Original Research

FACTORS ASSOCIATED WITH TIMELINESS OF HEPATITIS B BIRTH DOSE: A CROSS-SECTIONAL STUDY IN NORTH-WESTERN NIGERIA

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ABSTRACT

No studies focused on the hepatitis B birth dose (HepB-BD) vaccine since Nigeria adopted the strategy to reduce hepatitis B viral infection. Hence, we determined the uptake of HepB-BD, factors associated with timeliness, and those that contributed to delay. This study was a cross-sectional descriptive study carried out at an immunization post in north-western Nigeria. We recruited 400 mother-infant pairs that presented for the first immunization and obtained relevant information, including socio-demographics and reasons for the delays. Of the 400 infants, 44 (11.0%) received HepB-BD within 24 hours (timeliness), 105 (26.3%) and 274 (68.5%) by day 7 and 14, respectively. Multivariate analysis showed that mothers' education (primary adjusted odds (AOR) 17, 95% CI 1.404, 204.611), secondary AOR 5.9, 95% CI 1.148, 29.895), and tertiary AOR 7.7, 95% CI 1.228, 48.545), and ^{third} born AOR 8.2, 1.625, 41.018) were associated with HepB-BD timeliness. Maternal-related factors were the commonest (129; 46.6%) for delayed HepB-BD, with maternal illness the most commonly cited reason (37; 28.7%). This study showed a deficient level of uptake of HepB-BD vaccines among infants. Factors that were associated with timeliness included maternal education and higher birth order. The commonest reason for delayed HepB-BD was maternal illness.

Keywords: *Hepatitis B birth dose vaccine; hepatitis B viral infection; hepatitis; public health; newborns*

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Highlights:

1. Uptake of hepatitis B birth dose vaccine within 24 hours of birth is low in Katsina, north-western Nigeria.
2. The most common reason for delay presentation for hepatitis B birth dose vaccine is maternal illness.

INTRODUCTION

Viral hepatitis B is the most common chronic hepatitis of public health significance (World Health Organization 2020a). It remains a leading cause of morbidity and mortality, rivaling Tuberculosis and Human Immunodeficiency Virus in recent (World Health Organization 2007). Besides, about one-third of the world's population had at least serological evidence of hepatitis B virus (HBV) infection (Trépo et al. 2014). In 2015, 257 million people were living with chronic HBV infection, with over 800 thousand deaths from hepatocellular carcinoma and liver cirrhosis, the two most common long-term complications (World Health Organization 2007, 2020b).

Although the global burden of HBV is enormous, there are still marked variations in the prevalence; with the classification of endemicity into high, intermediate, and low risk based on the proportion of the population that tested positive for hepatitis B surface antigen (HBsAg) (Trépo et al. 2014). The prevalence of HBV infections is highly endemic in some parts of South East Asia and African countries, inclusively Nigeria, where ≥ 8% of the population are carriers of HBsAg (Alter 2003, Hou et al. 2005). A nationwide survey in Nigeria that involved children and adults (aged 2 to 90 years) showed an overall seroprevalence of 12.2% for HBsAg, with more significant variability across age groups (Nasidi et al. 2016).

In addition, studies in Nigeria showed marked variation in the prevalence among children with a range of 3.9 to 19.0% depending on the geographical locations and population of the study (Ndako et al. 2011, Ashir et al. 2010, Jibrin et al. 2014, Lawal et al. 2020). Whereas viral hepatitis B is highly endemic in Nigeria, the predominant mode of spread of the disease is vertical transmission from mothers to their children, with a lesser contribution from child to child in early childhood (Ashir et al. 2010). The impact of viral hepatitis B infection is more in children, where the propensity to progress to chronic disease could be as high as 90% for the perinatally acquired infection (Stevens et al. 1979).

A critical and most effective strategy for reducing the burden of new HBV infection to less than 90% by 2030 (World Health Organization (WHO) strategy goal towards making HBV more minor public health threat) is birth dose vaccination (World Health Organization 2016a, World Health Organization 2017). The Hepatitis B vaccine has an efficacy of 95%, and dramatically reduces the chance of mothers transmitting the disease to their children when given early. Indeed, the more tremendous success recorded in reducing the burden of viral hepatitis B in Europe, some Asian countries, and Americans was attributed to vaccination, including birth dose (Alter 2003, Álvarez et al. 2017). HBV vaccination led to a reduction from about 8.3% (regional average) to less than 1% in the Western Pacific region (Wiesen et al. 2016).

