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Timing of initiation, patterns of breastfeeding, and infant survival: prospective analysis of pooled data from three randomised trials



NEOVITA Study Group*



Summary

Background Although the benefits of exclusive breastfeeding for child health and survival, particularly in the post-neonatal period, are established, the independent beneficial effect of early breastfeeding initiation remains unclear. We studied the association between timing of breastfeeding initiation and post-enrolment neonatal and post-neonatal mortality up to 6 months of age, as well as the associations between breastfeeding pattern and mortality.

Methods We examined associations between timing of breastfeeding initiation, post-enrolment neonatal mortality (enrolment 28 days), and post-neonatal mortality up to 6 months of age (29–180 days) in a large cohort from three neonatal vitamin A trials in Ghana, India, and Tanzania. Newborn babies were eligible for these trials if their mother reported that they were likely to stay in the study area for the next 6 months, they could feed orally, were aged less than 3 days, and the primary caregiver gave informed consent. We excluded infants who initiated breastfeeding after 96 h, did not initiate, or had missing initiation status. We pooled the data from both randomised groups of the three trials and then categorised time of breastfeeding initiation as: at ≤ 1 h, 2–23 h, and 24–96 h. We defined breastfeeding patterns as exclusive, predominant, or partial breastfeeding at 4 days, 1 month, and 3 months of age. We estimated relative risks using log binomial regression and Poisson regression with robust variances. Multivariate models controlled for site and potential confounders.

Findings Of 99 938 enrolled infants, 99 632 babies initiated breastfeeding by 96 h of age and were included in our prospective cohort. 56 981 (57.2%) initiated breastfeeding at ≤ 1 h, 38 043 (38.2%) at 2–23 h, and 4608 (4.6%) at 24–96 h. Compared with infants initiating breastfeeding within the first hour of life, neonatal mortality between enrolment and 28 days was higher in infants initiating at 2–23 h (adjusted relative risk 1.41 [95% CI 1.24–1.62], $p < 0.0001$), and in those initiating at 24–96 h (1.79 [1.39–2.30], $p < 0.0001$). These associations were similar when deaths in the first 4 days of life were excluded (1.32 [1.10–1.58], $p = 0.003$, for breastfeeding initiation at 2–23 h, and 1.90 [1.38–2.62], $p = 0.0001$, for initiation at 24–96 h). When data were stratified by exclusive breastfeeding status at 4 days of age (p value for interaction = 0.690), these associations were also similar in magnitude but with wider confidence intervals for initiation at 2–23 h (1.41 [1.12–1.77], $p = 0.003$) and for initiation at 24–96 h (1.51 [0.63–3.65], $p = 0.357$). Exclusive breastfeeding was also associated with the lower mortality during the first 6 months of life (1–3 months mortality: exclusive vs partial breastfeeding at 1 month 1.83 [1.45–2.32], $p < 0.0001$, and exclusive breastfeeding vs no breastfeeding at 1 month 10.88 [8.27–14.31], $p < 0.0001$).

Interpretation Our findings suggest that early initiation of breastfeeding reduces neonatal and early infant mortality both through increasing rates of exclusive breastfeeding and by additional mechanisms. Both practices should be promoted by public health programmes and should be used in models to estimate lives saved.

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Introduction

Child mortality has decreased over the past decade, with an estimated 5.9 million deaths in children younger than 5 years reported in 2015 compared with 12.7 million in 1990.¹ The reduction in neonatal mortality has been much slower, with almost 2.7 million deaths occurring in 2015 (46% of all child

deaths). Even a greater number of children are affected by serious consequences of prematurity, intrauterine growth retardation, and sepsis during the neonatal period, manifesting as poor physical and cognitive development and long-term effects on human capital.² Interventions that can be deployed at scale starting before birth and continuing throughout the postnatal

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See [Comment](#) page e219

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Research in context

Evidence before this study

We searched PubMed and the Cochrane Library for publications between 1963 and May, 2015, and identified four systematic reviews examining the effects of breastfeeding patterns or timing of breastfeeding initiation on risks of neonatal and early infant mortality. We found no relevant papers published beyond those identified in these reviews, using combinations of the following search terms: “breastfeeding”, “breast feeding”, “breast milk”, “exclusive breastfeeding”, “partial breastfeeding”, “predominant breastfeeding”, “initiation”, “start”, “begin”, “neonatal mortality”, “newborn mortality”, “infant mortality”.

Two reviews by Lamberti and colleagues indicated that there was moderate quality evidence that exclusive breastfeeding was associated with reduced neonatal and 0–5 month mortality. Two reviews (Debes and colleagues, and Khan and colleagues) suggested that early breastfeeding initiation was associated with reduced neonatal mortality. Early initiation of breastfeeding was not proposed as an independent intervention in the *Lancet* 2013 Nutrition Series, in the expectation that it might only operate through effects on exclusive breastfeeding.

Added value of this study

This is the first study to examine the association between early breastfeeding initiation and post-neonatal mortality. Our findings from almost 100 000 infants substantially strengthen the evidence base showing that both early initiation and exclusive breastfeeding are associated with reduced neonatal and infant mortality.

