Review Article

Breastfeeding protects against infectious diseases during infancy in industrialized countries. A systematic review

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Abstract

Firstly, this review was performed to assess the effect of breastfeeding on infections during infancy in industrialized countries. Secondly, the effect of duration and exclusiveness of breastfeeding were explored. Studies were identified using Medline, Cochrane Library, Science Citation Index and by a manual search from bibliographies of articles from August 1986 to January 2008. Follow-up, case-control and randomized controlled trial (RCT) studies performed in an industrialized country, published in English, with breastfeeding as a determinant, with overall infections, gastrointestinal or respiratory tract infections as a major outcome, and at least 40 participants in the study were included. Using Bauchner's criteria published in a review in 1986, two reviewers and a peer reviewer assessed the internal validity of those studies. Twenty-one studies that met the inclusion and internal validity criteria were included. These included 16 follow-up and four case-control studies and one RCT. Four out of five studies observed decreased effects on overall infections in breastfed infants. With regard to gastrointestinal infections, six out of eight studies suggested that breastfeeding had a protective effect. Thirteen out of 16 studies concluded that breastfeeding protects infants against respiratory tract infections. Five studies combined duration and exclusiveness of breastfeeding. All studies observed a protective dose/duration-response effect on gastrointestinal or respiratory tract infections. These studies strongly suggest that breastfeeding protects infants against overall infections, gastrointestinal and respiratory tract infections in industrialized countries. The optimal duration of exclusive breastfeeding for protection against infectious diseases needs to be studied in more detail.

Keywords: breastfeeding, duration or exclusiveness of breastfeeding, gastrointestinal infections, infants, review, respiratory tract infections.

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Introduction

The World Health Organization (WHO) recommends mothers to breastfeed their infants, due to an accumulating evidence of the breastfeeding's benefits to growth, development and health (World Health Organization and Department of Nutrition for Health and Development 2001). There are several mechanisms explaining how human milk can protect infants from infectious diseases. Breast milk contains secretory IgA antibodies which contribute directly or indirectly to an anti-inflammatory response (Hanson *et al.* 2002; Lawrence & Pane 2007). Breast milk also contains other protective factors like lactoferrin and oligosaccharides, functioning as analogues for microbial receptors preventing microbes to attach to the mucosa (Newburg *et al.* 1998; Hanson *et al.* 2002; Lawrence & Pane 2007). Furthermore, the transfer of numerous cytokines and growth factors via breast milk may contribute to an active stimulation of the infant's immune system (Hanson *et al.* 2002). Consequently, the risks of infectious diseases like gastrointestinal infections, otitis media (OM), other respiratory tract infections and infection-induced wheezing may be reduced for several years after the termination of breastfeeding (Hanson *et al.* 2002).

In developing or low-income countries, it has been persistently shown that breastfeeding has a protective effect mostly on two major infectious diseases in infancy, gastrointestinal and respiratory tract infections (Brown *et al.* 1989; World Health Organization 2000). Research results are often conflicting in developed or industrialized countries, where overall sanitation and health care are better, although infections because of, for example, contaminated water or feeding vessels probably cannot be fully prevented (Bauchner *et al.* 1986; Habicht *et al.* 1986; Cunningham *et al.* 1991). The conflicting results may be mostly because of methodological flaws as suggested by Bauchner *et al.* in 1986. The most important flaws included failure to prevent detection bias, failure to control for confounding variables and lack of precision in specifying the categories of feeding and health outcomes (Bauchner *et al.* 1986).

Firstly, this review was performed to assess the effect of breastfeeding on the risks of overall infec-

tions, gastrointestinal and respiratory tract infections during infancy in industrialized countries, using studies started after the publication of the article of Bauchner *et al.* Secondly, the duration and exclusiveness of breastfeeding were taken into account.

