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Optimal Breastfeeding Practices and Infant and Child Mortality– A Systematic Review and Meta-analysis

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Abbreviations: BF-breastfeeding; CI – confidence interval; FE – fixed effect; HIV-Human Immunodeficiency Virus; LiST -Lives Saved Tool; LMIC – Low and Middle income country; OR – Odds Ratio; RCT – randomized control trial; RE – random effects; RR – relative risk; SE – Standard Error; WHO – World Health Organization; UNICEF -United Nations Children's Fund

ABSTRACT

Aim: To synthesize the evidence for effects of optimal breastfeeding on all-cause and infection-related mortality in infants and children aged 0-23 months.

Methods: We conducted a systematic review to compare the effect of predominant, partial, or no breastfeeding versus exclusive breastfeeding on mortality rates in the first 6 months of life and effect of no versus any breastfeeding on mortality rates between 6 and 23 months of age. A systematic literature search was conducted in PubMed, Cochrane CENTRAL, and CABI.

Results: The risk of all-cause mortality was higher in predominantly (RR 1.5), partially (RR 4.8), and no breastfed (RR14.4) infants compared to exclusively breastfed infants 0-5 months of age. Children 6-11 and 12-23 months of age who were not breastfed had 1.8 and 2.0 fold higher risk of mortality respectively, when compared to those who were breastfed.

Risk of infection-related mortality in 0-5 months was higher in predominantly (RR 1.7), partially (RR 4.56), and non breastfed (RR 8.66) infants compared to exclusive breastfed infants. The risk was 2-fold higher in non breastfed children when compared to breastfed children aged 6-23 months.

Conclusion: The findings underscore the importance of optimal breastfeeding practices during infancy and early childhood.

Key words: breastfeeding, newborn, infant, child, mortality, meta-analysis

Key notes

- Infants 0-5 months of age who were predominantly, partially or not breastfed had significantly higher risk of all-cause and infection-related mortality compared to exclusively breastfed infants.
- Children aged 6-23 months who were not breastfed had higher risk of all-cause and infection-related mortality than children who were continued on breastfeeding.
- Better the breastfeeding practice, higher the protection. Even partial breastfeeding had modest protective effect compared to no breastfeeding.

INTRODUCTION

Breastfeeding is one of the few interventions where the survival benefits span the entire continuum of childhood: newborn, infancy, and early childhood. Both the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) recommend early initiation of breastfeeding, exclusive breastfeeding during the first six months of life, and continued breastfeeding until 24 months of age (1). Yet breastfeeding rates globally generally remain low. Only 43% of the world's newborns are put to the breast within one hour of birth and 40% of infants aged six months or less are exclusively breastfed (2).

A number of reviews have evaluated the impact of breastfeeding on child mortality. The Bellagio Child Survival Series, published in *The Lancet* in 2003, identified optimal breastfeeding as the key intervention that could prevent up to 13% of under-five child deaths(3). Subsequent reviews in the Lancet Neonatal Survival Series and Nutrition series, used the Lives Saved Tool (LiST) to model the effect of scaling up breastfeeding and reaffirmed the importance of breastfeeding in reducing neonatal, infant, and child mortality.

Recent estimates suggest that optimal breastfeeding could prevent around 12% deaths in under five children every year, amounting to around 800,000 lives in low- and middle-income countries (LMICs)(4). However, the systematic reviews that formed the evidence base for the estimates were either restricted to a specific age group, such as neonates(5), or examined the effect of breastfeeding on specific infections such as pneumonia and diarrhoea. Such a focused approach restricts the search of the available literature as well as selection of studies, thereby risking the exclusion of some studies that had reported on other beneficial effects of breastfeeding. Here, we

systematically review the available literature and estimate the effects of optimal breastfeeding on i) all-cause mortality and ii) infection-related mortality in infants and children aged 0-23 months.

METHODS

Objectives

To estimate the effect of sub-optimal breastfeeding practices namely, predominant, partial, or no breastfeeding in the first 6 months of life compared to exclusive breastfeeding, and no breastfeeding between 6 and 23 months of age compared to any breastfeeding on a) all-cause mortality, and b) infection-related infant and child mortality rates.

Types of studies

We included randomized controlled trials (RCTs), both cluster randomized and quasi-randomized trials as well as observational studies - prospective/retrospective cohort and case-control - that had evaluated the effects of predominant/partial/no breastfeeding in the first 6 months of life or the effects of no breastfeeding beyond 6 months of life in infants and children aged 6 to 23months. Studies that reported all-cause mortality or mortality due to infectious causes were included. We excluded studies that provided information on only one of the infectious causes (e.g. deaths due to diarrhoea alone) or enrolled potentially HIV exposed infants due to risk of confounding by HIV status.

Types of participants

Studies that enrolled infants and children aged 2 years or less were considered for inclusion.

Types of intervention/exposure

Exposure: Predominant, partial, or no breastfeeding in first 6 months (objective 1); no breastfeeding between 6and 23 months of age (objective 2)

Control: Exclusive breastfeeding in first 6 months of life (objective 1); any breastfeeding between 6and 23 months of age (objective 2)

Outcomes and definitions

All-cause mortality and infection-related mortality were evaluated in the following time periods: 0 to 5 months, 6-11 months, and 12-23 months of age. Infection-related mortality included deaths due to any infection including sepsis, meningitis, pneumonia, diarrhea, measles, malaria, etc. The current WHO definitions were used for classifying breastfeeding exposure categories(6).

