Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis

*WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality**

Summary

Background The debate on breastfeeding in areas of high HIV prevalence has led to the development of simulation models that attempt to assess the risks and benefits associated with breastfeeding. An essential element of these simulations is the extent to which breastfeeding protects against infant and child mortality; however, few studies are available on this topic. We did a pooled analysis of studies that assessed the effect of not breastfeeding on the risk of death due to infectious diseases.

Methods Studies were identified through consultations with experts in international health, and from a MEDLINE search for 1980–98. Using meta-analytical techniques, we assessed the protective effect of breastfeeding according to the age and sex of the infant, the cause of death, and the educational status of the mother.

Findings We identified eight studies, data from six of which were available (from Brazil, The Gambia, Ghana, Pakistan, the Philippines, and Senegal). These studies provided information on 1223 deaths of children under two years of age. In the African studies, virtually all babies were breastfed well into the second year of life, making it impossible to include them in the analyses of infant mortality. On the basis of the other three studies, protection provided by breastmilk declined steadily with age during infancy (pooled odds ratios: 5·8 [95% CI 3·4–9·8] for infants <2 months of age, 4·1 [2·7–6·4] for 2–3-month-olds, 2·6 [1·6–3·9] for 4–5-month-olds, 1·8 [1·2–2·8] for 6–8-month-olds, and 1·4 [0·8–2·6] for 9–11-month-olds). In the first 6 months of life, protection against diarrhoea was substantially greater (odds ratio 6·1 [4·1–9·0]) than against deaths due to acute respiratory infections (2·4 [1·6–3·5]). However, for infants aged 6–11 months, similar levels of protection were observed (1·9 [1·2–3·1] and 2·5 [1·4–4·6], respectively). For second-year deaths, the pooled odds ratios from five studies ranged between 1·6 and 2·1. Protection was highest when maternal education was low.

Interpretation These results may help shape policy decisions about feeding choices in the face of the HIV epidemic. Of particular relevance is the need to account for declining levels of protection with age in infancy, the continued protection afforded during the second year of life, and the question of the safety of breastmilk substitutes in families of low socioeconomic status.

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Introduction

The recognition that HIV is transmitted through breastmilk raised the important question of whether strategies that promote breastfeeding in areas of high HIV prevalence should be changed.[1] This policy decision is particularly difficult, given that breastfeeding provides important protection against infectious diseases,[2–6] which account for over two-thirds of the 12 million annual deaths in children younger than 5 years in less developed countries.[7]

Theoretical models have been developed to assess the advantages and disadvantages of breastfeeding for HIV-positive women, as well as for women of unknown HIV status who live in areas of high HIV prevalence.[8–13] These models have taken into account the risk of transmission through breastfeeding with regard to the age of the infant, the protection afforded by breastmilk against infectious disease mortality, the underlying HIV prevalence, and the rate of infant and child mortality. However, according to a recent WHO/UNAIDS review,[14] an important limitation of these models was the poor quantification of the relative risks for mortality associated with lack of breastfeeding. Such models used relative risk estimates ranging from 1·3 to 7·9, and no model allowed for variable levels of protection within the first year of life. We did a comprehensive pooled analysis of existing studies of the effect of not breastfeeding on risk of infant and child mortality due to infectious diseases.

Methods

Through consultations with experts in international health, the Division of Child and Adolescent Health (WHO, Geneva, Switzerland) obtained a list of published and unpublished datasets that might provide information on the risk of infant and childhood mortality according to feeding practices. The search was limited to studies carried out in the 1980s and 1990s, to those that provided data on deaths in the first year of life (and if possible on second-year deaths as well), and to those in which the cause of death was ascertained. This list was complemented by a MEDLINE search from 1980 to December, 1998, with the keywords “breastfeeding” and “mortality”. These sources revealed a total of 13 research groups who might have had datasets containing the information required.

The datasets were revised to make them compatible in terms of the names of variables, and of coding. All deaths that occurred in the first week of life were excluded, since breastfeeding is unlikely to have had a marked impact on these deaths (which were mainly due to perinatal causes and congenital malformations). Also, deaths not attributed to infectious diseases and deaths for which the cause was not known, were excluded from most analyses. For the Ghana study, two independent raters defined the cause of death, and there was no attempt to reach a consensus. The κ statistic for inter-rater agreement was 0·65 ($p<0·001$). We arbitrarily chose to use the opinion of the first rater, but since the study contributed only 33 deaths to the analysis, we assumed that the pooled estimate would not be markedly affected. For the Philippines study, deaths classified as due to “diarrhoea and acute respiratory infections” were included in both categories. Information on AIDS-related deaths was not specifically collected in the studies—all but one were carried out in the

