Tab 1

Early initiation of breastfeeding, immediate skin-to-skin contact, and postnatal outcomes

EXECUTIVE SUMMARY

Early initiation of breastfeeding (EIBF)—defined as starting breastfeeding within one hour of birth—is strongly associated with reduced neonatal mortality in low and middle-income countries. This report synthesizes evidence on EIBF's impact, mechanisms, and implementation.

The association between EIBF and decreased neonatal mortality is supported by four large cohort studies conducted in Ghana, Tanzania, India, and Nepal. These studies consistently show that delayed breastfeeding initiation is associated with approximately 1.3 to 2.4-fold increased mortality risk in high-mortality settings. The relationship shows a dose-response pattern, with mortality risk increasing stepwise with longer delays in initiation. While no experimental studies directly assess EIBF's impact on mortality (which would require impractically large sample sizes), the observational evidence collectively supports causality due to strength of association, biological gradient, consistency across studies, and plausible causal pathways.

Several likely biological mechanisms explain EIBF's potential impact: (1) EIBF increases the likelihood of exclusive and prolonged breastfeeding; (2) it reduces prelacteal feeding (giving newborns substances other than breast milk in the first days of life); (3) it provides colostrum—the first milk produced after birth—which contains concentrated immune components; and (4) EIBF involves early skin-to-skin contact (SSC). Observational evidence suggests EIBF's mortality reduction is primarily mediated through decreased infection-related deaths, which is consistent with the effects of its mechanisms.

Immediate SSC—placing newborns on the mother's bare skin directly after birth—has particularly robust evidence for multiple benefits from randomized trials, including improved temperature regulation, reduced hypoglycemia, enhanced breastfeeding success, and possibly reduced maternal postpartum hemorrhage. Immediate SSC leads to EIBF, and appears to be a critical intervention underlying many of the observed benefits of EIBF.

Risks associated with EIBF and SSC appear minimal but include rare cases of sudden unexpected postnatal collapse and potential maternal discomfort. A possible concern with actively promoting SSC and EIBF is that it could induce feelings of guilt or shame in mothers who are unable to practice them.

EIBF rates vary substantially between and within countries. Interventions shown to increase EIBF rates include educational programs, peer counseling, health worker training, and multi-component programs that combine interpersonal counseling with mass media and policy

elements. Cesarean delivery consistently reduces EIBF rates, while facility-based delivery and skin-to-skin contact increase rates. While breastfeeding promotion is supported by many prominent international organizations, EIBF specifically has not been identified as a stand-alone intervention focus by major global health actors.

Given the strong association with reduced mortality, plausible biological mechanisms, and the relative simplicity of implementation, encouraging EIBF —primarily through interventions that promote early SSC—appears to be a promising intervention for reducing neonatal mortality in high-burden settings. Further research on optimal implementation strategies and cost-effectiveness would strengthen the case for increased attention to this intervention.

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ABOUT THIS REPORT

What is EIBF?

Early initiation of breastfeeding (EIBF) refers specifically to starting breastfeeding within one hour of birth. This definition is endorsed by the World Health Organization (WHO) and UNICEF, and the percentage of children receiving EIBF is among their core infant feeding indicators. A closely related practice is **immediate or early skin-to-skin care or contact (SSC)**, when newborn infants are placed on the mother directly after birth (ideally within the first 10 minutes) and maintaining skin contact for at least one hour or until the first breastfeeding is complete. Evidence indicates that skin-to-skin contact strongly promotes EIBF.

By definition, EIBF and early SSC can only happen shortly after birth and may occur regardless of whether breastfeeding or skin contact continues afterward. This distinguishes them from the longer-term practices of exclusive breastfeeding (feeding only breast milk for 6 months) and "kangaroo care" (an intervention targeted at premature and/or low birth weight infants involving early and prolonged skin-to-skin contact over many days or weeks and typically paired with exclusive breastfeeding, though definitions are not standardized).

Author, goals, scope, & methodology

Author: I (<u>Vijay Kotecha</u>) am a board-certified internal medicine physician in the United States, with >10 years of clinical experience, >5 years of research experience, and a strong interest in evidence-based medicine. I recently completed <u>Ambitious Impact's Research Training Program</u> (a full-time, 12-week program in applied research for global health interventions whose approach is strongly informed by principles of <u>Effective Altruism</u>). I have no prior specialized knowledge of this topic.

Usage of Artificial Intelligence: I used <u>Claude</u> and <u>Google Gemini</u> Large Language Models (LLMs) to help familiarize myself with some broad questions relevant to this report. LLMs were not used for other purposes such as analyzing, writing, or editing, with the exception of the executive summary which was drafted by Claude.ai.

Goals: The primary goal of this report is to better inform HealthLearn about the impact of early initiation of breastfeeding (EIBF), which is a practice addressed in their *Newborn Care Foundations* course. Additional goals include evaluating whether promoting EIBF is a potentially underappreciated pathway to impact for the broader global health community (particularly by those interested in highly cost-effective opportunities) and providing the foundation for a more concise writeup to disseminate beyond HealthLearn.

Scope & its evolution during this research process: The main questions addressed in this report are reflected in the section headings and were originally outlined to me by HealthLearn. I reorganized and prioritized the questions in conjunction with HealthLearn as I proceeded through my research. The focus is primarily on evidence from low- and middle-income countries.

The focus was initially just EIBF, but through this research process I became increasingly persuaded that we also needed to consider literature on early skin-to-skin contact (SSC). Therefore several questions were reworked to incorporate evidence on SSC (though I did less of a "deep dive" on SSC, since I'd already spent much of my available time on EIBF).

Methodology: Due to the applied, non-academic nature of this project, I prioritized a pragmatic, priority-driven, time-conscious approach at some expense of systematic rigor. I approached each question using internet-based searches of English-language, peer-reviewed academic literature. My search strategy was not systematic. Studies were first identified using Google, Google Scholar, and/or Pubmed, with search terms generally resembling the headings within this document. From there, "snowballing" was used to examine citations within those studies. I aim to clearly state the type of evidence (e.g., observational, experimental, consensus opinion) behind each conclusion and to share how strongly I believe each conclusion is supported, though it should be noted that my confidence is based largely on subjective judgements.

Abbreviations used in this report

BF: breastfeeding CI: confidence interval

DHS: Demographic & Health Survey

EBF: exclusive breastfeeding until age 6 months

EIBF: early initiation of breastfeeding

IQR: interquartile range

MICS: Multiple Indicator Cluster Survey

OR: odds ratio

RCT: randomized controlled trial

RR: relative risk

SES: socioeconomic status

SSC: skin-to-skin contact between newborn and mother

WHO: World Health Organization

RESEARCH QUESTIONS & FINDINGS

A. What is the association between EIBF and infant mortality?

Summary

I am very confident, based on five large cohort studies, that there is a strong association between EIBF and decreased mortality in the neonatal period (the first 4 weeks of life) in areas with high underlying infant mortality rates (inferring causality from these studies will be discussed in later sections).

- All study designs were secondary analyses of cohorts derived from randomized trials on a different topic (vitamin A supplementation, chlorhexidine, or micronutrient supplementation).
- Studies were carried out from 1998 to 2014 and conducted in Ghana, Tanzania, India, and Nepal, in areas with high underlying infant mortality.
- All examined a very large number of infants (~10,000 to 100,000, depending on the study); along with the high infant mortality rates, this means they include a large number of mortality outcomes (making it possible to detect and quantify differences in mortality rates with reasonable statistical precision).
- Findings were directionally consistent: delayed initiation (beyond 24 hours) was associated with increased neonatal mortality across all trials. The magnitude of effect was also fairly consistent (ranging from approximately a 1.3 to 2.4-fold increase in mortality with delayed initiation).
- There appeared to be a stepwise increase in mortality risk with each increment of delay (e.g. <1 hour, 1-24 hours, 24-48 hours...), suggesting a "dose-response" relationship.
- My impressions are most strongly influenced by the study published by the NEOVITA Study Group, 2016, which was by far the largest, as well as the most recent and best-conducted.

The association between EIBF and decreased mortality appears to persist after the neonatal period (i.e., after 28 days), at least up to 6 months of age.

