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Immune response and associated factors to Hepatitis B vaccination among children under five attending care at mulago hospital

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Abstract

Background Hepatitis B is a major global health concern, with chronic infections affecting approximately 296 million people yearly. A 2009 survey in East Africa showed a prevalence rate of 6.5%, with Uganda's rate at 10.3% and Northern Uganda at 20.7%. Therefore, this study sought to determine the immune response to Hepatitis B vaccination and associated factors among children under five attending outpatient care at Mulago Assessment Centre Pediatrics clinic.

Methods A cross-sectional study involving 301 children aged 1 to under 5 years at Mulago National Referral's Pediatrics clinic was conducted in February 2023. Children were consecutively enrolled and screened for Hepatitis B core antibodies, with anti-HBs antibody titers measured. A pretested semi-structured questionnaire was administered to caregivers. Data analysis was conducted using STATA Version 13.0. Logistic regression analysis was done to determine factors associated with immune response, a binary outcome.

Results All 301 children tested negative for Hepatitis B core antibodies. Children's ages ranged between 1 and 4 years with most aged 2 years, 89/301(29.6%). The immune response varied from 2 IU/ml to 1000 IU/ml, with a median of 86.2 IU/ml (IQR: 14.5-239.4). The prevalence of good immune response was 77.4% (233/301) (95% CI: 72.3-81.8%), with 58.4% (95% CI: 51.9-64.6%) classified as very good responders. The factors associated with immune response were child age (aOR = 0.40; 95% CI: 0.16–0.97; $p = 0.044$) and caregiver HIV status (aOR = 0.17; 95% CI: 0.04–0.71; $p = 0.014$).

Conclusion Children had protective antibody levels against the Hepatitis B virus, but it is still below the expected level by the World Health Organization. The child's age and caregiver's HIV status were associated with immune response. Emphasis needs to be made on the Hepatitis B birth dose and booster vaccinations, especially for children over 1 year and at-risk groups, to lower transmission rates and enhance long-term Hepatitis B protection.

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Keywords Immune response, HBs antibody, Hepatitis B vaccination, Children under five years, Mulago hospital, Uganda

Introduction

Hepatitis B Virus (HBV) infection, is a life-threatening viral liver infection, that is transmitted through various means, including vertically by mother-to-child transmission; horizontally from an infected child to an uninfected child, sexual intercourse, blood, and sharps [1, 2]. Globally, around 296 million individuals are affected by Chronic Hepatitis B (CHB) [3], leading to 1.5 million new cases annually, and causing 887,000 deaths each year due to HBV infection or related complications [1, 4, 5]. Approximately 820,000 deaths were associated with hepatitis B in the single year of 2019 [6]. In Uganda, a cross-sectional population-based study in Northern Uganda uncovered a prevalence of HBV infection in children, reaching 21.9%, with a corresponding lifetime exposure of 48% [7]. Additionally, the National serosurvey indicated high endemicity of HBV in the country, occurring in both childhood and adulthood, with a prevalence of 4.3% [6, 8].

The natural history of Hepatitis B involves stages like immune tolerance, immune activity, immune control, and immune escape, with children often in the immune-tolerant stage, characterized by a positive HBeAg, normal ALT, and a high viral load [9]. However, the infection can progress to CHB with associated complications like cirrhosis, and fibrosis, which can lead to Hepatocellular carcinoma [10]. Chronic Hepatitis B follows four phases such as the immune-tolerant phase, with high viral load but minimal liver damage; the immune-active phase, where the immune system attacks the liver, leading to elevated liver enzymes (ALT); the inactive phase, characterized by low viral replication and stabilized liver inflammation; and the immune escape phase, where viral replication and liver damage fluctuate [11].

Although no virologic cure is currently available for HBV, improving access to care through vaccination and treatment strategies has been found helpful to patients with co-infections, family history of liver disease, and comorbidities, regardless of viral load [8, 12]. The World Health Organization (WHO) guidelines recommend initiating treatment for individuals with fibrosis or cirrhosis at an HBV DNA level of > 2000 IU/mL and raised ALT, compared to the previous threshold of > 20,000 IU/mL [11]. Following WHO guidelines for CHB prevention, birth dosing was recently introduced in Uganda where it is recommended that children be vaccinated right from birth within 24 h [13]. This is then followed by 2–3 subsequent shots to protect them against HBV for at least 20 years or lifelong immunity without the need for booster doses [14, 15]. Catchup doses can be done for adolescents or older children who might have missed without the need for booster doses [14, 15].

This approach has demonstrated a 90% effectiveness in reducing the disease's impact, preventing infections, and decreasing prevalence in children under 5 years [16, 17]. Research suggests receiving two doses of HBV vaccine in specific groups can lead to an improved immune response, providing enhanced protection [18, 19]. Administering three doses of the hepatitis B vaccine typically induces protective antibody levels in over 90% of healthy infants and children [20], yet a considerable proportion of vaccinated infants in Uganda exhibit low antibody titers, and only half show a good immune response, even with a booster dose [21, 22].