Importantly, our analysis gives the first epidemiological evidence that early initiation has both a direct and indirect effect on reducing mortality. This finding concurs with research on the complex role of breastmilk in terms of immunology, epigenetics, the microbiome, and stem cells that strengthens the plausibility that early exposure to breastmilk has beneficial effects that go above and beyond a mere increase in the duration of exclusive breastfeeding.

Implications of all the available evidence

Our findings emphasise the crucial importance of prioritising the promotion of early breastfeeding initiation both to mothers and to the health workers who assist and support them. Although this promotion is already part of WHO recommendations for newborn care, it is not a universal practice with only half of newborn babies in the world being breastfed in the first hour of life.

Second, our findings strengthen the scientific basis for including early initiation in addition to exclusive breastfeeding in models, such as the LiST tool, that estimate survival benefits of scaling up key interventions to end preventable child deaths. Early initiation is currently omitted because it has been assumed that this only works through its influence on exclusive breastfeeding. Our findings challenge this assumption and suggest that the total number of deaths that could be saved if both breastfeeding best practices (early initiation and exclusivity) were adopted are currently being underestimated.

period are therefore needed to address neonatal mortality and morbidity.

Exclusive breastfeeding for the first months of life is one such intervention, which has been recommended in view of established benefits of reducing the risks of morbidity and mortality in the first 6 months of life.^{3,4} However, there is little evidence about the effects of exclusive breastfeeding on neonatal mortality.^{3,4}

Another intervention reported to be associated with improved newborn survival is early initiation of breastfeeding.^{5–8} However, it has not been elucidated whether the benefits of early initiation are only mediated through increased exclusive breastfeeding, or are also through independent mechanisms such as earlier and more frequent exposure to colostrum, improved thermal status conferred through contact with the mother, strengthened gastrointestinal barrier resulting in decreased risk of microbial translocation, or improved nutritional or immunological status.^{9–11}

Currently, only 50% of infants in the world are breastfed during the first hour of life.¹² Barriers to early initiation include facility practices leading to separation of mother and infant in the early hours after birth, tiredness after lengthy labour, caesarean sections, and

cultural norms that lead mothers to discard colostrum and give other traditional foods and fluids. Concerted programmatic action is required to address this situation. A strong evidence base for the survival benefits of early initiation, with a better understanding of whether these benefits include independent effects beyond those conferred by improvements in exclusive breastfeeding, is necessary to increase investment in this intervention.

Data from randomised trials are not and will not be available since it would not be ethical to randomly assign infants to a delayed initiation of breastfeeding. Analyses of well designed cohort studies would greatly advance our understanding of the magnitude and extent of the protective effects of early initiation of breastfeeding.⁹ We used data from a large cohort of mothers and infants who participated in three large neonatal vitamin A trials^{13–15} in Ghana, India, and Tanzania for such analyses. We aimed to study the association between timing of breastfeeding initiation and post-enrolment neonatal and post-neonatal mortality up to 6 months of age. Our secondary objectives were to assess the relation between breastfeeding patterns and mortality, and whether the association between early initiation and mortality was modified by exclusive breastfeeding status.

Methods

Study overview

We used prospectively collected data from the three methodologically standardised trials that took place in Ghana, India, and Tanzania between 2010 and 2014. The protocol and results of these studies are published elsewhere.^{13–16}

The trials were done in seven districts in the Brong Ahafo region of central rural Ghana, the rural and urban neighbourhoods of two districts in the state of Haryana in India, and in Dar es Salaam and Morogoro regions of Tanzania.¹⁶ The total population in the three sites was roughly 4·7 million. Infant mortality at the three sites was high: 60 deaths per 1000 livebirths in Ghana and India, and in Tanzania, 73 per 1000 livebirths in urban areas and 85 per 1000 livebirths in rural areas. Neonatal mortality was also high and ranged between 35 and 45 deaths per 1000 livebirths in the three sites.¹⁶ HIV prevalence was low and vitamin A deficiency was reported to be an important public health problem. In a subset of post-partum mothers whose serum retinol was measured in the trials, 13 (2%) of 542 mothers in Ghana, 34 (7%) of 515 mothers in Tanzania, and 68 (12%) of 562 mothers in India had low serum retinol (<0·70 µmol/L).

Trained fieldworkers in Ghana and India made home visits to all women of reproductive age residing in the study area every 3 months to interview them and ask them if they were pregnant. In Tanzania, pregnant women were identified during their regular antenatal visits, in the labour wards of public health facilities, and during regular household visits as a part of the health and demographic surveillance system. All pregnant women were followed up until delivery. Newborn babies were eligible for the randomised study if their mother reported that they were likely to stay in the study area for the next 6 months, they could feed orally, were aged less than 3 days, and the primary caregiver gave informed consent. Neonates were randomly assigned into either the intervention group (receiving 50 000 IU vitamin A on the day of birth or in the next 2 days) or the control group receiving placebo. Home visits were made by study workers on days 1 and 3 after supplementation to ascertain possible adverse events. Subsequently, workers visited homes at 1, 3, 6, and 12 months to obtain information on morbidity and mortality.