Only two studies I identified examined mortality beyond 28 days. The first, much larger (n=99,632) and higher-quality study found that mortality rates remained elevated in the periods of 1-3 months and 3-6 months in infants who initiated breastfeeding after 1 hour (mortality after 6 months was not examined). A much smaller (n=4,203) observational study, which did not consider the neonatal period, found delayed initiation was associated with increased morbidity, but not mortality, from 6 weeks to 12 months (primarily before 6 months). No morbidity or mortality benefits were found from 12-24 months.

My main concerns are listed below, in order of importance. Overall they don't meaningfully reduce my confidence in the EIBF-mortality association.

- Though the studies were large and consistent, I only identified five primary sources.
 There were a few additional case-control studies I omitted from this review due to my perception that they provided lower quality evidence and would not provide enough additional value for the time required.
- All studies I reviewed were secondary analyses, raising my concern for publication bias.
 In two, over 10 years elapsed from data collection to publication, suggesting that the
 data may have been "dredged" later and tested against the EIBF hypothesis. It seems
 plausible that other cohorts could have been retrospectively analyzed but not published
 because of negative results.
- One could speculate that women of higher socioeconomic status (whose infants are
 more likely to survive for numerous reasons) may know more about medical
 recommendations for breastfeeding and be more sensitive to social desirability,
 potentially biasing them to report earlier breastfeeding than actually occurred, (which
 would systematically exaggerate the association).¹
- Authorship is concentrated, with several authors involved in multiple primary studies as well as the available systematic reviews. This could be seen as limiting the "independence" of the results. In the very unlikely case of true research misconduct, multiple studies could be affected.
- Since the cohorts in these trials were derived from randomized trials on other topics, the
 populations were likely selected in order to increase the sensitivity for the original
 research question. However, since infant mortality was an important outcome for the
 original studies, it seems the main way participants were "not representative" was in
 having very high underlying rates of infant mortality (which also increases our sensitivity
 for detecting a benefit of EIBF, and would be similar to populations where EIBF
 interventions would be targeted).
- In all studies, time to initiate breastfeeding was based on the mother's recollection when asked (depending on study) between ~1 day and several weeks later. Recall bias is a legitimate concern, particularly with longer durations from birth until assessment. But importantly, recall bias in this setting (resulting in greater misclassification of timing intervals) should systematically favor the null hypothesis. The largest and most important study also had rapid follow up periods.

Evidence considered

(Presented chronologically)

¹ However, in some cases breastfeeding in low-income countries has the opposite socioeconomic pattern, i.e. women with lower SES may be more likely to breastfeed - see, e.g., Victoria et al., 2016.

- 1. Edmond et al. (2006)² analyzed data from a cohort of >10,000 infants in rural Ghana whose mothers were being followed for a vitamin A supplementation trial.
 - Design: Cohort study (secondary analysis of prospectively-collected data from a vitamin A supplementation trial)
 - Setting: Rural GhanaStudy period: 2003-2004
 - Participants: The study included all singleton infants born to mothers in that trial who a) initiated breastfeeding, b) survived to day 2, and c) whose mothers were visited by study staff during the neonatal period (i.e., first 4 weeks of life).
 - Data collection: Women were visited every 4 weeks by village-based fieldworkers. When a birth was reported, the fieldworker administered a multi-part "birth" questionnaire (based on mothers' recall). At the subsequent 4-week visit, an "infant" questionnaire was administered with questions on morbidity and mortality.
 - Sample size: 10,947 infants
 - Exposure: Mothers' self-reported timing of breastfeeding initiation after birth (< 1 hour, 1 hour to 1 day, day 2, day 3, or after day 3) and self-reported breastfeeding pattern (exclusive, predominant, or partial).
 - Primary outcome: Infant deaths from day 2-28
 - Statistical analysis: Logistic regression was used to calculate crude and adjusted odds ratios of mortality.
 - Controls for confounding and reverse causation:
 - Deaths within the first day were excluded to help reduce the risk of reverse causation.
 - Odds ratios were adjusted for potential confounders³ and for possible confounders PLUS the pattern of breastfeeding established (exclusive, predominant, or partial).
 - Additional analyses excluded infants with evidence of illness (reported as unwell on the day of birth, congenital abnormalities, premature, and unwell at the time of interview) and with early deaths (days 2–7).

Results:

esuits.

- 145 primary outcomes (infant deaths day 2-28) occurred.
- 43% of mothers started breastfeeding in <1 hour, and 71% within 1 day.
- All adjusted odds ratios of mortality showed stepwise increases ("dose response") for each period of delay in the initiation of breastfeeding.
- Breaking breastfeeding timing into two groups, "early" (within first day; NB this is different from EIBF in the first hour) and "late" (after the first day), the authors found a 2.4-fold (95% CI 1.69-3.40) increase in the risk of

² Karen M. Edmond et al., "Delayed Breastfeeding Initiation Increases Risk of Neonatal Mortality," *Pediatrics* 117, no. 3 (March 2006): e380-386, https://doi.org/10.1542/peds.2005-1496.

³ Gender, birth size, gestational age, presence of a congenital anomaly, health on the day of birth, health at the time of interview, mother's health at the time of delivery, age of mother, parity, educational level of mother, mother having cash income, household water supply, place of defecation, number of antenatal visits, place of birth, and birth attendant.

- neonatal mortality for late initiation (this was adjusted for the same confounders previously footnoted).
- Effect sizes were similar when analyses excluded infants with evidence of illness and deaths from day 2-7.
- When also considering the pattern of breastfeeding (exclusive, predominant, or partial) the odds of mortality remained >2-fold higher with late initiation for all patterns. This suggests benefits of EIBF above and beyond helping establish a pattern of exclusive breastfeeding.

Concerns:

- There was a substantial delay between birth and initial fieldworker visit (median of 14 days, IQR 7-21 days), leading to the possibility of recall bias.
- Potential for social desirability bias.
- Only approximately ½ of infants had a weight recorded within 48 hours, so authors used self-reported infant size (from "very tiny" to "very big") in regression analysis for birth weight.
- 2. Mullaney et al. (2008)⁴ conducted a similar study in southern Nepal among a cohort of approximately 23,000 infants who were being followed for a randomized control trial of chlorhexidine antiseptic treatment.
 - Design: Cohort study (secondary analysis of prospectively-collected data from a chlorhexidine trial)
 - Setting: Southern Nepal
 - Study period: 2002-2006
 - Participants: Infants surviving to 48 h of life whose mother reported breast-feeding and for whom a breast-feeding initiation time could be estimated.
 - Data collection: "Notification of live-born infants to study workers was facilitated by local female staff who visited infants as soon as possible after birth and then followed up during the neonatal period on a standard schedule (d 1-4, 6, 8, 10, 12, 14, 21, and 28). In this population, over 90% of newborns are delivered at home." Breast-feeding initiation time in hours was estimated by mothers' recall at the earliest recorded follow-up interval.
 - o Sample size: 22,838 infants
 - **Exposure:** Self-reported timing of breastfeeding initiation (<1 hour, 1-24 hours, 24-48 hours, 48-72 hours, >72 hours).
 - o **Primary outcome:** Infant deaths from 48 hours to 28 days
 - o Statistical analysis: Relative risks calculated with regression modeling
 - Controls for confounding and reverse causation:
 - Deaths within 48 hours of birth were excluded (this accounted for 54% of all neonatal deaths in this sample).

⁴ Luke C. Mullany et al., "Breast-Feeding Patterns, Time to Initiation, and Mortality Risk among Newborns in Southern Nepal," *The Journal of Nutrition* 138, no. 3 (March 2008): 599–603.

- As an additional step to assess reverse causality, the authors repeated the analysis excluding infants who exhibited signs of severe illness⁵ within the first 48 hours.
- Relative risks were adjusted for possible confounders⁶.

Results:

- 297 primary outcomes occurred (deaths from day 3-28).
- Only 3.4% of infants began breastfeeding in the first hour, and 57% within the first 24 hours.
- As in Edmonds et al. (2006), a stepwise increase in odds of neonatal mortality was seen for each delay in breastfeeding.
- Unlike the prior study, when adjusted for possible confounders, the increased odds at each delay did not reach statistical significance.
 - "The most important confounders of the main relationship were birth weight and prematurity; after adjustment for these variables, the relationship between initiation time and mortality was not significant for any individual category, although there was a trend (P = 0.03) toward increasing risk with delayed initiation time."
- However, grouping "early" (<24hrs) and "late" (>24hrs) initiators, late initiators had a 1.41-fold greater adjusted odds of mortality.
- Over 80% of infants had morbidity data recorded, and 741 met the criteria for severe illness. Excluding these infants (who were found to be 1.78-fold more likely to die), late-initiators still had 1.35-fold greater odds of mortality (95% CI 1.02-1.78).
- Compared to the Ghana trial by Edmonds et al. (2006), there was a higher incidence of low-birth-weight babies (29.8% vs 7.4%); authors speculate that the benefits of breastfeeding may be lower in LBW babies, who have been found to be less likely to continue breastfeeding. [Also note that birth weights in Edmonds et al. (2006) were estimated by mothers, not directly measured.]

