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Protective effect of breastfeeding: an ecologic study of *Haemophilus influenzae* meningitis and breastfeeding in a Swedish population

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Background	In Örebro County, Sweden, a 2.5-fold increase in the incidence of *Haemophilus influenzae* (HI) meningitis was found between 1970 and 1980. In a case-control study of possible risk factors for invasive HI infection conducted in the same area, 1987–1992, breastfeeding was found to be a strong protective factor.
Material and methods	In order to study the relation between incidence rates of HI meningitis between 1956–1992 and breastfeeding rates in the population an ecologic study was performed.
Results	A strong (negative) correlation between breastfeeding and incidence of HI infection 5 to 10 years later (ρ_{xy} (s) ≈ –0.6) was seen, whereas no relation seems to exist for the time lag 15 years and beyond. The correlation for contemporary data was intermediate. There were similar results for the breastfeeding proportions at 2, 4 as well as 6 months of age.
Discussion	Our ecologic data are consistent with results from our case-control study. The time-lag for the delayed effect on the population level could be estimated although sparse data make the estimates vulnerable to sampling fluctuations. Limitations with ecologic studies are discussed.
Conclusion	There seems to be an association between high breastfeeding rate in the population and a reduced incidence of HI meningitis 5 to 10 years later. These results do have implications on strategies for breastfeeding promotion, especially in countries where Hib vaccination is too costly and not yet implemented.

Keywords	*Haemophilus influenzae* infection, breastfeeding, ecologic study
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Invasive *Haemophilus influenzae* (HI) infection is a world-wide disease. The yearly incidence in children 0–4 years of age reported in different studies, before introduction of general Hib vaccination, vary between 30/100 000 in Caucasians and 600/100 000 in Native Alaskans.[1–3] Meningitis is the most common form in areas with a high incidence, with a peak incidence below the age of one year. In Scandinavia the incidence of invasive HI meningitis in children 0–4 years of age has been around 30/100 000 person years.[4–6] An increasing incidence of HI meningitis has been reported in the US, Sweden and Scotland.[7–10] In the US two studies have reported a fourfold increase in the incidence of HI meningitis from 1940 to 1970, with the most dramatic increase from 1955 to 1970. In Scotland, a similar increase in incidence of HI meningitis from the mid-1970s was reported, and it was most evident in the age 1–3 years. In Sweden a two- to three-fold increase in incidence of HI meningitis during the 1970s was reported and it was most evident in children less than 12 months of age. A high incidence persisted in this population until the introduction of a general Hib vaccination in 1993 when a dramatic decrease was seen.[5,11] The use of polysaccharide vaccine prior to general Hib vaccination was very small and cannot explain the slight decline in HI meningitis in the late 1980s.

A case-control study was conducted in Örebro County, Sweden, during a 6-year period, 1987–1992.[12] Multivariate analyses showed a significant association between invasive HI infection and two independent factors, i.e. short duration (<13 weeks) of exclusive breastfeeding (odds ratio [OR] = 3.79; 95% confidence interval [CI] : 1.6–8.8) and history of frequent infections (OR = 4.49; 95% CI : 1.0–21.0). For age at onset ⩾12 months, the associations were stronger. The association of decreased risk for invasive HI infection and long duration of breastfeeding persisted beyond the period of breastfeeding itself and the associations were strongest for meningitis. Other studies have shown that ongoing breastfeeding is beneficial

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against infections but the mechanisms are not fully understood. It has been shown that breast-milk has an inhibiting effect on the attachment of bacteria to the nasopharyngeal mucosa, which will reduce the colonization rate.

Aim of the Study

The aim of the study was to perform an ecologic investigation of the incidence rates of HI meningitis in relation to breastfeeding rates in the population over a period of time. Our hypothesis is that data on breastfeeding rates are related to data on the incidence of HI meningitis over time, and if so to estimate the time lag between the two series where the strongest correlation exists.

