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Breastfeeding and post-immunisation fever amongst infants receiving Diphtheria-Pertussis-Tetanus vaccine at a tertiary health institution in Ibadan, Nigeria

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Abstract *Objective*: To determine the incidence of fever after vaccination with the first dose of diphtheria-pertussis-tetanus (DPT) among exclusively breastfed and non-exclusively breastfed infants in Ibadan, Nigeria.
Methods: A prospective study was conducted on a cohort of 710 infants who received first dose of DPT vaccine at the Immunisation Clinic of a tertiary health institution in Ibadan, between July and October 2011. Based on the feeding pattern in a 24-hour feeding recall by mothers, infants were classified into exclusive and non-exclusive breastfeeding groups. Each of the infant's mothers was provided with a digital thermometer and instructed on how to measure the temperature of her infant. The information about the incidence of fever was obtained by telephone on the third day after vaccination.
Results: Only 682 completed the study. The overall rates of exclusive and non-exclusive breastfeeding were 48% and 52%, respectively. Compared with the infants who were non-exclusively breastfed, those who were breastfed exclusively had a risk for fever of 0.675 (95% CI, 0.558-0.817). The place of delivery and the highest level of education were confounders and effect modifiers of the association between breastfeeding and fever.
Conclusions: These findings suggest that exclusive breastfeeding is associated with a decreased incidence of fever after immunisation.

Keywords: Exclusive breastfeeding; Post-immunisation fever; Diphtheria-pertussis-tetanus vaccination; Nigeria

Introduction

Nigeria's immunisation coverage for children is among the lowest in the world.[1] The percentage of children fully immunised has only minimally increased from 14% in 2003 to 17% in 2008, with approximately 30% of children 12-23 months of age having had no vaccinations at all. Only 32% of children receive all three doses of the diphtheria-pertussis-tetanus (DPT) vaccine and only 47% of children receive the Bacillus-Calmette-Guerin (BCG) vaccination.[2] A study on maternal determinants of complete child immunisation showed that 32.4% of children completed the immunisation schedule.[3] One of the reasons given by mothers for not vaccinating or completing the immunisation schedule is the fear of side effects, which include fever following immunisation.[2, 3]

Fever is a frequent systemic adverse event following immunisation, especially in infants and young children. Although generally benign and self-limiting, fever is a common concern for parents and health-care professionals fuelled by fears of febrile convulsions. It is estimated that one of every four children develops fever following the administration of the DPT vaccine.[4] Fever after immunisation may be caused by immunisation or may coincide temporally as an indication of underlying, usually infectious, disease. The fever caused by immunisation is triggered by immune and inflammatory responses to vaccine components and is of short duration.[4-7] Prophylaxis or therapeutic administration of analgesics (acetaminophen or paracetamol) for fever following immunisation has been shown to reduce vaccine immunogenicity.[8, 9]

Breastfed infants have different immune responses to diseases and some vaccines compared with infants who are not breastfed.[5] Such responses might be attributable

to the several anti-inflammatory and immunomodulatory factors that are present in breast milk.[6, 7] Epidemiologic research has provided compelling evidence for the effects of human milk in decreasing infant mortality and morbidity from acute and chronic diseases.[10, 11] In spite of the evidence supporting the importance of breastfeeding during the first year of life, however, data on the effect of breastfeeding on fever following immunisation are limited. Indeed, only one study (known to the authors) has evaluated the effect of breastfeeding on fever following immunisation; it was reported that breastfed infants are less likely to have a fever after immunisation compared with those that are not breastfed.[12]

Fever associated with vaccinations is usually mild and of short duration. Nevertheless, it would be useful to know if there is a consistent association between breastfeeding and post-immunisation fever in different races and cultures. Such evidence can help promote breastfeeding practices and improve infant vaccination across the globe, especially in developing countries, including Nigeria. This study was therefore conducted to determine the incidence of fever after immunisation among exclusively breastfed and non-exclusively breastfed infants who received the first dose of the DPT vaccination at a tertiary health facility in Ibadan, Oyo State.

