ACTA PÆDIATRICA
PROMOTING CHILD HEALTH

Acta Pædiatrica ISSN 0803–5253

REGULAR ARTICLE

Breast-feeding and a subsequent diagnosis of measles

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Keywords
Breast feeding, Cohort study, Measles, Measles vaccine, Protection

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Received
26 July 2008; revised 26 October 2008; accepted 26 November 2008.

DOI:10.1111/j.1651-2227.2008.01180.x

Abstract

Background: Breast-feeding protects against many infectious diseases and may also influence immunization outcomes.

Aim: This study investigated if breast-feeding protects against clinical measles and if it modified the effect of immunization.

Methods: We used logistic regression with data for 10 207 individuals from the 1970 British Cohort study (BCS70). Breast-feeding data were collected at five years of age, and information on clinical measles infection, as well as socio-economic measures was collected at the age of ten years. Breast feeding was categorized as: breast-fed <1 month (n = 1611), breast-fed for 1–3 months (n = 1016), breast-fed for more than three months (n = 1108), breast-feeding of uncertain duration (n = 21) and never breast-fed (n = 6451).

Results: Breast-feeding for more than three months was negatively associated with a diagnosis of clinical measles infection after adjustment for crowding, social class, measles vaccination, parity and sex with an odds ratio (95% confidence interval) of 0.69 (0.60–0.81) compared with those who never breast-fed. Measles vaccination was highly associated with low risk for measles with: 0.14 (0.13–0.16). Age at acute measles infection was not associated with breastfeeding. Breast-feeding did not notably alter measles immunization efficacy.

Conclusion: Immunization against measles provides effective protection against the disease. A more modest reduction in the risk of a measles diagnosis is associated with breast-feeding. The associations with a diagnosis of measles for breast-feeding and measles immunization are independent of each other.

INTRODUCTION

Measles is a potent pathogen causing about 40 million cases of acute measles each year with over one million deaths among children (1). Measles virus infection causes a transitory depression of the immune function in children (1), especially evident in poor settings where there is a high load of infections. Measles vaccination was introduced in 1968 in Great Britain (2) when single measles vaccine was given to children between 12 and 15 months of age. Between 1970 and 1980, the vaccine coverage was approximately 50% in 2-year old children, but this was insufficient to control measles (3–6).

Breast-feeding is protective against many infectious diseases during the period that the child is breast-fed (7). Recent findings indicate that breast-feeding may have long-lasting protective effects against infectious diseases beyond the period of breast-feeding itself, as well as long-lasting effects on the immune responses to vaccines (8). This study was performed in order to investigate if breastfeeding has any long-term protective effect against clinical measles infection or if it modified the association of monovalent measles vaccination with measles infection.

METHODS

The 1970 British Cohort Study (BCS70) is following the lives of everyone born between the 5th and 11th of April 1970 and living in Great Britain (9). The study began with approximately 17000 birth events throughout the United Kingdom during the target week. After early mortality and the exclusion of Northern Ireland, 16 135 subjects were available for subsequent follow-up studies (10). Some 13 135 were involved in the five-year sweep in 1975 and 14 875 were involved in the ten-year sweep in 1980. The participating subjects remained representative of the original cohort from birth to age of ten years and after age of 30 years (11), (Fig. 1). This analysis was restricted to data on 10 207 individuals with breast-feeding data collected at five years of age and information on clinical measles infection up to ten years of age. When cohort members were aged five years, parents were interviewed by health visitors and information was taken from the cohort members' health records. These records provided the age in months of all immunizations. Crowding was recorded at the age of five years as the number of persons per room and categorized into equal fifths of its distribution. Parity, that is live births, is a marker of both in utero influences associated with previous

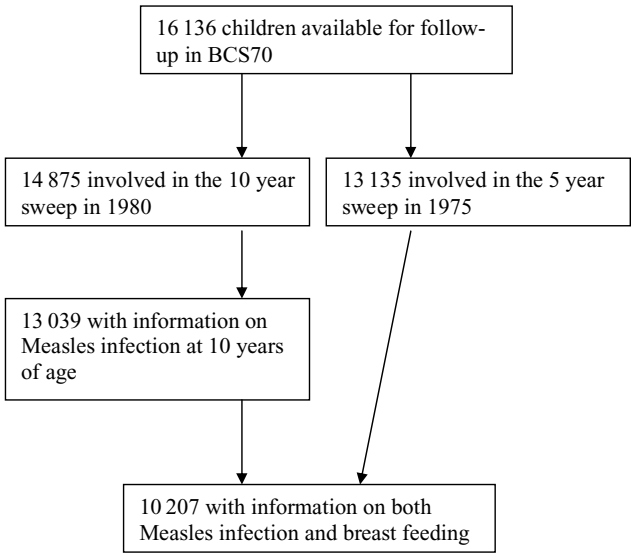

Figure 1 Flow chart of participation in the 1970 British Cohort Study.

pregnancies and later exposures resulting from the presence of older siblings, and this measure was coded into; 0, 1, 2 and 3 or more. Breast-feeding was defined as: breast-fed <1 month, breast-fed for 1–3 months, breast-fed >3 months, breast-fed but not known for how long and never breast-fed.