	Brazil[18]	The Gambia[19]	Ghana[20]	Pakistan[21]	Philippines[22]	Senegal[23]
Number of children	1070	431	1099	2166	9682	3534
Site	Pelotas	Upper River Division	Upper East Region	Lahore	Cebu	Niakhar
Design	Case-control	Case-control	Cohort	Cohort	Cohort	Cohort
Setting	Urban	Mostly rural	Rural	Rural and urban slums	Urban	Rural
Year	1984	1988–90	1990–91	1984–87	1988–91	1983–86

Table 1: **Characteristics of studies included in pooled analysis**

	Brazil	The Gambia	Ghana	Pakistan	Philippines	Senegal
Total deaths	357	202	33	41	165	425
Deaths by age (months)*						
0–1	51 (14·3%)	61 (30·1%)	1 (3·0%)	17 (41·5%)	19 (11·5%)	30 (9·3%)
2–3	113 (31·7%)	16 (7·9%)	5 (15·2%)	8 (19·5%)	16 (9·7%)	29 (8·9%)
4–5	84 (23·5%)	29 (14·3%)	10 (30·3%)	8 (19·5%)	22 (13·3%)	34 (10·5%)
6–8	80 (22·4%)	26 (12·8%)	7 (21·2%)	3 (7·3%)	48 (29·1%)	41 (12·6%)
9–11	29 (8·1%)	28 (13·8)	3 (9·1%)	0	27 (19·4%)	43 (13·2%)
12–23	··	42 (20·7%)	7 (21·2%)	5 (12·2%)	33 (20·0%)	148 (45·5%)
Deaths by cause						
Acute respiratory infections	127 (35·6%)	131 (49·3%)	10 (30·3%)	30 (69·8%)	39 (15·1%)	140 (13·5%)
Diarrhoea	170 (47·6%)	27 (10·2%)	5 (15·2%)	9 (10·9%)	62 (24·0%)	288 (27·8%)
Diarrhoea and acute respiratory infections	··	··	··	··	44 (17·1%)	··
Other infections	60 (16·8%)	45 (16·9%)	13 (39·4%)	2 (4·7%)	20 (7·8%)	··
Other causes	··	63 (23·7%)	5 (15·2%)	2 (4·7%)	93 (36·1%)	607 (58·7%)†
Breastfeeding prevalence by age (months) among controls						
0–1	84%	100%	100%	98%	80%	100%
2–3	60%	100%	100%	95%	77%	100%
4–5	39%	100%	100%	92%	72%	100%
6–8	28%	100%	100%	88%	64%	100%
9–11	26%	96%	100%	80%	57%	99%
12–23	··	75%	99%	46%	26%	91%

*Excluding deaths occurring in the first week of life, and deaths from non-infectious causes. †Including deaths due to infections other than acute respiratory infections or diarrhoea.

Table 2: **Distribution of deaths by age and cause, and breastfeeding prevalence among controls**

1980s—but HIV is unlikely to have caused more than a few deaths at any of the sites.

Since maternal education varied markedly across countries, this variable was classified separately for each study, according to approximate terciles. In Brazil, the classifications used were 0–2 years, 3–5 years, and 6–17 years of education; in Pakistan, women were classed as either illiterate, able to read, or able to read and write; and in the Philippines, women were grouped into those having 0–5 years, 6–10 years, or 11–16 years of education. For the African studies, stratification by maternal education was not possible.

To allow pooling of the data from case-control studies and cohort studies, results from the latter were stratified by age groups (0–1, 2–3, 4–5, 6–8, 9–11, 12–15, 16–19, and 20–23 months); the numbers of deaths and of survivors (ie, those who remained in the study until the end of each age stratum) were used in the analyses. An 11-month-old child from a cohort study, therefore, provided information on breastfeeding frequency for the first four age strata. Stratification was not required for the preparation of the data files for case-control studies, since each control child only provided information on breastfeeding at a single age. This pooling of case-control and cohort data, which has been used in other collaborative reanalyses,[15] is analogous to treating cohort studies as nested case-control studies.

In the analysis of cases, we assessed breastfeeding status before the onset of the fatal disease to avoid reverse causality—ie, feeding changes as a result of illness. When this information was not available, we used breastfeeding status 7 days before death. For controls, we assessed breastfeeding in the middle of each of the age intervals described. In the Brazilian study, most deaths took place in a hospital, and although hospital-acquired infections may have contributed to mortality,[16] the underlying cause of death was diarrhoea severe enough to warrant hospital admission. In Brazilian children who had one or more admissions due to diarrhoea in the 2 months before their death, breastfeeding status was classified before the first of these admissions. For the analyses of infant mortality stratified by sex, maternal education, and cause, the same strategy was used, but due to smaller sample sizes, only two age groups were used (0–5 and 6–11 months).