Data for feeding practices and key covariates were collected at enrolment through maternal report using methods recommended by the WHO.^{17,18} The enrolment visits were on the day of birth or the next 2 days of life (median age at enrolment: 17 h, IQR 8–25). Data recorded included the time of breastfeeding initiation in hours after birth, feeding of colostrum, feeding of other fluids and foods since birth, place of delivery, type of birth attendant, type of delivery, education and occupation of the mother, single or multiple births, birth order, and other information on socioeconomic characteristics such

as main sources of drinking water, type of toilet facilities, type of household, and household ownership of durable assets. Infants were weighed by study staff. Infants were visited on the first and third day after enrolment to obtain information on the time of breastfeeding initiation (if not already initiated at the enrolment visit) and colostrum intake. Data for feeding of other fluids and foods given since enrolment, the wellbeing of the infant, and potential intervention side-effects were recorded. Infants with adverse events were referred to health facilities and managed as per standard care. Study workers visited enrolled infants at 1, 3, 6, and 12 months in India and Tanzania, and monthly in Ghana to document feeding practices in the previous 24 h (including intake of breastmilk, plain water, other milk, other fluids, medicines, and food). Data for vital status, hospital admission since the last visit, and vaccination were recorded at each timepoint. Deaths were reported to a separate study team, who verified the death and completed a verbal autopsy interview.

Study staff underwent rigorous training for data collection. An independent team of study supervisors did random spot checks of all workers once a month and monitored quality of activities. Six monthly training sessions were held to standardise collection of birthweight data. The three studies used standardised questionnaires with a defined set of core variables, and these questionnaires were completed by interview, examination, anthropometry, or laboratory analyses. Each core variable had a standard definition, acceptable range limits, and an agreed-on data format. The questions were translated into the local language and back translated. Data were captured either electronically with tablet computers or netbooks (India and Tanzania), or on paper forms and double data-entered (Ghana). Detailed range and consistency checks were encoded within the electronic data-entry system to ensure data quality. Any discrepancies were returned to the field for verification. Data were sent every month to a central repository at WHO, where further quality checks were applied and feedback provided to the investigators at each site. WHO undertook site monitoring, including observation of data collection, in all three sites twice every year.

The three trials were approved by the WHO Ethical Review Committee. Additionally, the trial in India was approved by the Ethics Review Committee of the Society for Applied Studies (New Delhi, India). The trial in Ghana was approved by the ethics committees of Kintampo Health Research Centre (Kintampo, Ghana) and the London School of Hygiene & Tropical Medicine (London, UK). The trial in Tanzania was approved by the Harvard T H Chan School of Public Health Institutional Review Board (IRB; Boston, MA, USA), the Ifakara Health Institute IRB (Ifakara, Tanzania), the Tanzania Food and Drug Administration (Dar es Salaam, Tanzania), and the Tanzania National Institute of Medical Research (Dar es Salaam, Tanzania).

Procedures

We pooled the data for both randomisation groups. We then categorised time of breastfeeding initiation into three groups: less than 1 h, 2–23 h, and 24–96 h. We excluded infants who never initiated breastfeeding or who initiated after 96 h because the primary focus of our study was to examine the effect of early breastfeeding initiation.

Breastfeeding pattern was determined by the reported type of breastfeeding in the 24 h period preceding the interview and was categorised as exclusive, predominant, or partial. Exclusive breastfeeding meant that infants had received only breastmilk from their mother, or a wet nurse, or expressed breastmilk, and had not received any other liquids or solids with the exception of drops or syrups consisting of vitamins, mineral supplements, or medicines. Predominant breastfeeding meant that the infant's predominant source of nourishment had been breastmilk. However, the infant might also have received water and water-based drinks (sweetened and flavoured water, teas, infusions, etc), fruit juice, and ritual fluids. Partial breastfeeding meant that the infant had received breastmilk as well as other milk or cereal, or other food. Infants were categorised as not breastfeeding if the mother reported that no breastmilk had been given (either by herself or a wet nurse).^{17,18}

Outcomes

The primary outcomes in this analysis were post-enrolment neonatal mortality (between enrolment and 28 days), mortality between 1 and 3 months (29–90 days), and mortality between 3 and 6 months (91–180 days). We additionally chose 5–28 day mortality as an outcome to reduce the possibility of reverse causality, where the outcome (ill health leading to mortality) is a determinant of the predictor (initiation of breastfeeding), and not vice versa.¹⁹ Excluding deaths occurring in the first 4 days of life would remove infants who might have been too sick to initiate breastfeeding from the analysis. We restricted the examination of the association of early initiation of breastfeeding with infant deaths to 6 months of age because this is the period when there is the highest plausibility of timing of initiation affecting mortality.

The secondary objectives were to examine associations between breastfeeding patterns and mortality, and between breastfeeding initiation and breastfeeding patterns.

