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Pediatrics 2010;125:e1448; originally published online May 17, 2010;

DOI: 10.1542/peds.2009-1911

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<http://pediatrics.aappublications.org/content/125/6/e1448.full.html>

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Breastfeeding and Risk for Fever After Immunization



WHAT'S KNOWN ON THIS SUBJECT: Immune response to some vaccines is different among breastfed infants compared with those who are not breastfed.



WHAT THIS STUDY ADDS: Breastfed infants are less likely to have fever after routine immunizations.

abstract

FREE

OBJECTIVE: The objective of this study was to evaluate the effects of breastfeeding on the risk for fever after routine immunizations.

METHODS: A prospective cohort study was conducted at a pediatric vaccination center in Naples, Italy. The mothers of the infants scheduled to receive routine immunizations were instructed on how to measure and record infant temperature on the evening of the vaccination and for the subsequent 3 days. The information about the incidence of fever was obtained by telephone on the third day after vaccination. The relative risk for fever in relation to the type of breastfeeding was estimated in multivariate analyses that adjusted for vaccine dose, maternal education and smoking, and number of other children in the household.

RESULTS: A total of 460 infants were recruited, and information on the outcome was obtained for 450 (98%). Fever was reported for 30 (25%), 48 (31%), and 94 (53%) of the infants who were being exclusively breastfed, partially breastfed, or not breastfed at all, respectively ($P < .01$). The relative risk for fever among infants who were exclusively and partially breastfed was 0.46 (95% confidence interval: 0.33–0.66) and 0.58 (95% confidence interval: 0.44–0.77), respectively. The protection conferred by breastfeeding persisted even when considering the role of several potential confounders.

CONCLUSIONS: In this study, breastfeeding was associated with a decreased incidence of fever after immunizations. *Pediatrics* 2010;125:e1448–e1452

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KEY WORDS

breastfeeding, fever, immunization

ABBREVIATION

CI—confidence interval

www.pediatrics.org/cgi/doi/10.1542/peds.2009-1911

doi:10.1542/peds.2009-1911

Accepted for publication Jan 22, 2010

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

Fever is 1 of the most common adverse effects after infant immunizations,^{1,2} and it is triggered by immune and inflammatory responses to vaccine components. Fever associated with vaccinations is usually mild and of short duration; nonetheless, it would be useful to know whether preventive measures are available. Breastfed infants have different immune responses to disease as well as to some vaccines^{3,4} compared with infants who are not breastfed. Such different responses might be attributable to the several anti-inflammatory and immunomodulatory factors that are present in breast milk.^{5,6} Nevertheless, because no data have been published on reactivity to vaccines according to feeding habits, the objective of this study was to investigate the incidence of fever after immunizations among breastfed and nonbreastfed infants.

METHODS

Study Design

We conducted a cohort study to compare the incidence of fever during the 3 days after immunizations among breastfed and nonbreastfed infants.

Setting

The study was conducted at the vaccination center of District 49 of Naples between October 1, 2008, and May 31, 2009.

Participants

All infants who were scheduled to receive the first or second dose of a hexavalent combination vaccine (diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio virus, and *Haemophilus influenzae* type b), co-administered with a heptavalent pneumococcal conjugate vaccine, were enrolled. Infants were excluded when their birth weight was <2500 g, when they had major congenital defect or serious chronic illness, and when they

had had acute febrile illness in the week before the vaccination. No infant was included twice during the study period. After informing the parents and obtaining their written consent, data were collected about socioeconomic characteristics, and the type of infant feeding was investigated by means of a 24-hour dietary recall. The mothers were then instructed on how to measure infant rectal temperature and to record the exact values on a diary card. Parents were asked to measure body temperature on the evening of the vaccination and twice a day for the subsequent 3 days, once in the morning and once in the afternoon before meals,^{7,8} and whenever fever was suspected. A standard thermometer (Pic-Artsana, Como, Italy) and a fever diary card were provided to the mothers. One of the authors, unaware of the feeding habits of the infants, contacted all of the families by telephone on the third day after vaccination. The study was approved by the institutional review board of the ASL Napoli 1.