Concerns:

■ The authors note that national Demographic and Health Survey data report much higher rates of early breastfeeding in Nepal (~35% within 1 hour and ~85% within 24 hours), compared to what they determined in this study (~3% within 1 hour, ~55% within 24 hours) with very short followup assessments after birth.

 In my view, this more strongly calls into question the DHS survey data (self-reported timing but likely to occur far longer after birth perhaps years), rather than the self-reported timing in this study.

⁵ "Infants were defined as such if 2 or more of the following conditions were present: 1) difficulty breathing; 2) stiffening of the back or convulsions; 3) dysentery; 4) 5 or more watery stools within 24 h; 5) severe chest in-drawing; 6) axillary temperature >37.8°C; 7) respiratory rate <70 breaths/min."

⁶ Here, "low birth weight (LBW, <2500 g) status, prematurity (<37 wk), cord and skin cleansing treatment allocation in the parent trial, maternal literacy, sex, maternal hand-washing, previous death of a sibling, ethnicity, parity, and maternal report of fever in the 7 d prior to delivery."

- Recall and social desirability biases may be at play (for further on social desirability in breastfeeding studies, bias see Stewart et al. (2024).
- 3. Garcia et al. (2011)⁷ analysed data from approximately 10,000 newborns being followed for a randomized trial on vitamin A supplementation in southern India.
 - Design: Cohort study (secondary analysis of prospectively-collected data from a vitamin A supplementation trial)
 - Setting: Rural southern India (Tamil Nadu)
 - Study period: 1998-2001
 - Participants: Infants were included if they survived to 48 hours, breastfeeding timing could be ascertained, and they were visited by study staff within 7 days of birth.
 - Data collection: "When a birth occurred, local staff notified a supervisor who visited the site of delivery... At this visit, information on delivery and newborn characteristics, including breast-feeding initiation time, weight and gestational age were collected. Weight was measured using a Seca Model 727 electronic infant scale... Project staff visited infants every 2 weeks to record daily vital status and morbidity history. In the event of an infant death, cause of death was assigned through an independent review by two pediatricians of verbal autopsy data provided by family members. Data regarding breast-feeding were collected during the first visit."
 - Sample size: 10,464 infants
 - **Exposure:** Data on initiation of breastfeeding within the first hour was not available; timing intervals were defined as <12 h after birth, 12 to 24 after birth and more than 24 h after birth. As with prior studies, analysis was also conducted for "early" (<24 hrs) versus "late" (>24 hrs) initiators.
 - o **Primary outcome:** Mortality from 2-28 days
 - Statistical analysis: Relative risks calculated with regression modeling.
 Kaplan-Meier survival curves.
 - Controls for confounding and reverse causality:
 - As with prior studies, deaths in the first 48 hours were excluded to reduce risk of reverse causation (in this study, ~50% of neonatal deaths were in the first 48hrs, similar to the study by Mullaney et al. (2008).
 - Additionally, this study only included infants for whom the first visit occurred within 7 days after birth, to reduce likelihood of recall bias.
 - As with prior studies, analysis was repeated after excluding infants with signs of severe illness⁸ within the first 48 hours [this is defined differently in each study, based on available data]

⁷ C. R. Garcia et al., "Breast-Feeding Initiation Time and Neonatal Mortality Risk among Newborns in South India," *Journal of Perinatology: Official Journal of the California Perinatal Association* 31, no. 6 (June 2011): 397–403, https://doi.org/10.1038/jp.2010.138.

⁸ In this case, "(1) diarrhea; (2) dysentery; (3) fever; (4) difficulty/fast breathing; (4) took child for medical treatment."

- Additionally, analysis was repeated excluding deaths within 7 days.
- Additionally, analysis was repeated excluding infants whose weight was measured after 72 hours ("to assess the sensitivity of the conclusions to the timing of measurement of birth weight."

Results:

- 202 primary outcomes occurred (neonatal deaths after 48 hrs)
- Data on initiation of breastfeeding within the first hour was not available
- 82% were breastfed within the first 12 hours, and only 4% after 24 hours.
- Compared to early initiators, late initiators had 1.78-fold higher adjusted mortality (95% CI 1.03 3.10)
 - Note the low percent of late initiators: 430/10,464
- In contrast to prior studies, no stepwise mortality difference was seen with delay within earlier periods (<12 hour versus 12-24 hour initiators had similar mortality).
- Repeat analysis with additional data excluded to reduce risk of reverse causality (excluding severe illness in first 48 hours, excluding deaths within 7 days, excluding infants weighed after 72 hours) showed no attenuation of the main finding.

Concerns:

- Low number of late initiators.
- Time from birth to initial visit was <7 days, but not reported in finer detail, raising some concern of recall bias.
- Many of the authors overlap with the trial in Nepal.
- Long duration from study dates until publication, suggesting "data dredging" once the EIBF-mortality link became known.
- 4. Systematic reviews by Debes et al. (2013)⁹ and Khan et al. (2015)¹⁰ did not identify any studies predating the ones I mention here, increasing my confidence that I have not omitted important earlier evidence. They also confirm the centrality of these three studies in establishing the association between EIBF and mortality.
- 5. The NEOVITA Study Group (2016)¹¹ published a pooled analysis of data from three methodologically-standardized vitamin A supplementation trials conducted between 2010-2014.

⁹ Amanda K. Debes et al., "Time to Initiation of Breastfeeding and Neonatal Mortality and Morbidity: A Systematic Review," *BMC Public Health* 13 Suppl 3, no. Suppl 3 (2013): S19, https://doi.org/10.1186/1471-2458-13-S3-S19.

¹⁰ Jehangir Khan et al., "Timing of Breastfeeding Initiation and Exclusivity of Breastfeeding during the First Month of Life: Effects on Neonatal Mortality and Morbidity--a Systematic Review and Meta-Analysis," *Maternal and Child Health Journal* 19, no. 3 (March 2015): 468–79, https://doi.org/10.1007/s10995-014-1526-8.

¹¹ NEOVITA Study Group, "Timing of Initiation, Patterns of Breastfeeding, and Infant Survival: Prospective Analysis of Pooled Data from Three Randomised Trials," *The Lancet. Global Health* 4, no. 4 (April 2016): e266-275, https://doi.org/10.1016/S2214-109X(16)00040-1.

- Design: Cohort study (secondary analysis of prospectively-collected data from a multi-site vitamin A supplementation trial)
- Setting: Ghana, India, and Tanzania
- Study Period: 2010-2014
- Participants: Infants in three study areas who initiated breastfeeding within 96 hours.
- Data collection: Study workers visited mothers at home on day of birth or the next 2 days (median age at enrolment: 17 h, IQR 8–25). Subsequent visits were conducted 1 and 3 days later, then at 1, 3, 6, and 12 months. Timing of breastfeeding initiation was self-reported by mothers. Infants were weighed by the study staff. "An independent team of study supervisors did random spot checks of all workers once a month and monitored quality of activities...WHO undertook site monitoring, including observation of data collection, in all three sites twice every year."
- o Sample size: 99,632 infants
- Exposure: Self-reported initiation of breastfeeding within <1 hour, 2-24 hours, or 24-96 hours. 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.
- Primary outcome: Neonatal mortality (between enrollment and 28 days), 5–28 day mortality, mortality between 1 and 3 months (29–90 days), and mortality between 3 and 6 months (91–180 days).
- Statistical analysis:
 - Relative risks adjusted for potential confounders¹² as well as pattern of breastfeeding.
 - "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."
 - "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".
- Controls for confounding and reverse causality:
 - 5-28 day mortality (excluding deaths within first 4 days)
 - Analysis controlled for breastfeeding pattern (exclusive, predominant, or partial)
- Results:

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¹² "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."