The importance of vaccines in the global eradication of viral hepatitis B made the WHO recommend that newborns receive hepatitis B birth dose (HepB-BD), preferably within 24 hours of birth (World Health Organisation 2017). This WHO position has been adopted by many countries, inclusive of Nigeria. Nigeria adopted HepB-BD in 2004 (Sadoh & Sadoh 2014). Nigeria gives HepB-BD within a designated period of 24 hours of birth. Though the HepB-BD vaccine is monovalent, it is usually given along with oral polio and BCG vaccines; both of which are allowed up to the 14th day of life; which means it may be delayed (Sadoh et al. 2013, Chido-Amajuoyi et al. 2018).

Although there is no universally acceptable definition of timeliness for the HepB-BD vaccine, WHO recommends the first 24 hours of life (World Health Organization 2007). The provision of hepatitis B birth dose reduced the chance of perinatal transmission and remained a crucial strategy in preventing HBV infection in the endemic countries (Wiesen et al. 2016).

A few years after the hepatitis B vaccine became available in Nigeria, few studies have assessed the timeliness of birth dose vaccines in Nigeria, and none focused on the HepB-BD vaccine (Sadoh & Eregie 2009; Ibraheem et al. 2019, David et al. 2020). Besides, the studies were carried out in the other regions of the country, excluding the north-western geopolitical zone, the region with the least immunization coverage (National Bureau of Statistics (NBS) and United Nations Children's Fund (UNICEF) 2018).

The Nigeria Demographic and Health Survey in 2017 indicated that the region has the least coverage for routine immunizations coverage rate of 13.7% for Pentavalent 3 (National Bureau of Statistics (NBS) and United Nations Children's Fund (UNICEF) 2018). Thus, the implementation of the HepB-BD vaccine remains unknown, mainly in the north-western geopolitical region of the country. This calls for an appraisal of the level of HepB-BD vaccine, identifying the gaps, and probably proffer solutions as the country strife to meet the global target of a 90% reduction in the burden of HBV infection by 2030.

Thus, we hypothesized that the uptake of HepB-BD was low and influenced by some local factors. Hence, we determined the timeliness HepB-BD vaccine and associated factors. We also described factors that cause the delay of HepB-BD to identify measures that may improve coverage.

MATERIALS AND METHODS

Ethical considerations

We obtained ethical approval from the Ethical Review Committee of the Federal Medical Centre, Katsina, Nigeria. We obtained informed consent from the mothers or caregivers after clearly explaining the study details to them. The confidentiality of the data was also ensured. All mothers were educated about the importance of immunization and the number and timing of each immunization appointment.

Study design and location

This descriptive cross-sectional study was conducted in Federal Medical Centre, Katsina, Katsina State, from February to July 2019. Katsina state is located in the northwest geopolitical zone of Nigeria. It lies approximately 12^{o}59 N and 7^{o}36 E. Based on the last census (2006) in Nigeria, the Katsina Local Government Area had a population size of 318,459 with an annual growth rate of 3%.

Though a tertiary health facility, the hospital provides routine immunization services in collaboration with Katsina State Primary Health Care Development Agency. The immunization post runs daily on weekdays (Monday to Friday) from 8:00 am to 3:00 pm. The average number of newborns attending routine vaccination was 141 per month (Immunization record).

Sample size estimation

We estimated the minimum sample size required for the study from the proportion formula (Kasiulevičius et al. 2006).

$$n = \frac{z^2 pq}{d^2}$$

Where:
n = minimum sample size
z = the standard normal deviate usually set at 1.96 and corresponds to a 95% confidence interval.
p = the proportion in the target population estimated to have a particular characteristic, using 53.8% obtained in a study in Northcentral Nigeria (David et al. 2020)
q =1-p
d = tolerable margin of error was set at 5%. Hence, the minimum size obtained was 381. However, 400 mothers-infants paired were recruited.

Study population

The study populations were the infants and their respective mothers/caregivers who presented at the immunization clinic for their first vaccination dose during the study period.

Study inclusion criteria

Mothers/caregivers who brought their newborns for the first round of vaccines gave consent to participate in the study.