After preparing the data, we did the analyses using standard meta-analytic procedures—ie, Mantel-Haenszel pooled estimates and Cornfield confidence intervals.[17] We added 0·5 to all table cells containing a value of zero, so that calculation of the odds ratio was possible. The analyses were done with Stata 5.0 (Stata Corporation, College Station, TX, USA) and the "metan" procedure.

Results

We identified eight studies that met our criteria; data were obtainable from six of them.[18–23] Of those we could not obtain, one dataset had been destroyed, and the author of the other failed to respond to repeated attempts to contact him. The studies were all done between 1983 and 1991, and covered both urban and rural areas (table 1). Table 2

Age-group (months)	Brazil			Pakistan			Philippines			Pooled		Pooled†	
	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Cases	Odds ratio (95% CI)
0–1	51	7·2 (3·3–15·9)	43·7	17	21·3 (7·9–57·7)	6·2	18	2·5 (1·0–6·3)	50·1	86	5·8‡ (3·4–9·8)	125	4·2 (2·8–6·3)
2–3	113	3·8 (2·3–6·1)	83·3	8	11·8 (3·1–45·4)	2·5	15	5·1 (1·9–13·7)	14·2	136	4·1 (2·7–6·4)	144	3·6 (2·4–5·5)
4–5	84	2·5 (1·4–4·5)	67·2	8	1·6 (0·0–10·3)	5·0	22	2·6 (1·1–5·8)	27·8	114	2·5 (1·6–3·9)	119	2·5 (1·6–4·0)
6–8	80	2·4 (1·2–4·7)	37·0	3	3·5 (0·0–27·1)	1·7	47	1·5 (0·8–2·6)	61·4	130	1·8 (1·2–2·8)	149	1·7 (1·1–2·5)
9–11	29	1·9 (0·7–5·3)	31·9	0	··	0	27	1·2 (0·6–2·5)	68·1	56	1·4 (0·8–2·6)	68	1·4 (0·8–2·4)
All	357	3·2 (2·3–4·2)	··	36	7·9 (3·8–16·3)	··	129	1·9 (1·3–2·7)	··	522	··	605	··

Deaths due to non-infectious causes, and deaths in the first week of life were excluded.
*Weight of data in pooled estimate. †Including deaths due to non-infectious causes. ‡Heterogeneity test, p=0·009.

Table 3: **Infant mortality associated with not breastfeeding, by country and age-group**

Age (months) and sex	Brazil			Pakistan			Philippines			Pooled	
	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)
0–5											
Boys	140	3·5 (2·3–5·4)	70·2	16	10·7 (3·9–29·4)	3·4	32	2·4 (1·2–4·9)	26·4	188	3·5 (2·4–5·0)
Girls	108	3·8 (2·4–6·2)	73·8	17	6·8 (2·2–20·7)	4·9	25	4·5 (2·1–9·7)	21·3	150	4·1 (2·8–6·1)
6–11											
Boys	63	1·5 (0·8–3·1)	58·7	2	5·7† ··	1·3	26	2·0 (0·9–4·3)	40·0	91	1·8 (1·1–3·0)
Girls	46	3·9 (1·5–10·3)	36·0	3	11·9† ··	2·2	24	2·0 (0·9–4·3)	61·9	73	2·9 (1·6–5·2)

Deaths due to non-infectious causes, and deaths in the first week of life were excluded.
*Weight of data in pooled estimate. †Confidence interval undefined owing to small sample size.

Table 4: **Infant mortality associated with not breastfeeding, by country, age-group, and sex**

Age-group (months)	Gambia			Ghana			Pakistan			Philippines			Senegal			Pooled†	
	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Weight (%)*	Cases	Odds ratio (95% CI)	Weight (%) *	Cases	OR (95% CI)
12–15	15	0·7 (0·1–4·0)	20·1	4	23·8‡§ ··	0·3	3	1·1 (0·0–8·0)	10·3	18	1·5 (0·6–4·0)	54·0	51	3·0 (1·0–9·3)	15·4	91	1·6 (0·8–3·2)
16–19	16	1·3 (0·3–6·7)	18·0	2	11·0‡ (0–138·7)	0·7	2	4·5§ ··	4·4	11	1·0 (0·3–3·5)	36·2	35	2·9 (1·3–6·4)	40·6	66	2·1 (1·1–4·0)
20–23	7	0·8 (0·1–4·5)	9·8	1	3·9‡§ ··	0·9	0	·· ··	0	4	1·7‡§ ··	3·3	62	1·8 (1·1–2·9)	86·0	74	1·7 (1·0–2·7)
All	38	0·9 (0·3–2·6)	··	7	7·9 (1·2–53·2)	··	5	2·0 (0·4–11·5)	··	33	1·4 (0·6–2·9)	··	148	2·0 (1·4–3·1)	··	231	··