- Breastfeeding initiation intervals were <1 hour (57% of neonates), 1-24 hours (38%), and 24-96 hours (4%)
- Stepwise increase in 5-28 day mortality was seen for each period of delay.
- Mortality between 1-3 months and 3-6 months was also higher in neonates who initiated breastfeeding after 1 hour; the magnitude of elevated risk was broadly similar for each time period (RR ~1.3 to 1.9)
- Adjusting for breastfeeding pattern (exclusive, predominant, or partial) did not meaningfully reduce the effect of early initiation, suggesting that EIBF works not simply by increasing rates of exclusive breastfeeding.

Concerns:

- Only a small percentage of initiators after 24 hours
- Social desirability bias.
- Although time from birth to initial assessment was very rapid, there is still some possible recall bias.
- 6. A systematic review and meta-analysis by Smith et al. (2017a)¹³ does not identify significant studies that are not included above. It does identify a few additional case-control and cross-sectional studies which I omit here, due to quality concerns and my perception that they would not be sufficiently informative for the time invested.
- 7. An additional study by Smith et al. (2017b)¹⁴ reports on post-neonatal outcomes for approximately 4,000 newborns being followed for a randomized trial on micronutrient supplementation in Tanzania.
 - Design: Cohort study (secondary analysis of prospectively-collected data from two micronutrient supplementation trials)
 - Setting: Urban Tanzania
 - Study Period: 2004-2009
 - Participants: One cohort of infants born to HIV-positive women, and one cohort
 of infants born to HIV-negative women, for whom breastfeeding was initiated and
 timing could be assessed.
 - Data collection: Enrollment 5-7 weeks postpartum. Mothers came to monthly clinic visits.
 - **Exposure:** Self-report breastfeeding initiation (<1 hour or >1 hour).
 - Primary outcome: "Outcomes of interest included time to death, morbidity, and growth failure... We assessed the risk of death at 3, 6, 12, and 24 months.
 Morbidities were defined as specific symptoms assessed by nurses at monthly clinic visits by reviewing illustrated daily diaries kept by caregivers: diarrhea; cough; difficulty breathing; fever; refusal to eat, drink, or breastfeed; pus draining

Emily R. Smith et al., "Delayed Breastfeeding Initiation and Infant Survival: A Systematic Review and Meta-Analysis," *PloS One* 12, no. 7 (2017): e0180722, https://doi.org/10.1371/journal.pone.0180722.
 Emily R. Smith et al., "Delayed Breastfeeding Initiation Is Associated with Infant Morbidity," *The Journal of Pediatrics* 191 (December 2017): 57-62.e2, https://doi.org/10.1016/j.jpeds.2017.08.069.

- from ears; and vomiting. We also considered maternal reports of hospitalizations and unscheduled outpatient visits as indicators of all-cause morbidity."
- Statistical analysis: "To examine the relationship between delayed breastfeeding and time to death or growth failure, we used Cox proportional hazard models. We used inverse probability weights to create an adjusted survival curve (15). We assessed the association between delayed breastfeeding and morbidity using generalized estimating equation (GEE) models with binomial distribution, log link, and exchangeable covariance structure in order to account for repeated observations. We a priori stratified time into three categories: 0-6, 6-12, and 12-24 months. Parent study was included as a fixed effect in all models, and treatment (i.e. zinc or multivitamins) was included in the morbidity models based on the results of the parent trials (12)."

Controls for confounding and reverse causality:

- Adjustments for possible confounders¹⁵.
- "Because ongoing breastfeeding may be a confounder, or possibly a mediator, of the relationship between early breastfeeding initiation and infant health, we included exclusive breastfeeding (yes, no) at 6 weeks in models as a sensitivity analysis."
- "In a second sensitivity analysis, we also excluded HIV-infected children from the analysis."

Results:

- Only 13% reported breastfeeding after 1 hour ("delayed").
- Higher risk of symptoms associated with pneumonia (cough, etc) with delayed breastfeeding within the first 6 months.
- No significant morbidity associations after 6 months.
- No association with growth failure.

Concerns:

- Smallest sample and (implausibly?) high rates of EIBF.
- Neonatal period was not examined.
- Long duration from study dates until publication, suggesting "data mining" once the EIBF-mortality link became known.
- Long delay from birth until data collection; recall bias.

B. Does EIBF and/or early SSC directly cause a reduction in mortality?

Are there experimental studies that directly assess the impact of EIBF or early SSC on mortality?

Summary

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¹⁵ Woman's age (≥20 years, <20 years), woman's education (<2 years, ≥2 years), wealth tertile, birth weight of recent delivery (continuously), infant sex (male or female), cesarean section (yes, no), and health facility delivery (yes, no)

No.

Evidence considered

In my literature search I was unable to identify any experimental (i.e., not observational) studies directly assessing the impact of EIBF or early skin-to-skin care (e.g., via promotional interventions) on mortality.¹⁶

Are there experimental studies that link EIBF promotion to intermediate outcomes that are linked to lower mortality?

Summary

Overall I found a paucity of experimental evidence examining EIBF and *any* health outcomes (let alone mortality). I identified only a single cluster randomized trial of an intervention promoting EIBF which followed growth and morbidity and found small effects, though the intervention also promoted exclusive breastfeeding (making it impossible to attribute the benefits to EIBF alone). My impression is that this study is weakly supportive of a causal relationship of EIBF, though the experimental evidence remains very thin.

- The intervention was primarily designed to increase EIBF and exclusive breastfeeding rates, and was not powered to detect health outcomes. However, the researchers found slightly lower morbidity among the breastfeeding promotion group (mid-upper arm circumference - MUAC - was slightly higher, and infants had fewer caregiver-reported episodes of "fever with cough" by age 6 months).
- The study appears well-conducted, though social desirability bias may have inflated the caregiver-reported outcomes (particularly the rates of early and exclusive breastfeeding).

While studies directly linking EIBF to improvements in health outcomes are lacking, there is much stronger evidence that EIBF is associated with other practices which themselves may be causally linked to reductions in mortality. These will be discussed under Heading E.

Evidence considered

¹⁶ This is unsurprising: an ethically-conducted study could only promote EIBF (not prevent it), so there will not be a dichotomous difference between groups, and mortality is an infrequent occurrence even in places with relatively high infant mortality. Thus conducting an EIBF promotion study with adequate power to detect a mortality difference would require an enormous number of participants. [Using a power size calculator at clincalc.com, assuming a baseline neonatal mortality rate of 35/1000 (a figure I obtained for Nigeria), a 20% EIBF rate in the control group, an 80% EIBF rate in the promotion group, and a 20% mortality reduction due to EIBF, achieving 80% power would require randomizing over 50,000 newborns.]

- 1. Abdulahi et al. (2021)¹⁷ conducted a cluster randomized trial of a breastfeeding education and support intervention in rural Ethiopia, with 249 women-infant pairs in the intervention arm and 219 women-infant pairs in the control.
 - Design: Cluster RCT
 - Setting: Rural Ethiopia. "The study was conducted in the Manna district located in Jimma Zone in southwest Ethiopia, where there was no similar ongoing intervention or project. From the total of 78 sub-districts under Mana, 36 sub-districts were selected for the study. The 36 sub-districts selected for the study were randomly assigned to either an intervention group (n = 18) receiving the BFESI or a control group (n = 18) receiving the routine Ethiopian healthcare service."
 - Study period: 2017
 - Participants:
 - Inclusion: Women in their second or third trimester of pregnancy, who were willing to participate with no intention of leaving the study area during the intervention period.
 - Exclusion: severe mental illness that could interfere with consent and study participation, serious illness or clinical complications warranting hospitalization, the occurrence of maternal death, abortion, stillbirth, infant death, twin gestation, preterm birth (at <37 weeks gestation), or any child congenital malformation that could interfere with breastfeeding.
 - 100% of eligible women consented; 249 women-infant pairs in intervention arm, 219 women-infant pairs in control
 - Data collection:
 - Randomization and data collection processes were blinded to the study group.
 - Data were collected at enrollment, plus 1 and 6 months postpartum by trained nurses. ¹⁸ Aside from anthropometry, data were obtained by interviewing mothers.
 - Intervention: Enhanced breastfeeding education and support program, delivered by trained peer supporters, consisting of two in-home prenatal visits (months 8 and 9) and multiple postnatal visits for the first 5 months.
 - Control: Usual care (which includes prenatal visits where EIBF and EBF are discussed, though it is felt that health workers are overburdened and may not be able to provide optimal lactation education and support).