The presence of anti-HBs is indicative of an immune response following vaccination [23]; however, studies have shown that cellular immunity can provide long-term protection [24]. Memory T-cells and B-cells generated during vaccination can increase a good immune response upon re-exposure to the virus, even if circulating antibody levels decline over time [25]. Variability in the immune response to the hepatitis B vaccine, especially in infants, is associated with various factors [22, 26–28]. Individual differences, including genetic variations [29, 30]; the age of vaccine administration [6, 22]; and maternal antibodies transferred during pregnancy [31] influence how the immune system reacts to vaccination. Other factors like the type of vaccine [21], disease-induced immune suppression, storage conditions, timing, dosage of vaccine administration, and population-specific elements, collectively influence immune responses.

Studying the immune response to the HBV vaccine is important since it bridges the information gap on how protected children under five are against the Hepatitis B virus. Therefore, this study sought to determine the immune response among children under five who attend the Mulago Assessment Center (MAC) Pediatric Clinic that were previously vaccinated and possible factors that may be associated with the immune response. This study provides information on the level of protection in children under five to inform other interventional strategies like the introduction of additional booster doses at the National level. The information can also be used in educational programs or campaigns to increase uptake and adherence to Hepatitis B vaccination. The research will provide a basis for further studies in the area that can further help fight the HBV epidemic in Uganda.

Materials and methods

Study design and setting

Across-sectional study, employing a purely quantitative approach, was conducted in February 2023 at the Mulago Assessment Centre (MAC) Pediatrics Clinic in Mulago National Referral Hospital (MNRH). Mulago National Referral Hospital is located in the Kampala District, the central region of Uganda. It serves as the teaching hospital for the Makerere University College of Health Sciences (MAKCHS). Mulago Hospital has MAC Pediatrics clinic founded in 2010 to serve as a general outpatient facility for children aged 1 day to 12 years. The clinic has a mission to provide quality pediatric services in Neurology, Endocrinology, Pulmonology, Cardiology, and Orthopedic to all children within that age bracket. In 2020, it attended to a total of 15,560 children, with a monthly average of 1,300 patients and a daily estimated average of 46 children across all age groups. The clinic runs from 8 am to 4 pm every day of the week offering non-specialized care to the children and acts as a point of referral to specialized clinics. The clinic is staffed by both medical and non-medical personnel, the team includes one medical officer who heads the unit, three clinical officers, two nursing aids, six nurses, one records officer, and one cleaner.

Population and eligibility criteria

The study recruited a total of 301 children receiving outpatient care at MNRH in February 2023. Eligible participants were children aged 1 to less than 5 years, and their caregivers who willingly consented to participate in the study. The children whose caregivers had evidence (history) of hepatitis B vaccination such as child health card or maternal recall of the of the number of doses received, sites of vaccination, and the location where the vaccine was administered were also included in the study. In contrast, those who were chronically ill but stable were included in the study. The study excluded children confirmed to have HBV infection and those experiencing severe illness requiring urgent medical attention.

Sample size and sampling procedure

We employed Fleiss's statistical methods for rates and proportions to determine the required sample size, using vaccination status as the binary predictor. Assumptions were based on a study by Kumar et al. (2021) where protective antibodies were present in 69.9% of fully vaccinated individuals, compared to 52.7% in partially vaccinated individuals [32]. A 2-sided confidence level of 95% and 80% power was utilized, with 0.05 as the absolute sampling error, aiming for 274 children (137 fully vaccinated and 137 partially vaccinated). Accounting for a 10% error rate, the final sample size was adjusted to 301. The Outpatient Department (OPD) register was used to identify children aged 1 to <5 years who attended care at the clinic on working days. Those meeting eligibility criteria were consecutively enrolled in the study, with an average of 20 participants daily.

Study variables

The main outcome variable was immune response to HBV vaccination in children under five attending OPD care at MAC Pediatrics clinic. Independent variables were socio-demographic characteristics of the children (age, gender, place of residence; caregiver characteristics (relationship to child, marital status, education level, employment status, history of Hepatitis B testing, Hepatitis B status, history of HIV testing, HIV status) and Clinical characteristics of children like BMI, history of Hepatitis B vaccination, facility where child got Hepatitis B vaccine, number of Hepatitis B vaccine shots, intervals of Hepatitis B shots, gestation at birth, congenital abnormalities, HIV serostatus, previous admissions and treatments in past 12 months, birth weight, HBcAb Test.

Data collection tool and measurement

Data collection involved face-to-face interviews with caregivers using structured questionnaires. For participants not fluent in English, the questionnaire was translated into Luganda to obtain information on factors associated with immune response. We also inquired about both the birth dose and the subsequent 3-dose series as part of the national immunization schedule. Intervals at which Hepatitis B vaccine was administered were classified as; "On Schedule" or "Not on schedule/Off schedule" based on guidelines set by the Uganda National Expanded Program on Immunization (UNEPI) {Minisstry of Health, 2016 #65}. On schedule meant a child received the Hepatitis B vaccine according to the UNEPI schedule for vaccination within 0, 6, 10, and 14 weeks. Not on schedule/Off Schedule meaning: The child did not receive their Hepatitis B vaccination within these recommended intervals.