At the age of ten years, an interview was conducted by health visitors and a community medical officer examined the child and extracted information from medical records. The age when cohort members had a diagnosis of measles was recorded and the interview ascertained father's current or most recent occupation, and this was used to establish the Registrar General's social class that was coded into I, II, III non-manual, III manual, IV, V and with a separate category where the class could not be estimated (usually due to the absence of a father).

Statistical methods

Logistic regression with measles infection as the dependent variable investigated associations with breast-feeding duration. Adjustment was for measles vaccination, social class, household crowding, sex and number of older siblings. All measures were modelled as series of binary dummy variables. We performed stratified analyses for measles vaccination and for breast-feeding. To assess potential effect modification we performed an interaction test for the association of immunization with a measles diagnosis by breast-feeding.

To assess whether breast-feeding only influenced the risk of receiving a diagnosis of measles during the pre-school period or contemporaneously with breast-feeding, an additional analysis began follow-up for infections at the age of five years (when all breast-feeding had ceased).

The statistical package SPSS (SPSS Inc., Chicago, IL, USA) was used for the analyses.

RESULTS

Immunization against measles provided effective and statistically significant protection against a diagnosis of measles (Table 1). Breast-feeding was negatively associated with a measles diagnoses and was independent of crowding, social class, measles vaccination, number of older siblings and sex. This association is statistically significant for the two categories with the longest duration of breast-feeding. There is a dose-dependent association, with a greater reduction in the risk of a measles diagnosis with increased duration of breast-feeding. The inverse association of measles diagnosis with breast-feeding was found also in children vaccinated against measles with an odds ratio (and 95% confidence interval) of 0.74 (0.60–0.90) for those breast-fed for more than three months compared with those who were never breast-fed. Among children not vaccinated against measles the odds ratio for breast-feeding for more than three months was 0.63 (0.50–0.79) compared with those who were never breast-fed. Interaction testing confirmed that there was no effect modification for the association of immunization and clinical measles risk by breast-feeding, even when duration of breast-feeding was taken into account (data not shown).

High social class was associated with less risk of clinical disease, while crowding brought an increased risk with a statistically significant association when the most and least crowded groups were compared. No difference between the sexes was found. Parity was associated with a modest increased risk after adjustment for potential confounding factors. The results were unaltered when number of older siblings were used in place of parity. There was no statistically significant association of the age at clinical measles with breast-feeding (among those who had an infection): the mean age was 4.5 years (median five years) for children breastfed for more than three months and 4.4 years (median four years) for children never breast-fed.

When the follow-up for measles infections began at the age of five years with after adjustment for the other covariates, breast-feeding >3 months remained statistically significantly associated with a reduction in the risk of measles infection: 0.82 (0.70–0.97). Measles immunization was also associated with a lower risk of measles infection, which, as expected, was of lower magnitude than the main results when the follow-up for measles began at the age of five years: 0.33 (0.30–0.36).

DISCUSSION

This study shows a negative association between a diagnosis of clinical measles infection and duration of breast-feeding with a decreased risk of 30% in children who were breastfed for more than three months in comparison with those who were never breast-fed. Some studies, but not all, have shown a protective effect of breastfeeding far beyond the period of breast-feeding itself (4). There is a dose-dependent negative association with increasing duration of breast-feeding underlining the consistency in the results. We speculate

Table 1 Risk for clinical measles infection associated with measles immunization, breastfeeding, social class, crowding, sex and parity