Statistical analyses

We summarised baseline data regarding household, maternal, and infant characteristics using means or medians for continuous data and proportions for

	≤1 h (N=56 981)	2–23 h (N=38 043)	24–96 h (N=4608)
Infant characteristics			
Male sex	29 558 (51.9%)	19 685 (51.7%)	2455 (53.3%)
Birthweight, g (mean, SD)	2928 (479)	2784 (454)	2726 (477)
Low birthweight (<2500 g)	8517 (14.9%)	8303 (21.8%)	1240 (26.9%)
Multiple births	1394 (2.4%)	922 (2.4%)	153 (3.3%)
Colostrum given	55 026 (96.6%)	33 346 (87.7%)	2164 (47.0%)
Vitamin A supplementation	28 395 (49.8%)	19 070 (50.1%)	2351 (51.0%)
Maternal or delivery characteristics			
Age			
Mother's age, years (median, IQR)	25 (21–29)	24 (21–28)	24 (21–27)
Number of mothers aged <20 years	6710 (11.8%)	3719 (9.8%)	338 (7.3%)
Education			
None or less than primary	15 577 (27.3%)	16 025 (42.1%)	1998 (43.4%)
Primary completed and secondary incomplete	30 093 (52.8%)	12 583 (33.1%)	1347 (29.2%)
Secondary completed and higher	11 311 (19.9%)	9435 (24.8%)	1263 (27.4%)
Primiparous	13 160 (23.1%)	11 293 (29.7%)	1617 (35.1%)
Skilled birth attendant at delivery	44 369 (77.9%)	24 095 (63.3%)	3262 (70.8%)
Caesarean delivery	2120 (3.7%)	2664 (7.0%)	1461 (31.7%)
Family characteristics			
Wealth quintile			
1 (most poor)	10 001 (17.6%)	8255 (21.7%)	1239 (26.9%)
2	12 558 (22.0%)	7666 (20.2%)	964 (20.9%)
3	8826 (15.5%)	6934 (18.2%)	817 (17.7%)
4	14 828 (26.0%)	7769 (20.4%)	758 (16.5%)
5 (least poor)	10 768 (18.9%)	7419 (19.5%)	830 (18.0%)

Data are n (%), unless otherwise indicated.

Table 1: Baseline characteristics of mothers and infants by breastfeeding initiation time

categorical data, and have presented them by breastfeeding initiation time categories.

As part of the analysis plan, we had decided to pool the data only if the results from all sites were qualitatively similar. We therefore initially analysed the data individually by country, and upon finding that the results were similar in direction and magnitude between countries, we pooled the data. All univariate and multivariate models included country (study site) as a fixed effect. We used log binomial models to assess the relation between breastfeeding initiation or breastfeeding patterns and mortality in the time periods of interest.^{20,21} We used Poisson regression models with robust variances if the log binomial models failed to converge.²² We assessed for effect modification (ie, potential interaction) between timing of initiation and breastfeeding pattern using likelihood ratio tests comparing models with and without interaction terms. We also examined the relation between timing of breastfeeding initiation and not exclusive breastfeeding at 1 and 3 months, as well as the relation between timing of breastfeeding initiation and not breastfeeding at 1 and 3 months. Potential confounders considered in all multivariable models included: study site, sex, birthweight, singleton babies, maternal age, maternal

education, parity, skilled birth attendant, caesarean section, and wealth quintile. We also repeated all analyses in the control group only to determine if there was any modification of the effect of breastfeeding on mortality by vitamin A status. For deaths between 1 and 3 months, only infants who were alive at 1 month of age and for whom breastfeeding initiation status was known were included in the analysis. For deaths between 3 and 6 months, only infants who were alive at 3 months of age and for whom breastfeeding initiation status was known were included in the analysis. For breastfeeding pattern at 1 and 3 months, only infants alive at 1 month and 3 months of age, respectively, for whom breastfeeding initiation status and breastfeeding pattern were known were included in the analysis. These are similar methods to those used in other breastfeeding studies.^{5-9,23-24} Adverse reactions to supplementation were rare (bulging fontanelle 0.1–0.9%) and these infants were not excluded from any analyses. All p values were two-sided. Missing data for potential confounders were imputed using unconditional mean imputation. We analysed the data using Stata statistical software version 13.0.²⁵

Post-hoc calculations of statistical power showed that we had 90–99% power for all except two comparisons at

	Number of deaths (rate per 1000 livebirths)	Number of newborn babies	Univariable		Multivariable model 1*		Multivariable model 2†	
			RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
Neonatal mortality (from enrolment to 28 days)‡								
Total number	..	99 632
Initiation ≤1 h	623 (10.9)	56 981 (57.2%)	1.00	..	1.00
Initiation 2–23 h	559 (14.7)	38 043 (38.2%)	1.53 (1.34–1.74)	<0.0001	1.41 (1.24–1.62)	<0.0001
Initiation 24–96 h	79 (17.1)	4 608 (4.6%)	1.82 (1.42–2.33)	<0.0001	1.79 (1.39–2.30)	<0.0001
Neonatal mortality (5–28 days)§								
Total number	..	98 480
Initiation ≤1 h	301 (5.4)	56 135 (57.0%)	1.00	..	1.00	..	1.00	..
Initiation 2–23 h	313 (8.3)	37 768 (38.4%)	1.43 (1.19–1.7)	0.0001	1.32 (1.10–1.58)	0.003	1.33 (1.10–1.60)	0.003
Initiation 24–96 h	53 (11.6)	4 577 (4.6%)	1.97 (1.45–2.69)	<0.0001	1.90 (1.38–2.62)	0.0001	1.80 (1.29–2.52)	0.001
Infant mortality from 1 to <3 months (29–90 days)¶								
Total number	..	97 707
Initiation ≤1 h	332 (6.0)	55 772 (57.1%)	1.00	..	1.00	..	1.00	..
Initiation 2–23 h	359 (9.6)	37 416 (38.3%)	1.40 (1.18–1.66)	0.0001	1.34 (1.13–1.59)	0.001	1.28 (1.08–1.52)	0.005
Initiation 24–96 h	49 (10.8)	4 519 (4.6%)	1.46 (1.07–2.00)	0.018	1.48 (1.07–2.06)	0.017	1.25 (0.90–1.72)	0.180
Infant mortality from 3 to <6 months (91–180 days) 								
Total number	..	96 606
Initiation ≤1 h	286 (5.2)	55 145 (57.1%)	1.00	..	1.00	..	1.00	..
Initiation 2–23 h	289 (7.8)	36 998 (38.3%)	1.49 (1.23–1.79)	<0.0001	1.42 (1.18–1.72)	0.0002	1.39 (1.15–1.68)	0.001
Initiation 24–96 h	33 (7.4)	4 463 (4.6%)	1.36 (0.93–1.99)	0.108	1.35 (0.93–1.97)	0.113	1.21 (0.83–1.76)	0.317

