that universal vaccination at birth was cost-saving (16).

On the other hand, in highly-endemic countries especially in Sub-Saharan Africa, there is a paucity of health economic evaluations. These few studies highlighted that vaccination of neonates (without prior screening of the mothers) within 24 hours is the best option on the basis of cost-effectiveness (33,52,54). Results from economic evaluations in the Gambia and Mozambique (14,40) also indicated immunizing infants against HBV is cost-effective.

Our study corroborates the result of a study in Vietnam, also a highly endemic country, that reported universal HBV vaccination at birth was highly cost-effective from a payer's perspective, and cost-saving from the societal and health care perspectives (39). In Mozambique, an additional dose of HBV at birth was found to be a highly cost-effective 251 US$ per averted DALY (40).

Our finding indicates that introducing a universal newborn vaccination for HBV in Cote d'Ivoire is very likely to be a cost-saving intervention. The major limitation (that causes an overestimate of costs per DALY averted) is the fact that our model is static and not dynamic and therefore excludes positive effects of herd immunity. However, these might be small as herd immunity primarily affects horizontal transmission. Indeed, it has been postulated that for countries with high endemicity, static models could be a better choice to appraise the cost-effectiveness of a universal HBV vaccine (35).

Among health staff, morning hours are devoted to immunization activities and afternoons are allotted to administrative tasks. So, it is possible that no extra health personnel would have to be hired to administer the birth dose if implemented. Therefore, the true marginal labour cost of providing the extra birth dose is far lower, thus rendering our net cost savings underestimated.

Finally, obviously, our model could not take into account any possible future technological innovations that might decrease (or even increase) the costs of treating HBV along with attendant gains in averted DALYs (12). If radiotherapy and/or chemotherapy treatments and/or liver transplants, which are currently not available, become available, then the effect on the cost per DALY ratio is unknown as this would increase treatment costs but would also increase averted DALY by a currently unknown factor.

A further underestimation of treatment costs is caused since pharmaceutical costs (other than for palliative care) were not associated with liver cancer, since most cases in Africa are discovered at a very late stage and median survival times are subsequently short (32). However, despite the expected advantages of instituting a dose at birth, the main constraint is the ability (in the post-GAVI support era) to get funding now for a project whose gains are generated mainly in the future.

It can only be hoped that this paper would give a basis for designing an optimal strategy for the introduction of the HB vaccine for preventing perinatal transmission of HBV in Cote d'Ivoire. It is also hoped that this paper will stimulate similar cost-utility analyses in other African nations that have not yet adopted giving a Hepatitis B vaccination at birth.

Conclusion

Univariate sensitivity analyses showed that introducing a fourth dose of HBV immunization is a cost-saving strategy. Therefore, we recommend moving from the three doses to the proposed four-dose immunization schedule, adding a dose at birth in Cote d'Ivoire.

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Appendix 1: Summary Base Case Estimates

Parameters	**Base case estimates**	**Range for sensitivity analysis**	**Source**
Epidemiologic, Demographic and Economic			
Birth cohort (2018)	947,687		(39)
Coverage rate	93%	60%-95%	Assumption
Discount rate	3%	1.5%-5%	Assumption
Exchange rate for 1 $	528.304		http://www.exchangerate.com
GNP per Capita (2018) $2303			IMF (2020)
Vaccination			
Vaccination price	$0.245	$0.19-$0.29	(63)
Vaccine efficacy 3-dose schedule	81.69%	80.7%-82.7%	(31)

Vaccine efficacy 4-dose schedule	84.52%	83.5%-84.5%	(25,37)
Wastage rate vaccine	15%		(45)
Wastage rate Injection syringes	10%		(48)
Time to vaccinate (to inject one dose of Hep monovalent) in minutes	5		Expert opinions
Time spent for explanation (prevention) in minutes	5		Expert opinions
Percentage of sick days taken by a nurse in a year	50%		Expert opinions
Time taken Nurse to treat side effects (min)	5		Expert opinions
Time taken MD treat side effects (min)	7		Expert opinions
Burden of the disease			
Mothers who are HB+	7.70%		(31)
Transmission at birth	5.40%		(31)
% Born HB+	0.44%		
Disability weight (DW) for carrier state (CS)	0.075		(74)
Disability weight (DW) for chronic active Hepatitis (CAH)	0.36		(44)
Disability weight (DW) for cirrhosis	0.33		(44)
Disability weight (DW) for HCC	0.58		(44)
% Cirrhosis attributable to HB Average age at diagnosis of cirrhosis	39 35		(15) Expert opinions
Average age at death of cirrhosis	60		Expert opinions
ALOS in-patient Acute Hep B	15 days		UFH Hospital
ALOS inpatients for Cirrhosis	7.1 days		UFH Hospital
Stay inpatients for HCC	7.0 days		UFH Hospital
Cirrhosis	24.70 death rate per 1000		Expert opinions
Chronic	9.56 death rate per 1000		Expert opinions
Variables of the Hepatitis B Virus Natural History Model for Perinatal			
Outcome of carrier state			
CAH	1.2 per 1000		(43)
Cirrhosis	0.7 per 1000		(43)
HCC	0.5 per 1000		(43)
Outcome of CAH state †			
Cirrhosis	20 per 1000		(43)
HCC	5 per 1000		(43)
Cirrhosis -HCC	33 per 1000		(44)