Modeling a BCG Birth Dose-based Vaccination Program for Improved Hepatitis B Control in Uganda: Mixed-methods study

Anthony Makhoba (drmakhoba@gmail.com)
St. Francis Hospital Nsambya
Victoria Nakibuuka
St. Francis Hospital Nsambya
Martin Mugenyi
St. Francis Hospital Nsambya
Plaxeda Nanjobe
St. Francis Hospital Nsambya
Michael Lwetabe
St. Francis Hospital Nsambya
Felistas Nyaranga
St. Francis Hospital Nsambya
Stella Kyoyagala
Mbarara Regional Referral Hospital
Elias Kumbakumba
Mbarara Regional Referral Hospital
David Scheifele
[1] BC Children's Hospital Research Institute

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Abstract

Background: Hepatitis B virus (HBV) is mainly transmitted perinatally. Delaying the first dose of HBV vaccine to 6 weeks of age as is the current practice in Uganda may increase the risk of perinatal transmission. In this study, we aimed to assess the uptake of BCG vaccine within 24 hours after birth and to assess the feasibility of BCG/HBV vaccine co-administration in Uganda.

Methods: This was a mixed-methods study. We retrospectively collected data on BCG vaccine uptake, the timing of vaccination, and reasons for missed/delayed vaccination, at two hospitals: capital city-based St. Francis Hospital Nsambya (SFHN), and upcountry-based Mbarara Regional Referral hospital. We also conducted a cross-sectional study at SFHN to explore factors associated with delayed or missed BCG vaccination within 24 hours after birth.

Results: Of the 2,002 newborn babies randomly sampled, 1,534 (76.5%) received BCG vaccine within 24 hours. On chart review, 140 participants had identifiable reasons for delayed BCG vaccination as follows: admission to neonatal unit with birth asphyxia (56.2%, n= 73), and birth weight <2.5kg (30.8%, n=40). On interviewing 73 mothers at vaccination clinics, admission to a neonatal unit for prematurity (n= 42, 57.5%), birth asphyxia (n= 73, 56.2%) or birth weight < 2.5kg (n=40, 30.2%) were the reasons for missed/delayed vaccination. The median human cost for the BCG vaccination process was $0.14.

Conclusions: Over three-fourth of neonates received their BCG vaccine within 24 hours after birth, providing a convincing basis for co-administration of BCG and HBV vaccines.

Background

Hepatitis B virus (HBV) infection is still a major global public health problem, with an estimated 2 billion people exposed globally, over 350 million chronic carriers, and annual deaths of about 600,000 (1). The burden of HBV is disproportionately high on the African continent where it is highly endemic with seroprevalence reported at approximately 9% (2). It is therefore not surprising that chronic complications of HBV infection such as liver cirrhosis and its sequelae hepatocellular carcinoma remain a big health problem in Africa, associated with significant morbidity and mortality (3).

HBV infection in a pregnant woman poses a serious risk to her infant as perinatal transmission from mother to infant at birth is very efficient(4). If a mother is positive for both hepatitis B surface antigen (HBsAg) and HB e antigen (HBeAg), 70% – 90% of infants will become infected in the absence of post-exposure prophylaxis (5). The risk of perinatal transmission is about 10% if the mother is positive only for HBsAg. Without post-exposure immunoprophylaxis, approximately 40% of infants born to HBV-infected mothers will develop chronic HBV infection, approximately one-fourth of whom will eventually die from chronic liver disease (5, 6).

HBV is highly prevalent in Uganda(7). Following the introduction of the pentavalent vaccine, consisting of DPT-Hib-HepB in the Uganda National Expanded Program on Immunisation (UNEPI) schedule at 6 weeks

after birth in 2002, the national HBV seroprevalence of HBV has decreased to from about 10% (7) to 4.1% (Uganda guidelines for prevention, testing, care, and treatment of hepatitis B and C virus infection the republic of Uganda, 2019). However, the current prevalence of about 4.1% remains unacceptably high. Most chronic HBV infections in highly endemic areas like Uganda are acquired perinatally through mother-to-child transmission(6). One study reported an HBV seroprevalence of 11.8% among pregnant women attending antenatal care (ANC) in Northern Uganda(8) and another study reported a prevalence of 2.9% in Central Uganda (9).

In Uganda, routine ANC screening of pregnant mothers for HBV is not available at most health facilities offering antenatal care and HBV immunoglobulin is not available for babies born to hepatitis B positive mothers. In Uganda, the first dose of HBV is given at 6 weeks of life, with other infant vaccines (Immunization guidelines in Uganda by UNEPI, n.d.). World Health Organization (WHO) advocates that in regions of high endemicity where HBV is mainly spread from mother to infant at birth, a first HBV vaccine dose given at birth (within 24 hours) is critical for preventing HBV infection(1). Therefore, delaying the first dose of the HBV vaccine to 6 weeks after birth is a missed opportunity to prevent perinatal transmission of HBV.