¹⁷ Misra Abdulahi et al., "Breastfeeding Education and Support to Improve Early Initiation and Exclusive Breastfeeding Practices and Infant Growth: A Cluster Randomized Controlled Trial from a Rural Ethiopian Setting," *Nutrients* 13, no. 4 (April 6, 2021): 1204, https://doi.org/10.3390/nu13041204.

¹⁸ "At baseline, data on demographic and socio-economic characteristics, information on various maternal factors, and maternal knowledge and attitude towards breastfeeding were assessed. At one month postpartum, information about pregnancy outcome and other study exclusion criteria, and maternal practice on early initiation of breastfeeding including information about colostrum and pre-lacteals feeding were gathered. Data collected at around six months postpartum included maternal knowledge and attitude towards breastfeeding, EBF practice, infant anthropometry measurements, and morbidity."

Outcomes: "The primary study outcomes were rates of EI and EBF for six months and infant growth. Secondary outcomes included maternal knowledge and attitude towards breastfeeding at the endline. We further included morbidity for common childhood illnesses over the past two weeks as an additional secondary outcome, although this was not considered a priori in the study protocol."

Statistical analysis:

- Intention to treat
- Study was powered for detecting changes in EBF rates (not morbidity outcomes)

Results:

- No red flags in randomization outcome; groups were similar at baseline (slightly more 15-19yo mothers in control)
- The intervention improved EIBF rates to 72.7%, compared with 40.6% in the control group. Exclusive breastfeeding also rose to 68.3% vs 54.8% in control.
- "In the adjusted analysis, BFESI significantly increased the rate of EI of breastfeeding by 25.4% (95% CI: 14.5, 37.3%; p = 0.001) and EBF by 14.6% (95% CI: 3.77, 25.5%; p = 0.010), as compared to the control group."
- Low attrition; 90% of participants completed 1-month follow-up, and 87% completed 6-month follow-up.
- "From the several growth and morbidity outcomes evaluated, the only outcomes with significant intervention effect were a higher mid-upper arm circumference (ES: 0.25cm; 95% CI: 0.01, 0.49cm; p = 0.041) and a lower prevalence of respiratory infection (ES: -6.90%; 95% CI: -13.3, -0.61%; p = 0.033)."
- However, most morbidity outcomes were slightly lower (~30%) in the intervention group (though statistically not significant). While not reaching statistical significance, 18.9% of intervention infants had "serious illness" (defined as illness requiring medical attention), versus 27.4% in the control condition.
- This was not commented on by the authors, but among the reasons for attrition prior to the 1-month follow-up interval were 4 infant deaths in the intervention group and 7 infant deaths in the control. In 1-month to 6-month attrition, there were 2 infant deaths in the intervention group and 0 in the control.
 - It seems clear that statistical analysis would conclude this
 difference is well within the bounds of chance. But it's the closest
 we have to our "holy grail" of direct experimental evidence for a
 mortality benefit in the neonatal period.

o Concerns:

■ Both EIBF and exclusive breastfeeding rates went up in the intervention group, so health benefits cannot be attributed to EIBF alone.

As the study participants could not be blinded, it seems plausible that women who received extensive breastfeeding promotion education may have had a social desirability bias to report earlier and more exclusive breastfeeding (which would inflate the study's findings). Stewart et al. (2024) find evidence for recall bias in EIBF and social desirability bias in EBF in a population that received an intervention that included promotion of breastfeeding practices.

Does the observational evidence suggest that EIBF directly causes a reduction in mortality?

Summary

My impression is that the large cohort studies associating EIBF and mortality are supportive of a causal interpretation. Here I consider a subset of the <u>Bradford-Hill</u> <u>"criteria"</u> (truly "viewpoints", as they were described by their originator).

- Strength of association: Neonatal mortality is strikingly lower in infants who received early breastfeeding. Smith et al. (2017a)¹⁹ pool the previously-discussed cohorts for a meta-analysis, and conclude: "Compared to infants who initiated breastfeeding 1 hour after birth, infants who initiated breastfeeding 2–23 hours after birth had a 33% greater risk of neonatal mortality (95% CI: 13–56%, I2 = 0%), and infants who initiated breastfeeding 24 hours after birth had a 2.19-fold greater risk of neonatal mortality (95% CI: 1.73–2.77, I2 = 33%)."
 - The possibility of reverse causation is explicitly considered by multiple studies, and early deaths (within the first 1-7 days, depending on study) are excluded for this reason. Two of the studies performed additional analyses excluding infants with evidence of severe illness in the first 48 hours, and the relationship remained intact.
 - Findings are only partially attenuated (and in some cases, essentially unaffected)
 by adjustment for expected confounders.
 - Though there are other probable residual confounders, it's not obvious that they should be strong enough to fully explain the association.
- **Biological gradient**: In cohorts where breastfeeding initiation was grouped into multiple time periods (e.g., <1hr, 1-24hrs, 24-48hrs...), there was generally a stepwise increase in associated mortality risk (though this was not seen in Garcia et al., 2011²⁰).
- **Consistency**: Studies were conducted in diverse settings (four countries) over a span of 16 years (1998-2014). All were directionally consistent, and effect sizes were reasonably similar. Only one study²¹ did not detect a mortality benefit to EIBF, but the neonatal

¹⁹ Smith et al., "Delayed Breastfeeding Initiation and Infant Survival."

²⁰ Garcia et al., "Breast-Feeding Initiation Time and Neonatal Mortality Risk among Newborns in South India."

²¹ Smith et al., "Delayed Breastfeeding Initiation Is Associated with Infant Morbidity."

period was not examined, there were relatively few "late initiators", it was the smallest study, and the risk of recall bias was highest. Even so, there was evidence of decreased serious illness from 6 weeks to 12 months of life (primarily in the first 6 months) for infants who received EIBF. [As a caveat to the consistency argument, studies were remarkably similar in design²², potentially exposing them to the same pitfalls across studies.]

The strongest counterarguments, in my view, are that residual confounders account for a substantial portion of the observed effect. While we can't directly find evidence for this in the observational data, there are several potential confounders²³ that are not addressed in all of the trials²⁴.

• For example, maternal health and nutrition may be an important predictor of both EIBF and neonatal mortality. A randomized study by Jahan et al. (2014)²⁵ in poor urban women in Bangladesh found that promoting prenatal nutrition (with a focus on consumption of khichuri, a rice and lentil dish) resulted in increased pregnancy weight gain, higher mean birth weights, and a substantial increase in EIBF rates (86.0% vs. 56.7%).

Additionally, I think there are reasonable counter-arguments to be made regarding the risk of bias (such as publication bias and "p-hacking") in secondary analysis of prior datasets (see, e.g., Baldwin et al., 2022²⁶ for further discussion). But even if this reduced the strength or consistency of the association, my impression is that this would be very unlikely to "explain it away" entirely.

Evidence considered

- 1. Edmond et al. (2006)
- 2. Mullaney et al. (2008)
- 3. Garcia et al. (2011)
- 4. NEOVITA Study Group (2016)
- 5. Smith et al. (2017a)
- 6. Smith et al. (2017b)

²² E.g. all were secondary analyses of cohorts from RCTs, all relied on self-reported initiation timing, all had risk of social desirability bias, and all could be affected by unmeasured confounders.

²³ A few that come to mind are duration and complications of labor (likely to lead to later breastfeeding, and probably associated with neonatal mortality, e.g. because mother is in worse condition to care for the neonate), prenatal care quality (e.g., EIBF mothers receive more breastfeeding education and have other relative socioeconomic advantages), and health facility and/or provider quality.

²⁴ The largest and most important trial by the NEOVITA Study Group (2016), and others, adjust their findings for many important factors, including birth weight, maternal age and parity, presence of skilled birth attendants, and surrogate markers of socioeconomic status (see footnote #6).

²⁵ Khurshid Jahan et al., "Short-Term Nutrition Education Reduces Low Birthweight and Improves Pregnancy Outcomes among Urban Poor Women in Bangladesh," *Food and Nutrition Bulletin* 35, no. 4 (December 2014): 414–21, https://doi.org/10.1177/156482651403500403.