Search methods for identification of studies

We searched published literature from PubMed (Medline), Cochrane Library, and CABI Global Health databases to identify studies examining the effects of breastfeeding on neonate, infant or child mortality. Panel 1 provides the search strategy used for searching PubMed. Similar terms were used for searching the other databases. No language restrictions were applied.

Three review authors (BS, RC, and MJS) screened the titles and abstracts independently to identify potentially relevant citations. The full texts of all potentially relevant articles were retrieved and independently assessed for eligibility using pre-defined inclusion criteria and data were extracted. Any disagreements or discrepancies between reviewers were resolved by discussion and, if necessary, by consulting the fourth review author (ST).

Data extraction

For studies that met the final inclusion criteria, double data abstraction using standardized forms was performed to capture study identifiers and context, study design and limitations, intervention/exposure specifics (breastfeeding categories as per WHO definitions(6) and outcome effects (mortality). For each outcome, the total number of participants and the number of participants experiencing an event in different groups were extracted.

Statistical analysis

Data entry and meta-analysis were performed with user written programs on Stata 11.2 software (StataCorp, College Station, TX). Pooled estimates of the outcome measures were calculated from the relative risks (RR) and 95% confidence intervals (CI)/standard errors (SE) of the individual studies by generic inverse variance method by the user written "metan" command in Stata. For studies that provided odds ratios (OR), we converted the effect size to RR and then used these in the meta-analysis, whenever possible. The intention was to include the largest number of studies for the analyses. We examined for heterogeneity amongst the included studies by inspecting the forest plots and quantifying the impact of heterogeneity using a measure of the degree of inconsistency in the studies' results (I^2 statistic). We used the fixed-effect model if the I^2 statistic was less than 60%; if the I^2 was 60% or more, we used the random-effects model providing no major causes for heterogeneity could be identified.

Two separate analyses were performed to evaluate the effects of sub-optimal breastfeeding practices in infants aged 0-5 months and subsequent mortality. In the first, we compared the effect of exclusive breastfeeding with other categories, strictly

following the WHO definitions of breastfeeding categories. In the second, we collapsed the two breastfeeding categories – exclusive and predominant – to form a combined category and then compared this with the remaining categories in the 0-5 month age group.

For infants aged 6 months and above, we derived two estimates for all-cause mortality (6 to 11 and 12-23 month time periods) and a single estimate for infection-related mortality (6-23 months age). The proportion of infectious deaths was available for all but two studies (information provided in the study or obtained from the study authors). For the remaining two studies, we assumed the infection-related mortality to be 90% based on the study setting and the data from other studies. (Panel S1 and Table S1). We used the Guideline Development Tool (GDT) developed by the GRADE Working Group for assigning the quality of evidence(7).

RESULTS

We conducted the search in October 2014. Of the total 19636 citations retrieved in the search, 18874 were excluded after screening the title. Of the remaining, 57 full-text articles were assessed for eligibility after screening the abstract. Finally, a total of 13 articles were included in the review (8-20).Of these, 9 were prospective cohort studies, 2 were case-control studies, and 2 were secondary analyses from RCTs. About half of the studies were from Africa (n=6), while the others were conducted in Latin America (n=2), South East Asia (n=5), Eastern Mediterranean (n=1), and the Western Pacific (n=1) regions. One study reported data from three different regions.

All-cause mortality

Table 2 depicts the pooled effects of respective breastfeeding practices on all-cause mortality (Table S1 lists the individual studies included under each comparison). When compared to exclusively breastfed infants, predominantly breastfed infants aged 0-5 months had 48% more risk of mortality (RR 1.48, 95% CI 1.14 -1.92, 3 studies); the risk of mortality was almost 3-fold higher in partially breastfed infants (RR 2.84, 95% CI 1.63 -4.97, 3 studies) and 14-fold higher in infants who were not breastfed (RR 14.4, 95% CI 6.13 -33.9; 2 studies).When the two breastfeeding categories – exclusive and predominant – were combined and then compared with other categories, infants who were partially breastfed and not breastfed were found to have 2.3 and 2.5 fold higher risk of mortality, respectively (Table 2). Compared to breastfed infants and children 6-23 months of age, those who were not breastfed had about 1.8 and 2.0 fold increase in the risk of mortality in 6-11 months and 12-23 months of age, respectively.

Among all breastfeeding groups, there was a dose-response relation between different breastfeeding exposure categories and the risk of mortality. When compared to predominantly and partially breastfed infants, those who were not breastfed had 6.1 and 3.9 fold increase in the risk of mortality in 0-5 months of age (Table 2).

Infection-related mortality

The pooled effects of respective breastfeeding practices on infection-related mortality are provided in Table 3 (Table S2 enlists the individual studies included under each comparison). When compared to exclusive breastfeeding, predominant breastfeeding had a 70% higher risk of infection-related mortality in infants aged 0-5 months (RR 1.7, 95% CI 1.18 -2.45, 3 studies). The risk was 4.6 and 8.7 fold higher in partial and 'no breastfeeding' categories, respectively. When compared to the combined category of

exclusive/predominant breastfeeding, infants who were partially breastfed had a 3.2 fold higher risk while those who were not breastfed had a 2.2 fold higher risk of infection-related mortality in 0-5 months of age. Compared to breastfed infants and children 6-23 months of age, those who were not breastfed had 2.1 fold increase in the risk of mortality between 6 and 23 months of age (RR 2.09, 95% CI 1.68 -2.60). The pooled effect did not differ when studies in which the infection-related mortality was derived from all-cause mortality were excluded (RR 2.26, 95% CI 1.71-3.0 vs. RR 1.85, 95% CI 1.31 -2.62) (Figure 3).