Methods

Articles were searched using the medical databases Medline, Cochrane Library and Science Citation Index. The keywords we used were: breastfeeding, breast milk; infant; gastrointestinal infection, respiratory tract infection, infectious diseases; developed, Western or industrialized countries; and combinations of those terms. References of each obtained article were screened on additional relevant studies. The last search was performed in January 2008 and 273 abstracts were found. Two reviewers assessed the abstracts using the following inclusion criteria: the article had to be written in English and published after 1986, the year in which the review of Bauchner *et al.* was published; the study design had to be case-control, follow-up or randomized controlled trial study, and the study had to be performed in an industrialized country. An industrialized country was defined as a country that the World Bank considered to have a high income. In January 2008, this income applied to 60 countries, mostly in Western and Northern Europe, Northern America, Australia and some Asian countries (http://www.worldbank.org/data/countryclass/classgroups.htm#High_income). Furthermore, breastfeeding had to be at least one of the determinants and overall infections, gastrointestinal or respiratory tract infections had to be one of the major outcomes. The study had to contain a minimum of 40 participants, since studies with smaller sample sizes are likely to have inadequate statistical power (Bauchner *et al.* 1986). Differences in opinion between the reviewers were proposed to a third reviewer and discussed to get consensus. A meta-analysis was not applied since the variety in study design, the definition and timing of determinants and outcomes would lead to a much smaller number of studies included. Therefore, we performed a descriptive review and included all studies based on quality criteria.

Table 1. Studies included in the review based on inclusion and internal validity criteria

Year	Studies found according to the inclusion criteria*	Internal validity criteria				Studies included in this review based on inclusion and internal validity (≥ 3) criteria
		Avoidance of detection bias	Adjustment for confounders	Clear definition of determinant	Clear definition of outcomes	
1986	Leventhal	+	+	+	+	Yes
1989	Takala	–	±	+	+	No
1990	Howie	+	+	+	±	Yes
1990	Rubin	+	+	+	+	Yes
1991	Holberg	+	+	+	+	Yes
1993	Duncan	+	+	+	+	Yes
1994	Aniansson	+	+	+	+	Yes
1994	Pisacane	±	±	+	+	Yes
1995	Beaudry	–	+	+	+	Yes
1995	Dewey	+	+	+	+	Yes
1996	Nafstad	–	+	+	±	No
1997	Scariati	+	+	+	±	Yes
1997	Silfverdal	–	+	±	±	No
1998	Cushing	+	+	+	+	Yes
1999	Raisler	–	±	+	±	No
1999	Silfverdal	–	–	±	+	No
1999	Levine	–	+	±	+	No
2001	Kramer	+	+	+	+	Yes
2003	Koch	+	+	+	+	Yes
2003	Oddy	–	+	+	+	Yes
2003	Sinha	+	+	+	+	Yes
2003	Kramer	+	+	+	+	Yes
2003	Pettigrew	–	+	+	±	Yes
2004	Pardo-Crespo	+	+	±	±	Yes
2006	Paricio Talayero	+	+	+	+	Yes
2006	Chantry	–	+	+	+	Yes
2007	Quigley	–	+	+	+	Yes

*Inclusion criteria were that studies had to be performed in an industrialized country, written in English, published after 1986, be a case-control, follow up or randomized controlled trial study, have at least 40 participants, have breastfeeding at least as one of the major determinant and overall infections, gastrointestinal or respiratory tract infections at least as one of the major outcomes.

Twenty-seven studies met the inclusion criteria (Table 1) (Leventhal *et al.* 1986; Takala *et al.* 1989; Howie *et al.* 1990; Rubin *et al.* 1990; Holberg *et al.* 1991; Duncan *et al.* 1993; Aniansson *et al.* 1994; Pisacane *et al.* 1994; Beaudry *et al.* 1995; Dewey *et al.* 1995; Nafstad *et al.* 1996; Scariati *et al.* 1997; Silfverdal *et al.* 1997; Cushing *et al.* 1998; Raisler *et al.*, 1999; Silfverdal *et al.* 1999; Levine *et al.* 1999; Kramer *et al.* 2001; Koch *et al.* 2003; Oddy *et al.* 2003; Sinha *et al.* 2003; Kramer *et al.* 2003; Pettigrew *et al.* 2003; Pardo-Crespo *et al.* 2004; Paricio Talayero *et al.* 2006; Chantry *et al.* 2006; Quigley *et al.* 2007). The internal validity of those studies were assessed using Bauchner's criteria (Bauchner *et al.* 1986): (1) avoid-

ance of detection bias; (2) adjustment for confounding variables, such as socioeconomic status, size of the family, smoking by the mother, and the mother's level of education; (3) a definition of infant feeding; and (4) a definition of outcome events (Bauchner *et al.* 1986). We standardized the term 'formula-fed' or 'bottle-fed' into 'non-breastfed' for uniformity. Studies that met at least three criteria were included and 21 articles matched those pre-specified criteria. From those valid studies, four were case-control and 16 were follow-up studies and one was a randomized controlled trial. We categorized those studies according to the outcome measured (Table 2). There were 12 studies which met four of the internal validity