Initially, we found that only one out of the ten participants had a vaccination card on 3 random visits to the clinic before the study, making it unfeasible to completely rely on the child's health cards to confirm vaccination status. As a result, we included maternal recall i.e. asking mothers to recall the number of shots given in the first 3 months, age, site of vaccination, and location where the vaccine was administered to verify it is indeed a vaccination center. The questionnaire was further validated through a pre-test conducted with a sample group involving 10 participants from MNRH, specifically the MAC Pediatrics clinic, to assess clarity and reliability before preceding actual data collection. Additionally, we adopted a core antibody test to determine whether the presence of antibodies was due to disease exposure or immunization.

The principal investigator provided one-day training on the data collection tool and procedures to research assistants, and continuous supervision by investigators ensured thorough checks for clarity, completeness, and accuracy in the collected data. Eligibility screening for immune response was conducted, followed by the acquisition of informed consent from all participants.

Serological testing

Data was also obtained from laboratory-analyzed samples. From each child whose caregiver had provided consent, blood samples were collected under aseptic conditions in a red vacutainer, amounting to 2–3 mLs of venous blood. These samples were centrifuged for an hour to obtain serum, and subsequently tested for qualitative core antigen antibodies and quantitative antibodies against Hepatitis B surface using the Cobas 6000 analyzer series. The collected samples were batched in groups of 50, and those not processed immediately were stored at 2–8 °C for up to a week. Sample collection and storage procedures were executed as promptly as possible, following the standard protocol, and were completed within a maximum timeframe of 6 h.

Serological examinations took place at MNRH Laboratory-Block 5, utilizing Electrochemoluminescence (ECL) [33] to analyze serological markers for HBV, including HBsAg, hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), and hepatitis B e antibody (HBeAb). All tests were conducted and interpreted following the manufacturers' instructions. Children with anti-HBs Ab titer between 2 and <10 U/mL were classified as poor responders, while those with an anti-HBs Ab titer of ≥ 10 U/mL were considered good responders against HBV vaccination.

Statistical analysis

The collected data was cleaned, coded, entered into EpiData version 3.0, and exported to STATA version 13 for analysis. Categorical variables were summarized using frequencies and percentages, while continuous variables were presented with either the mean (standard deviation) or median (interquartile range). Immune response is a dichotomous variable categorized as poor response and good response. The Immune response was determined by obtaining the proportion of the eligible participants who quantitatively fell under these categories; Poor responders i.e. non-responders (0 IU/mL) and Moderate responders (1-<10 IU/ml); and good responders (>/= 10IU/ml) [23]. The numerator was the number of eligible participants per category and the denominator was the total number of eligible participants from the study ($n = 301$). The immune response was then reported as a percentage with the corresponding 95% confidence interval.

After testing for all assumptions, bivariate logistic regression was done to determine the relationship between each independent factor and immune response since the outcome is binary. The independent factors considered were the children's sociodemographic factors, the children's clinical factors, and the caregiver factors. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were used to quantify the associations between factors influencing the immune response to HBV vaccination. All variables with a p-value less than 0.2 were considered for multivariate analysis. Collinearity (similarity in variable information) was also tested to determine which variables could be included in the multivariate regression model. Thereafter, multivariate logistic regression was done to determine the factors that were dependently associated with immune response in the Children under five at the MAC-Pediatrics clinic. Interaction and confounding were tested to develop the final model. A p-value of less than 0.05 was deemed statistically significant.

Results

Study profile

In the one-month study period, 1500 children presented to the MAC Pediatrics clinic, and 316 children were screened for eligibility. The remaining 15 children were not enrolled due to their blood samples being coded insufficient ($n = 12$) and blood samples without study IDs ($n = 3$). There were 301 children enrolled in the study and included in the analysis.

Socio-demographic characteristics of children and their caregivers

The 301 children recruited had ages ranging between 1 and 4 years with the highest number, 89/301(29.6%), aged 2 years. Half of the children were male, 51.5% (155/301) while the majority were from tribes within the central region of Uganda and were living in the urban area within rented houses. The majority were living with their biological parents. Almost 80% (240/301) of the children had 1 to 5 siblings and 54.5% (164/301) lived with 2 to 4 people at home (Table 1). The caregiver characteristics showed that 81.4% (245/301) of the caregivers were mothers and most were married and unemployed. Regarding education, the highest number of caregivers had attained secondary education (43.2%, 130/301). There were 52.5% (158/301) of the caregivers who had a household income of less than 100,000/= and 80.7% (243/301) of the caregivers' Hepatitis status was unknown (Table 1).

Table 1 Socio-demographic characteristics of children and their caregivers attending OPD at MAC Pediatrics in Mulago National Referral Hospital

Variable	Frequency (N = 301)	Percentage (%)
Age (Completed years)		
1 year	67	22.3
2 years	89	29.6
3 years	84	27.9
4 years	61	20.3
Sex		
Male	155	51.5
Female	146	48.5
Tribe		
Central region	199	66.1
Western region	67	22.3
Eastern region	27	9.0
Northern region	6	1.9
Non-Ugandans (Kenyan and Tanzanian)	2	0.7
Residence		
Urban	293	97.3
Rural	8	2.7
Number of siblings at home		
None	53	17.6
1 to 5	240	79.7
>5	8	2.7
Number of people living at home		
2 to 4 people	164	54.5
5 to 7 people	127	42.2
8 to 13 people	10	3.3
Type of house the child stays in		
Rented	243	80.7
Own home	58	19.3
People child lives with		
Biological Parents	295	98
Others[1]	6	2
Characteristics of caregivers		
Relationship to child		
Mother	245	81.4
Father	41	13.6
Other	15	5
Marital status		
Married[2]	268	89
Never married	11	3.7
Divorced or separated	19	6.3
Widowed	3	1
Highest education level		
None	30	10
Primary school	116	38.5
Secondary school	130	43.2
Tertiary/university	25	8.3
Employment status		
Unemployed	157	52.2
Self-employed	112	37.2
Formal employment	30	10
Peasant farmer	2	0.7
Estimated monthly income		