As observed with all-cause mortality, there was a dose-response effect between the different breastfeeding categories and the infection-related mortality as well. Infants who were not breastfed had 7.2 and 3.7 fold higher risks of mortality in 0-5 months of age, when compared to predominantly and partially breastfed infants (Table 3).

Quality of evidence

Because of the type of studies included (cohort/case-control) and the serious risk of bias, the quality of evidence was Very Low to Low for predominant/partial/no breastfeeding vs. exclusive breastfeeding in 0-5 months, as well as for the comparison of no vs. any breastfeeding in 6-23 months of age with respect to all-cause and infection-related mortality (Table 4).

DISCUSSION

The major findings of the review were (1) significantly higher risks of all-cause and infection-related mortality with sub-optimal breastfeeding practices in the first 2 years of life; (2) almost similar effect sizes for all-cause and infection-related mortality; and (3) a

dose-response effect relation among the different breastfeeding categories, with even partial breastfeeding having a modest protective effect when compared to no breastfeeding. The findings may not be necessarily 'new' in the true sense: the findings rather reaffirm and quantify the harmful effects of suboptimal breastfeeding practices.

How different are the results of the present review from that of the recently published reviews by Lamberti et al (21, 22)? For all-cause mortality, there was virtually no difference between our review and the previous reviews in the individual comparisons of predominant, partial, or no breastfeeding with exclusive breastfeeding in 0-5 months of age. All the reviews included the same studies so identical results are expected. In contrast, the estimated effect sizes for the comparison of no versus any breastfeeding in 6-23 months of age were quite different from that of the previous reviews (Table S3). Our pooled effects were more conservative - RR 1.76 (95%CI 1.28 - 2.41) and RR 1.97 (95%CI 1.45 -2.67) in 6-11 and 12-23 months, respectively, when compared to the reported effect sizes of RR 5.66 (95% CI 1.86 - 17.2) and RR 2.23 (95% CI 0.65 -7.59) for the two time periods in a previous review(21). We included more studies: 4 and 6 studies, respectively while the previous review had only one study each in the two time periods.

The other outcome of the review – the effect of breastfeeding practices on infection-related mortality – has not previously been reported in earlier reviews (21, 22). The Lamberti review reported only diarrhoea specific or pneumonia specific mortality which precludes a direct comparison. The pooled effect sizes for the infection-related mortality seem to be relatively modest when compared to that of diarrhoea specific mortality but not so when compared to that of pneumonia specific mortality (Table S3).

The discrepancy is possibly because (a) optimal breastfeeding practices are more protective against diarrhoea specific than pneumonia specific mortality(19) and (b) pneumonia specific mortality may be more common(23), or infection-related mortality tends to approximate its effect size compared to diarrhoea specific mortality.

The LiST model currently uses only the effect sizes of pneumonia and diarrhoea specific mortality for evaluating the impact of optimal breastfeeding practices. This approach has its own pitfalls. It ignores the impact of breastfeeding on other causes of mortality such as neonatal sepsis, prematurity (particularly, necrotizing enterocolitis), measles, sudden infant death syndrome (SIDS), etc. The current estimates are therefore likely to underestimate the potential lives saved by scaling-up optimal breastfeeding practices in LMICs. In the current review, we have attempted to estimate the effect size for mortality due to any infection and not only due to diarrhoea or pneumonia. Our estimate is more likely to take account of 'other' infections such as neonatal sepsis, measles or malaria.

Having a more comprehensive effect size for infection-related mortality also allowed us to compare the effect sizes for all-cause and infection-related mortality. If optimal breastfeeding practices were to prevent only mortality due to infections and not due to other causes like malformations, trauma, and birth asphyxia, the effect size for all-cause mortality should have been roughly half the effect size for infection-related mortality (because infectious causes other than AIDS account for only about 45% of under-five mortality(23). But our findings do not conform to the expected results. The effect sizes for all-cause mortality were almost the same as that of infection-related mortality for most comparisons. This could be explained if the studies included for

estimating the pooled effects of all-cause mortality and infection-related mortality were different. Differences in settings or baseline risks, for example, could result in totally independent effect sizes for the two. But the studies included were mostly the same. The finding therefore raises a larger question: should we be using the effect size for all-cause mortality instead of the effect size for infection-related mortality (or pneumonia/diarrhoea specific mortality) to estimate the potential lives saved by optimal breastfeeding practices?

The quality of evidence was Very low to Low for both the outcomes. Given the importance of the intervention, the number of studies included in the review was also small (only 13 studies). While the lack of randomised controlled trials is understandable, the relative paucity of high quality observational studies on such a crucial topic is rather baffling. There is an urgent need for large multi centre studies to evaluate the effects of optimal breastfeeding practices on both all-cause and infection-related mortality.