Table 2. Characteristics of studies included in the review categorized by outcomes

Outcome	Study	Country	Design	Number of participants	Age included	Result (95%CI)
Overall infections	Leventhal <i>et al.</i> 1986	USA	Case-control	146 cases 151 controls	<90 days	OR 0.79 (0.47, 1.32) for hospitalized serious illness if BF OR 0.17 (0.03, 0.44) for mild illness if BF Reference: non-BF
	Beaudry <i>et al.</i> 1995	Canada	Retrospective cohort	776	0–6 months	IDR 0.67 (0.54, 0.82) for all illnesses if BF
	Pettigrew <i>et al.</i> 2003	USA	Prospective cohort	674	0–6 months	For firstborn infants, per week longer BF, 4% ($P < 0.01$) decrease of illness requiring a health care provider
	Pardo-Crespo <i>et al.</i> 2004	Spain	Case-control	336 cases and controls	0–24 months	Shorter BF duration in infants admitted for all causes (40.6 ± 5.4 vs. 99.5 ± 5.4 days; $P < 0.01$) or fever of unknown origin (40.8 ± 12.4 vs. 91.7 ± 12.4 days; $P < 0.01$) at the age of ≤ 6 months, not ≥ 6 months
	Paricio Talayero <i>et al.</i> 2006	Spain	Prospective cohort	1385	0–12 months	HR 2.45 (1.28, 4.66) for hospitalization for infections if exclusive BF < 4 months Reference: exclusive BF ≥ 4 months
Gastrointestinal infections	Howie <i>et al.</i> 1990	UK	Prospective cohort	750	0–24 months	Reduced rate of GI at ages 0–13 weeks and 14–26 weeks ($P < 0.01$) and ages 27–39 weeks and 40–52 weeks ($P < 0.05$) if BF > 13 weeks Average OR 0.16 (0.04, 0.73) for GI if BF 1–52 weeks Reference: non-BF
	Rubin <i>et al.</i> 1990	Denmark	Prospective cohort	500	0–12 months	IDR 1.067 (0.98, 1.23) for gastroenteritis if BF
	Beaudry <i>et al.</i> 1995	Canada	Retrospective cohort	776	0–6 months	IDR 0.53 (0.27, 1.04) for gastrointestinal illness if BF
	Dewey <i>et al.</i> 1995	USA	Prospective cohort	144	0–24 months	Incidence 0.31 episodes/100 days at risk for diarrhoeal illness 0–12 months (significant using log-linear analysis) if non-breast feeding vs. 0.15 episodes/100 days if BF
	Scariati <i>et al.</i> 1997	USA	Prospective cohort	2615	0–12 months	OR 1.8 ($P < 0.05$) for diarrhoea if non-BF Reference: exclusive BF
Respiratory tract infections	Kramer <i>et al.</i> 2001	Belarus	Randomized controlled trial	17 046	0–12 months	OR 0.60 (0.40, 0.91) for ≥ 1 episode of GI for intervention group (stimulate to initiate BF, support to maintain BF) Reference: control group (no intervention)
	Kramer <i>et al.</i> 2003	Belarus	Nested observational cohort	3483	0–12 months	IDR 0.35 (0.13, 0.96) for GI at age 3–6 months if exclusive BF 6 months IDR 0.90 (0.46, 1.78) for GI 6–12 months if exclusive BF 6 months Reference: exclusive BF < 3 months
	Quigley <i>et al.</i> 2007	UK	Prospective cohort	15 980	0–8 months	OR 0.37 (0.18, 0.78) for diarrhoea if exclusive BF OR 1.98 (1.32, 2.96) for diarrhoea 1–4 months; per month cessation of BF OR 1.28 (1.01, 1.61) for diarrhoea 5–7 months; per month cessation of BF
	Howie <i>et al.</i> 1990	UK	Prospective cohort	750	0–24 months	Reference: non-BF Reduced rate of RTI at ages 0–13 weeks and 4–52 weeks ($P < 0.05$) if BF > 13 weeks Average OR 0.44 (0.15, 1.31) for RTI if BF 1–52 weeks
	Rubin <i>et al.</i> 1990	Denmark	Prospective cohort	500	0–12 months	Reference: non-BF IDR 0.98 (0.88, 1.10) for URTI