Definition of Exposure

We used the 24-hour dietary recall method recommended by the World Health Organization to define exclusive (no other food or fluids given) and partial (food and nutritive fluids, including formula milk, added to breast milk) breastfeeding.⁹

Definition and Assessment of Outcome

The main outcome of this study was fever, defined as body temperature of $\geq 38^{\circ}\text{C}$ ¹⁰, when temperature was obtained by rectal route and using the thermometer provided to the families by the study team. The mothers were contacted by telephone and were asked to read the information that they had recorded on diary cards. For each infant, information was obtained on how many times temperature had been recorded, how and when it was

measured, and the exact values in degrees centigrade.

Potential Confounders

In this study we considered maternal education and smoking, the number of other children in the household, and the vaccine dose as potential confounders of the association between breastfeeding and fever. The information about such variables was obtained from the mothers at the time of the vaccination.

Vaccines and Vaccinators

Vaccines used were Infanrix HeXa (GlaxoSmithKline) and Prevnar (Wyeth Lederle Vaccines SA). The vaccines were administered via intramuscular injection into the anterolateral aspect of thighs by using a 16-mm-long needle. A pediatrician (Dr De Michele) and a pediatric nurse (Ms Palma) were the only vaccinators during the study period.

Statistical Analysis

Comparison between groups was performed by means of the χ^2 test. The relative risk with 95% confidence intervals (CIs) was used to compare the incidence of fever among the feeding groups. Stratified analysis was performed to investigate the role of confounding and effect modification of variables that were considered as potential confounders or effect modifiers of the association between breastfeeding and fever. As in this study the prevalence of the outcome is high (>10%), to estimate the relative risk or risk ratio adjusted for potential confounders, we used SAS software PROC GENMOD's log-binomial regression¹¹ (SAS Institute, Inc, Cary, NC).

Sample Size

Preliminary unpublished data of our group suggested that the incidence of fever after heptavalent immunization among nonbreastfed infants was

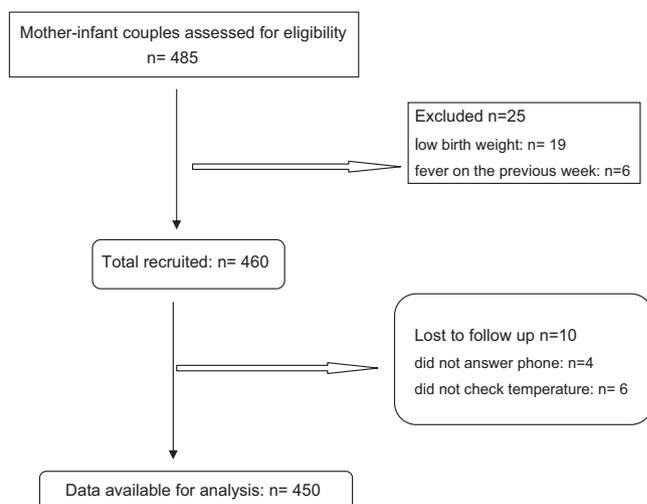


FIGURE 1
Flow diagram of the study.

~40%. Assuming a 20% loss to follow-up, we calculated that we would require ~110 infants in each feeding group to detect a statistically significant decrease of 50% ($\alpha = .05$, $1 - \beta = 80\%$) in the rate of fever after immunization.

RESULTS

Participants

A total of 485 mother–infant pairs were assessed for eligibility. Among them, 25 were excluded (19 infants had

low birth weight, and 6 had fever in the week before immunization). All mothers recruited ($n = 460$) accepted to participate in the study, and data for analysis were available for 450 (98%; Fig 1). Ten mothers were lost to follow-up: 4 of them did not answer 3 consecutive telephone calls, and 6 did not collect and record information on infant body temperature. Of these 10 children, 2 were exclusively breastfed, 4 were partially breastfed, and 4 were not breastfed.

Characteristics of Study Participants

Table 1 shows some baseline characteristics of the mothers and infants enrolled in the study. A total of 206 infants (46%) received the first vaccine dose and 244 (54%) the second 1; their mean ages were 101 days (SD: 90 days) and 176 days (SD: 86 days), respec-

TABLE 1 Characteristics of Infants Enrolled in the Study ($n = 450$)

Characteristics	Value
Gender, M/F	220/230
Presence of other children in the household, n (%)	224 (50)
Maternal education ≤ 8 y, n (%)	172 (38)
Maternal smoking, n (%)	118 (26)
Fever in family members in the 3 d before immunization, n (%)	14 (3)
First vaccine dose, n (%)	206 (46)
Age, mean (SD), d	101 (90)
Breastfeeding, n (%)	
Exclusive	84 (41)
Partial	60 (29)
None	62 (30)
Second vaccine dose, n (%)	244 (54)
Age, mean (SD), d	176 (86)
Breastfeeding, n (%)	
Exclusive	36 (15)
Partial	94 (38)
None	114 (47)