Methods

Study setting

The study was conducted in the Immunisation Clinic of the Institute of Child Health of the College of Medicine, which is located within the University College Hospital (UCH), a tertiary health institution in Ibadan.[13] The Immunisation Clinic opens three times each week, on Mondays and Wednesdays for infants from birth to 6 months of age and Thursdays for infants 9-11 months of age, who are due to receive yellow fever and measles according to the Nigerian immunisation schedule.[3] On average, 60 mothers and their infants are seen each day the clinic is open, which usually opens at 9am and closes at 4pm.[13]

Study design

A prospective cohort study design was used to determine the incidence of post-immunisation fever 3 days post-vaccination among exclusively breastfed and non-exclusively breastfed infants who received the first dose of the DPT vaccine. The study participants were mother-infant pairs who came to the Immunisation Clinic between 1 July and 30 October 2011, and the infants received the first dose of the DPT vaccine. Mother-infant pairs were excluded if the infant had an acute febrile illness in the 3 days preceding the vaccination, was the product of a multiple birth, or had a birth weight < 2.5 kg, or the mother could not read or write. We estimated that 358 infants in each feeding group (exclusive and non exclusive breastfeeding) were required to detect a statistically significant difference (31.0% rate of fever after immunisation) between the groups, with an absolute precision of 10%, a 5% α level, a 20% β level, and assuming a 10% loss to follow-up.[12]

Data collection

Mothers of infants were informed about the study and written consent was obtained. Data on demographics, telephone numbers, socio-economic characteristics, delivery history, infant feeding habits, and pre- and post-immunisation health status of the infant were collected using a semi-structured questionnaire. Infants were classified into exclusively breastfed (no other food or fluids given) or non-exclusively breastfed (food and nutritive foods added to breast milk or no breast milk at all) based on their current feeding patterns using a 24-hour dietary recall. Each of the mothers was provided with a standard digital thermometer and a fever diary card, and was taught how to measure and record the body temperature of her baby on the evening of the vaccination and twice a day for the next two days (once in the morning and once in the evening before meals, and whenever fever was suspected). The baseline temperature before vaccination was taken by mothers and cross-checked by the investigators before recording on the questionnaire. This was done to ensure that mothers had acquired competency in handling and taking the temperature. One of the authors, who was unaware of the feeding habits of the infants, contacted all of the mothers by telephone on the third day after vaccination. For every mother contacted, information was obtained on how many times temperature had been recorded and the exact values in degrees Centigrade. An infant was defined as having a fever after immunisation if any oral temperature reading was $\geq 38^0$C.[14]

Data analysis

Data were analysed using the statistical package for social sciences (SPSS) software (version 15.0). Descriptive statistics were used to summarise variables and inferential statistics using the chi-square test was used to determine the association between categorical variables including infant feeding habits categorised into exclusively breastfed and partially breastfed infants and post-immunisation fever. The incidence of post-immunisation fever for the different levels of the variables was calculated and the relative risk (RR) with 95% confidence intervals (CIs) was used as a measure of association. Stratified analyses with adjusted RRs were used to determine the role of socio-demographic and child-related variables that were significant with both exclusive breast-feeding and post-immunisation fevers as confounders or effect modifiers in the relationship between exclusive breastfeeding and post-immunisation fever. Ethical approval for the study was obtained from the joint University College Hospital and University of Ibadan Ethics Committee.

Results

Seven hundred ten mother-infant pairs who attended the clinic within the study period and met the eligibility criteria consented to participate; however, only 682 completed the three day follow-up period. Of the 28 mother-infant pairs that were lost to follow-up, 24 dropped out because their telephone numbers were not accessible and the remaining four were not included because they did not collect and provide information on the infants' body temperatures. Table 1 shows the characteristics of the mothers and infants who completed the study and those who were lost to follow-up. The mother-infant pairs who were lost to follow-up differed from the remaining infants with respect to mother's age (p=0.006), parity (p<0.004), mother's occupation (p<0.041), and the presence of other children within the household (p< 0.001). Among mother-infant pairs that completed the follow-up period, 332 (48.7%) mothers exclusively breastfed the infants.

The socio-demographic profile of the mother-infant pairs and birth-related characteristics according to breastfeeding practices are presented in Table 2. As indicated, exclusive feeding practice was associated with the mother's level of education, marital status, and parity. The place of delivery and delivery mode were also shown to be significantly associated with the breastfeeding pattern. Exclusive breastfeeding was observed in 55.1% of the newborns delivered in public health facilities compared to 48.2% and 36.1% delivered in private health facilities and at home, respectively (p=0.039). The majority of the mothers who exclusively breastfed had normal vaginal deliveries (52.2%) compared to caesarean deliveries (14.3%; p<0.0001).