Holberg <i>et al.</i> 1991	USA	Prospective cohort	1179	0–12 months	RR 8.0 (2.80, 22.80) for LRTI at 1–3 months if non-BF Reference: exclusive BF
Duncan <i>et al.</i> 1993	USA	Retrospective cohort	1120	0–12 months	Significant difference in mean number of episodes of acute and recurrent OM ($P < 0.01$) if exclusive BF for 4 and 6 months, respectively. Reference: BF and exclusive BF < 4 months, respectively
Aniansson <i>et al.</i> 1994	Sweden	Prospective cohort	448	0–12 months	Significant lower frequencies of acute OM if BF ($P < 0.05$) Reference: no BF
Pisacane <i>et al.</i> 1994	Italy	Case–control	74 cases 88 controls	0–6 months	OR 0.22 (0.09, 0.55) for acute LRTI if BF on admission Reference: non-BF
Beaudry, 1995	Canada	Retrospective cohort	776	0–6 months	IDR 0.78 (0.61, 1.00) for RTI
Dewey, 1995	USA	Prospective cohort	144	0–24 month	No significant difference in incidence of RTI if BF Incidence 0.53 vs. 0.45 episodes/100 days at risk (significant using log-linear analysis) for OM 0–12 months if non-BF Reference: BF
Cushing <i>et al.</i> 1998	USA	Prospective cohort	1202	0–6 months	OR 1.10 (0.98, 1.24) for URTI if full BF OR 0.79 (0.67, 0.91) for LRTI if full BF Reference: non-BF
Kramer, 2001	Belarus	Randomized controlled trial	17 046	0–12 months	OR 0.87 (0.59, 1.28) for ≥ 2 episodes of RTI for intervention group (stimulate to initiate BF, support to maintain BF) Reference: control group (no intervention)
Koch <i>et al.</i> 2003	Greenland	Prospective cohort	288	0–24 months	RR 2.98 (0.91, 9.71) for LRTI if partly BF RR 3.66 (1.06, 12.6) for LRTI if stopped BF Reference group: exclusive BF
Oddy <i>et al.</i> 2003	Australia	Prospective cohort	2602	0–12 months	OR 1.43 (1.02, 2.01) for URTI if predominant BF < 2 months Reference group: predominant BF > 2 months
Sinha <i>et al.</i> 2003	USA	Nested case control	12 420	0–30 days	OR 1.1 (0.64, 2.0) for neonatal RTI in boys if exclusive BF OR 1.4 (0.78, 2.4) for neonatal RTI in boys if mixed feeding OR 0.5 (0.29, 0.79) for neonatal RTI in girls if exclusive BF OR 0.6 (0.34, 0.93) for neonatal RTI in girls if mixed feeding Reference group: non-BF
Kramer, 2003	Belarus	Nested observational cohort	3483	0–12 months	No significant differences for ≥ 2 episodes of any RTI, URTI, hospitalization for RTI or ≥ 1 episode of OM if exclusive BF 3 months Reference group: exclusive BF ≥ 6 months
Chantry <i>et al.</i> 2006	USA	Cross-sectional cohort	2277	6–24 months	OR 4.27 (1.27, 14.35) for pneumonia if full BF 4–6 months OR 1.95 (1.06, 3.59) for recurrent otitis media if full BF 4–6 months Reference group: full BF ≥ 6 months
Quigley, 2007	UK	Prospective cohort	15 980	0–8 months	OR 0.66 (0.47, 0.91) for LRTI if exclusive BF OR 1.46 (1.19, 1.80) for LRTI 1–4 months; per month cessation of BF OR 1.12 (1.00, 1.27) for LRTI 5–7 months; per month cessation of BF Reference group: non-BF

BF, breastfeeding; RTI, respiratory tract infection/illness; URTI, upper respiratory tract infection/illness; LRTI, lower respiratory tract infection/illness; OM, otitis media; CI, confidence interval; OR, odds ratio; RR, relative risk; HR, hazard ratio; IDR, incidence density ratio; Ratios presented as those reported in the original papers.

criteria, and nine studies which met three of the internal validity criteria.

Results

Breastfeeding and overall infections

A limited number of articles studied the effects of breastfeeding on overall infectious morbidity.