Study exclusion criteria

Mothers/caregivers whose babies had received the first doses of vaccines (before presentation), and those whose vaccination cards could not be cited for verification.

Data collection

We enrolled every mother-baby pair who fit the inclusion criteria till the sample size was attained. A trained research assistant administered a pretested semi-structured interview-based questionnaire. The research attendant was a nursing student trained in filling the study proforma. Information obtained included the sociodemographic details of the mother-child pair presenting for vaccination, such as sex of the child, age of mother, religion, marital status, level of education, and occupation of the child's parents. We classified the socioeconomic class based on Oyedeji's socioeconomic classification (Oyedeji 1985). Details of antenatal care clinic (ANC) attendance, place of birth for the index child, and the child's birth order were also recorded.

Definition of terms

Timeliness for HepB-BD vaccine was defined as those that received the vaccine within 24 hours of birth (WHO).

Outcomes measured

The primary outcome measure for this study was the proportion of newborns that received their HepB-BD within 24 hours of life. The secondary outcomes included variables associated with the timeliness of HepB-BD and factors that contributed to the delayed HepB-BD vaccine.

Data analysis

We analyzed the data using the IBM® SPSS version 25.0 (*IBM corporation, Virginia, U.S.A.*). Parents' ages were normally distributed and expressed as mean with standard deviation (SD), while the infants' age (not normally distributed) was summarised as median with interquartile range (IQR). The categorical variables were summarized as frequency and percentage. The number of children that received the HepB-BD was expressed over the total number of children recruited to determine the proportion of children on day 1 (timeliness), day 7, and day 14. A simple odds ratio expressed the relationship between timeliness and other variables. Variables that were less than 0.02 from the odds ratio were entered into binary logistic regression and expressed as adjusted odds ratio (AOR) with a 95% confidence interval to identify factors associated with timeliness. We summarized the reason for delayed vaccination with a frequency and percent Table. A p-value of less than 0.05 was taken as the level of statistical significance.

RESULTS

The median age of the infants was 12 (interquartile range-6.25 to 17) days. The age ranges from 0 (day of birth) to 197 days. Of the 400 recruited babies, 216 were males (54.0).

The mean (SD) age of the mothers was 27.65 (5.71) years, ranging from 16 to 45 years, and the mean (SD) age of the fathers was 37.63 (7.09) years. Most mothers were married (99.8%) and from monogamous family settings (66.3%). Also, 96.5% (386) had more than three antenatal clinics (ANC) visits, and most were delivered at a government health facility (88.5%). About 50.0% of the mothers had a secondary level of education, though most were unemployed (59.0%). Table 1 also shows that most respondents were from the middle class (47.8%). Of the 400 children paired with their mothers, 135 (33.8%) were fourth born and above.

Out of 400 infants, 44 (11.0%) received hepatitis B birth dose vaccine within 24 hours of life. At the end of the first and second weeks of life, 105 (26.3%) and 274 (68.5) infants received hepatitis B birth dose vaccine, respectively (Table 2). The median (interquartile range) duration of the first dose of the Hepatitis B vaccine was 12 (6.25, 17) days (Table 2).

Factors associated with hepatitis B birth dose vaccine within 24 hours of life included a higher birth order-3rd born (odds ratio 5.906, 95% CI 1.342, 26.339). In contrast, mothers whose occupation belongs to group 2 are less likely to receive the hepatitis B vaccine within 24 hours (odds ratio 0.215, 95% CI 0.072, 0.639), as shown in Table 3.

Table 1. General characteristics of the study population

Variables		Frequency(n=400)	Percent
Mothers' age group (years)	Less than 25	168	42.0
	26 to 35	195	48.7
	36 to 45	37	9.3
Fathers' age group (years)	Less than 25	13	3.3
	26 to 35	170	42.5
	36 to 45	170	42.5
	Greater than 45	47	11.7
Marital status	Married	396	99.0
	Unmarried	4	1.0
Family type	Monogamous	265	66.2
	Polygamous	135	33.8
ANC attended	None	6	1.5
	1 to 3 visits	8	2.0
	More than three visits	386	96.5
Place of birth	Home delivery	31	7.8
	Government hospital	354	88.4
	Private hospital	15	3.8
Mothers' educational level	None	14	3.4
	Primary/Islamic	33	8.3
	Secondary	196	49.0
	Tertiary	157	39.3
Fathers' educational level	None	19	4.8
	Primary/Islamic	8	2.0
	Secondary	81	20.2
	Tertiary	292	73.0
Mothers' occupations*	Group 1	18	4.5
	Group 2	16	4.0
	Group 3	89	22.2
	Group 4	41	10.3
	Group 5	236	59.0
Socioeconomic class	Upper	112	28.0
	Middle	191	47.7
	Lower	97	24.3
Child's birth order	1st born	114	28.5
	2nd born	86	21.5
	3rd born	65	16.2
	4th and above	135	33.8