The incidence of post-immunisation fever among those who completed the follow-up period was 274 (40.2%). As shown in table 3, the incidence of post-immunisation fever in infants was significantly less among those who were exclusively breastfed (107/332, 32.2%) compared to those who were not exclusively breastfed (167/350, 47.7%). Post-immunisation fever in infants was also shown to be significantly associated with the place of delivery of the infant, marital status, and the highest level of education attained by the mother. Evaluating the role these variables played in the relationship between type of infant feeding and post-immunisation fever indicated that place of delivery and level of education attained by the mothers were both confounders and effect modifiers (Table 4).

Table 1: Comparison of mothers and infants who completed the study and those who were lost to follow-up on key demographic and socio-economic characteristics

Characteristics	Completed study n = 682(%)	Lost to follow-up n = 28 (%)	P-value
Infant gender			
Female	359 (52.6)	12 (42.9)	0.312
Male	323 (47.4)	16 (57.1)	
Place of delivery			
Home	61 (8.9)	4 (14.3)	0.06
Public health facility	158 (23.2)	11 (39.3)	
Private health facility	463 (67.9)	13 (46.4)	
Mode of delivery			
Caesarean section	63 (9.2)	0 (0.0)	0.14*
Vaginal delivery	619 (90.8)	28 (100)	
Other children in the household	465 (68.2)	11 (39.3)	0.001
Yes	217 (31.8)	17 (60.7)	
No			
Mother's parity			
1	217 (31.8)	17 (60.7)	0.004
2-4	417 (61.1)	11 (39.3)	
5+	48 (7.0)	0 (0.0)	
Age of mother in years			
≤ 20	22 (3.2)	2 (7.1)	0.006
21-30	330 (48.4)	21 (75.0)	
Above 30	330 (48.4)	5 (17.9)	
Mother's marital status			
Unmarried	272 (39.9)	9 (32.1)	0.412
Married	410 (60.1)	19 (67.9)	
Religion			
Christianity	371 (54.4)	17 (60.7)	0.511
Islam	311 (45.6)	11 (39.3)	
Ethnic group			
Yoruba	631 (92.5)	25 (89.3)	0.464
Others	51 (7.5)	3 (5.6)	
Highest level of education			
Primary	155 (22.7)	7 (25.0)	0.06
Secondary	237 (34.8)	15 (53.6)	
Tertiary	290 (42.5)	6 (21.4)	
Current working status			
Yes	167 (24.5)	8 (28.6)	0.623
No	515 (75.5)	20 (71.4)	
Maternal occupation			
Housewife	66 (9.7)	6 (21.4)	0.041
Trading	318 (46.6)	16 (57.1)	
Artisan	122 (17.9)	1 (3.6)	
Private sector employee	116 (17.0)	5 (17.9)	
Public sector employee	60 (8.8)	0 (0.0)	
Type of infant feeding			
Exclusive breastfeeding	332 (48.7)	9 (32.1)	0.086
Non-exclusive breastfeeding	350 (51.3)	19 (67.9)	
Fever among family member 3 days before immunisation			>0.99*
Yes	12 (1.8)	0 (0.0)	
No	670 (98.2)	28 (100)	

* Fishers' exact text

Table 2: Relationship between exclusive breastfeeding (EBF) and maternal socio-demographic and birth-related characteristics

Characteristics	EBF	n=332 (%)	Row total	P-value
Infant gender				
Female	170	(47.4)	359	0.465
Male	162	(50.2)	323	
Place of delivery				
Home	22	(36.1)	61	
Public health facility	87	(55.1)	158	0.039
Private health facility	223	(48.2)	463	
Mode of delivery				
Caesarean section	9	(14.3)	63	<0.0001
Vaginal delivery	323	(52.2)	619	
Other infants in the household				
No	223	(48.0)	465	0.580
Yes	109	(50.2)	217	
Parity				
1	95	(43.8)	217	
2-4	223	(53.5)	417	0.001
5+	14	(29.2)	48	
Age of mother				
≤ 20	8	(36.4)	22	
21-30	153	(46.4)	330	0.188
Above 30	171	(51.8)	330	
Marital status				
Unmarried	112	(41.2)	272	0.0014
Married	220	(53.7)	410	
Religion				
Christianity	178	(48.0)	371	0.689
Islam	154	(49.5)	311	
Ethnic group				
Yoruba	306	(48.5)	631	0.733
Others	26	(51.0)	51	
Highest level of education attained by mother				
Primary	66	(42.6)	155	
Secondary	104	(43.9)	237	0.005
Tertiary	162	(55.9)	290	
Current working status of mother				
Working	82	(49.1)	167	0.90
Not-working	250	(48.5)	515	
Maternal occupation				
Housewife	31	(47.0)	66	
Trading	165	(51.9)	318	
Artisan	48	(39.3)	122	0.209
Private sector employee	59	(50.9)	116	
Public sector employee	29	(48.3)	60	