In contrast, BCG immunization within 24 hours of birth is relatively successful in Uganda. BCG coverage was estimated at 89% in 2006 (Bureau, 2007) and increased to 94% in 2016 (UNICEF Uganda Vaccination Coverage, n.d.). In Kampala metropolitan area, BCG coverage was found to stand at 92.7% in 2012(10). Health facility deliveries have significantly increased in Uganda from 57% in 2011, to 73% in 2016 and to 90.2% in a recent study carried out in rural Uganda (11). Most of the newborn babies who receive birth dose BCG vaccine within 24 hours are delivered within health facilities. The rest get vaccinated at their initial visit to the hospital. However, the vaccination coverage reported by the Uganda Ministry of Health does not distinguish between those who received the BCG vaccine within 24 hours of birth and those who got it later.

Therefore, the aim of this study was to evaluate the uptake of the BCG vaccine within 24 hours as the “Gold Standard” and assess if this model can be used as a yardstick to advocate for change in Uganda’s vaccination schedule for the introduction of a birth dose of HBV vaccine.

Methods

Study designs and settings:

We conducted a mixed-methods study, involving a retrospective chart review and a cross-sectional study design.

The retrospective study involved a review of all delivery charts from health records of St. Francis Hospital Nsambya (SFHN) and Mbarara Regional Referral Hospital (MRRH) over a three-year period, June 2017 to June 2020. Data was collected on BCG vaccine uptake, the timing of vaccination, and reasons for

missed/delayed vaccination. SFHN has approximately 5,000 deliveries annually while MRRH has over 8,000 deliveries per year.

In the cross-sectional study conducted at SFHN between June and September 2020, we collected data on reasons for delayed or missed vaccination that may have not been established from chart review. In-depth interviews were conducted with mothers of babies who missed 24-hour birth dose BCG vaccination. Also, direct observation of 20 BCG vaccinations was done at SFHN to document the time taken to complete the vaccination process, from obtaining consent to completing documentation. The human cost of vaccination was estimated from the salary scales of the nurses and midwives who carried out vaccination at SFHN and the time required.

Eligibility Screening

For the retrospective study, we enrolled participants who delivered at either of the two hospitals in the past 3 years, with accessible vaccination records at the hospital archive. Those with grossly missing data were excluded. For the cross-sectional study, mothers of babies born in the hospital whose babies missed BCG vaccination within 24 hours of birth. This included mothers who delivered within the previous 9 months, who were willing to provide an informed written consent. Nurse or midwife on official payroll of St. Francis hospital Nsambya.

Study Tools

Data abstraction form was used to capture the BCG vaccination information from the records. (See appendix). The same form was administered by the research assistant during the maternal interviews to capture any additional reasons for missed or delayed BCG vaccination. A survey questionnaire and stopwatch were used to record the duration of the BCG vaccination process.

Data analysis

The rate of birth dose BCG vaccination coverage was calculated as follows: The number of newborns ascertained to have received BCG within 24 hours of birth out of the total sample gave a rate of birth dose BCG vaccination. Univariate analysis was employed to present reasons for delayed or missed BCG birth dose vaccination.

Study Ethics

Ethics Review

We obtained Research Ethical Committee (REC) approval from Mbarara University of Science and Technology REC. Approval Number **07/12–18, and** the Uganda National Council of Science and

Technology (UNCST). UNCST Registration Number **HS415ES.** Administrative clearance was obtained from SFHN and MRRH authorizing access to the patient records.

All research methods were performed in accordance with the relevant guidelines and regulations governing good clinical practice.

All participants interviewed provided written informed consent and a waiver of consent was provided by the REC for the chart reviews.

Results

Retrospective study results

Baseline characteristics of the participants

The retrospective review included 2,002 mothers and infants. The mean maternal age was 28 years (SD 5.0). Five hundred thirteen mothers (51%) had a vaginal delivery and 493 (49%) were delivered by Caesarean section. ANC attendance stood at 90.9% (n = 910) for 3 visits and 81.8% (n = 819) for 4 visits. HIV prevalence was 4.3%. HBsAg was positive in 0.3% (n = 3) of 457 participants who tested, while hypertension and diabetes were present in 5.5% (n = 55) and 0.7% (n = 7), respectively (Table 1).