RR=relative risk. *Controlling for study site, sex, birthweight, singleton, maternal age, maternal education, primiparity, skilled birth attendant, caesarean section, and wealth quintile. †Controlling for study site, sex, birthweight, singleton, maternal age, maternal education, primiparity, skilled birth attendant, caesarean section, wealth quintile, and breastfeeding pattern. ‡Among all livebirths who initiated breastfeeding. §Among all livebirths who initiated breastfeeding, who survived until 5 days. ¶Among all livebirths who initiated breastfeeding, who survived until 28 days. ||Among all livebirths who initiated breastfeeding, who survived until 90 days.

Table 2: Neonatal and infant mortality risk by hour of breastfeeding initiation

	Number of deaths (rate per 1000 livebirths)	Number of newborn babies	Univariable		Multivariable*	
			RR (95% CI)	p value	RR (95% CI)	p value
Neonatal mortality (5–28 days) by exclusively breastfed status at 4 days† (N=98 203; p value for interaction with exclusivity=0.690)						
Among exclusively breastfed infants at 4 days						
Total number	..	64 097
Initiation ≤1 h	244 (5.1)	47 442 (74.0%)	1.00	..	1.00	..
Initiation 2–23 h	135 (8.4)	16 128 (25.2%)	1.53 (1.22–1.91)	0.0002	1.41 (1.12–1.77)	0.003
Initiation 24–96 h	5 (9.5)	527 (0.8%)	1.78 (0.74–4.30)	0.201	1.51 (0.63–3.65)	0.357
Among not exclusively breastfed infants at 4 days						
Total number	..	34 106
Initiation ≤1 h	56 (6.5)	8678 (25.4%)	1.00	..	1.00	..
Initiation 2–23 h	177 (8.2)	21 469 (62.9%)	1.29 (0.95–1.75)	0.106	1.22 (0.9–1.66)	0.197
Initiation 24–96 h	45 (11.4)	3959 (11.6%)	1.79 (1.20–2.67)	0.004	1.80 (1.19–2.73)	0.006
Infant mortality (1–3 months) by exclusively breastfed status at 1 month‡ (N=87 576; p value for interaction with exclusivity=0.921)						
Among exclusively breastfed infants at 1 month						
Total number	..	52 655
Initiation ≤1 h	127 (3.7)	34 174 (64.9%)	1.00	..	1.00	..
Initiation 2–23 h	98 (5.8)	16 998 (32.3%)	1.37 (1.02–1.85)	0.039	1.39 (1.02–1.89)	0.036
Initiation 24–96 h	10 (6.7)	1483 (2.8%)	1.36 (0.7–2.64)	0.371	1.65 (0.82–3.31)	0.157
Among not exclusively breastfed infants at 1 month						
Total number	..	34 921
Initiation ≤1 h	92 (6.8)	13 577 (38.9%)	1.00	..	1.00	..
Initiation 2–23 h	189 (10.2)	18 513 (53.0%)	1.23 (0.95–1.59)	0.116	1.17 (0.9–1.52)	0.237
Initiation 24–96 h	27 (9.5)	2831 (8.1%)	1.10 (0.71–1.70)	0.664	1.09 (0.7–1.69)	0.710
Infant mortality (3–6 months) by exclusively breastfed status at 3 months§ (N=86 692; p value for interaction with exclusivity=0.925)						
Among exclusively breastfed infants at 3 months						
Total number	..	35 579
Initiation ≤1 h	75 (3.2)	23 525 (66.1%)	1.00	..	1.00	..
Initiation 2–23 h	48 (4.3)	11 095 (31.2%)	1.40 (0.93–2.09)	0.106	1.31 (0.89–1.93)	0.177
Initiation 24–96 h	4 (4.2)	959 (2.7%)	1.32 (0.46–3.74)	0.604	1.25 (0.44–3.58)	0.675
Among not exclusively breastfed infants at 3 months						
Total number	..	51 113
Initiation ≤1 h	128 (5.3)	24 019 (47.0%)	1.00	..	1.00	..
Initiation 2–23 h	184 (7.7)	23 832 (46.6%)	1.25 (0.98–1.59)	0.078	1.19 (0.94–1.5)	0.154
Initiation 24–96 h	27 (8.3)	3262 (6.4%)	1.29 (0.84–1.98)	0.246	1.17 (0.76–1.8)	0.465
RR=relative risk.*Controlling for site, sex, birthweight, singleton, maternal age, maternal education, primiparity, skilled birth attendant, caesarean section, and wealth quintile. †Among all livebirths who initiated breastfeeding, who survived until 5 days, whose breastfeeding pattern at 4 days was known. ‡Among all livebirths who initiated breastfeeding, who survived until 28 days, whose breastfeeding pattern at 1 month was known. §Among all livebirths who initiated breastfeeding, who survived until 90 days, whose breastfeeding pattern at 3 months was known.						