Table 3: Mothers' socio-demographic and birth-related characteristics with the absolute and relative risks of post-immunisation fever

Characteristics	Risk of post-immunisation fever n (%)	Row total	Risk Ratio (95 Confidence Interval)
Infant gender			
Female	146 (40.7)	359	1.03 (0.85-1.23)
Male	128 (39.6)	323	1
Place of delivery			
Home	32 (52.5)	61	1
Public health facility	40 (25.3)	158	0.48 (0.34-0.69)*
Private health facility	202 (43.6)	463	0.83 (0.64-1.08)
Mode of delivery			
Caesarean section	25 (39.7)	63	1
Vaginal delivery	249 (40.2)	619	1.01 (0.74-1.40)
Other infant in the household			
No	179 (38.5)	465	1
Yes	95 (43.8)	217	1.14 (0.94-1.38)
Fever in family member in the 3 days before immunisation			
Yes	7 (58.3)	12	1
No	267 (39.9)	670	0.68 (0.42-1.11)
Parity			
1	95 (43.8)	217	1.05 (0.73-1.52)
2-4	159 (38.1)	417	0.92 (0.64-1.31)
5+	20 (41.7)	48	1
Age of mother			
≤ 20	8 (36.4)	22	1
21-30	145 (43.9)	330	1.21 (0.69-2.13)
Above 30	121 (36.7)	330	1.01 (0.57-1.78)
Marital status			
Unmarried	126 (46.3)	272	1
Married	148 (36.1)	410	0.78 (0.65-0.93)*
Religion			
Christianity	139 (37.5)	371	0.86 (0.72-1.04)
Islam	135 (43.4)	311	1
Ethnic group			
Yoruba	257 (40.7)	631	1.22 (0.82-1.82)
Others	17 (33.3)	51	1
Highest level of education attained by mother			
Primary	78 (50.3)	155	1
Secondary	101 (42.6)	237	0.85 (0.69-1.05)
Tertiary	95 (32.8)	290	0.65 (0.52-0.82)*
Current working status of mother			
Working	74 (44.3)	167	1.14 (0.93-1.40)
Not-working	200 (38.8)	515	1
Maternal occupation			
Housewife	21 (31.8)	66	1
Trading	146 (45.9)	318	1.44 (0.99-2.10)
Artisan	44 (36.1)	122	1.13 (0.74-1.73)
Private sector employee	41 (35.3)	116	1.11 (0.72-1.71)
Public sector employee	22 (36.7)	60	1.15 (0.71-1.87)
Type of infant feeding			
Exclusive breast-feeding	107 (32.2)	332	0.68 (0.56-0.82)*
Non-exclusive breastfeeding	167 (47.7)	350	1

Table 4: Association between breastfeeding and fever stratified by potential confounders

Confounder	Breastfeeding pattern	Adjusted Relative risk for fever	95% CI
Place of delivery			
Home	Exclusive	0.647	0.365-1.144
Public health facility	Exclusive	0.925	0.542-1.581
Private health facility	Exclusive	0.663	0.533-0.824
Marital status of mother			
Not married			
Married	Exclusive	0.683	0.515-0.905
	Exclusive	0.697	0.537-0.904
Highest level of education attained by the mother			
Primary			
Secondary	Exclusive	0.544	0.373-0.792
Tertiary	Exclusive	0.944	0.701-1.271
	Exclusive	0.608	0.434-0.850

Discussion

The role of exclusive breastfeeding in post-immunisation fever in infancy is not fully understood. The results of the current study indicated that exclusive breastfeeding reduces the risk of post-immunisation fever in infants. We found that exclusively breastfed infants were less likely to have fever following the first dose of DPT vaccination compared with infants that were not exclusively breastfed. However, the level of education of mothers, and where the mothers delivered the infants were both confounders and effect modifiers in the relationship. While the reduction in risk of post-immunisation fever was statistically significant if mothers exclusively breastfed and reported having a tertiary education, this reduction was not significant if mothers exclusively breastfed and reported a primary or secondary education. The significant reduction in risk of post-immunisation fever was also found if mothers exclusively breastfed and reported having delivered the newborn at a private health facility. This finding was not the case if the exclusively breastfed infant was delivered at home or at a public health facility.