Leventhal *et al.* (1986) found that breastfeeding protects infants from hospitalization for illnesses (Table 2). The protective effect of breastfeeding in their study was substantially diminished when the data were stratified according to the severity of infections in order to minimize the potential surveillance bias. An odds ratio (OR) of 0.79 (95% confidence interval: 0.47 to 1.32) for infants with serious infections was found and an OR of 0.17 (0.03, 0.44) for infants with mild infections. Beaudry *et al.* (1995) observed an incidence density ratio (IDR) of 0.67 (0.54, 0.82) for infections at the age of 0–6 months in breastfed infants. The IDR controlled for potential confounders was not presented. Recent studies that adjusted for confounders showed that infants who were breastfed for a shorter period had higher risks of infections or illnesses that required a doctor's visit or hospital admission (Pardo-Crespo *et al.* 2004; Paricio Talayero *et al.* 2006).

Breastfeeding and gastrointestinal infections

Eight studies studied the effects of breastfeeding on gastrointestinal infections (e.g. gastroenteritis, diarrhoea, vomiting) (Table 2). Six studies suggested a protective effect of breastfeeding of which the size varied according to the duration and exclusiveness of breastfeeding.

Howie *et al.* (1990) found that infants who were breastfed for 13 weeks or more had significantly fewer gastrointestinal infections at the age of 0 to 13 weeks ($P < 0.01$; reduction in incidence 6.6%–16.8%), at 14 to 26 weeks ($P < 0.05$), at 27 to 39 weeks ($P < 0.05$) and at 40 to 52 weeks ($P < 0.05$), than those who were never breastfed. Infants who were breastfed but less than 13 weeks had a similar rate of gastrointestinal infections as infants who were never breastfed.

Dewey *et al.* (1995) observed an increased incidence of episodes of gastrointestinal infections during the first year of life among non-breastfed infants compared to breastfed infants, even after adjusting for day care use and number of siblings. Scariati *et al.* (1997) concluded that, after adjusting for potential confounders, the risk of gastrointestinal infections was 1.8-fold increased in infants who received no breast milk compared to those who received exclusively breast milk ($P < 0.05$). In a randomized controlled trial done by Kramer *et al.* (2001), the intervention group of mothers was stimulated to initiate breastfeeding, supported to maintain breastfeeding and helped to resolve common breastfeeding problems. Infants of mothers of the intervention group had fewer episodes of gastrointestinal infections [OR 0.60 (0.40, 0.91)] than infants of mothers of the control group. Compared with infants exclusively breastfed for 3 months, Kramer *et al.* (2003) showed a reduced risk of gastrointestinal infections at the age of 3 to 6 months in infants exclusively breastfed for 6 months [IDR 0.35 (0.13, 0.96)]. No reduced risk was observed for gastrointestinal infections at the age of 6–12 months. Quigley *et al.* (2007) found a protective effect for diarrhoea in the first 8 months of life if infants were exclusively breastfed [OR 0.37 (0.18, 0.78)].

Two studies did not observe a protective effect of breastfeeding (Rubin *et al.* 1990; Beaudry *et al.* 1995). Beaudry *et al.* concluded that breastfeeding was protective against gastrointestinal infections during the first 6 months of life (IDR) 0.53 (0.27, 1.04). However, after adjusting per potential confounders (socio-economic status, infant's age, mother's age or maternal cigarette consumption) the IDRs mostly became non-significant. Rubin *et al.* found no substantial protective effect of breastfeeding against gastrointestinal infections, with an adjusted IDR of 1.07 (0.98, 1.23).

Breastfeeding and respiratory tract infections

Sixteen studies assessed the association between infant feeding habits and respiratory tract infections or illnesses (Table 2).

Howie *et al.* (1990) observed a significant reduction of respiratory tract infections at ages 0 to 13 weeks and 40 to 52 weeks if the infants were breastfed for 13