Table 3: Neonatal and infant mortality risk by hour of breastfeeding initiation, stratified by exclusive breastfeeding status

the levels of risk ratios observed. The exceptions were power for comparing breastfeeding initiation at ≤1 h and at 24–96 h (64%) and power for comparing mortality at 1–3 months and 3–6 months (41%).

Role of the funding source

The study was conceptualised and implemented by investigators from Ghana, India, and Tanzania, and coordinated by the WHO. A Senior Program Officer employed by the funder provided expert technical advice during discussions on the study design, the interpretation of the results, and the drafting of the paper.

Results

116 906 livebirths were recorded in the three study areas. Of them, 99 938 (85%) were enrolled in the trials: 22 955 (84%) of 27 330 identified livebirths were enrolled in Ghana, 31 999 (94%) of 34 133 livebirths in Tanzania, and 44 984 (81%) of 55 443 livebirths in India. Post-enrolment mortality to 6 months was 23 deaths per 1000 livebirths in Ghana, 31 deaths per 1000 livebirths in India, and 24 deaths per 1000 livebirths in Tanzania. Breastfeeding initiation prevalence was high in all three sites, with 99% initiating breastfeeding within 24 h in Ghana (22 640 of 22 984) and Tanzania (31 648 of 31 891),

	Number of deaths (rate per 1000 livebirths)	Number of newborn babies	Univariable		Multivariable*	
			RR (95% CI)	p value	RR (95% CI)	p value
Neonatal mortality (5–28 days) by patterns of breastfeeding at 4 days†	..	98 203
Exclusively breastfed at 4 days	384 (6.0)	64 097 (65.3%)	1.00	..	1.00	..
Predominantly breastfed at 4 days	180 (7.9)	22 785 (23.2%)	1.10 (0.88–1.39)	0.395	0.99 (0.78–1.25)	0.927
Partially breastfed at 4 days	97 (8.6)	11 316 (11.5%)	1.19 (0.91–1.56)	0.208	1.34 (1.01–1.78)	0.042
Not breastfed at 4 days	1 (200.0)	5 (0.0%)	NE	NE	NE	NE
Mortality from 1 to <3 months by patterns of breastfeeding at 1 month‡	..	87 576
Exclusively breastfed at 1 month	235 (4.5)	52 655 (60.1%)	1.00	..	1.00	..
Predominantly breastfed at 1 month	143 (5.5)	25 785 (29.4%)	0.87 (0.7–1.08)	0.216	0.84 (0.68–1.05)	0.132
Partially breastfed at 1 month	104 (12.7)	8 173 (9.3%)	2.01 (1.58–2.55)	<0.0001	1.83 (1.45–2.32)	<0.0001
Not breastfed at 1 month	61 (63.3)	963 (1.1%)	12.05 (9.13–15.91)	<0.0001	10.88 (8.27–14.31)	<0.0001
Mortality from 3 to <6 months by patterns of breastfeeding at 3 months§	..	86 692
Exclusively breastfed at 3 months	127 (3.6)	35 579 (41.0%)	1.00	..	1.00	..
Predominantly breastfed at 3 months	104 (3.9)	26 652 (30.7%)	0.93 (0.71–1.22)	0.609	0.93 (0.71–1.23)	0.623
Partially breastfed at 3 months	154 (6.7)	22 850 (26.4%)	1.70 (1.33–2.18)	<0.0001	1.62 (1.26–2.07)	0.0001
Not breastfed at 3 months	81 (50.3)	1611 (1.9%)	12.19 (9.08–16.36)	<0.0001	11.98 (8.98–16)	<0.0001

NE=not estimable because numbers too small. *Controlling for site, sex, birthweight, singleton, maternal age, maternal education, primiparity, skilled birth attendant, caesarean section, and wealth quintile. †Among all livebirths who initiated breastfeeding, who survived until 5 days, whose breastfeeding pattern at 4 days was known. ‡Among all livebirths who initiated breastfeeding, who survived until 28 days, whose breastfeeding pattern at 1 month was known. §Among all livebirths who initiated breastfeeding, who survived until 90 days, whose breastfeeding pattern at 3 months was known.

Table 4: Mortality risk by breastfeeding pattern at 4 days, 1 month, and 3 months

and 91% in India (40 735 of 44 793). A total of 99 632 babies initiated breastfeeding within 96 h of birth and were included in this prospective cohort (table 1). A group of 306 (0.3%) infants either initiated breastfeeding after 96 h, did not initiate, or had unknown initiation status and they were excluded from this analysis. This group had very high mortality (45.8 deaths per 1000 livebirths between enrolment and 28 days; 52.3 deaths per 1000 livebirths between 1 and 3 months, and 36.9 deaths per 1000 livebirths between 3 and 6 months of age).