Strengths and limitations

Unlike previous reviews, we adopteda more inclusiveapproach which included those cross referenced in the aforementioned reviews. Also, we estimated the effect sizes for infection-related mortality as a whole instead of focusing on only pneumonia and diarrhoea specific mortality. Our review has major limitations too. First, we did not include mortality due to exposure to HIV. The estimated infection-related mortality could still be an underestimate of the true effect, particularly in regions with high rates of deaths due to HIV exposure. Second, due to practical difficulties, we could not contact all the study authors to obtain the relative risks for some of the comparisons. Instead,

we used the values provided in the previously published reviews. Because the adjusted relative risks could not be used in the pooled analyses, the quality of evidence was only very low to low. Third, for more than half of the studies included in the comparison of no vs. any breastfeeding in 6-23 months of age, we derived infection-related mortality from the all-cause mortality. The approach has its limitation, but the results of 'sensitivity analysis' including only those studies that had reported infection-related mortality were not much different from the overall results (Figure 3).

CONCLUSIONS

The findings of the present review underscore the importance of optimal breastfeeding practices during infancy and early childhood. The pooled effect sizes – particularly that of infection-related mortality – obtained in the review could be used to more accurately estimate the number of potential lives saved by scaling up the coverage of optimal breastfeeding practices.

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Panel 1

SEARCH STRATEGY (PubMed)

1. (("breast feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breast feeding"[All Fields] OR "breastfeeding"[All Fields]) OR ("breast feeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breast feeding"[All Fields])) OR "human milk"[All Fields] OR "breast milk"[All Fields] OR ("exclusive breastfeeding"[All Fields] OR "exclusive breast feeding"[All Fields]) OR continuation[All Fields] OR continuing[All Fields] OR continued[All Fields] OR "stopping"[All Fields] OR stopped[All Fields] OR stop[All Fields]
2. ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) OR ("infant mortality"[MeSH Terms] OR ("infant"[All Fields] AND "mortality"[All Fields]) OR "infant mortality"[All Fields] OR ("neonatal"[All Fields] AND "mortality"[All Fields]) OR "neonatal mortality"[All Fields]) OR ("infant mortality"[MeSH Terms] OR ("infant"[All Fields] AND "mortality"[All Fields]) OR "infant mortality"[All Fields]) OR ("child mortality"[MeSH Terms] OR ("child"[All Fields] AND "mortality"[All Fields]) OR "child mortality"[All Fields])
3. ("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields]) OR ("diarrhoea"[All Fields] OR "diarrhea"[MeSH Terms] OR "diarrhea"[All Fields]) OR ("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) OR ("infection"[MeSH Terms] OR "infection"[All Fields] OR "infections"[All Fields]) OR (preterm[All Fields] OR ("infant, premature"[MeSH Terms] OR ("infant"[All Fields] AND "premature"[All Fields]) OR "premature infant"[All Fields] OR "prematurity"[All Fields])) OR ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields])
4. (Addresses[ptyp] OR Autobiography[ptyp] OR Bibliography[ptyp] OR Biography[ptyp] OR pubmed books[filter] OR Case Reports[ptyp] OR Congresses[ptyp] OR Consensus Development Conference[ptyp] OR Directory[ptyp] OR Duplicate Publication[ptyp] OR Editorial[ptyp] OR Festschrift[ptyp] OR Guideline[ptyp] OR In Vitro[ptyp] OR Interview[ptyp] OR Lectures[ptyp] OR Legal Cases[ptyp] OR News[ptyp] OR Newspaper Article[ptyp] OR Personal Narratives[ptyp] OR Portraits[ptyp] OR Retracted Publication[ptyp] OR Twin Study[ptyp] OR Video-Audio Media[ptyp])
5. #1 AND (#2 OR #3)
6. #5 NOT #4

Table 1: Brief description of studies included in the review

S No.	Author	Year	Country	Setting	Study Design	Sample Size	Breastfeeding Groups Assessed	Age	Results (All-cause mortality)	Results (Infection-related mortality)	Comments
1	Arifeen (9)	2001	Bangladesh	Urban Slum, LMIC	Cohort	1677	Predominant vs. exclusive	3d-5mo	1.88 (1.12-3.17)	1.86 (0.74-4.67)	Effect sizes for some comparisons not provided in original study; the same were obtained from Lamberti et al (21, 22)
							Partial vs. exclusive	3d-5mo	2.4 (1.52-3.8)	2.87 (1.31-6.31)	
							Partial vs. predominant	3d-28d	1.94 (0.58-6.43)	1.6 (0.4-7.01)	
							Partial vs. excl./predominant	3d-28d	1.33 (0.61-2.94)	1.54 (0.38-6.11)	
							No vs. exclusive	3d-5mo	21.6 (12.3-37.9)	3.81 (0.67-21.7)	
							No vs. predominant	3d-28d	1.94 (.58-6.43)	1.11 (0.06-19.8)	
							No vs. partial	3d-28d	1.46 (0.4-5.29)	0.62 (0.03-11.9)	
							No vs. excl./predominant	3d-28d	1.92 (0.58-6.25)	1.02 (0.06-18.0)	
							No vs. any	6-9mo	5.66 (1.86-17.2	2.05 (0.26-16.06)	
							No vs. any	9-11 mo	-	7.66 (2.64-22.3)	
2	Bahl (11)	2005	Ghana India Peru	Urban/ Periurban, LMIC	Secondary data from RCT	9424	Predominant vs. exclusive	6-26wks	1.11 (0.6-2.07)	1.52 (0.61-4.55)	Effect sizes for some comparisons not provided in original study; the same were obtained from Lamberti et al (21, 22)
							Partial vs. exclusive	6-26wks	1.88 (1.02-3.49)	2.99 (1.22-8.78)	
							Partial vs. predominant	6-26wks	1.69 (1.1-2.61)	1.96 (1.11-3.51)	
							Partial vs. excl./predominant	6-26wks	1.69 (1.1-2.63)	2.17 (1.26-3.72)	
							No vs. exclusive	6-26wks	8.99 (4.29-18.8)	12.9 (3.95-45.4)	
							No vs. predominant	6-26wks	8.08 (4.45-4.7)	8.53 (3.31-19.6)	
							No vs. partial	6-26wks	4.77 (2.65-8.61)	4.35 (1.72-9.71)	
							No vs. excl./predominant	6-26wks	8.33 (4.55-14.3)	9.42 (3.7-21.0)	
3	Awasthi (10)	1991	India	LMIC	Cohort	507	No vs. excl./predominant	0-6 mo	1.63 (0.88-3.01)	1.51 (0.77-2.96)	Infants in 'BF group'