*Weight of data in pooled estimate. †All cases were breastfed. ‡Contains one or more zero cells. Odds ratios and 95% CI calculated by adding 0·5 to all table cells. §95% CI undefined owing to small sample size.

Table 5: **Mortality at 12–23 months of age associated with not breastfeeding, by country and age-group**

shows the number of deaths by age, excluding deaths in the first week of life and non-infectious deaths. All studies except those from Ghana and Pakistan included more than 160 deaths. Taking into account the different widths of the age strata, the highest mortality rates were observed in infants younger than 2 months of age in The Gambia and Pakistan, in those 2·0–3·9 months old in Brazil, in those 4·0–5·9 months old in Ghana and Senegal, and in those 6·0–8·9 months old in the Philippines.

Acute respiratory infections or diarrhoea were the leading cause of death from infectious diseases in three studies. However, some differences in design and the classification of the cause of death affected the comparability of the studies. The Brazilian study was restricted to deaths due to infections. The study from the Philippines had a category of "diarrhoea and acute respiratory infections" for deaths of children with symptoms of both disorders, whereas in the other studies the referees assigned such deaths to the single cause that initiated the chain of events leading to death. Deaths due to infections other than acute respiratory infections or diarrhoea in Senegal were grouped with non-infectious deaths.

Breastfeeding patterns varied markedly between studies (table 2). In the three African sites, virtually every child was breastfed during the whole of their first year of life. Therefore, these studies could not be included in the analyses of lack of breastfeeding and infant mortality. In the Gambian study, breastfeeding status was ignored because mothers were unable to provide information on breastfeeding duration in 14 cases (6·9%) and 19 controls (8·3%); in the study in the Philippines, it was ignored in three cases (1·8%) and 113 controls (1·2%). Table 3 shows the odds ratios for infant mortality associated with lack of breastfeeding in each group in each study. Pooled data are also shown. The protection against mortality provided by breastmilk tended to decline with age in all three studies. When deaths due to non-infectious causes were included in the pooled estimate, odds ratios for the youngest age ranges were affected the most (table 3).

The protection provided by breastfeeding against all infant deaths (ie, in any age group) was greatest in Pakistan, intermediate in Brazil, and lowest in the Philippines (table 3). Protection provided by breastfeeding was slightly greater for girls than for boys, but the fact that the confidence intervals overlap should be noted (table 4). In the first 6 months of life, protection against diarrhoea was substantially greater (odds ratio 6·1 [95% CI 4·1–9·0]) than against acute respiratory infections (2·4 [1·6–3·5]), but all 6–11 months of age, similar levels of protection were observed against both causes of death (1·9 1·2–3·1] *vs* 2·5 [1·4–4·6], respectively). Whereas protection against diarrhoea declined markedly with age, protection against acute respiratory infections was constant.

Lack of breastfeeding was associated with a substantially larger risk in 0–5-month-old children of poorly educated mothers (1st tercile; odds ratio 7·6 [4·7–12·3]) than in those with more educated mothers (2·7 [1·8–4·1] and 3·5 [2·0–6·1] for 2nd and 3rd terciles, respectively). This effect was also seen in 6–11-month-old children (5·1 [2·8–9·3], 2·0 [1·1–3·8], and 1·1 [0·5–2·6] for 1st, 2nd, and 3rd terciles, respectively).

All studies except the Brazilian one provided data on deaths in the second year of life. Except for two studies (Ghana and Senegal), there was no clear pattern of decreasing risk with age. There was no significant heterogeneity. The overall odds ratio for the second year was greatest in Ghana (7·9, based on only seven deaths). The Senegal and Pakistan studies showed odds ratios of 2·0, but the latter was not significant. No significant effect was observed in the Gambian and Filipino studies (table 5).

Discussion

This paper presents the findings from a comprehensive attempt to obtain available data on all studies on cause-specific mortality according to breastfeeding. A large number of investigators were contacted by WHO, and datasets from those willing and able to participate were included. Nevertheless, only three datasets provided information on deaths in the first year of life, and six provided data on deaths in the second year. Also, we have not been able to rule out publication bias, which is likely to result in the exclusion of small studies with negative findings. Of the two datasets that were identified but could not be included, one showed a protective effect of breastfeeding, and the other was not published.