Among enrolled infants initiating breastfeeding by 96 h of age, 56 981 (57.2%) initiated in 1 h or less, 38 043 (38.2%) initiated between 2 h and 23 h, and 4608 (4.6%) initiated between 24 h and 96 h (table 1).

Table 1 shows the characteristics of the infants and their mothers by timing of initiation of breastfeeding. The study population had low literacy (34% of mothers reported having no education or not completing primary school), 11% of mothers were teenagers, and 72% of mothers reported having a skilled attendant at birth. Less than 20% of infants were low birthweight (18 060; 18.1%). Additional information on the baseline characteristics of the study sites are presented in previous publications.^{13–15}

Among infants with known breastfeeding status, 64 097 (65.3%) of 98 203 infants were exclusively breastfed at 4 days, 52 655 (60.1%) of 87 576 were exclusively breastfed at 1 month, and 35 579 (41.0%) of 86 692 were exclusively breastfed at 3 months of age.

Among infants who initiated breastfeeding within the first hour, the mortality between enrolment and 28 days of age was 10.9 deaths per 1000 livebirths (table 2). Compared with babies who initiated breastfeeding within the first hour of life, infants who initiated breastfeeding between 2 h and 23 h of life had an increased risk of mortality from enrolment to 28 days after birth (adjusted relative risk [adjRR] 1.41 [95% CI 1.24–1.62], $p<0.0001$), as did those who initiated breastfeeding between 24 h and 96 h after birth (1.79 [1.39–2.30], $p<0.0001$; table 2).

This association remained similar when deaths in the first 4 days of life were excluded to address the possibility of reverse causality (table 2). Mortality between 5 and 28 days of life was higher in babies who initiated breastfeeding after the first hour of life than in babies who initiated breastfeeding in the first hour (aRR 1.32 [95% CI 1.10–1.58], $p=0.003$, for breastfeeding initiation between 2 h and 23 h, and 1.90 [1.38–2.62], $p<0.001$, for breastfeeding initiation between 24 h and 96 h). Additional adjustment for breastfeeding pattern at day 4 of life did not change these estimates, suggesting that it was not an important confounder (table 2). Further, breastfeeding pattern was not an effect modifier in the relation between early initiation of breastfeeding and 5–28 day mortality (table 3). The relative risks were similar in exclusively and non-exclusively breastfed infants (p for interaction=0.690; table 3).

Among infants who initiated breastfeeding in the first hour, the mortality between 1 and 3 months of age was

6.0 deaths per 1000 livebirths. Compared with these infants, those who initiated breastfeeding between 2 h and 23 h of life had an increased risk of mortality between 1 and 3 months of life after adjusting for potential confounders (adjRR 1.34 [95% CI 1.13–1.59], $p=0.001$). Infants who initiated breastfeeding between 24 h and 96 h also had an increased risk of mortality between 1 and 3 months (adjRR 1.48 [1.07–2.06], $p=0.017$).

The association between time of initiation of breastfeeding and 1–3 month or 3–6 month mortality remained similar after additional adjustment for breastfeeding pattern (table 2). Further, breastfeeding pattern was not an effect modifier in the relation between early initiation of breastfeeding and 1–3 month or 3–6 month mortality. The relative risks were similar in exclusively and non-exclusively breastfed infants (table 3).

We also examined the association between breastfeeding patterns at three ages (4 days, 1 month, and 3 months) and mortality in the subsequent periods (5–28 days, 1–<3 months, 3–<6 months; table 4). Infants who were not breastfed at the three ages of assessment had substantially higher mortality in subsequent periods than those who were exclusively breastfed (table 4). The adjusted RR for the period 5–28 days was not estimated because of the small number of non-breastfed infants at 4 days of age.

Infants who were partly breastfed at the three ages of assessment also had a higher risk of mortality in subsequent periods than did those who were exclusively breastfed (table 4). Infants who were predominantly breastfed at the three ages of assessment had similar risks of mortality in subsequent periods to those who were exclusively breastfed (table 4).

Initiation of breastfeeding after the first hour of life was associated with an increased risk of not being exclusively breastfed, and not being breastfed at all at 1 month and 3 months of age (appendix).

To confirm that receiving neonatal vitamin A did not modify the association between early initiation of breastfeeding and mortality, we did an additional analysis in which only the infants who were randomly assigned to receive placebo were included. The analyses limited to the placebo group showed that the results were similar to the overall (vitamin A and placebo groups combined) results presented in table 2 (appendix). Finally, site-specific analyses showed that the results were similar in Ghana, India, and Tanzania (appendix).

Discussion

The results from our study indicated that both early initiation and exclusive breastfeeding were significantly associated with reduced mortality from study enrolment (median 19 h after birth) to at least 3 months after birth. The findings are supported by strong biological plausibility. Early breastfeeding initiation reduces the use of prelacteal feeds that carry a high risk of contamination, while breastfeeding appears to both protect and have

positive regulatory effects over the intestinal mucosa.²⁶ Breastmilk, and particularly colostrum, is rich in immune and non-immune substances that protect against respiratory infections, neonatal sepsis, and enteric pathogens.^{10–11} Breastfeeding promotes intestinal maturation and epithelial recovery from infection. The protective effect of early initiation is probably due to some of the above direct effects and to an effect on later breastfeeding practices. Thus, both early initiation and exclusive breastfeeding are important and should be promoted by programme and policy makers.