ANC-antenatal clinic; Group 1-Professional senior civil servants, large business owner and contractors; Group 2-Non-academic professionals e.g., nurses, secondary school teachers, medium size business owner, intermediate grade public servants; Group 3-junior school teachers, non-manual skilled workers such as clerks, drivers, artisans; Group 4- Petty traders, messengers, labourers; Group 5- Unemployed, students.

Mothers' age, family type, place of delivery, attendance of antenatal clinics, family socioeconomic status, and days of the weeks the infants were delivered were not associated with the timeliness of the hepatitis B birth dose vaccine (Table 3).

After controlling for confounders, multivariate analysis (binary logistic regression) showed that mothers being educated (primary- adjusted odds (AOR) 17, 95% CI 1.404, 204.611), secondary- AOR 5.9, 95% CI 1.148, 29.895), and tertiary AOR 7.7, 95% CI 1.228, 48.545). Higher birth order (3rd born AOR 8.2, 1.625, 41.018) was significantly associated with an infant receiving a hepatitis B dose vaccine within 24 hours. In contrast, mothers whose occupation belongs to group 2 are less likely to receive the hepatitis B vaccine within 24 hours (AOR 0.143, 95% CI 0.037, 0.554), as shown in Table 3.

Table 2. Hepatitis B vaccination status of the infants (n=400)

Hepatitis B vaccination status	Frequency	Percent	95% Confidence interval
Hepatitis B vaccine within 24 hours (birth dose)	44	11.0	8.0, 14.0
Hepatitis B vaccine received from day 0 to 7	105	26.3	21.9, 30.6
Hepatitis B vaccine received from day 0 to 14	274	68.5	64.0, 73.0
Median (IQR) duration (days) of first dose of hepatitis B vaccine	12.0 (6.25, 17.0)		
Range (days) of the first dose of Hepatitis B vaccine	0 to 197		

Table 3. Multivariate analysis of factors that were associated with Hepatitis B birth dose vaccination within 24 hours

Variables	N (44)	OR	95% CI	p-value	AOR	95% CI	p
Mothers' age (years)							
Less than 25	20 (45.5)	1					
26 to 35	19 (43.1)	1.252	0.644, 2.434	0.508			
36 to 45	5 (11.4)	0.865	0.302, 2.476	0.787			
Fathers' age (years)							
Less than 25	2 (4.5)	1					
26 to 35	16 (36.4)	1.750	0.356, 8.600	0.491			
36 to 45	21 (47.7)	1.290	0.267, 6.228	0.751			
Above 45	5 (11.4)	1.527	0.260, 8.958	0.639			
Family type							
Monogamous	34 (77.3)	1					
Polygamous	10 (22.7)	1.840	0.880, 3.848	0.105	2.353	0.966, 5.729	0.060
ANC attended							
None	0 (0)	1					
1 to 3 visits	0 (0)	1.615	0.627, 4.161	0.321			
> 3 visits	44 (100.0)	1.328	0.640, 2.758	0.447			
Place of birth							
Home delivery	1 (2.3)	1					
Govt. hospital	42 (95.4)	0.467	0.027, 8.015	0.599	0.437	0.023, 8.889	0.590
Private hospital	1 (2.3)	0.248	0.033, 1.863	0.175	0.270	0.031, 2.374	0.238
Mothers' educ.							
No formal educ.	3 (6.8)	1					
Primary	1 (2.3)	8.727	0.820, 92.854	0.073	16.952	1.404 204.611	0.026
Secondary	21 (47.7)	2.273	0.587, 8.806	0.235	5.859	1.148, 29.895	0.033
Post-secondary	19(43.2)	1.981	0.507, 7.747	0.326	7.720	1.228 48.545	0.029
Fathers' educ.							
No formal educ.	1 (2.3)	1					
Primary	1 (2.3)	0.389	0.021, 7.111	0.524			
Secondary	7 (15.9)	0.587	0.068, 5.081	0.629			
Post-secondary	35 (79.5)	0.408	0.053, 3.151	0.390			
Mothers' occupation.							
Group 5 ref	27 (61.4)	1					
Group 1	1 (2.3)	2.196	0.281,17.166	0.453	1.514	0.168, 13.622	0.711
Group 2	6 (13.6)	0.215	0.072, 0.639	0.006	0.143	0.037, 0.554	0.005
Group 3	9 (20.5)	1.148	0.517, 2.548	0.734	1.220	0.506, 2.938	0.658