Observational studies of breastfeeding and infant health may be affected by a number of methodological problems, including self-selection, reverse causality, and confounding, which have been reviewed in detail elsewhere.[24–27] In this analysis, an attempt was made to avoid reverse causality by recording breastfeeding before the fatal illness episode. Also, stratification by maternal education—a potential confounder and effect modifier—showed a consistent increase in risk for weaned infants in most education categories.

An extensive review of the literature on breastfeeding and all-cause mortality revealed one meta-analysis published in 1984[28] (which covered eight pre-1950 studies and one 1979 study), and 13 other studies.[29–40] Most of these consisted of reanalyses of existing datasets, which were mainly retrospective demographic surveys. These studies were not included in the present analysis because they did not provide information on cause of death. The studies vary substantially in terms of definitions of breastfeeding variables, in the types of analyses used, and on how the results were presented. Most investigators did not attempt to rule out reverse causality. Owing to these limitations, most of the results could not be compared with our findings. However, all studies showed significant protective effects of breastfeeding, at least for some age groups. The review confirmed that our reanalysis included most of the well-designed, published studies of breastfeeding and mortality.

Even studies that made specific attempts to control for bias have shown a protective effect of breastfeeding,[18,22,24] and several reviews agree that the overall evidence is compelling.[2–6] Randomised trials of breastfeeding promotion and infant mortality would be prohibitively difficult and ethically questionable, but one trial in India compared the effects of different types of milk given by bottle to high-risk newborns.[41] Raw human milk provided substantial protection against the incidence of septicaemia, conjunctivitis, diarrhoea, and umbilical sepsis. Our decision to exclude first-week deaths from this analysis—in order to avoid reverse causality—will underestimate the protection provided by breastmilk against neonatal infections. Another issue to bear in mind in this reanalysis is that studies did not employ a uniform protocol for defining causes of death. Most studies used verbal autopsy methods which are substantially more accurate for some causes (such as measles and diarrhoea) than for others (such as acute respiratory infections or malaria).[42,43] Nevertheless, a higher level of protection was provided against diarrhoea than against acute respiratory infections in the first six months of life within each study. Unfortunately, most studies did not provide sufficient information on breastfeeding pattern (exclusive, predominant, or partial) to allow a pooled analysis of this variable. Breakdown by sex suggested a slightly larger protection for girls, but, as noted, the confidence intervals overlap.

Our reanalysis showed that infants who are not breastfed have a six-fold greater risk of dying from infectious diseases in the first 2 months of life than those who are breastfed, but that protection decreases steadily with age, and is probably due to lower intakes by older children who also receive complementary feeding. There was significant heterogeneity within the pooled estimate for the first age group, so this estimate should be regarded with caution. The heterogeneity was mainly due to the very high odds ratio observed in Pakistan (21·3, based on 17 deaths); when Pakistan was excluded, there was no significant heterogeneity. Since 98% of infants under 2 months of age in Pakistan were reportedly breastfed, those who were not breastfed may have had underlying morbidity. In the first year of life, protection was observed in three studies from three different continents. For the second year, results were less consistent, but still suggested a protective effect.

We suggest that our data should be used in future simulations of the impact of withholding breastfeeding in HIV-positive mothers. Since our estimates refer to mortality due to infectious diseases, the relative weight of infections in overall infant and child mortality should be taken into account in the simulations. Our results will also help assess the risks and benefits associated with breastfeeding for children of different ages, since the risk of HIV transmission also depends on duration of breastfeeding.[44,45] Of direct relevance to the debate on HIV and breastfeeding are the higher levels of protection seen among less educated women, particularly for deaths at ages 6–11 months. Such results are consistent with the finding that infant-mortality differentials according to breastfeeding status are virtually non-existent in more developed countries where maternal education is high.[46] The main policy issue is whether or not HIV-positive mothers with low levels of schooling and income will be able to feed their infants with safe breastmilk substitutes. Earlier research from Malaysia showed that the association between breastfeeding and mortality is twice as strong in households without piped water or a toilet than in those with such facilities.[29] This question exceeds the scope of our analysis, but our results suggest that it will be difficult, if not impossible, to provide safe breastmilk substitutes to children from underpriviledged populations.

There is a wide agreement that the final decision on whether or not to breastfeed if a woman is HIV-positive should reside with the mother and the family.[1] We hope that our results will provide a firmer basis for policy decisions on how to help families in this difficult situation.

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