Table 1 (continued)

Variable	Frequency ($N=301$)	Percentage (%)
Age (Completed years)		
<100,000 UGX	158	52.5
100,000 to 300,000 UGX	61	20.3
300,000 to 1,000,000 UGX	77	25.6
>1,000,000 UGX	5	1.7
History of Hepatitis B testing		
Yes	58	19.3
No	243	80.7
Hepatitis B status		
Negative	57	18.9
Positive	1	0.3
Unknown	243	80.7
History of HIV testing		
Yes	292	97
No	9	3
HIV status		
Negative	284	94.4
Positive	8	2.6
Unknown	9	3.0

[1]Other people the child lives with include Aunt, Uncle, and Grandparents.

[2]Married is defined as those who are legally married or cohabiting.

Clinical characteristics of children

Regarding children's clinical characteristics, children had a mean weight of 14.8 kg (SD = 8.3) and a mean height of 89.1 (SD = 12.5). The majority of the children had a normal nutritional status and had received all three Hepatitis B vaccine shots (Pentavalent vaccine) from a government facility. There were 67.8% (204/301) of the children with a normal body temperature and only 11.3% (34/301) had been admitted in the past 12 months. Most of the children, 97.7% (294/301) had been born at term and only 1.3% (4/301) had congenital abnormalities (Table 2). There were 79.0% (225/301) of the children born with a normal birth weight (2.5 to 3.5 kg). Among the 301 children, 1 child had cerebral palsy, 1 child had a congenital heart defect and none of the children had diabetes, malabsorption syndrome, nephrotic syndrome, or spinal muscular atrophy.

HBsAg tests were not done; however, all patients underwent HBcAb testing to ensure that antibodies were not from exposure to disease. All the children tested negative for the Hepatitis B core antibody screen. Findings on intervals of Hepatitis B shots indicated that 97.7% (294/301) of the children were off schedule, implying they did not receive the Hepatitis B vaccination within the intervals of 0, 6, 10, 14 weeks as recommended by the Uganda National Expanded Program on Immunization (UNEPI).

Immune response to hepatitis B vaccine among children

The immune response, represented by the Hepatitis B antibody titers, ranged from 2 IU/ml to 1000 IU/ml. The children had a median Hepatitis B antibody titer of 86.2 IU/ml (IQR: 14.5, 239.4). The proportion of the Immune response was determined by eligible participants who quantitatively fell under the good immune response (Titer values greater than 10 IU/ml). The prevalence of a good immune response was 77.4% (95% CI: 72.3 – 81.8%), which was calculated by getting the percentage of the number of children with a good response (233) out of the total number of children recruited in the study (301) multiplied by 100. The 233 good responders were further divided into good responders with titer values from 10 to < 100 IU/ml and very good responders with titer values over 100 IU/ML. The proportion of very good responders was 58.4% (95% CI: 51.9 – 64.6%) which was obtained by getting the percentage of children with very good responses (136) divided by the total number of children with good responses (233) (Fig. 1).

Factors associated with the immune response to Hepatitis B vaccine among children attending mulago assessment center

Bivariate analysis

Bivariate analysis was done using logistic regression, and the factors with a p-value of less than 0.2 were considered for further analysis. The children's sociodemographic characteristics considered were age and type of house lived in (Table 3). Children aged 2, 3, and 4 years

Table 2 Clinical characteristics of children under five attending OPD care at MAC

Variable	Measure	Frequency (*N* = 301)	Percentage (%)
Weight (kg) Mean (SD)	14.8(8.3)		
Median (IQR)	14.0 (12,16)		
Height (cm) Mean (SD)	89.1 (12.5)		
Median (IQR)	89 (81,98)		
z-score (nutritional status)			
<-3 SD to <-2SD (SAM/MAM)		4	1.3
-2 to + 2 SD (NORMAL)		258	85.7
>+2 SD to > + 3 SD (OVERWEIGHT/OBESITY)		32	10.6
Temperature			
<35.5 C		2	0.7
35.5 to 37.5 C		204	67.8
>37.5 C		95	31.6
Facility where child got Hepatitis B vaccine			
Government facility		279	92.7
Private Hospital		22	7.3
Number of Hepatitis B vaccine shots			
3 shots		299	99.3
1 shot		2	0.7
Intervals of Hepatitis B shots			
On schedule (6, 10 and 14 weeks)		7	2.3
Not on schedule		294	97.7
Gestation at Birth			
Preterm		7	2.3
Term		294	97.7
Congenital abnormalities (*n* = 297)			
Yes[1]		4	1
No		293	98.7
HIV serostatus			
Exposed		3	1
Positive		1	0.3
Negative		297	98.7
Previous admissions in past 12 months			
Yes		34	11.3
No		267	88.7
Previous treatments in past 12 months			
Steroids		2	0.7
Antibiotics		241	80.1
Anticancer treatments		1	0.3
Birth weight (kg)			
Underweight (1.4 to 2.4 kg)		21	7.4
Normal (2.5 to 3.5 kg)		225	79.0
Overweight (3.6 to 4.6 kg)		39	13.6
HBcAb Test Results			
HBcAb Positive		0	0
HBcAb Negative		301	100