	Ever had measles				Unadjusted	Adjusted
	No	(%)	Yes	(%)	Odds ratio (95% CI)	Odds ratio (95% CI)
Measles vaccination						
Yes	4011	(77.0%)	1558	(31.2%)	0.14 (0.12 – 0.15)	0.14 (0.13–0.16)
No	1195	(23.0%)	3443	(68.8%)	1.0	1.0
Breastfeeding						
Breastfeeding 0–1 months	873	(16.8%)	738	(14.8%)	0.76 (0.68–0.85)	0.90 (0.79–1.02)
Breastfeeding 1–3 months	586	(11.3%)	430	(8.6)	0.66 (0.58–0.75)	0.83 (0.71–0.96)
Breastfeeding > 3 months	688	(13.2%)	420	(8.4%)	0.55 (0.48–0.62)	0.69 (0.60–0.81)
Breastfeeding not known how long	9	(0.2%)	12	(0.2%)	1.20 (0.50–2.84)	0.87 (0.33–2.30)
Never breastfed	3050	(58.6%)	3401	(68.0%)	1.0	1.0
Father's social class						
I	390	(7.5%)	172	(3.4%)	0.40 (0.33–0.48)	0.51 (0.41–0.63)
II	1315	(25.3%)	892	(17.8%)	0.61 (0.55–0.68)	0.73 (0.65–0.83)
III non-manual	436	(8.4%)	391	(7.8%)	0.81 (0.70–0.94)	0.96 (0.81–1.14)
III manual	1951	(37.5%)	2159	(43.2%)	1.0	1.0
IV	530	(10.2%)	594	(11.9%)	1.01 (0.89–1.16)	0.93 (0.80–1.08)
V	142	(2.7%)	206	(4.1%)	1.31 (1.05–1.64)	1.01 (0.79–1.30)
Social class not assigned	442	(8.5%)	587	(11.7%)	1.20 (1.05–1.38)	1.16 (1.00–1.36)
Crowding (persons per room ratio in fifths)						
1 least crowded	903	(17.3%)	589	(11.8%)	1.0	1.0
2	1115	(21.4%)	844	(16.9%)	1.16 (1.01–1.33)	1.11 (0.95–1.30)
3	1468	(28.2%)	1247	(24.9%)	1.30 (1.15–1.48)	1.18 (1.02–1.37)
4	1030	(19.8%)	1243	(24.9%)	1.85 (1.62–2.11)	1.39 (1.19–1.63)
5 most crowded	690	(13.3%)	1078	(21.6%)	2.40 (2.08–2.76)	1.36 (1.14–1.62)
Child's sex						
Male	2654	(51.0%)	2569	(51.4%)	1.0	1.0
Female	2552	(49.0%)	2432	(48.6%)	0.99 (0.91–1.06)	1.02 (0.94–1.12)
Parity						
0	2203	(42.3%)	1610	(32.2%)	1.0	1.0
1	1796	(34.5%)	1680	(33.6%)	1.28 (1.17–1.40)	1.03 (0.93–1.15)
2	730	(14.0%)	892	(17.8%)	1.67 (1.49–1.88)	1.09 (0.95–1.25)
3+	477	(9.2%)	819	(16.14%)	2.35 (2.06–2.68)	1.21 (1.03–1.42)
Total	**5206**		**5001**			

that breast-feeding may result in a milder form or sub-acute measles infection, reducing the likelihood of diagnosis. The most effective protection against measles was immunization, which was administered in the monovalent form for this cohort. Breast-feeding did not influence the efficacy of measles immunization.

Immediately following the introduction of the monovalent measles vaccine in Great Britain in 1968, measles morbidity and notifications declined markedly, but due to a low uptake rate (approximately 50%) the average measles notification rates did not continue to fall so rapidly and were relatively stable (with seasonal and annual fluctuations) between 1970 and 1980 (4–6) when the data used here were collected. The situation in 1982 was similar to that between 1970 and 1980 and paper from 1982 reported the following. There were over 100 000 notifications in the United Kingdom, of which 10 589 occurred in Scotland. During that epidemic year 1492 cases were notified with a rate of 436 per 100 000 population, of whom 50 required hospital care; 42% of those admitted had respiratory complications, including bronchiolitis and bronchopneumonia, 28% had otitis media and 20% had convulsions (12).

There might be a potential for misclassification and recall bias among our data. The information on measles infection was based on interviews with the parents and with reference to health records but without confirmation by serology or culture. Parents are likely to remember children with a clinical measles infection, and those with the sickest children will have had medical consultations indicated by health records. However, we focused on those with obvious clinical measles infection, which normally is visible and clinically evident. Those with a sub-clinical infection will not be reported here, but we are concerned with a clinical manifestation of the disease. It is possible that breast-feeding does not protect against clinical measles, but might be associated with an atypical manifestation that is as severe as the typical disease, but less likely to have been diagnosed. We know of no study that indicates this is likely. While

there may be bias, there is nothing to suggest that this is differential by the exposure so, while the results may be somewhat imprecise, it is unlikely that they are spurious. We adjusted for markers of socio-economic circumstances including social class and crowding which may be relevant to infection risk. Parity was included in the models, as previous pregnancies can influence the in utero environment and the number of older siblings can influence the severity of measles in childhood. The results were not notably altered when number of older siblings were used in place of parity.