Group 4	1 (2.3)	5.167	0.682, 39.125	0.112	5.643	0.714, 44.613	0.101
SEC							
Lower	7 (15.9)	1					
Upper	13 (29/5)	0.592	0.226, 1.550	0.286	0.607	0.139, 2.648	0.507
Middle	24 (54.5)	0.541	0.224, 1.305	0.172	0.404	0.142 1.151	0.090
Birth order							
1st born	18 (40.9)	1					
2nd born	11 (25.0)	1.278	0.569, 2.870	0.552	1.656	0.695 3.950	0.255
3rd born	2(4.5)	5.906	1.342, 26.339	0.020	8.165	1.625, 41.018	0.011
4th and above	13 (29.5)	1.760	0.821, 3.770	0.146	3.831	0.677 4.008	0.272
Birth day **							
Weekend	10 (22.7)	1					
Weekdays	34(77.3)	0.713	0.340, 1.495	0.370			

OR- odds ratio, AOR-Adjusted odds ratio; ANC-antenatal clinic; educ-education; Occup-occupation; ** days of the weeks the infants were born. Occupational classifications (Group 1-Professional senior civil servants, large business owners, and contractors; Group 2-Non-academic professionals, e.g. nurses, secondary school teachers, medium-size business owners, intermediate grade public servants; Group 3-junior school teachers, non-manual skilled workers such as clerks, drivers, artisans; Group 4- Petty traders, messengers, laborers; Group 5- Unemployed, students)

Table 4. Factors or reasons for delay in hepatitis B birth dose

Variables n=277		Frequency	Percent
Maternal-related factors n=129	Mother was sick	37	13.4
	Not aware she needs to bring the child within 24 hours for hepatitis B dose vaccine	26	9.4
	Delivered weekend	25	9.0
	Decides to come after naming ceremony	18	6.5
	Mother traveled	6	2.2
	Mother had cesarean delivery	17	6.1
Healthcare-related factors n=45	Given appointment to come later at the delivery facility	31	11.2
	Out of stock	14	5.1
Infants' factors n=29	Baby was sick	29	10.5
Others n=74	No reasons	72	26.0
	Father declined	2	0.6

Out of 277 respondents that provided reasons, maternal-related factors were the commonest (129; 46.6%) for delayed hepatitis B birth dose, with maternal illness the most commonly cited reason (37; 28.7%). Other reasons included being given an appointment to come later at the delivery facility (31; 11.2%) and baby sickness (29; 10.5%). Worthy of note is that only two fathers declined vaccination (0.6%), as shown in Table 4.

DISCUSSION

Hepatitis B birth dose vaccine remains a crucial strategy to combat the HBV infection in an endemic country like Nigeria. This study showed low uptake (11%) of hepatitis B dose vaccine based on the timeliness within 24 hours recommended by WHO. The percentage of children that received the HepB-BD vaccine was low compared with 50% and 53.8% reported in Ilorin (Ibraheem et al. 2019) and Jos (David et al. 2020), respectively in Northcentral Nigeria;. However, both studies included oral polio and BCG vaccines. The number of children that had HepB-BD based on timeliness was also far less than 62.8% of children that received the HepB-BD vaccine within 24 hours of birth among Vietnamese children (Álvarez et al. 2017) and other high-income countries (Wiesen et al. 2016, Álvarez et al. 2017). In contrast, the value obtained in this study was higher than 1.3% reported in Benin (Sadoh & Eregie 2009), south-south Nigeria, which may reflect the years apart in the studies. The Benin study was done more than a decade before the present study.