weeks or more, compared to infants who were never breastfed. Holberg *et al.* (1991) studied 1179 infants in the US. They observed that the adjusted relative risk (RR) of having respiratory syncytial virus(RSV)-lower respiratory tract infections between 1 and 3 months of age increased from 5.6 (2.00, 15.30) to 8.0 (2.80, 22.80) if infants were not breastfed. At older ages, breastfeeding did not significantly affect the RR for RSV infections. Duncan *et al.* (1993) showed that the mean number of acute OM episodes of infants who were exclusively breastfed for 4 or more months was half of that of infants who were never breastfed. Furthermore, infants who were exclusively breastfed had 40% fewer episodes of acute OM than infants whose diets were supplemented with other foods before 4 months. Aniansson *et al.* (1994) studied 448 infants and observed that the frequency of acute OM was significantly lower in breastfed infants than in non-breastfed infants in each age group. The first acute OM episode occurred significantly earlier in infants who were weaned <6 months than infants who were still breastfed or partially breastfed at 6 months of age. Pisacane *et al.* (1994) studied 74 cases and 88 controls and found that infants with a pneumonia or bronchiolitis were less likely to have been breastfed until admission [OR 0.22 (0.09, 0.55)]. Severely ill infants had had fewer breastfeeding than infants with mild illnesses. No protective effect of breastfeeding was found for infants with pertussis. Beaudry *et al.* (1995) observed an adjusted incidence density ratio of 0.78 (0.61, 1.00) for respiratory tract infections (including upper respiratory tract infections, lower respiratory tract infections and OM) if infants were breastfed. Dewey *et al.* (1995) concluded that in the first year of life, the percentage of OM was 19% lower and the prolonged episodes of OM (>10 days) was 80% lower in breastfed infants compared with non-breastfed infants. No significant differences in rates of other types of respiratory tract infections were observed. In their study, Cushing *et al.* (1998) found no significant protective effect of breastfeeding on total respiratory tract infections or upper respiratory tract infections after adjustment for important confounders. Full breastfeeding was associated with fewer lower respiratory tract infections [OR 0.79 (0.67, 0.91)]. Koch *et al.* (2003) studied several risk

factors for respiratory tract infections in infants less than 2 years of age. Compared with infants who were exclusively breastfed, partly or never breastfed infants had higher risks of lower respiratory tract infections [OR 2.98 (0.91, 9.71) and 3.66 (1.06, 12.6), respectively]. However, in the adjusted model, partly breastfeeding was not significant although a tendency of a protective effect for lower respiratory tract infections was observed. Oddy *et al.* (2003) concluded that predominant breastfeeding for at least 6 months and partial breastfeeding for up to 1 year might reduce the prevalence and subsequent morbidity of respiratory tract infections in infancy. Hospital, doctor, or clinic visits for four or more upper respiratory tract infections were significantly more frequent if predominant breastfeeding was stopped before 2 months or partial breastfeeding was stopped before 6 months. Compared with neonates who were non-breastfed, Sinha *et al.* (2003) observed an inverse association of exclusive breastfeeding with neonatal respiratory tract infections among girls [OR 0.5 (0.29, 0.79)] but not among boys [OR 1.1 (0.64, 2.00)], after adjustment for confounders. Mixed feeding showed a protective effect on neonatal respiratory tract infections, again only among girls [OR 0.6 (0.34, 0.93)]. Infants fully breastfed for 4 to 6 months had higher risks for pneumonia or recurrent OM, compared with infants fully breastfed ≥ 6 months [OR 4.27 (1.27, 14.35) and OR 1.95 (1.06, 3.59)], according to Chantry *et al.* (2006). Associations of breastfeeding with recurrent upper respiratory tract infections or wheezing were not found. Quigley *et al.* (2007) found a protective effect of exclusive breastfeeding on lower respiratory tract infections [OR 0.66 (0.47, 0.91)]. Furthermore, per month shorter breastfeeding, an OR of 1.46 (1.19, 1.80) was observed for lower respiratory tract infections at the age of 1 to 4 months, and an OR of 1.12 (1.00, 1.27) for lower respiratory tract infections at the age of 5 to 7 months.

Rubin *et al.* (1990) did not find an association between breastfeeding and upper respiratory tract illnesses. The adjusted incidence density ratio was 0.98 (0.88, 1.10). Kramer *et al.* found (2001, 2003) no associations between episodes of respiratory tract infections, upper respiratory tract infections, hospitalization for respiratory tract infections or OM

and duration of exclusive breastfeeding (<3 months vs. ≥ 6 months).

Some studies differentiated between upper and lower respiratory tract infections. Two (Duncan *et al.* 1993; Aniansson *et al.* 1994) out of seven studies (Rubin *et al.* 1990; Duncan *et al.* 1993; Aniansson *et al.* 1994; Cushing *et al.* 1998; Oddy *et al.* 2003; Kramer *et al.* 2003; Chantry *et al.* 2006) observed a protective effect of breastfeeding on upper respiratory tract infections. All studies with lower respiratory tract infections as the outcome found decreased risks of these infections if infants were breastfed (Pisacane *et al.* 1994; Cushing *et al.* 1998; Koch *et al.* 2003; Chantry *et al.* 2006; Quigley *et al.* 2007).