											were considered to be exclusive/ predominantly breastfed
4	Srivastava (18)	1994	India (Patna)	LMIC	Cohort	500	No vs. excl./predominant	0-6 mo	1.62 (1.07-2.47)	1.73 (1.09-2.75)	Infants in 'BF group' were considered to be exclusive/ predominantly breastfed
5	Briend (12)	1988	Bangladesh	Rural, LMIC	Cohort	4612	No vs. any	12-23 mo	-	2.23 (0.65-7.62)	Effect size obtained from Lamberti et al (21, 22)
6	de Francisco (13)	1993	Gambia	Rural, LMIC	Case control	431	No vs. any	12-23 mo	0.9 (0.3-2.6)	0.87 (0.16-4.64)	Effect size for infection-related mortality derived from all-cause mortality
7	Edmond (14)	2006	Ghana	Rural, LMIC	Secondary data from RCT	10947	Predominant vs. exclusive Partial vs. exclusive Partial vs. excl./predominant Partial vs. predominant	3 - 28 d 3 - 28 d 3 - 28 d 3 - 28 d	1.45 (1.02-2.04) 5.0 (2.86-9.09) 4.55 (2.63-7.69) -	1.7 (1.1-2.64) 7.4 (3.9-14.0) 6.16 (3.33-11.4) 4.34 (2.22-8.45)	Effect size available for only the neonatal period
8	Garenne (15)	2006	Senegal	Rural, LMIC	Cohort	3534	No vs. any	12-23 mo	2.0 (1.4 to 3.1)	2.11 (1.46-3.05)	Effect size for infection-related mortality derived from all-cause mortality
9	Hanson (16)	1994	Pakistan	LMIC	Cohort	2166	No vs. any	6 -11 mo 12-23 mo	1.59 (1.14-2.2) 2.0 (0.4 to 11.5) -	2.05 (0.33-12.81) 3.5 (0.07-182.2)	Data for 6-11 mo refers to pooled effect of 3 studies (Victora/ Hanson/ Yoon) that was obtained

											from WHO collaborative study (24)
10	Molbak (17)	1994	Guinea Bissau	Semi urban, LMIC	Cohort	849	No vs. any	12-35 mo	3.45 (1.41-8.33)	3.72 (1.58-8.76)	
11	Victora (19)	1987	Brazil	LMIC	Case Control	1071	No vs. any	6- 11 mo -	1.59 (1.14-2.2) -	2.4 (1.21-4.75) 1.9 (0.69-5.23)	Data for 6-11 mo refers to pooled effect of 3 studies (Victora/ Hanson/ Yoon) that was obtained from WHO collaborative study (24)
12	Yoon (20)	1996	Philippines	Urban, LMIC	Cohort	9682	No vs. any	6-11 mo 12-23 mo	1.59 (1.14-2.2)[-] 1.4 (0.6-2.9)[†]	1.2 (0.59-2.45) 1.62 (0.67-3.92)	Data for 6-11 mo refers to pooled effect of 3 studies (Victora/ Hanson/ Yoon) that was obtained from WHO collaborative study (24)
13	Ghana VAST Study Team (8)	1994	Ghana	Rural, LMIC	Cohort	1099	No vs. any	12-24 mo	7.9 (1.2-53.2)[†]	9.1 (1.38-60.06)	Effect size for infection-related mortality derived from all-cause mortality

Baseline mortality rates available for Arifeen 114/1000 and Victora 40/1000

Table 2: Effect of respective breastfeeding (BF) on all-cause mortality

BF practice	Relative Risk (95% CI)	Number of studies*
Predominant, partial or no BF vs. exclusive BF in 0-5 months of age		
Exclusive BF	1.0	-
Predominant BF	1.48 (1.13 to 1.92)	3
Partial BF	2.84 (1.63 to 4.97)	3
No BF	14.4 (6.13 to 33.9)	2
Partial, no BF vs. predominant BF in 0-5 months of age		
Predominant BF	1.0	-
Partial BF	1.6 (1.09 to 2.33)	2
No BF	6.09 (3.57 to 10.4)	2
Partial, no BF vs. exclusive/predominant BF in 0-5 months of age		
Exclusive or predominant BF	1.0	-
Partial BF	2.27 (1.66 to 3.1)	3
No BF	2.47 (1.86 to 3.3)	4
Partial vs. no BF in 0-5 months of age		
Partial BF	1.0	-
No BF	3.89 (2.28 to 6.65)	2
Any vs. no BF in infants aged 6-23 mo		
Any BF	1.0	-
No BF 6-11 m	1.76 (1.28 to 2.41)	4
No BF 12-23 m	1.97 (1.45 to 2.67)	6

* Not all studies reported the respective infant feeding practices and the numbers of studies contributing to each comparison therefore differed.