1 The congenital abnormalities include cerebral palsy, Down syndrome, and hydrocephalus. 2 Other treatments include antimalarials, antifungals, Panadol, vitamin C and hydroxyurea, steroids, anticancer

had lower odds of being immune responders compared to 1-year-olds, with odds ratios of (cOR 0.53, 95% CI: 0.23–1.22), (cOR:0.53; 95% CI: 0.23–1.21) and (cOR:0.54; 95% CI 0.22–1.31) respectively. However, these differences were not statistically significant since the p-value was greater than 0.05). This could be attributed to factors such as vaccination timing (on-schedule vs. off-schedule), vaccine quality, or individual biological variation. The caregiver characteristics considered were employment status, Hepatitis B status, and HIV status (Table 3).

There were none of the children's clinical characteristics that were considered for further analysis (Table 4).

Multivariate analysis

Multivariate logistic regression analysis was done to determine the factors that were independently associated with immune response to Hepatitis B vaccination. Interaction and confounding were assessed for and were not found present between the variables. Table 5 shows the details of the results from multivariate analysis where the age of the child and the HIV status of the caregiver were found to be significant factors associated with immune response.

Regarding age, children aged 3 years were 60% less likely to have a good immune response compared to children aged 1 year (aOR = 0.40; 95% CI: 0.16–0.97; $p = 0.044$). Conversely, children aged 2 years (aOR = 0.44; 95% CI: 0.18–1.06; $p = 0.067$) and 4 years (aOR = 0.42; 95% CI: 0.16–1.07; $p = 0.070$) did not show a significant difference in immune response compared to their counterparts aged 1 year (Table 5**)**. Concerning the HIV status of caregivers, children whose caregivers had positive HIV status were 20% less likely to display a good immune response than those with caregivers testing negative for HIV (aOR = 0.20; 95% CI: 0.05–0.87; $p = 0.032$). Similarly, children with caregivers of unknown HIV status showed an 84% reduced likelihood of having a good response compared to those with caregivers having a known HIV status (aOR = 0.16; 95% CI: 0.04–0.65; $p = 0.011$) **(**Table 5**).**

Discussion of results

The study set out to determine the immune response to Hepatitis B Virus vaccine The factors associated with the

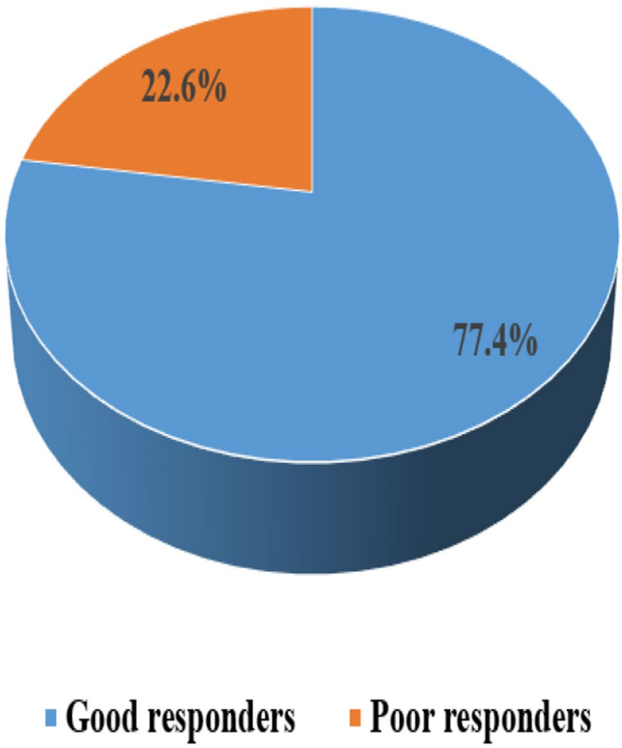

Fig. 1 Prevalence of good immune response to Hepatitis B vaccination among children under five attending OPD care at MAC Pediatrics in MNRH

immune response were the HIV status of the mother and the age of the child.

Immune response among children under 5 at mulago assessment centre pediatrics clinics in mulago

The immune response of 77.4% found in this study shows that the HBV vaccine confers protection to majority of the children at Mulago Assessment Centre Pediatrics clinic. The protective immune response could largely be explained by the incorporation of birth dosing that is meant to reduce the hepatitis B global burden among children under 5 to less than 1% according to WHO [20]. However, it is still lower than the 90% global target [11]. The failure to meet the WHO target may be due to the reduction in the antibody titers over time among participants who were over 9 months after immunization. Despite the vaccine's protective effect, a poor response rate (22.6%) was noted among children. This could be due to their immature immune systems and interference from maternal antibodies acquired through breastfeeding or prenatal transfer [31, 34]. According to the Hepatitis B Foundation (HBF), this reduction in antibody titers could still explain the steady increase of new cases registered globally of 1.5 million annually mostly diagnosed in adulthood [1].