²⁶ Jessie R. Baldwin et al., "Protecting against Researcher Bias in Secondary Data Analysis: Challenges and Potential Solutions," *European Journal of Epidemiology* 37, no. 1 (2022): 1–10, https://doi.org/10.1007/s10654-021-00839-0.

- 7. Jahan et al. (2014)
- 8. Baldwin et al. (2022)

C. To what extent might EIBF directly reduce mortality?

Summary

Due to systematic ways in which research findings may be generally prone to overestimating effect sizes, as well as some specifics related to this topic, I think it's most appropriate to consider the mortality reductions of EIBF²⁷ summarized in Smith et al. (2017a)²⁸ more like "upper limits" than central point estimates of the true effect.

- It seems that incorporating all possible confounders should reduce the estimated effect; however, comparisons of observational versus experimental evidence in other domains suggests that the effect size estimates from observational evidence are not systematically higher, suggesting that substantially discounting the estimated effect may not be warranted.
 - In the limited cases where we have randomized data on breastfeeding interventions, studies find evidence of clinical benefits that seem compatible with observational data.
- Factors such as false positives, regression to the mean, publication bias, and others seem to create a general bias towards overestimation of effects in many areas of scientific inquiry (when these factors lead to challenges replicating early findings, they are sometimes described as the "decline effect").
 - Though the observational studies of EIBF are strong in many ways, they are vulnerable to some of these pitfalls.
- Studies were conducted at least 10 years ago, and it is possible that changes over time (such as improvements in water and sanitation) could make breastfeeding less impactful.
- We should consider how the estimates by Smith et al. (2017a)²⁹, which exclude mortality in the first 1-4 days of life due to the potential for reverse causation, might apply to the entire neonatal period and beyond.
 - Approximately half of all neonatal deaths occur within ~48 hours. If we suspected that EIBF has little impact on mortality in the first 1-4 days, we should reduce its expected effects on total neonatal mortality by around 50%.
 - In contrast, if we think that EIBF has similar effects in the first 1-4 days, we could apply the expected mortality reduction to all neonatal deaths.

 $^{^{27}}$ "Compared to infants who initiated breastfeeding 1 hour after birth, infants who initiated breastfeeding 2–23 hours after birth had a 33% greater risk of neonatal mortality (95% CI: 13–56%, I2 = 0%), and infants who initiated breastfeeding 24 hours after birth had a 2.19-fold greater risk of neonatal mortality (95% CI: 1.73–2.77, I2 = 33%)."

²⁸ Smith et al., "Delayed Breastfeeding Initiation and Infant Survival."

²⁹ Smith et al.

- The most important study, by the NEOVITA Study Group (2016)³⁰, actually does include data on mortality in the entire neonatal period, i.e. from birth to 28 days, as well as data excluding the first 4 days. Relative risks in the 0-28 day period, compared to the 5-28 day period, are very similar.
- The estimated effect by Smith et al. (2017a)³¹ is only for neonatal mortality reductions, though evidence from the NEOVITA Study Group (2016)³² suggests a mortality benefit extending to 6 months.

Taking what I see as the most optimistic ("best-case") plausible scenario:

- The true neonatal mortality reduction, excluding the first 2 days, matches the point estimates of Smith et al. (2017a)³³. Residual confounders are minimal, the observational effect sizes match what would have been found in randomized trials, there are no "decline effect" pitfalls, and negative changes to the impact of EIBF since the studies were conducted.
 - o RR of neonatal mortality from day 3-28 with EIBF in first hour = 1.0
 - RR from day 3-28 with initiation between 1-24 hours = 1.33
 - o RR from day 3-28 with initiation after 24 hours = 2.19
- 50% of neonatal deaths occur from day 3-28 (a conservative estimate: see Sankar et al., 2016; a higher percent would be "worse" for the intervention, making this a generous scenario)
- Reverse causation accounts for only 10% of the link between EIBF and mortality in the first 2 days of life.
 - 50% of neonatal deaths occur from day 0-2
 - RR of neonatal mortality from day 0-2 with EIBF in first hour = 1.0
 - o RR from day 0-2 with initiation between 1-24 hours = 1.297
 - o RR from day 0-2 with initiation after 24 hours = 2.071
- The reduction in infant mortality rates continues from age 28 days to 6 months and is only 30% lower than the reduction in the neonatal period.
- In this scenario:
 - RR of neonatal mortality across the entire neonatal period is 1.31 for a delay of
 1-24 hours and 2.13 for delay of >24 hours.
 - RR of infant mortality from 28 days to 6 months is 1.231 for a delay of 1-24 hours and 1.833 for a delay of >24 hours
- In a hypothetical intervention (the numbers I chose are broadly consistent with the evidence reviewed):
 - At baseline, 50% of children begin breastfeeding in the first hour, an additional 40% within 24 hours, and the final 10% beyond 24 hours (or not at all)
 - An EIBF intervention increases rates to 75% within the first hour, an additional
 15% within 24 hours, and 10% beyond 24 hours

³⁰ NEOVITA Study Group, "Timing of Initiation, Patterns of Breastfeeding, and Infant Survival."

³¹ Smith et al., "Delayed Breastfeeding Initiation and Infant Survival."

³² NEOVITA Study Group, "Timing of Initiation, Patterns of Breastfeeding, and Infant Survival."

³³ Smith et al., "Delayed Breastfeeding Initiation and Infant Survival."

- Ideal state with 100% EIBF rates: RR of neonatal mortality = 1.0
- Before intervention:
 - 50% begin in first hour: 0.50 × 1.00 = 0.50
 - 40% begin within 1-24 hours: 0.40 × 1.31 = 0.524
 - 10% begin after 24 hours: 0.10 × 2.13 = 0.213
 - Weighted average RR = 0.50 + 0.524 + 0.213 = 1.237
- After intervention:
 - 75% begin in first hour: 0.75 × 1.00 = 0.75
 - 15% begin within 1-24 hours: 0.15 × 1.31 = 0.1965
 - 10% begin after 24 hours: 0.10 × 2.13 = 0.213
 - Weighted average RR = 0.75 + 0.1965 + 0.213 = 1.1595
- Relative reduction in neonatal mortality (from day 0 to 28) due to intervention = (1.237 1.1595) / 1.237 = 0.0627 = 6.27%
- Relative reduction in infant mortality from 28 days to 6 months (with analogous calculations) = 5.3%
- The most optimistic case would also incorporate substantial gains beyond mortality³⁴, which I do not attempt to quantify here.

Taking what I see as the most pessimistic ("worst-case") plausible scenario:

- The causal link between EIBF and mortality (including any causal link between practices associated with EIBF and mortality) is greatly exaggerated due to unmeasured confounders and "decline effect" factors, together accounting for a 60% of the effect size.
- The full effect is only seen from days 5-28 (excluding days 1-4). Reverse causation accounts for 60% of the association between EIBF and mortality in the first 4 days of life.
- 65% of neonatal deaths occur in the first 4 days of life (see again Sankar et al., 2016)³⁵.
- No benefits extend beyond the neonatal period.
- We fully discount any effects on morbidity.
- In this scenario, with analogous calculations to those above:
 - RR of neonatal mortality across the entire neonatal period is 1.08 for a delay of
 1-24 hours and 1.29 for delay of >24 hours.
- In the same hypothetical intervention scenario:
 - Ideal state with 100% EIBF rates: RR of neonatal mortality = 1.0
 - Pre-intervention (50% EIBF, 90% <24 hours): RR of neonatal mortality = 1.061
 - Post-intervention (75% EIBF, 90% <24 hours): RR of neonatal mortality = 1.041
 - Relative reduction in neonatal mortality (day 0 to 28) due to intervention = 1.9%

In addition to questions about the "true" attributable reductions in mortality, a hypothetical intervention's effect is sensitive to the baseline percent of infants with

³⁴ For example, EIBF appears to promote EBF, and EBF is associated with many benefits including fewer childhood infections, higher intelligence, lower rates of metabolic disorders, and reduced rates of breast and ovarian cancer in mothers (for further discussion of EBF, see Heading E.II).

³⁵ M. J. Sankar et al., "When Do Newborns Die? A Systematic Review of Timing of Overall and Cause-Specific Neonatal Deaths in Developing Countries," *Journal of Perinatology* 36, no. 1 (May 2016): S1–11, https://doi.org/10.1038/jp.2016.27.

delayed breastfeeding, particularly those beyond 24 hours (as our evidence suggests the RR of >24 hour delay is substantially higher than 1-24 hour delay), as well as the intervention's effectiveness in improving EIBF rates and rates of delay >24 hours.