Table 1
Maternal characteristics.

Maternal characteristics	Number (%)		
Maternal age			
Overall, Mean, (SD), years	28 (5.0)		
Mbarara, Mean (SD), years	27 (4.6)		
Nsambya, Mean (SD), years	29 (5.1)		
Type of delivery			
Vaginal delivery	513 (51)		
Caesarean Section	493 (49)		
Antenatal visit			
1	993 (99.2)		
2	978 (97.7)		
3	910 (90.9)		
4	819 (81.8)		
Comorbidities	Negative	Positive	Unknown
HIV status	924 (91.2)	44 (4.3)	45 (4.4)
Hepatitis B	454 (45.5)	3 (0.3)	542 (54.3)
Diabetes Mellitus	970 (96.9)	7 (0.7)	24 (2.4)
Hypertension	931 (93)	55 (5.5)	15 (1.5)
Rheumatic fever	981 (98)	1 (0.1)	19 (1.9)
TB status	986 (98.5)	0 (0.0)	15 (1.5)
STD status	980 (97.9)	5 (0.5)	16 (1.6)

Characteristics Of The Newborns

In total, 2,002 newborn babies were evaluated. Equal numbers at each of the study sites. Fifty-one percent (n = 1022) were female, 87.8% (n = 1742) had normal birth weight of 2.5 — 3.5kg and 8.2% (n = 163) low birthweight (< 2.5kg). (Table 2)

Birth-dose BCG vaccination rate.

Of the 2002 newborn babies, 1,534 (76.5%) received BCG within the first 24 hours (Table 2).

Reasons for missing or delayed BCG vaccination from chart review.

On chart review, 140 participants had identifiable reasons for delayed BCG vaccination. The major reasons for missing or delaying the birth dose of BCG included admission to neonatal unit with birth asphyxia (56.2%, n = 73) or birth weight < 2.5kg (30.8%, n = 40) (Table 2). There were no reasons recorded in the charts for missing the vaccine for 331 of the 471 affected newborns.

Cross-sectional study results.

Reasons For Delayed Bcg Vaccination

Of the 73 others interviewed at vaccination clinics confirmed that principal reasons for delayed BCG vaccination of their infants were prematurity (57.4%, n = 42) and admission to the Neonatal Intensive care unit (38.4%, n = 28).

Table 2
Newborn babies' characteristics from retrospective review.

Characteristics	Number (%)
Gender	
Male	980 (49)
Female	1022 (51.1)
Birth weight	
Normal Birth Weight (2.5–3.5 kg)	1742 (87.8)
Low Birth Weight (< 2.5kg)	163 (8.2)
High Birth Weight (> 4kg)	80 (4.0)
BCG was given within 24 hours of birth	
No	471 (23.5)
Yes	1534 (76.5)
Reasons for missing/delayed BCG vaccination (N = 140)	
Birth asphyxia	73 (56.2)
Birth weight < 2.5 Kg	40 (30.8)
Severe jaundice	10 (7.7)
No vaccine in Hospital	6 (4.6)
Other handicaps or illness	1 (0.8)
Other reasons for missing BCG (From Maternal Interviews, N = 73)	
NICU admission	28 (38.4)
Premature	42 (57.5)
Prolonged rupture of membranes	1 (1.4)
Sepsis	1 (1.4)
Down syndrome	1 (1.4)

Time to BCG vaccination.

The median time to BCG vaccination for these hospital-born babies was 1 (IQR: 1 — 3) day. (Table 3)

Table 3
Babies who received BCG vaccine with their respective dates of birth.

Time, days	Frequency.	Percent
0 — 1	1534	76.51
2 — 7	349	17.41
8 — 14	42	2.09
15 — 21	27	1.35
22 — 28	16	0.8
29 — 35	19	0.95
36 — 42	7	0.35
42 — 49	5	0.25
50 — 56	2	0.1
57 — 63	4	0.2
Total	2002	100

Time for completion of the vaccination process.

The median time required for completion of the vaccination process from the time of obtaining maternal consent to filling the vaccination record was 9 minutes (95% CI: 7 — 9).

Human Cost of BCG vaccination.

Using the current salary structure of enrolled nurses of 450,000 Ugandan shillings (UGX) and registered nurses of 650,000 UGX (1 UGX = $3, 650) together with the time required per newborn vaccination session, the estimated human cost of vaccination to the hospital was 500 UGX (IQR): 416 — 583). The vaccine is provided for free by UNEPI through the Ministry of health.