Studies conducted in diverse regions, including South-Western Uganda, Poland, and Morocco, reported lower seroprotection rates of 5.5%, 53.5%, and 29%, respectively [6, 35, 36]. The immune response in this study was far less than the response denoted in other studies like Italy that found seroprotection to be 84.2% for those vaccinated in infancy [37]. The seroprotection level of 92% was found in a cross-sectional study among 128 children in Cameroon which was also higher than that found in this study [38]. Other studies that showed higher responses included; Accra (84.4%) and rural Nigeria (84.6%) among the vaccinated children [3, 34]. This difference may be due to a difference in the age groups studied which brings in the aspect of age as a factor highlighted in our study as a factor to the response. The age factor also denotes time since the vaccine was received which is an important factor in antibody response according to the current study.

Antibody titers, particularly levels above 100 IU/ml, are commonly used to assess protective immunity. The proportion of children with good immune response from our study was found higher than 68.86% found in a cross-sectional study among 122 children within a tertiary hospital in India [32]. This response proportion was also higher than results found in similar studies done within Africa including a study done in Senegal (58%) [38] and one done in Ethiopia (54.3%) [39]. However, antibody titres alone may not fully represent immune protection, since a strong immune response is always expected post-vaccination. Findings from various settings, including our study at Mulago Hospital, indicate that some children fail to meet the WHO-recommended 90% antibody response threshold [20]. Studies, such as those by BC Simons, PR Spradling, DJ Bruden, C Zanis, S Case, TL Choromanski, M Apodaca, HD Brogdon, G Dwyer and M Snowball [40], have shown that even when antibody titers are low or undetectable, individuals can still be protected through cellular immunity, which involves memory B-cells and T-cells [40]. Cellular immunity, especially T-cell responses, can provide additional protection. Memory T-cells and B-cells formed during vaccination enable a rapid immune response upon future exposure to the virus, even if circulating antibody levels decrease over time [25].

The poor response rate from our study was 22.6% which is twice the expected global registered poor response rate of 5–10% according to the CDC [15]. This further underscores the more recent increases in the prevalence globally and the numerous outbreaks registered in Uganda, especially the Northern region [1, 7]. This could be due to vaccine efficacy being altered during vaccination in the community due to transport and storage conditions, brand of the vaccine, or having only 3 doses that may not be sufficient. The striking disparity between our results may also be explained by the inadequate information obtained regarding the number of doses obtained by the children enrolled in the study.

Table 3 Bivariate analysis of children and caregiver socio-demographic characteristics and immune response to Hep B vaccine

Variable	Immune response		cOR	95% CI	*p*-value
	Poor responders	Good responders			
	N (%)	*N*(%)			
Age* **					
1 year	10(14.9)	57(85.1)	1		
2 years	22(24.7)	67(75.3)	0.53	0.23–1.22	0.137
3 years	21(25)	63(75)	0.53	0.23–1.21	0.131
4 years	15(24.6)	46(75.4)	0.54	0.22–1.31	0.172
Sex					
Male	33(21.3)	122(78.7)	1		
Female	35(24)	111(76)	0.86	0.50–1.47	0.578
Tribe					
Muganda	43(23.1)	143(76.9)	1		
Munyankole	10(20.8)	38(79.2)	1.14	0.53–2.48	0.736
Other	15(22.4)	52 (77.61)	1.04	0.53–2.03	0.903
Residence					
Urban	67(22.9)	226(77.1)	1		
Rural	1(12.5)	7(87.5)	2.08	0.25–17.17	0.498
Number of siblings at home					
None	10(18.9)	43(81.1)	1		
1 to 5	55(22.9)	185(77.1)	0.78	0.37–1.66	0.522
>5	3(37.5)	5(62.5)	0.39	0.08–1.90	0.242
Number of people living at home					
2 to 4 people	34(20.7)	130(79.3)	1		
5 to 13 people	34(24.8)	103(75.2)	0.79	0.46–1.36	0.399
Type of house child lives in					
Rented	50(20.6)	193(79.4)	1		
Own home	18(31)	40(69)	0.58	0.30–1.09	0.089
Who the child lives with					
Biological Parents	67(22.7)	228(77.3)	1		
Others	1(16.7)	5(83.3)	1.47	0.17–12.79	0.727
Caregiver Characteristics					
Relationship to child					
Mother	55(22.4)	190(77.6)	1		
Father	8(19.5)	33(80.5)	1.19	0.52–2.73	0.675
Other	5(33.3)	10(66.7)	0.58	0.19–1.76	0.337
Marital status					
Married	58(21.6)	210(78.4)	1		
Never married/ Divorced or separated /Widowed	10(30.3)	23(69.7)	0.64	0.29–1.41	0.265
Highest education level (Caregiver)					
None/Primary	34(23.3)	112(76.7)	1		
Secondary school	27(20.8)	103(79.2)	1.16	0.65–2.05	0.615
Tertiary/university	7(28)	18(72)	0.78	0.30–2.03	0.611
Employment (Caregiver)					
Unemployed	29(18.5)	128(81.5)	1		
Employed	39(27.1)	105(72.9)	0.61	0.35–1.05	0.076
Estimated monthly income					
<100,000 UGX	29(18.4)	129(81.6)	1		
300,000 to > 1,000,000 UGX	39 (27.3)	104(72.7)	0.07	0.35–1.03	0.657
Hepatitis B status					
Unknown	59(24.3)	184(75.7)	1		
Known (Negative/Positive)	9(15.5)	49(84.5)	1.75	0.81–3.77	0.156