Duration and exclusiveness of breastfeeding and infections

Of all studies included in our study, several assessed the effects of exclusiveness, others the duration and some the combination of duration and exclusiveness of breastfeeding on infectious diseases.

Compared with exclusive breastfeeding, Holberg and Koch observed higher risks of RSV-lower respiratory tract infections and respiratory tract infections, respectively, if infants were not breastfed (Holberg *et al.* 1991; Koch *et al.* 2003). They found no difference in these outcomes if infants were partially breastfed. Scariati *et al.* (1997) found an increased risk of gastrointestinal infections with decreased amounts of breastfeeding (high mixed, middle mixed, low mixed, non-breastfeeding) compared with exclusively breastfeeding. A similar dose-response effect of breastfeeding was observed on OM infections. Compared with never breastfed infants, exclusively breastfed infants had lower risks of lower respiratory tract infections (Cushing *et al.* 1998), neonatal respiratory tract infections [only girls (Sinha *et al.* 2003)], respiratory tract infections and gastrointestinal infections (Quigley *et al.* 2007). Sinha *et al.* (2003) and Howie *et al.* (1990) observed protective effects of partial breastfeeding on infectious diseases but other studies did not.

According to the duration of breastfeeding, Pettigrew *et al.* (2003) observed a 4% decrease of infants with illnesses who required a health care provider per week longer the infants received breastfeed-

ing. Infants with different admission causes or admitted with fever of unknown origin had been breastfed for a shorter period, as shown by a study of Pardo-Crespo *et al.* (2004). Howie *et al.* (1990) found a significant protective effect on gastrointestinal and respiratory tract infections if the infants were breastfed for more than 13 months (full or partial) compared to those who were never breastfed. Both the risk of diarrhoea and lower respiratory tract infections at the age of 1 to 4 months and the risk of lower respiratory tract infections at the age of 5 to 7 months increased with increasing months since breastfeeding cessation, observed by Quigley *et al.* (2007).

Some studies combined the exclusiveness and duration of breastfeeding. The mean number of episodes of acute OM both at the age of 0 to 6 months and 6 months to 12 months decreased significantly with increasing duration and exclusivity of breastfeeding, shown by Duncan *et al.* (1993). Oddy *et al.* found that predominantly breastfeeding less than 2 months increased the risk of upper respiratory tract infections with 1.43 (1.02, 2.01), compared with infants predominantly breastfed for >2 months. An increased risk of hospitalization for infections was found for infants exclusively breastfed less than 4 months, compared with infants exclusively breastfed for ≥ 4 months, according to Paricio-Talayero *et al.* (2006). The risks of respiratory tract infections were not different between infants who were exclusively breastfed for ≥ 6 months vs. exclusively breastfed for 3 months (Kramer *et al.* 2003) or fully breastfed for ≥ 6 months vs. fully breastfed for 4 to 6 months (Chantry *et al.* 2006).

Discussion

With the improvement of the general quality of recent published studies on breastfeeding and infectious diseases in industrialized countries, the positive protective effects of breastfeeding seem to be clear. It has been persistently shown that breastfeeding is protective against infections, gastrointestinal and respiratory tract infections, even in industrialized countries.

Important reviews about the methodological flaws of studies on breastfeeding were done by Kovar *et al.* (1984) and Bauchner *et al.* (1986). Their criteria are adequate for assessing validity, even though there are

more aspects for assessing internal validity such as the presence of reverse causality or selection bias. Kovar and Bauchner concluded in their article that breastfeeding has at least a minimal protective effect in industrialized countries based on the few studies with adequate methodology and controlling for confounding variables. Our review took their criteria into account and confirms this suggestion. The results and are in line with former reviews mostly published in the nineties (Kovar *et al.* 1984; Cunningham *et al.* 1991; Kalter *et al.* 1991 al-Ali *et al.* 1997; Yngve & Sjostrom 2001; Oddy *et al.* 2003) and an extensive recent published review (Ip *et al.* 2007).