Our findings are in accord with previously reported associations between delayed breastfeeding initiation and increased risk of neonatal mortality.^{5–7,9,23–24} In our study, associations were strong and persisted in infants who were exclusively breastfed and when we addressed reverse causality by excluding all deaths in the first 4 days of life. We observed a dose–response association between the time of breastfeeding initiation and risk of neonatal mortality. Infants who started breastfeeding at 24 h or later after birth were at the highest risk of mortality, and those who started between 2 h and 23 h were at higher risk of mortality in the neonatal period compared with infants who were breastfed in the first hour. Our analysis suggests that the association between early breastfeeding initiation and reduced risk of mortality cannot be fully explained by improvements in exclusive breastfeeding. After adjusting for the patterns of breastfeeding at the beginning of each of the age periods studied, the lower risk of mortality in those who started breastfeeding in the first hour was still observed in the neonatal period (between 5 and 28 days after birth), between 1 and 3 months, and between 3 and 6 months. We observed a strong protective effect of early initiation of breastfeeding in infants who were exclusively breastfed in the neonatal period, at 1 month and at 3 months of life. The meta-analysis of three previous studies conducted in Ghana, Nepal, and India (with relative risks ranging from 0.43 to 0.71) found that early initiation of breastfeeding was associated with a 44% lower risk of neonatal mortality.⁹ The investigators of this meta-analysis postulated that the effect was principally mediated through exclusive breastfeeding rather than the distinct effect of early initiation.⁹ The findings of our study provide evidence against this hypothesis.

We also confirmed the previously reported association between exclusive breastfeeding and a lower risk of mortality in the first half of infancy, when compared with partial or no breastfeeding.^{23,24} However, we did not find a difference in risk of mortality between infants with exclusive breastfeeding and predominant breastfeeding, by contrast with the previous systematic review, which showed that exclusive breastfeeding was associated with a lower risk of mortality than predominant breastfeeding.^{23,24}

To our knowledge, this is the largest cohort in which associations between early breastfeeding initiation and exclusive breastfeeding with infant survival have been

See Online for appendix

examined to date. Almost 100 000 infants were followed up in this study, compared with previous studies in Ghana (10 947 infants), Nepal (22 838), and south India (10 464).⁵⁻⁷ This high number of participants gave our estimates a higher degree of precision than that of previous studies. Moreover, this seems to be the first study to show that the association between early initiation and survival extended beyond the neonatal period. Our findings also show that early initiation has an independent effect, in addition to its effect mediated through increasing exclusive breastfeeding. The quality of our data was high, with low levels of attrition (ranging from 0.2% at the 6 month follow-up visit in India to 3.5% in Tanzania). Data for timing of breastfeeding initiation were collected from mothers during home visits that occurred very close to the initiation event, reducing the risk of recall bias. We measured and adjusted for confounders in the analysis. The proportion of newborn babies enrolled in each of the study populations included in our analysis was high, strengthening the generalisability of the study results.

Our study, however, has limitations inherent to its observational design. Reverse causality is possibly the most relevant concern when examining the effects of breastfeeding patterns on risk of infant mortality, as it might lead to overestimates of the protective effects of early initiation and of breastfeeding. Infants who are severely ill are likely to initiate breastfeeding later and might never breastfeed. We attempted to address this concern by excluding infants who died in the first 4 days of life and by restricting analyses to infants who were exclusively breastfed at 4 days. This adjustment did not weaken the association between early initiation and lower risk of mortality. We also only recruited infants who were able to feed, so at the time of the first interview none of the infants were likely to be severely ill.

Misclassification could have affected our findings, but given the timing of data collection so close to birth (median 19 h), it is unlikely that misclassification of the primary exposure would have been a serious problem in this dataset. Our data on breastfeeding pattern were obtained using standard 24 h recall methods,^{17,18} and misclassification of breastfeeding patterns (ie, babies reported as exclusively breastfed when they were really predominately or partially breastfed) would have biased results towards reducing the effects of exclusive breastfeeding on mortality. Although we measured and adjusted for many potential confounders, there may be some risk of residual confounding.

There are important implications of our findings. Our study suggests that effects of both early breastfeeding initiation and exclusive breastfeeding should be taken into account when models, such as those used in the Lives Saved Tool (LiST),²⁷ are applied to estimate the survival benefits of breastfeeding in the first 6 months of life. Early breastfeeding initiation is already part of WHO recommendations for newborn care.²⁸ However,

this is not a universal practice. A study¹² published in *The Lancet* indicates that only half of infants in the world are breastfed in the first hour of life. It is critical to prioritise the promotion of this practice to mothers and to the health workers who can assist and support them for early breastfeeding initiation. Such effort holds the promise of reducing mortality throughout the first 6 months of life, the period of highest vulnerability in childhood, and increasing exclusive breastfeeding duration, with its additional benefits for both health and development of infants.

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Contributors

All authors participated in the design of the study during a workshop. CSS, ERS, and SY analysed the data. All authors contributed to the drafting and review of the report.

Declaration of interests

We declare no competing interests.

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