The number of children vaccinated within 24 hours was also far higher than 1.1% in the Gambia (Miyahara et al. 2016). The low value obtained in this study compared with the north-central studies may be due to the focus on the hepatitis b birth dose received within 24 hours compared with the other studies that included other vaccines (polio and BCG), both of which can be given up to 14 days after birth. Besides, the low value in this study could also reflect low coverage of immunization in north-western Nigeria, inclusive of the state where this study was conducted. Also worthy of note is the progressive increase in the number of children that received the first dose within 14 days

(68.0%), raising the possibility that a continuous schedule along with other antigens that allowed up to two weeks of life may have contributed to the delayed HepB-BD vaccine. The import of this low level of HepB-BD vaccine suggests an urgent need for a scale-up, especially if the country will meet the set global target of a reduction to 90% in the burden of new HBV infection since the vertical route remains the leading route of transmission in the country.

This study also showed that a higher birth order (3rd born) was associated with six times the likelihood of timeliness of HepB-BD vaccine compared with the firstborn. In contrast to the observation in this study, findings in the Western Region of Gambia showed that higher birth order was associated with delayed timeliness for vaccination (Miyahara et al. 2016). This finding also contradicted the observation in Ilorin, which showed that the timeliness of birth dose vaccines was unrelated to birth orders. The observation that the older birth order likely got HepB-BD within 24 hours may have reflected the maternal experience and probably improved knowledge as they gave birth to more children. Hence, they may have recognized the importance of early vaccination.

This study also showed that maternal age, place of delivery, and socioeconomic class were not related to the timeliness of the HepB-BD vaccine. In Ilorin (Ibraheem et al. 2019), place of birth (hospital delivery), and attendance at the antenatal clinic were the factors that were associated with the timeliness of birth dose vaccines. In contrast, Jos' study showed that socioeconomic status and maternal age were associated with timeliness for birth dose vaccines (David et al. 2020). In Vietnam, low birth weight, age less than 20 years, and socioeconomic status were associated with timeliness for the HepB-BD vaccine. This observation affirms the previous findings of variability in factors that may contribute to the timeliness of HepB-BD and the need to identify local factors that will help in planning and policy formation (World Health Organization 2016b, Moturi et al. 2018).

After controlling for confounders, factors associated with timeliness of hepatitis B birth dose included mothers being educated, with those with primary education 17 times more likely to bring their children for HepB-BD vaccine within 24 hours compared with those without formal education. This finding supported most studies that showed education as the key determinant of timeliness presentation for vaccination (Miyahara et al. 2016, Chido-Amajuoyi et al. 2018, Anh et al. 2019). Maternal education (at least at the primary level) has been shown to improve women's understanding and knowledge and encourage better child health care practices, including attendance at immunization clinics. We also observed that those at middle occupational levels are less likely to vaccinate their children for HepB-BD vaccine at birth. This may be related to their work because they may be busy at work while pregnant and see the delivery period as the time to rest.

The common reasons for delayed HepB-BD vaccine were maternal-related factors, with the commonest being maternal illness (13.4%). This finding differs from other parts of Nigeria, where out-of-stock (Sadoh et al. 2013, David et al. 2020) and delivery at the weekend (Ibraheem et al. 2019) were identified as the leading cause of delay in the timeliness of birth dose vaccines. The focus of attention on the sick mothers may have prevented the relatives and caregivers from remembering the newborns for vaccination. This also calls for a review of health facilities policy that allows immunization to be taken to the mothers who just delivered and afford the babies the opportunity not to miss vaccination.

Strength and limitation

The limitation of this study was being a single-center study and may not have been a reflection of the number of newborns who received HepB-BD vaccine in the state.

CONCLUSION

A very low level of HepB-BD vaccine uptake among the infants presented at an immunization post in the North-western part of Nigeria. This finding calls for urgent interventions to scale up the delivery of HepB-BD if the country meets the global goal of a 90% reduction in the new HBV infection. Factors that were associated with vaccination within 24 hours of birth included maternal education (at least primary level) and higher birth order. The most typical reason for delayed HepB-BD was a maternal illness, which calls for a review of a hospital policy that would allow birth dose vaccines to be taken to mothers in their words. By doing so, the missed opportunity can be avoided.

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Conflict of interest

None.

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Author contribution

OKI and KMI conceptualized, wrote, and revised the manuscript. KA reviewed, finalized the manuscript and managed the administration. IML and OKI were final check.

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