TABLE 3 Association of Some Potential Confounders With Outcome

Characteristic	Infants With Fever ($n = 172$)	P
Maternal education, y		
≤ 8 ($n = 172$)	77 (45)	$<.05$
> 8 ($n = 278$)	95 (34)	
Maternal smoking		
Yes ($n = 118$)	59 (50)	$<.01$
No ($n = 332$)	113 (34)	
Other children in the household		
Yes ($n = 224$)	98 (44)	$<.05$
No ($n = 226$)	74 (33)	
First vaccine dose ($n = 206$)	54 (26)	$<.01$
Second vaccine dose ($n = 244$)	118 (48)	

Data are n (%).

tively. The infants who received the first dose were significantly more exclusively breastfed compared with those who received the second dose (41% vs 15%; $P < .01$).

Potential Confounders

Table 2 provides information on the distribution of some potential confounders among feeding groups. Maternal smoking and education, the number of other children in the household, and vaccine dose were associated with breastfeeding (Table 2), as well with fever (Table 3), and could then confound the association between breastfeeding and fever.

Outcome Data

Table 4 shows the frequency of fever among feeding groups. Among the infants who were exclusively breastfed, partially breastfed and not breastfed, the incidence of fever was, respec-

TABLE 2 Association of Some Potential Confounders With Exposure

Characteristics	Exclusive Breastfeeding ($n = 120$)	Partial Breastfeeding ($n = 154$)	No Breastfeeding ($n = 176$)	P
Maternal education ≤ 8 y	34 (28)	44 (28)	94 (53)	$<.01$
Maternal smoking	14 (12)	30 (19)	74 (42)	$<.01$
Other children in the household	54 (45)	70 (45)	100 (57)	$<.05$
First vaccine dose	84 (70) ^a	60 (39)	62 (35)	$<.01$

^a Exclusive but not partial breastfeeding was associated with vaccine dose.

TABLE 4 Distribution of Fever According to Type of Feeding

Type of Feeding	Infants With Fever, <i>n</i> (%)	RR (95% CI)	Adjusted RR (95% CI) ^a
Exclusive breastfeeding (<i>n</i> = 120)	30 (25)	0.46 (0.33 to 0.66)	0.38 (0.21 to 0.73)
Partial breastfeeding (<i>n</i> = 154)	48 (31)	0.58 (0.44 to 0.77)	0.46 (0.27 to 0.84)
No breastfeeding (<i>n</i> = 176)	94 (53)	1.0	

RR indicates risk ratio.

^a Risk adjusted for maternal education, smoking, presence of other children in the household, and vaccine dose.**TABLE 5** Association Between Breastfeeding and Fever Stratified by Potential Confounders

Confounder	Breastfeeding	Relative Risk for Fever	95% CI	
Maternal smoking	Yes	Exclusive	0.23	0.07 to 0.80
		Partial	0.57	0.33 to 0.97
	No	Exclusive	0.56	0.38 to 0.81
		Partial	0.64	0.45 to 0.89
Other children at home	Yes	Exclusive	0.66	0.44 to 0.97
		Partial	0.56	0.37 to 0.83
	No	Exclusive	0.30	0.16 to 0.56
		Partial	0.62	0.42 to 0.91
Maternal education ≤8 y	Yes	Exclusive	0.51	0.30 to 0.88
		Partial	0.40	0.23 to 0.70
	No	Exclusive	0.49	0.31 to 0.77
		Partial	0.73	0.51 to 1.00
First vaccine dose	Yes	Exclusive	0.48	0.30 to 0.80
		Partial	0.42	0.22 to 0.79
	No	Exclusive	0.60	0.40 to 1.00
		Partial	0.66	0.49 to 0.88

Mantel-Haenszel adjusted risk ratio for exclusive breastfeeding = 0.50 (95% CI: 0.42 to 0.60); Breslow-Day test for interaction over strata: *P* = .48. Mantel-Haenszel adjusted risk ratio for partial breastfeeding = 0.59 (95% CI: 0.52 to 0.68); Breslow-Day test for interaction over strata: *P* = .66.**TABLE 6** Frequency of Temperatures Recorded and Mean Peak Temperature on the First Day After Vaccination According to the Type of Feeding