Table 4 Bivariate analysis of children's clinical characteristics and immune response to Hepatitis B vaccine

Variable	Immune response		cOR	95% CI	*p*-value
	Poor	Good			
	N(%)	*N*(%)			
Nutritional status of the child					
Normal	58(22.5)	200(77.5)	1		
Overweight/ obesity	9(23.1)	30(76.9)	0.97	0.43–2.15	0.934
SAM/MAM	1(25.0)	3(75.0)	0.87	0.09–8.52	0.905
Temperature					
35.5 to 37.5 C	48(23.5)	156(76.5)	1		
<35.5 or > 37.5	20(20.6)	77(79.4)	1.18	0.66–2.13	0.573
Place where vaccine was got					
Government facility	65(23.3)	214(76.7)	1		
Private Hospital	3(13.6)	19(86.4)	1.92	0.55–6.71	0.305
Interval of Hepatitis shots					
On schedule (6, 10 and 14 weeks)	67(22.5)	231(77.5)	1		
Not on schedule	1(33.3)	2(66.7)	0.58	0.05–6.50	0.659
Gestation at birth					
Term	68(23.1)	226(76.9)	1		
Preterm	0(0)	7(100)	1	-	-
Birth weight					
2.5 to 3.5 kg Normal weight	49(21.8)	176(78.2)	1		
1.4 to 2.4 kg underweight	6(28.6)	15(71.4)	0.7	0.26–1.89	0.477
3.6 to 4.6 kg overweight	9(23.1)	30(76.9)	0.93	0.41–2.08	0.856
HIV sero status of the child					
Exposed	1(33.3)	2(66.7)	1		
Positive	0(0)	1(100)	1	-	-
Negative	67(22.6)	230(77.4)	1.72	0.15–19.22	0.661
Congenital abnormalities					
Yes	64(21.8)	229(78.2)	1		
No	2(50.0)	2(50.0)	0.28	0.04–2.02	0.207
Previous admissions in last 12 months					
No	60(22.5)	207(77.5)	1		
Yes	8(23.5)	26(76.5)	0.94	0.41–2.19	0.89
Treatments given in last 12 months					
Antibiotics	51(21.2)	190(78.8)	1		
Other	17(28.3)	43(71.7)	0.68	0.36–1.29	0.236

Table 5 Multivariate analysis of factors associated with immune response to Hep B vaccine among under 5 children attending MAC

Variable	cOR (95% CI)	*p*-value	aOR(95% CI)	*p*-value
Age				
1 year	1		1	
2 years	0.53(0.23–1.22)	0.137	0.44(0.18–1.06)	0.067
3 years	0.53(0.23–1.21)	0.131	0.4(0.16–0.97)	0.044
4 years	0.54(0.22–1.31)	0.172	0.42(0.16–1.07)	0.07
HIV status of caregiver***				
Negative	1		1	
Positive	0.26(0.06–1.08)	0.064	0.20(0.05–0.87)	0.032
Unknown	0.21 (0.05–0.81)	0.023	0.16(0.04–0.65)	0.011

Current vaccination coverage surveys are based mainly on an assessment of immunization cards [41]. In this study, the information obtained may have been biased since there were only 5 cards received with the majority of the information not confirming whether all doses were obtained. Vaccination card registrations demonstrate a critical need for accurate monitoring of vaccine delivery and coverage. This poor response problem may extend well beyond hepatitis B since the vaccine is received through a pentavalent vaccine. The same children who may have not developed an immune response to the HBV vaccine may also be at risk for having a poor response to diphtheria, tetanus, pertussis, and Haemophilus influenzae B vaccines.

All the studies aforementioned showed that the WHO standard of seroprotection at > 90% was not attained. This failure could be due to problems with storage conditions which may be affected by the frequent power outages where there are limited power backup systems cold chain [42]. This in turn compromises the cold chain which may influence the quality of the Hepatitis B vaccines the children are receiving. There may also be a need to assess the quality of the pentavalent vaccine. Second, there may be a quality problem with the pentavalent QuinvaxemTM (Crucell) vaccine [43].

Factors associated with immune response among children under 5 at MAC pediatrics clinics in mulago

The study found child age and caregiver HIV status influenced immune responses among children at MAC. Three-year-olds were 60% less likely to have a good immune response than one-year-olds. These findings align with cross-sectional studies conducted in African countries; in Burkina Faso, and Cameroon, indicating an association between younger age and seroprotection [23, 44]. Similarly, another study done in Basel Switzerland suggested that older age at vaccination was associated with a poor antibody response, partly attributed to declining antibody levels with increasing age [45]. This could partly be due to the decreasing antibody levels over time described in the literature on Hepatitis B [22].