In the scenarios above, I assumed an EIBF intervention would be effective at shifting
more infants to <1 hour from 1-24 hours, but infants with >24 hour delays would not be
impacted since it seems likely that other factors than health worker practices would be
involved in such long delays

Evidence considered

In my view, this question can't be addressed by evidence alone (even if we had better data than we currently have). I attempt to explain my thought process below, which roughly follows a Bayesian approach.

The only quantitative estimates of the reduction in infant mortality associated with EIBF come from observational studies. It would be helpful to have a "base rate" of how effect sizes from observational evidence typically compare to effect sizes from randomized trials on the same topic. We could then consider how our specific case may differ from our base rate. We should also consider the extent to which experimental evidence may systematically differ from "the truth" (first in general, then considering our specific case). Finally, we should consider other relevant factors, such as changes that have occurred since the studies were conducted. Putting this all together, we can then speculate on how to adjust our estimates.

- To address the first part of this process, I searched for studies assessing how effect sizes in observational studies compare to the effect sizes found in randomized studies on the same topic. Fortunately, this is a well-studied problem.
 - Toews et al. (2024)³⁶ analyze this question for the Cochrane Library, updating a review by Anglemeyer et al. (2014)³⁷.
 - They examined a large number of systematic reviews, encompassing 2,869 RCTs involving 3,882,115 participants, and 3,924 observational studies with 19,499,970 participants.
 - "When pooling RORs and RRRs, the ratio of ratios indicated no difference or a very small difference between the effect estimates from RCTs versus from observational studies (ratio of ratios 1.08, 95% confidence interval (CI) 1.01 to 1.15). We rated the certainty of the evidence as low. Twenty-three of 34 reviews reported effect estimates of RCTs and observational studies that were on average in agreement."

³⁶ Ingrid Toews et al., "Healthcare Outcomes Assessed with Observational Study Designs Compared with Those Assessed in Randomized Trials: A Meta-epidemiological Study," *Cochrane Database of Systematic Reviews*, no. 1 (2024), https://doi.org/10.1002/14651858.MR000034.pub3.

³⁷ Andrew Anglemyer, Hacsi T. Horvath, and Lisa Bero, "Healthcare Outcomes Assessed with Observational Study Designs Compared with Those Assessed in Randomized Trials," *The Cochrane Database of Systematic Reviews* 2014, no. 4 (April 29, 2014): MR000034, https://doi.org/10.1002/14651858.MR000034.pub2.

- Their headline conclusion is that systematic differences between the effect estimates of RCTs and observational studies are small or nonexistent.
- This is in agreement with prior work by Golder et al. (2011)³⁸, Benson and Hartz (2000)³⁹, and Concato et al. (2000)⁴⁰. I did not find substantial disagreements in the literature.
- Therefore I take the default stance that we should not automatically discount the estimated effect sizes in well-conducted observational trials.
- Considering the specific case we are interested in, we can try also comparing observational and experimental evidence in other breastfeeding interventions.
 - My overall impression of the observational evidence (multiple studies, e.g. Sankar et al., 2015)⁴¹ is that it suggests widespread and profound benefits to breastfeeding across multiple domains, even after attempts to adjust for possible confounders.
 - Kramer (2010)⁴², the lead author of a landmark RCT on EBF (the "PROBIT trial"), comments that their study and 6.5 year follow-up confirmed some findings from observational studies (reductions in eczema and GI infections) but contradicted others (growth, asthma, and others).
 - The benefits of breastfeeding seen in observational trials seems more "impressive" than seen in experimental breastfeeding promotion trials, but an inherent limitation is that breastfeeding promotion does not create an "all or none" difference between groups, limiting the potential differences in outcomes.
 - In other words, I think that the typical "breastfeeding promotion" randomized study is probably underpowered to detect clinical effects.
 - Considering these limitations, it seems reasonable to stick close to the "base rate" assumption (i.e., no systematic difference between well-conducted observational and experimental trials).
- Next, we should consider the possibility of systematic differences between academic studies (on average) and our best estimate of "the truth".

³⁸ Su Golder, Yoon K. Loke, and Martin Bland, "Meta-Analyses of Adverse Effects Data Derived from Randomised Controlled Trials as Compared to Observational Studies: Methodological Overview," *PLOS Medicine* 8, no. 5 (May 3, 2011): e1001026, https://doi.org/10.1371/journal.pmed.1001026.

³⁹ Kjell Benson and Arthur J. Hartz, "A Comparison of Observational Studies and Randomized, Controlled Trials," *New England Journal of Medicine* 342, no. 25 (June 22, 2000): 1878–86, https://doi.org/10.1056/NEJM200006223422506.

⁴⁰ J. Concato, N. Shah, and R. I. Horwitz, "Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs," *The New England Journal of Medicine* 342, no. 25 (June 22, 2000): 1887–92, https://doi.org/10.1056/NEJM200006223422507.

⁴¹ Mari Jeeva Sankar et al., "Optimal Breastfeeding Practices and Infant and Child Mortality: A Systematic Review and Meta-Analysis," *Acta Paediatrica (Oslo, Norway: 1992)* 104, no. 467 (December 2015): 3–13, https://doi.org/10.1111/apa.13147.

⁴² Michael S. Kramer, "Breast Is Best': The Evidence," *Early Human Development*, Selected Proceedings of the Neonatal Update 2010, 86, no. 11 (November 1, 2010): 729–32, https://doi.org/10.1016/j.earlhumdev.2010.08.005.

- A highly skeptical take, expressed in a highly-cited work by loannidis (2005)⁴³, is that "most published research findings are false."
- The "decline effect" is a popular conceptualization that may include statistical phenomena such as false positives and regression to the mean, plus other contributors such as publication bias.
 - I briefly searched for "base rate" estimates of the magnitude of the decline effect (i.e., without knowing the specific case, by how much should we generally expect studies to overestimate findings?) and was unable to find any useful information.
- To operationalize these considerations into a "base rate" assumption, a reasonable heuristic seems to be to consider it more likely that published effect sizes are overestimates than underestimates. As a corollary to this, point estimates of effect sizes might be better viewed as more akin to "upper limits".
- I wasn't able to find much information on how the decline effect varies across fields, though it seems plausible that certain areas of research may be more vulnerable than others. In our specific case, the body of observational evidence for EIBF steers clear of many of the pitfalls that Ionnidis (2005) outlines in his "Corollaries" section. However I'm a little concerned that the evidence for EIBF comes from retrospective analysis of trials done for different reasons, and that other cohorts could have been retrospectively examined but not published due to null findings.
 - This very slightly downgrades my expectation of the size of EIBF's effect.
- Another consideration is whether to expect that the importance of breastfeeding may be changing over time. One notable occurrence since the study periods of our cohorts (1998-2014) has been the <u>substantial decline</u> in infant mortality in low-income and lower-middle income countries.
 - I don't think this should clearly impact the relative protection of EIBF, but certain mechanisms (such as EIBF promoting EBF, and EBF protecting against consumption of unsafe water) may be less relevant in certain contexts (such as areas that have experienced greater economic development).
 - It also means that a lower absolute number of neonatal deaths would be averted by EIBF interventions now compared to when the studies were conducted (assuming the same relative reduction).
- Finally, what other factors might matter?
 - Importantly, the meta-analysis reductions of mortality with EIBF take data from studies which all exclude mortality within the first 1-4 days.
 - When reported in our cohorts, first-48 hour mortality accounts for 50-54% of total neonatal deaths, and a brief survey of other literature seems to agree that ~40-50% of neonatal deaths are within 48 hours.

⁴³ John P. A. Ioannidis, "Why Most Published Research Findings Are False," *PLoS Medicine* 2, no. 8 (August 2005): e124, https://doi.org/10.1371/journal.pmed.0020124.

- So the mortality reduction should be scaled down based on the anticipated effects of EIBF on mortality in the first few days of life.
 - If we assume no effect in the first 2 days, and 50% of neonatal deaths occurring in the first 2 days, then EIBF would only account for half of the "headline" reduction.
- But mortality reductions may also extend beyond 28 days.
 - The NEOVITA Study Group (2016)⁴⁴ examine the EIBF-mortality association up to 6 months⁴⁵.
 - "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."