Material and Methods

Study population

During the study period, the population in Örebro County, in south central Sweden, was around 270 000. The child population, one month–16 years old, showed a slight decrease from 59 148 in 1955 to 52 490 in 1992.

Identification of cases

All patients aged one month to 16 years who developed HI meningitis between 1956 and 1992 within the county were included in this study. Incidence rates of HI meningitis 1956–1980 were based on an investigation of all records of bacterial meningitis in the Departments of Paediatrics, Infectious Disease, Oto-Rhino-Laryngology, Pathology and Forensic Medicine and these results have been published before.[9] For calculation of the incidence rates we used the same age-interval (one month–16 years) as in the previously reported study, instead of 0–4 years which is more common today. For the period 1981–1986 we performed an investigation of cases and records similar to the one described above, while for the period 1987–1992 the information originates from a prospective incidence study of invasive HI disease already presented.[4] All cases of childhood bacterial meningitis, 1956–1992, have been referred to the Örebro Medical Center Hospital.

Criteria for diagnosis

The diagnosis was based on clinical findings consistent with invasive HI infection with either a positive culture from cerebrospinal fluid (CSF); or a negative culture of CSF combined with any one of the following three criteria: (a) Leucocytosis in CSF ($>5 \times 10^6$/l) with demonstration of bacteria by direct microscopy or an antigen documentation with direct immunofluorescence, immunoelectrophoresis, co-agglutination or latex agglutination, or (b) Leucocytosis in CSF ($>5 \times 10^6$/l) and bacteria cultured from blood, or (c) Leucocytosis in CSF ($>5 \times 10^6$/l) and a significant rise in serum antibody titres.

Incidence rates

Incidence rates were calculated in 5-year periods and were defined as number of cases in the age range one month–16 years/100 000 person years (Table 1). The mean population/year in the county for the age group one month–16 years for each 5-year period was used.

Breastfeeding rates

We have used rates of exclusive breastfeeding based on data from two sources; the Swedish National Board of Health and

Table 1 Per cent children exclusively breastfed in Sweden at the ages of 2, 4 and 6 months, and incidence of *Haemophilus influenzae* (HI) meningitis in Örebro county, calculated as mean annual incidence in 5-year periods

	National averages for Sweden			Örebro county
Year	Breastfeeding 2 months (%)	Breastfeeding 4 months (%)	Breastfeeding 6 months (%)	Incidence of HI meningitis (per 100 000 person years)
1944	85	70	53	
1950[a]	77	58	42	
1953	73	52	36	
1955[a]	71	49	33	
1957/58[a]	68	45	28	5.1
1960	65	40	24	
1962/63[a]	59	34	19	6.1
1965	54	28	15	
1967/68[b]	45	21	10	4.8
1970	35	15	7	
1972/73	31	13	6	12.2
1975	46	25	14	
1977/78	50	40	12	13.8
1980	58	40	22	
1982/83	61	44	23	13.5
1985	62	45	21	
1987/88	67	46	24	10.3
1990	70	49	26	
1992/93	75	57	34	9.1

[a] The breastfeeding data for 1950, 1955, 1957/58 and 1962/63 were estimated by linear interpolation.

[b] The figure for 1967/68 is an average of 1967 and 1968. The same applies to 1972/73 and so on.

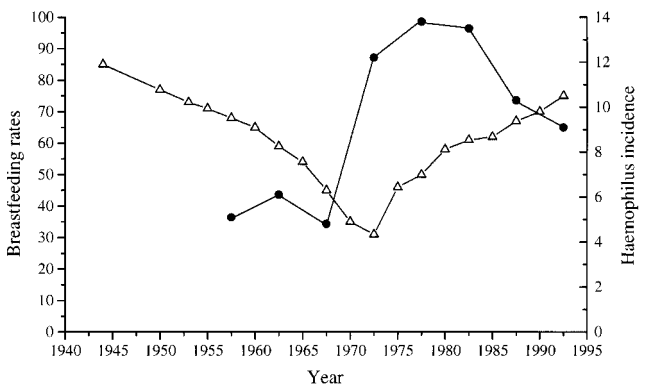

Figure 1 Time series for breastfeeding rates (%) (–△–) and *Haemophilus influenzae* meningitis incidence (per 100 000 person years) (–•–)