Table 3: Effect of respective breastfeeding (BF) practices on infection-related mortality

BF practice	Relative Risk (95% CI)	Number of studies
Predominant, partial or no BF vs. exclusive BF in 0-5 months of age		
Exclusive BF	1.0	-
Predominant BF	1.7 (1.18 to 2.45)	3
Partial BF	4.56 (2.93 to 7.11)	3
No BF	8.66 (3.19 to 23.5)	2
Partial, no BF vs. predominant BF in 0-5 months of age		
Predominant BF	1.0	-
Partial BF	2.64 (1.74 to 4.0)	3
No BF	7.16 (3.06 to 16.8)	2
Partial, no BF vs. exclusive/predominant BF in 0-5 months of age		
Exclusive or predominant BF	1.0	-
Partial BF	3.21 (2.17 to 4.74)	3
No BF	2.17 (1.54 to 3.07)	4
Partial vs. no BF in 0-5 months of age		
Partial BF	1.0	-
No BF	3.74 (1.63 to 8.59)	2
Any vs. no BF in infants aged 6-23 mo		
Any BF	1.0	-
No BF 6-23 m	2.09 (1.68 to 2.60)	9*

**9 studies providing data for 14 time-periods*

Table 4: Grade profile summary for 'Sub-optimal breastfeeding vs. optimal breastfeeding practices'

Quality assessment						Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	RR (95% CI)		
All-cause mortality (0-5 mo); Predominant vs. exclusive breastfeeding								
3	Cohort/ secondary analyses from RCTs	serious [1]	not serious	not serious	not serious	RR 1.48 (1.13 to 1.92)	□□◯◯ LOW	CRITICAL
All-cause mortality (0-5 mo); Partial vs. exclusive breastfeeding								
3	Cohort/ secondary analyses from RCTs	serious [1]	not serious [2]	not serious	not serious	RR 2.84 (1.63 to 4.97)	□□◯◯ LOW	CRITICAL
All-cause mortality (0-5 mo); No vs. exclusive breastfeeding								
2	Cohort/ secondary analysis from RCTs	serious [1]	not serious [2]	not serious	not serious	RR 14.4 (6.13 to 33.8)	□□◯◯ LOW	CRITICAL
All-cause mortality (6-11 mo); No vs. any breastfeeding								
4	Cohort/case-control	very serious [1,3]	not serious [2]	not serious	not serious	RR 1.76 (1.28 to 2.41)	⊕◯◯◯ VERY LOW	CRITICAL
All-cause mortality (12-23 mo); No vs. any breastfeeding								
6	Cohort/case-control	very serious [1,3]	not serious	not serious	not serious	RR 1.97 (1.45 to 2.67)	⊕◯◯◯ VERY LOW	CRITICAL
Infection-related mortality (0-5 mo); Predominant vs. exclusive breastfeeding								
3	Cohort/ secondary analyses from RCTs	serious [1]	not serious	not serious	not serious	RR 1.70 (1.18 to 2.45)	□□◯◯ LOW	CRITICAL
Infection-related mortality (0-5 mo); Partial vs. exclusive breastfeeding								
3	Cohort/ secondary analyses from RCTs	serious [1]	not serious	not serious	not serious	RR 4.56 (2.93 to 7.11)	□□◯◯ LOW	CRITICAL
Infection-related mortality (0-5 mo); No vs. exclusive breastfeeding								

2	Cohort/ secondary analysis from RCTs	serious [1]	not serious	not serious	not serious	RR 8.66 (3.19 to 23.5)	□□◯◯ LOW	CRITICAL
Infection-related mortality (6-23 mo); No vs. any breastfeeding								
9	Cohort/case-control	very serious [1,3]	not serious	not serious	not serious	RR 2.09 (1.68 to 2.60)	⊕◯◯◯ VERY LOW	CRITICAL

1. *Limitations in analysis (unadjusted RR used in the review)*
2. *Moderate heterogeneity (I^2>60%) but effects of all studies in same direction*
3. *Reverse causality in some of the studies*