Data on immunizations were based on health records, so reporting errors are less probable. There is a possible bias linked to the use of health care related to socio-economic circumstances. We tackled this problem through adjustment. Data on breast-feeding duration were collected at five years of age, thus there is a potential risk for recall bias. Mothers who breastfeed may be different from those mothers who do not breastfeed, for example in terms of level of education, number of children, smoking habits, social class, likelihood of vaccination, use of day-care and risk of exposure to measles. Adjustment using the regression models was performed to tackle these potential sources of confounding and the effect of adjustment was consistent with an independent association between breast-feeding and measles infections.

We conducted an analysis where measles infections were assessed between age five and ten years, rather than from birth, as in the main analysis. This was to rule out the possibility that the association with breast-feeding was due solely to a protective effect that operated only during the period of breast-feeding itself. This analysis would also limit the potential influence of contemporaneous effects due to differences in nursery attendance. Beginning follow-up at age of five years (by which time all breast-feeding had ceased) will introduce bias, such that those who had an earlier infection will not be at risk of a subsequent measles diagnosis. Thus, if the association were solely due to a contemporaneous influence of breast-feeding, the association with later infections should be eliminated or even reversed. In fact, breast-feeding remained associated with a reduced risk of measles infection indicating that the effect persists after breast-feeding has ceased. As expected, the bias deliberately introduced by this procedure attenuated the magnitude of protection associated with both breast-feeding and immunization (as the early beneficial effects are excluded and mask later protection). We also stratified the analysis by measles vaccination and the consistency of the results in both strata provide more evidence that the association of breast-feeding with clinical measles infection is not confounded by vaccination history. Although we adjusted for possible confounding factors we cannot totally rule out the possibility of a 'healthy mother effect', but this seems unlikely to be the main explanation because of the small influence of multiple adjustment. As the children were all followed up to the same age over the same period, differences in follow-up time or age are not a concern. Similarly, it is unlikely that temporal variation in breast-feeding rates and measles transmission could account for the results, as these children belonged to the same birth cohort.

Speculation on biological mechanisms

While this research cannot explain the biological mechanisms underlying the reduced risk of clinical measles reported among those who were breast-fed, we speculate on some biological mechanisms that may underlie this association. We have earlier documented that among children with invasive Haemophilus influenzae disease aged 18 months or more, children breast-fed 3 months or more showed a more rapid antibody response than those breastfed for a shorter duration (13) and a stimulatory effect of breast-feeding on the antibody response to Hib (13–15) and two of the Pneumococcal serotypes has been documented (16). Pabst et al. reported that breastfed children had a Th1 type response, less evident in formula-fed children, upon stimulation with measles vaccine and concluded that feeding mode has an important long-term immune modulating effect on infants beyond weaning (17). Breast-fed infants have shown greater maturity in development of the immune system (18). We did not find any significant difference between the sexes, but studies in developing countries with a high-titre measles vaccine, a higher mortality post-immunization has been reported for females (19) but not for standard titre vaccines. Garenne and Lafon speculated that males have stronger Th1 deviation early in life with increased vulnerability to diseases associated with cytotoxic activity compared with females (20). Interleukin-7 (IL-7) in human milk plays an important role in the development of the thymus (21), and Interleukin-2 (IL-2) in breast-milk has been associated with increased T cell response (22). Lactoferrin is an important defence protein involved in protection against various microbial infections and oral lactoferrin supplementation in human immunodeficiency virus-infected children resulting in more differentiated subpopulations of T-lymphocytes (23,24). A combination of these and other factors in human milk might enhance antibody mediated defence that protects against invasion, as well as cell mediated immunity rapidly activate cytotoxic functions, thus eliminating pathogens more effectively.

The measles virus is highly infectious and it is essential that high vaccination coverage is maintained to protect the population from epidemics. The measles vaccine strain in the currently used combined measles mumps and rubella (MMR) formulation is the same as for the monovalent vaccine investigated here. Therefore, we expect that MMR efficacy against clinical measles is similarly independent of breast-feeding. Thus differences in breast-feeding patterns between individuals and populations should not interfere with the success of immunization against measles. The level of protection conferred by breast-feeding is far lower than that by immunization and these influences are independent of each other: the most protected children would be immunized, but breast-feeding may provide some additional protection. The higher level of protection offered primarily by immunization but also combined with breast-feeding may

be particularly important where the risk of measles infection is high.

CONCLUSIONS

Breast-feeding may be associated with a modest reduced risk for clinical measles infection up to the age of ten years. Vaccination against measles is highly effective protection and this is not influenced by breast-feeding.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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