Parameter	Exclusive Breastfeeding (<i>n</i> = 120)	Partial Breastfeeding (<i>n</i> = 154)	No Breastfeeding (<i>n</i> = 176)
No. of temperature checks reported			
5–6	105 (88)	129 (84)	150 (85)
3–4	12 (10)	18 (12)	24 (14)
1–2	3 (2)	7 (4)	2 (1)
Peak temperature mean (SD), °C ^a	37.10 (0.84)	37.20 (0.88)	37.50 (0.89)

^a Analysis of variance: *F* = 8.74, *P* < .001.

tively, 25%, 31%, and 53% (*P* < .01). Compared with the infants who were not breastfed, those who were exclusively breastfed had a relative risk for fever of 0.46 (95% CI: 0.33–0.66) and those who were partially breastfed of 0.58 (95% CI: 0.44–0.77). None of the variables investigated turned out to be either an effect modifier (Table 5) or a confounder of the association between

breastfeeding and fever; actually, the adjusted relative risks, when considering all of the potential confounders, resulted 0.38 (95% CI: 0.21–0.73) and 0.46 (95% CI: 0.27–0.84), respectively, for exclusive and partial breastfeeding (Table 4).

Table 6 shows the distribution of temperature measurements and the mean

peak temperatures during the first day after the vaccination. The choice of this day was suggested by the observation that, for 155 (90%) of the 172 infants, fever was reported to have occurred during the first day after vaccination. Fever was for most children of short duration (75% of the infants had a 1-day duration of fever), and duration was not associated with the type of feeding. Body temperature >39.0°C occurred in 8 (1.7%) infants; 4 were partially breastfed, and 4 were not breastfed.

DISCUSSION

This study suggests that breastfed infants are less likely to have fever after immunization compared with those who are not breastfed. Actually, a significant difference of risk is still present after controlling for several potential confounders, and also the mean peak temperature is different among feeding groups on the first day after vaccination.

This study has several limitations. One is that body temperatures were taken by the mothers rather than by health professionals. Even if the mothers were accurately trained on how to measure rectal temperature, were provided a standard thermometer, and were compliant with taking and recording temperatures, it is not possible to exclude a bias in the assessment of fever. Actually, breastfeeding mothers had a higher education level and could have been more accurate in detecting fever; however, fever was less frequent among breastfed infants, and it is unlikely that mothers of lower education systematically reported biased body temperatures. A second limitation is that fever after immunization could be an infective episode. Even if it is not easy to deal with this potential confounder, that fever was usually of short duration and occurred during the 24 hours after immunization rules

out most infections; however, the limitations of our study are common to other investigations performed on this topic and reflect the difficulty of obtaining outcome data by means of health professionals.

Any explanation for an association between breastfeeding and fever after immunization must be conjectural. Different responses to *Haemophilus influenzae* type b and pneumococcal^{3,4} as well as to measles-mumps-rubella vaccine¹² have been reported among breastfed infants compared with those who were not breastfed; it is then conceivable that reactogenicity could be different, too.^{5,6} Because proinflammatory cytokines act as endogenous pyrogens, some antimicrobial or anti-inflammatory components of breast milk could reduce fever by decreasing the production of such in-

terleukins or of Toll-like receptor and their effects on the vascular network supplying the thermoregulatory center in the anterior hypothalamus.^{13,14}

The production of proinflammatory cytokines could be reduced not only by components of breast milk but also by breastfeeding itself. Actually, breastfeeding fulfills the function of meeting the infants' emotional needs, and it is conceivable that sick infants frequently breastfeed to reduce discomfort and to get emotional support from the intimate contact with their mothers. This could be a reason that a reduced caloric intake after immunization has been reported among infants who are not breastfed but not among those who are breastfed. Such reduced caloric intake has been associated with an increase of serum leptin and of proinflammatory interleukin 1 β

and tumor necrosis factor α ¹⁵ and could be 1 of the reasons that non-breastfed infants are at more risk for fever; however, breastfed infants could be less prone to illness-induced anorexia also because of the presence of docosahexaenoic acid in breast milk.¹⁶

CONCLUSIONS

Breastfeeding seems to be associated with a reduced risk for fever after immunization, but additional, well-organized studies are needed. The design of such studies should include more objective research methods, such as measurements taken by health care professionals at the same time of the day or night, and should evaluate the role of mild intercurrent infections by medical monitoring.

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