We recognise the limitations the design could have imposed on the findings of this study. First, misclassification bias in the assessment of exposure and outcome is possible. We relied on a 24-hour dietary recall method to classify infants into exclusively or non-exclusively breastfed infants. Although this method might minimise recall bias because of the short duration of memory recall required, it may not accurately provide information on feeding habits of infants during a long period prior to the study. However, it is a method recommended by the World Health Organization to measure current exclusive breastfeeding rate, and it provided a basis for comparing our results with a previous study which used the same indicator.[9] In addition, social desirability bias may be introduced as a result of mothers wanting to impress the investigators that they practiced exclusive breastfeeding, which is the desirable practice based on ongoing health education for nursing mothers in our environment. In the assessment of outcome, body temperatures were taken by the mothers rather than by health professionals. Although, the mothers were trained on how to measure their infant's temperature, provided with a standard digital thermometer, and were compliant with taking and recording temperatures, it was not possible to exclude a bias in the assessment of fever. The differences in characteristics, such as mother's age, parity, mother's occupation, and the presence of other children within the household of those that were lost to follow-up and those who completed the study, may indicate selection bias. We ensure that only those mother-infant pairs in which information was complete for both exposure and outcome data were included in the analysis. Although information about potential confounders was obtained, identified, and controlled for in the analysis, there is the possibility that our findings may have been influenced by unknown confounders. Lastly, our study design could not exclude fever following immunisation due to infective episodes.

Several epidemiologic studies have demonstrated the benefits of exclusive breastfeeding for the infant.[7, 10, 15-21] These benefits include an increase in immune responses, fewer infections, a reduction in sudden infant death syndrome, less childhood obesity, fewer tendencies to develop atopy and necrotizing enterocolitis, as well as higher intelligence later in life. Pisacane et al. suggested that breastfed infants are less likely to have fever after immunisation compared with those who are not breastfed is similar to the finding from the present study.[12] The two studies, although similar in design, differ in cultural and environmental settings, but demonstrated a consistent association between breastfeeding and post-immunisation fever. This has implications for policy and advocacy for immunisation, especially in our environment. Exclusive breastfeeding could be promoted to improve immunisation coverage because the risk of fever post-immunisation, which is one of the reasons for not completing the immunisation schedule, is reduced.[2, 3] Furthermore, the practice of prophylactic administration of analgesics (acetaminophen or paracetamol) before vaccination, with the antecedent risk of reducing vaccine immunogenicity, could be discouraged if health workers and household caregivers are aware of the safer alternative of exclusive breastfeeding. [8, 9].

The mechanism by which exclusive breastfeeding reduces post-immunisation fever is not well understood; however, the anti-inflammatory properties of human milk or the act of nursing itself could be responsible.[12] The hypothesis that human milk is anti-inflammatory is supported by studies documenting anti-inflammatory effects in animal models and suppression of humoral and cellular components of inflammation *in vitro*.[7] It is not clear whether or not this mechanism has topical effects within the digestive tract alone or whether or not absorption of milk components results in systemic effects. Inflammation benefits the host as a defense mechanism and precursor to immune responses. Inflammation also contributes to the clinical manifestations of illness. The biological effect of the anti-inflammatory

character of breast milk may be to minimise clinical symptoms without losing immune responsiveness for the breastfed infant.[22] It has also been observed that fever could be due to poor feeding, which is common when children are sick. As breastfed infants are less likely to have poor feeding, the likelihood of fever post-immunisation is also reduced.[12]

Conclusions

In conclusion, we showed that the incidence of fever after the first dose of the DPT vaccination among exclusively breastfed infants was lower compared with non-exclusively breastfed infants. Although the association was modified by level of education of mothers and the sites where the infants were delivered, consistency in the strength of association with a previous study conducted in a different cultural setting was demonstrated. Health care workers could promote exclusive breastfeeding as a safer alternative to prophylactic administration of acetaminophen or paracetamol to prevent post-immunisation fever. Apart from all the advantages of exclusive breastfeeding for mothers and infants, the practice has the potential of improving completion of the immunisation schedule through a reduction in adverse events following immunisation in our setting. In addition, further studies with assessment of fever by healthcare workers rather than the mothers and improved design are suggested.

Author's Contributions
AAF: conceived the study and draft
OO: Draft and analysis of data
Conflict of Interest: None
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