Figure 1: PRISMA Diagram

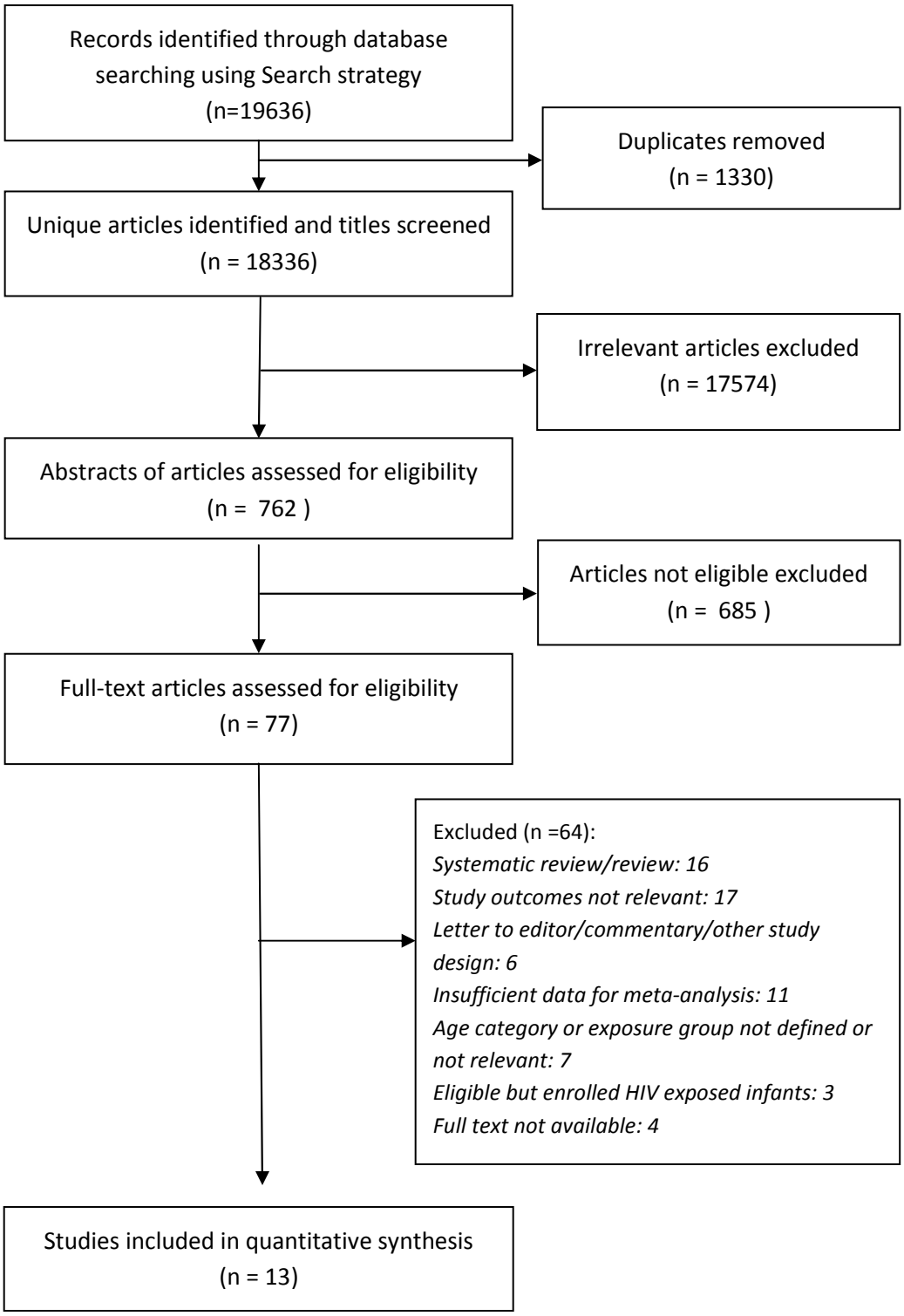


Figure 2: Sub-optimal vs. optimal breastfeeding in infants aged 0-5 months and all-cause mortality