Discussion

This study assessed the timing of BCG vaccination among babies born at two hospitals. The average BCG vaccination rate within 24 hours of birth was 76.5%. This figure is lower than the country average of 88% reported by WHO and UNICEF estimates of national immunization coverage in 2019 and that reported in Kampala of 92.7% in 2012 in a study done by Babirye et al (10). However, most of the babies who missed the 0–1day mark were vaccinated within the next seven days.

The main reason for the delayed/missed birth dose of BCG vaccination was admission to the neonatal unit due to birth asphyxia, prematurity, and low birth weight. These are plausible reasons leading to

delayed vaccination as these conditions need the baby to first receive lifesaving interventions before vaccination can be undertaken. The high number of babies suffering birth asphyxia could be a reflection of acute and chronic maternal illnesses as well as other pregnancy-related complications. This is supported by the high proportion (49%) of mothers delivered by Caesarean section. However, this study did not inquire into the indications for Caesarean section but the commonest indications include obstructed labour and fetal distress(12). Prematurity contributed to a significant number of delayed vaccinations. There has been a growing burden of prematurity in Uganda and it currently stands at 13.6 per 1,000 live births(13). The study by Ayebare found that poor antenatal attendance among other factors contributed to preterm delivery. The current study found good antenatal attendance with 90.9% of the women having attended a minimum of three antenatal visits and as such may not have contributed significantly to premature births. Vaccine stockout was not a significant factor as only 4.6% of babies missed a birth dose as a consequence of lack of vaccine. This reflects the great effort made by the Government of Uganda through UNEPI to make vaccines available. These same factors could favour the successful implementation of Hepatitis B birth-dose vaccination in the country.

The average time taken to complete the BCG vaccination process for each baby was 9 minutes from the time of obtaining consent up to filling in the vaccination card and record book. This would not pose many limitations to adding an HBV vaccine as the only extra time would be for drawing the vaccine and documentation both of which could be done at the same BCG session.

The cost of vaccination using the current salary structure of nurses came to 500 UGX ($0.14 USD per baby vaccinated. This could reflect the additional cost to be borne for introducing a birth dose of the HBV vaccine as the vaccine is supplied free by the government.

Limitations Of The Study

The sample of health records assessed at each hospital was large (about 16 — 20%) and randomly selected but might not be fully representative of the patient populations. Records were sometimes incomplete so available documentation of BCG vaccination may have under-estimated the true rate of vaccination. Some of the maternal information was missing among records of deliveries at MRRH and was not included in the analysis. Likewise, data from this hospital was often missing to explain missed/delayed birth doses of BCG. This hospital did not assess nurses' time taken for vaccination (and hence cost of vaccination) or conduct maternal interviews to establish additional reasons for missing BCG birth-dose because at the time of the study the research assistant could not access the clinical areas due to COVID-19 restrictions. This study was limited to hospital deliveries and does not consider deliveries that occur outside of the formal health facilities in Uganda. Such infants might miss out on the birth dose of BCG and HBV vaccine. However, with decreasing numbers of deliveries occurring outside health facilities, this would not disadvantage many newborns. This can also be minimized through health education during antenatal clinics where mothers are encouraged to deliver within health facilities so that their babies could benefit from birth doses of both BCG and HBV vaccines.

Conclusion

BCG vaccine uptake within 24 hours of birth was 76.5%. The major reason for delayed vaccination was admission to the neonatal care unit. Even though HBV vaccination starting at 6 weeks of birth has contributed to a significant reduction in HBV infections in the country, a birth dose is recommended by WHO for greater impact. This study shows that most babies get BCG within 24hrs of birth, a success that can inform a change in policy to bring the first HBV vaccine dose to within 24hrs and improve the impact of this important vaccination.

Abbreviations

ANC Antenatal care

BCG Bacillus Calmette Guerin

HBV Hepatitis B virus

HBsAg Hepatitis B surface antigen

MRRH Mbarara Regional Referral Hospital

REC Research Ethics Committee

UNCST Uganda National Council of Science and Technology

UNICEF United Nations Children's Fund

UNEPI Uganda National Expanded Program on Immunization.

Declarations

Ethics approval and consent to participate

We obtained Research Ethical Committee (REC) approval from Mbarara University of Science and Technology REC. Approval Number 07/12-18, and the Uganda National Council of Science and Technology (UNCST). UNCST Registration Number HS415ES.

All participants who were interviewed in the cross-sectional part of the study provided written informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AM, MM, VC, PN, SK, EK, ML conceived and wrote the study protocol.

AM, ML, FN, PN collected the data and performed data analysis

AM, FB lead the manuscript writing

DS International coach, advised on the study protocol and manuscript.

All authors read and approved the final manuscript

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- Appendix.docx