Table 2 Cross-correlations between breastfeeding proportions for children 2, 4 and 6 months of age (national averages for exclusive breastfeeding) at time t and incidence rates for *Haemophilus influenzae* meningitis at time t+s for children 1 month to 16 years old in Örebro county. The time period, t, covers 5-year intervals and the time lag, s, also refers to 5-year intervals

	Breastfeeding		
Time lag, s, in 5-year intervals	Children 2 months	Children 4 months	Children 6 months
0 years (no lag)	–0.37	–0.13	–0.23
5 years	–0.60	–0.41	–0.56
10 years	–0.58	–0.67	–0.64
15 years	+0.10	–0.03	+0.04

Welfare for the periods 1944–1975 and 1984–1993, and from Semper, a Swedish company producing formula milk, for the period 1976–1984[13–16] (Table 1).

Statistics

Statistical calculations based on a time series approach for analysing dependence between aggregated longitudinal data were used.[17] Our main hypothesis involved a possible relation between breastfeeding at time point t, and the incidence of HI meningitis at a later time point t + s, where s is an unknown time lag. In epidemiological terms s is analogous to latency time. With a formulation used in time series analysis breastfeeding is a leading indicator for meningitis; it precedes the outcome. To investigate this hypothesis we calculated cross-correlations between the two variables of interest ρ_{xy} (s) where X_t is the variable acting as leading indicator and Y_{t+s} the outcome variable. We used data for exclusive breastfeeding.

To comply with the assumption of stationary time series data, which is necessary for the interpretation of the cross-correlation coefficient, the calculations were performed on differenced data, that is, the data values applied were $\Delta X_t = X_t - X_{t-1}$ and similarly for Y_t. Since data were sparse the calculations were performed on 5-year interval data. This implies that the unit for time t is 0, 5, 10 years and so on, not yearly data. The aim of the study is one of an ecologic investigation and we regard the estimated coefficients as descriptive and exploratory in nature and have therefore not calculated any measure with respect to statistical inference, like confidence intervals or *P*-values. In addition the estimates of the standard errors should also be vulnerable due to the sparse data.

Results

The data on breastfeeding and incidence rates are given in Table 1. Figure 1 shows the relation between breastfeeding and incidence over the time interval studied. Cross-correlations are given in Table 2. In our data the strongest (negative) correlation between breastfeeding and incidence of HI infection is seen for a time lag 5–10 years (ρ_{xy} (s) ≈ –0.6), whereas no relation seems to exist for the time lag 15 years. The results for contemporary data are intermediate, with correlations in the interval –0.13 to –0.37. There are similar results for the breastfeeding proportions at 2, 4 as well as 6 months of age. The negative cross-correlation implies that low breastfeeding is followed by increased incidence rates 5 to 10 years later in time, provided that the aggregated data permit this interpretation.

Discussion

Protective effect of breastfeeding on HI infection at an individual level

There has long been controversy regarding the protective effect of breastfeeding against infections in general and HI disease in particular; some studies have failed while others have succeeded in demonstrating protective effects.[18,19] Several studies have shown that breastfeeding is beneficial for the child in the prevention of infections as reviewed by Hanson *et al.*[20–22] In a review Bauchner *et al.* assessed the extent to which 20 studies on association between breastfeeding and infection met important methodological standards and the conclusion was that breastfeeding has at most a minimal protective effect in industrialized countries.[18]

The protective effect of breastfeeding may be due to a direct and local effect on the mucosa as well as to a long lasting and general effect through, for example, priming the immunological system.[20,22,23] Results from our previous study support this hypothesis.[12]

Protective effect of breastfeeding on HI infection at a population level

We have earlier demonstrated possible causal associations between duration of breastfeeding and risk of HI infection at an individual level.[12] The present study is an ecologic study using aggregated data on a population level. Such studies are descriptive and explorative, not causal or explanatory.[24,25] The statistical relation between incidence rates of HI meningitis and the proportion of breastfeeding at the population level showed a cross-correlation of –0.6 with a time lag of 5–10 years. It is interesting to note that the case-control study indicated an increased level of protection of breastfeeding for age at onset over 12 months of age. Subsequently there seemed to be a long-lasting effect, an observation which could possibly be linked with the estimated time lag in the ecologic data.