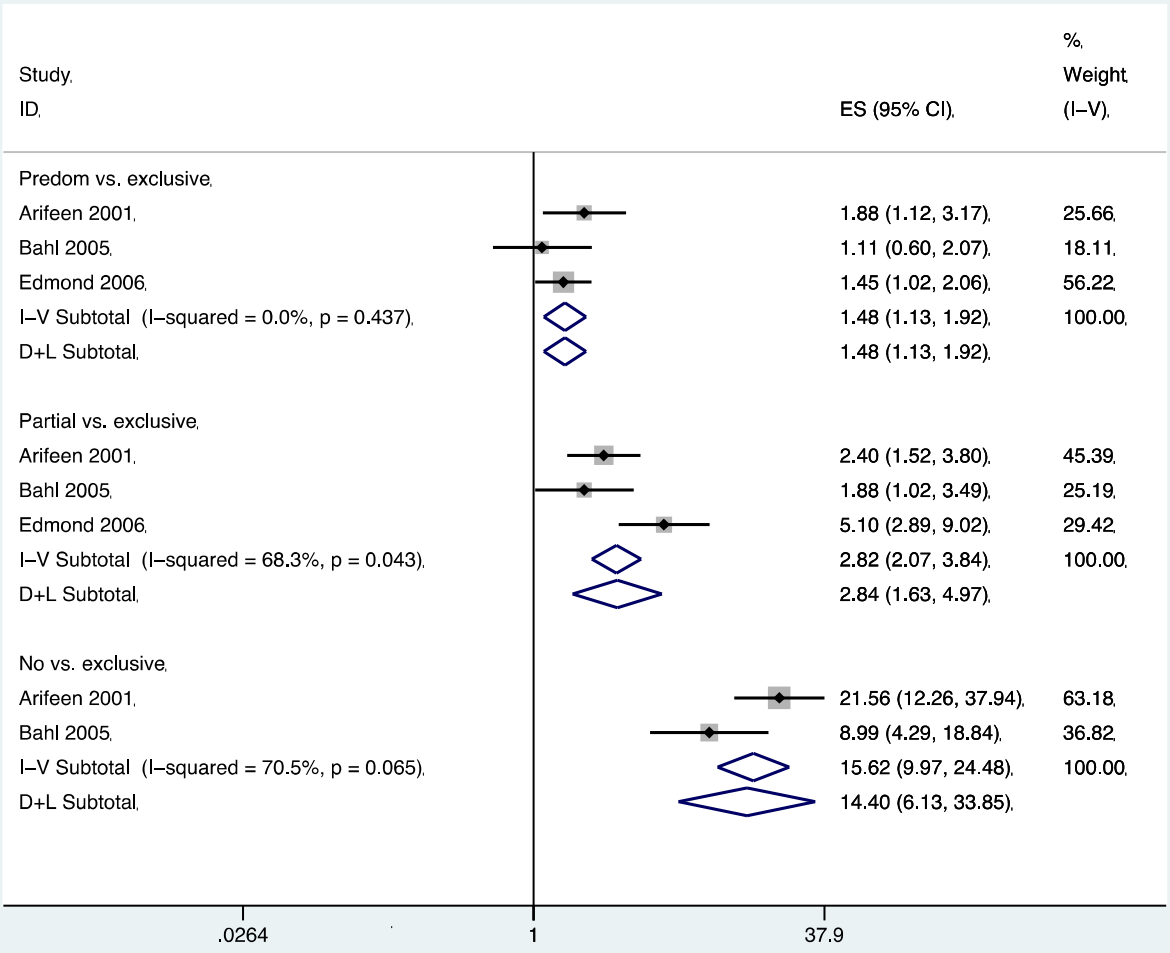
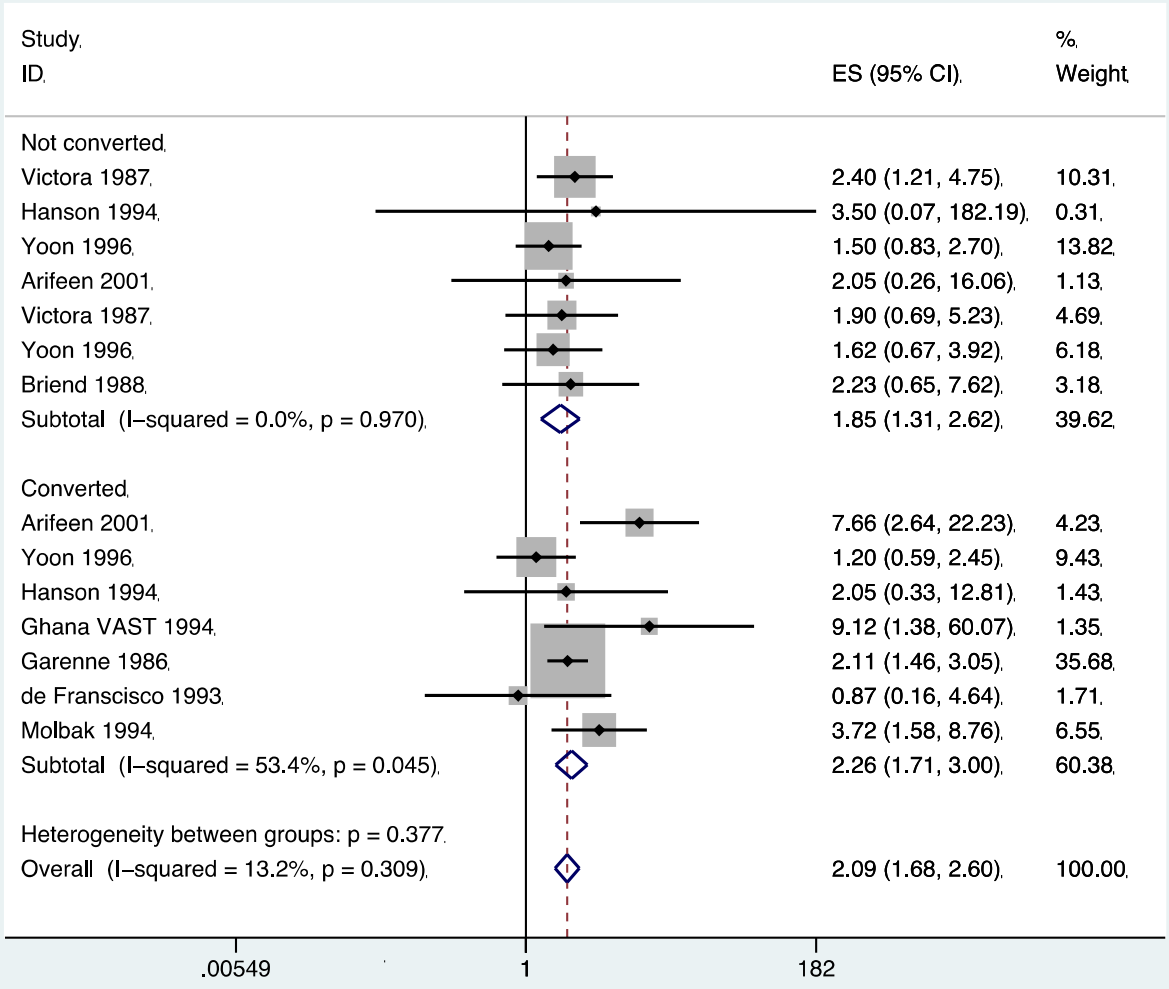


Figure 3: No vs. any breastfeeding in infants aged 6-23 months and infection-related mortality



NB: *'Not converted' refers to studies that directly reported infection-related mortality while 'converted' refers to those studies in which infection-related mortality was derived from the all-cause mortality and the proportion of infection-related deaths in the respective studies (see Text)*

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