However, the variance within the age group for our study showed that immune response among 2 and 4-year-olds did not differ significantly from that of 1-year-olds. This could be explained by the increase in the protective memory B-cell levels over time. It may also be due to a difference in timing when the four-year-old children got their vaccines compared to the three-year-olds. Other researchers argued that better immune responses are observed when administering the HBV vaccine to older children compared to infancy, possibly due to a more mature and dynamic immune system primed at that age [22, 46]. Despite the contradicting findings regarding the impact of age on immune responses to the HBV vaccine, healthcare providers should consider age-optimized vaccination strategies to enhance the effectiveness of the immunization process.

Among the caregiver factors, results indicated that children with caregivers testing positive for HIV were 80% less likely to develop protective antibodies. This is similar to a study conducted in America that showed a reduced response to the HBV vaccine in HIV-exposed or even infected children [47]. Additionally, children with caregivers of unknown HIV status showed an 84% reduced likelihood of a good response compared to those with known HIV status. The children of caregivers with unknown HIV status may be exposed to HIV without any PMTCT hence the poor response. This may lead them to be easily infected with HIV which greatly affects the immune system i.e. the antigen-presenting cells (cellular) and humoral (T & B lymphocytes affected) [22]. Similar findings have been reported indicating reduced response to HBV vaccine close to 29% in HIV-exposed or infected children [36]. Contrary to the previous findings, people living with HIV (PLWH) who received the HBV vaccine demonstrated a positive response with a pooled response rate of 71.5% [48]. This indicates successful immunization against Hepatitis B, highlighting the importance of maternal testing and participation in the prevention of mother-to-child transmission (PMTCT) programs to reduce seroexposure in infants [31, 37]. Another study conducted in Cameroon among HIV-infected children showed a non-response rate of 71% therefore pausing a great risk of poor response in sub-Saharan Africa which is highly endemic [36]. It is important to ensure all pregnant mothers are tested and undergo the PMTCT program to reduce the seroexposure of infants to HIV.

Strengths and limitations

Study strengths

This the first study in Uganda and East Africa as a whole to study the immunological response to Hepatitis B vaccination in children under five and influencing factors. The sample size, was sufficient for the study's objectives and provides valuable baseline data for future research, including cohort studies. The study employed Electroluminescence technology, considered superior to other testing methods like enzyme-linked immunosorbent assays (ELISA) utilized in prior studies. The use of Electroluminescence technology is considered a strength of the study since it is a simple procedure with high specificity and sensitivity and also has high efficiency. This test has greater sensitivity when detecting antibodies at much lower titre volumes, and requires less dilution and sample sparing to give results.

Study limitations

Despite the above findings, the study was susceptible to both information and recall bias, as it relied on caregivers' ability to remember if the child was vaccinated on schedule and disclose specific health details such as HIV status. These could not be verified as many participants could not provide vaccination cards or proof of HIV testing (only evidence of 5 cards had immunization cards). However, the good immune response with 100% anti-HBc negative may be indicative of previous exposure to the vaccine.Generalizability is an issue, the results may not apply to children in rural settings, given that the study exclusively involved children who sought care at Mulago Hospital, located in an urban setting. Children living in different parts of Uganda are exposed to different sets of societal and contextual factors influencing their growth and development.

Conclusion

Children under 5 years attending the MAC Paediatrics clinic have an overall protective immune response of 77.4%, with more than half having very good antibody titers of > 100 IU/ml, following Hepatitis B vaccination in infancy. However, this is still below the WHO-expected immune response of at least 90% following immunization. Efforts to improve protection in children at risk of poor immunological outcomes due to the HIV-positive or unknown status of their caregivers should prioritize early HIV screening. Strengthening HIV prevention and treatment services for guardians can lower the risk of vertical transmission and indirectly boost the child's immune system. Health policymakers should implement policies supporting booster doses of Hepatitis B for children under five and ensure their enforcement and evaluation within the health system. Researchers should focus on studying the immune response to Hepatitis B vaccination in high-risk children, such as those sero-exposed to or living with HIV. Additionally, cohort studies following children from birth are needed to assess how age affects the immune response, ensuring accuracy by confirming vaccination status during the study period.

Abbreviations

Anti HBsAg Ab	Antibodies to hepatitis B surface antigen titer levels
CHB	Chronic Hepatitis B
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
MAC	Mulago Assessment Center
MNRH	Mulago National Referral Hospital
OPD	Outpatients Department
OR	Odds Ratio
SOMREC	School of Medicine Ethics Review Committee
WHO	World Health Organization

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Author contributions
A.K. developed the research idea and design. J.R. and V.M. conceived the study, supervised the research process, and reviewed the manuscript. All authors read and approved the final manuscript. N.M., A.B., C.K.N., and R.N. participated in the analysis, interpreted the results, and reviewed the manuscript.

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Data availability
The data is available upon request from the main author.

Declarations

Ethical approval and consent to Participate
This study was accredited and approved by the School of Medicine Research and Ethics Committee (SOMREC) of Makerere University (Mak-SOMREC-2022-460). Permission to conduct the study was sought and obtained from the Mulago Ethics Committee and the head of MAC Pediatrics clinic, MNRH. Informed consent was obtained from all participants after clearly explaining the research objectives and procedures.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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