Methodological considerations

There are limitations to consider in this study. Regional incidence rates for HI meningitis were used because of lack of reliable national ones. Incidence studies of HI meningitis in Sweden in the 1980s have shown similar rates as our local figures and we claim that the incidence rates for HI meningitis from our county are valid and can be used at a national level.[4–6]

Breastfeeding rates in each county were reported to the Swedish Medical Board, later the Swedish National Board of Health and Welfare, from 1938 to 1975, after which such reporting ceased on a regular nationwide basis. In 1987 the official national registration of breastfeeding from all counties started again (children born after 1985) to be reported to the Swedish National Board of Health and Welfare. Between 1975 and 1986 registration was done in some counties, as well as by a formula-producing company, Semper, so that national breastfeeding rates for this period could be estimated. Semper has established their breastfeeding rates through repeated interviews of randomly selected samples. There could be weaknesses in the registrations done after 1975 and before 1987 although we have no indications to either refute or confirm this. The breastfeeding rates in Örebro county in 1955 and during the 1980s–1990s, have not been different from the national averages (L Ekholm, Child Health Unit, Örebro County, personal communication) but we can not totally exclude that a difference may have existed during the other years of the study period.

The time lag was estimated based on 5-year interval data. If data with denser time intervals could have been collected this might effect the estimate and a more precise figure could have been calculated. However, results at hand indicate that a time lag somewhere in the 5–10 year interval is most likely.

The cross-correlations were calculated on cumulative percentages for breastfeeding at 2, 4 and 6 months of age. An alternative could be to use the proportion of children who cease breastfeeding before 2 months and between the succeeding time points of observation 2, 4 and 6 months. Rough estimates for these proportions are easily derived from Table 1. We have not presented these calculations since they would introduce further assumptions and not provide us with information very different from that already given.

Although our ecologic data on HI incidence and breastfeeding have potential weaknesses and were not obtained on the desired yearly basis, they are to our knowledge unique and at present they seem to represent the most detailed data source readily avaliable.

In an ecologic study like this it is hardly possible to control for confounders. This is a drawback and one of the main reasons why ecologic studies should be interpreted very cautiously. In our previous case-control study we were able to introduce several confounders e.g parental smoking, different day-care practices and the child's history of other infections but such data are found on an individual level and not easily included in studies on highly aggregated data. However, we have tried to analyse the relation between HI meningitis incidence and day-care use (number of children in day-care as well as number of day-care units) and have found that the increase in HI meningitis to some extent preceded the increase in the use of day-care. Further, there has been almost no more use of baby day-care (before the age of one year) in Sweden due to changes in the health insurance system. Baby day-care existed in the 1960s and 1970s but only to a small extent and it cannot explain the increase in HI meningitis incidence.

Based on the statistical analysis alone, the interpretations of our results are tentative but they are consistent with other findings, e.g. the protective effect at the individual level of breastfeeding on HI meningitis, as well as on bacterial adherence and colonization.

Conclusion

In an earlier case-control study we found support for a protective effect of breastfeeding on the risk for HI meningitis at an individual level. The present communication is an ecologic study, using aggregated data at a population level. Ecologic studies are descriptive and explorative, not causal. The statistical relation between incidence rates of HI meningitis and the proportion of non-breastfeeding at the population level was analysed and there is an association between high breastfeeding rate in the population and a reduced incidence of HI meningitis 5–10 years later. These results could have implications on strategies for breastfeeding promotion, especially in countries where Hib vaccination is too costly and not yet implemented.

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