The methods used for obtaining articles for this review led to a selection of high quality studies with minimal methodological imperfections. However, some limitations should be mentioned. Due to a strict selection a limited number of studies were included. Studies performed in industrialized Asian countries were not presented in this review. One study from Asia was found, but did not meet our inclusion criteria for the validity of the study design (al-Ali *et al.*, 1997). The use of only English literature limited the number of studies included, and allowed for publication bias. Bauchner *et al.* (1986) found two studies that met all four of their criteria and four that met three criteria. Our review found 12 studies that met all four criteria and nine that met three criteria. All 21 studies controlled for at least one major confounder. Of all 21 studies included, five did not meet the first criterion for active surveillance because they used mailed questionnaires that were only sent once (Takala *et al.* 1989; Oddy *et al.* 2003; Pettigrew *et al.* 2003; Chantry *et al.* 2006; Quigley *et al.* 2007). But, as stated in their article (Takala *et al.* 1989; Chantry *et al.* 2006), detection bias, which would modify their results, would probably have underestimated the observed protective effect of breastfeeding. One study validated the questionnaires with hospital case notes in a subsample and concluded that 99% of the parental recall was valid (Oddy *et al.* 2003). Furthermore, assessing infectious diseases by questionnaires is currently widely accepted in epidemiological studies, and reliably reflects the true incidence of those infections (Kalter *et al.* 1991). Different definitions for gastrointestinal or respiratory illnesses were used and might contain a mix of infectious and

non-infectious aetiology. This could dilute or exaggerate the real protective effect of breastfeeding against infections and should be prevented.

Five out of eight studies suggested that breastfeeding had a protective effect against gastrointestinal infections. The qualities of those studies are equal, carefully designed to avoid biases and consequently lead to appropriate conclusions. One of the studies that did not support the protective effect of breastfeeding had an extensive definition of doctor diagnosed-gastroenteritis, but relatively small number of participants (Rubin *et al.* 1990). Overall, we may conclude that breastfeeding protects infants from gastrointestinal infections.

Thirteen out of 16 studies concluded that breastfeeding protects infants against respiratory tract infections. However, not all studies separated infectious from non-infectious respiratory tract illnesses since it is difficult to distinguish between these causes during infancy. The protective effect of breastfeeding seems to be different for upper respiratory tract infections and lower respiratory tract infections. Therefore, it is necessary to differentiate between upper respiratory tract infections, lower respiratory tract infections and acute OM, instead of analysing them under one entity. Our findings are in line with a meta-analysis, which observed an overall protective effect of breastfeeding and lower respiratory disease hospitalization in the first two years of life [Relative Risk (RR) 0.28 (0.14, 0.54)], adjusted for smoking and socio-economic status (Bachrach *et al.* 2003). They did not differentiate between lower respiratory tract infections and asthma.

Positive correlations of the duration, the exclusiveness and the combination of duration and exclusiveness of breastfeeding with gastrointestinal and respiratory infections were observed. This suggests a dose-response effect whereby a longer and more exclusive breastfeeding period leads to a better protection against infection diseases. However, not all studies took the effects of different types of formula feeding, other milk, fluids or solids into account. Different types of formula feeding might result in different effects since compositions of formulas have changed considerably during the last decades. Furthermore, the exact minimal duration of exclusive breastfeeding that still protects infants against infec-

tious diseases in industrialized countries needs to be further explored (Yngve & Sjöström 2001; Kramer & Kakuma 2004; Fewtrell *et al.* 2007). The benefits and general applicability of 4 vs. 6 months of exclusively breastfeeding are not completely clarified, although the WHO recommended in 2001 to exclusively breastfeed infants for 6 months in all countries (World Health Organization and Department of Nutrition for Health and Development, 2001).

We found an established protective association of breastfeeding with gastrointestinal and respiratory tract infections. These findings might be used to support the health policy in industrialized countries in order to promote breastfeeding as well for increasing the incidence and the duration of exclusive breastfeeding. However, the optimal duration of exclusive breastfeeding (4 or 6 months) for protection against infectious diseases needs to be further studied.

Conflicts of interest

None declared.

Key messages

- Results on the protective effect of breastfeeding on infectious diseases were often conflicting in industrialized countries, where overall sanitation and health care are better.
- Studies published from 1986, after which more strictly internal validity criteria were used, strongly suggest that breastfeeding protects infants against overall infections, gastrointestinal and respiratory tract infections in industrialized countries.
- Studies that combined the duration and exclusiveness of breastfeeding observed a protective dose/duration-response effect on gastrointestinal or respiratory tract infections. However, the benefits and general applicability of 4 vs. 6 months of exclusive breastfeeding are not completely clarified, as recommended by the World Health Organization.

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