D. Does EIBF have benefits beyond neonatal mortality reductions?

Summary

If we accept that EIBF directly reduces neonatal mortality, it is almost impossible to consider that it does so without also reducing morbidity.

The most plausible mechanisms by which EIBF could prevent neonatal deaths (discussed subsequently) primarily function through reducing risk factors for infection, and the limited experimental evidence on EIBF also points towards reductions in infection-related morbidity.

Evidence considered

- 1. As previously discussed, Abdulahi et al. (2021) found that by increasing EIBF and EBF (by 25% and 15%, respectively) through a promotion intervention, infants had fewer caregiver-reported respiratory infections by 6 months of age.
 - While not reaching statistical significance, 18.9% of intervention infants had "serious illness" (defined as illness requiring medical attention), versus 27.4% in the control condition.
 - Notably, the study was powered to detect differences in EIBF and EBF rates and not clinical outcomes, and I think the trends are noteworthy despite the absence of statistical significance.

⁴⁴ NEOVITA Study Group, "Timing of Initiation, Patterns of Breastfeeding, and Infant Survival."

⁴⁵ "...the period when there is the highest plausibility of timing of initiation affecting mortality."

- 2. The systematic review by Debes et al. (2013)⁴⁶, previously mentioned, found low-to-medium quality evidence of several morbidity outcomes associated with delays in initiation of breastfeeding.
- 3. Raihana et al. (2019)⁴⁷ conducted an observational study of almost 30,000 births in Bangladesh. "The proportion of children with severe illness increased as the delay in initiation increased from 1 hour (12.0%), 24 hours (15.7%), 48 hours (27.7%), and more than 48 hours (36.7%) after birth."

E. What mechanisms may account for the impact of EIBF, or practices that promote it (such as early skin-to-skin care)? Which mechanisms are only hypothesized vs. tested?

I. What is the biological plausibility?

Summary

There is strong biological plausibility that EIBF could reduce neonatal mortality, mediated through several possible mechanisms with theoretical and/or empiric evidence. These will be discussed below, and include a) increasing the exclusivity and/or duration of breastfeeding, b) effects of colostrum on immunity and/or intestinal development, c) reduction in prelacteal feeding, and d) effects of skin-to-skin contact on hypothermia and/or hypoglycemia. In addition, reduction in maternal postpartum hemorrhage and/or enhanced mother-child bonding could contribute (this evidence was not reviewed, as per my judgement these mechanisms seem less likely to be major factors).

Limited evidence indicates that the effects of EIBF on mortality are conferred primarily through reductions in infections and/or hypothermia.

Evidence considered

- 1. The causes of neonatal death are often multifactorial and have been well described by Mahtab et al. (2023)⁴⁸. EIBF could plausibly impact some of these factors (e.g., infection, hypothermia) but not others (e.g., severe congenital malformations, delivery-related complications).
 - Importantly, the two largest contributors to neonatal deaths are infection (40%) and/or prematurity (32%), and it seems likely that EIBF may help mitigate the effects of both.

⁴⁶ Debes et al., "Time to Initiation of Breastfeeding and Neonatal Mortality and Morbidity."

⁴⁷ Shahreen Raihana et al., "Early Initiation of Breastfeeding and Severe Illness in the Early Newborn Period: An Observational Study in Rural Bangladesh," *PLoS Medicine* 16, no. 8 (August 30, 2019): e1002904, https://doi.org/10.1371/journal.pmed.1002904.

⁴⁸ Sana Mahtab et al., "Causes of Death Identified in Neonates Enrolled through Child Health and Mortality Prevention Surveillance (CHAMPS), December 2016 –December 2021," *PLOS Global Public Health* 3, no. 3 (March 20, 2023): e0001612, https://doi.org/10.1371/journal.pgph.0001612.

- The large contributions of infection and prematurity to the overall burden of neonatal deaths demonstrates that it would be plausible for EIBF to result in the observed reductions in mortality via a reduction in deaths due to these factors alone (i.e., we don't need to invoke implausible pathways in order to account for the full observed impact).
- 2. Edmond et al. (2007)⁴⁹ further analyzed the data described in Edmond et al. (2006)⁵⁰, which was previously discussed, in order to determine the causes of neonatal mortality in the cohort.
 - Verbal autopsies were used to ascertain causes of death.
 - o Of neonatal deaths from day 2-28, 66% were due to infectious causes.
 - Risk of infection-related death increased stepwise with each increment of breastfeeding delay from 1 hour to 7 days.
 - Late initiation (defined as >1 day) was associated with a 2.6-fold adjusted OR (95% CI: 1.68-4.04) of infection-related death.
 - Partial breastfeeding was associated with 5.7-fold higher risk of infection-related death (adj OR: 5.73; 95% CI: 2.75, 11.91).
 - No significant associations were observed between feeding practices and noninfectious causes of death.

II. Exclusivity and/or duration of breastfeeding

Summary

EIBF probably leads to a small increase in longer-term breastfeeding. This effect could be indirectly mediated through a reduction in prelacteal feeding (which itself is a risk factor for breastfeeding cessation). The duration and exclusivity of breastfeeding is strongly linked to decreased mortality in observational studies, and EBF causes reductions in infection-related morbidity in a limited number of randomized trials (not powered for mortality). Thus, promoting longer-term breastfeeding is likely one mechanism of EIBF's impact.

• Exclusive and/or sustained breastfeeding is also linked to several other benefits with additional quality-of-life and economic implications.

Evidence considered

(Regarding the link from EIBF to EBF)

⁴⁹ Karen M. Edmond et al., "Effect of Early Infant Feeding Practices on Infection-Specific Neonatal Mortality: An Investigation of the Causal Links with Observational Data from Rural Ghana," *The American Journal of Clinical Nutrition* 86, no. 4 (October 2007): 1126–31, https://doi.org/10.1093/ajcn/86.4.1126. ⁵⁰ Edmond et al., "Delayed Breastfeeding Initiation Increases Risk of Neonatal Mortality."

- 1. The NEOVITA Study Group (2016)⁵¹ found a small association between EIBF and subsequent breastfeeding, reported in web appendix A and B.
 - "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."
 - This association was modest: the adjusted RR of non-exclusive breastfeeding at 3 months was 1.05 (95% CI: 1.04-1.06) for initiation of breastfeeding at 2-23 hours versus <1 hour, and 1.06 (95% CI: 1.04-1.08) for initiation beyond 24 hours. The adjusted RR of not breastfeeding at all at 3 months was 1.20 (95% CI: 1.07-1.35) for the 2-23 hour group, and 1.88 (95% CI: 1.56-2.26) for initiation beyond 24 hours.</p>
 - The authors note the association between EIBF and mortality was present regardless of breastfeeding pattern, implying that additional mechanisms must be involved.
- 2. Nguyen et al. (2020a)⁵² report on survey data from three impact evaluations of large-scale social and behaviour change communication interventions ("Alive & Thrive) in Bangladesh, Vietnam, and Ethiopia, in order to examine relationships among EIBF, prelacteal feeds, and EBF, and how the interventions affected these relationship.
 - "EIBF alone was not associated with EBF, whereas non-prelacteal feeding was associated with 1.6-3.5 higher odds of EBF."
 - "The pathway from EIBF to non-prelacteal feeding to EBF explained 13–18% of the intervention effect on EBF."
- 3. Mena-Tudela et al. (2023)⁵³ conducted a small retrospective cohort study (n=342) in Spain examining timing of breastfeeding and effectiveness of breast latching on exclusive breastfeeding outcomes.
 - Timing of initiation of breastfeeding was recorded by providers in the medical record and categorized as <1 hour versus >1 hour.
 - o EIBF was not significantly associated with EBF at 6 months postpartum.
- 4. Ahmmed et al. (2022)⁵⁴ examined DHS survey data from Bangladesh, finding that EIBF was significantly associated (adjusted OR 1.22, P < 0.05) with EBF.

(Regarding evidence for benefits of EBF)

1. A systematic review by Sankar et al. (2015)⁵⁵ synthesized observational evidence from 13 trials for the effects of breastfeeding on mortality.

⁵¹ NEOVITA Study Group, "Timing of Initiation, Patterns of Breastfeeding, and Infant Survival."

⁵² Phuong Hong Nguyen et al., "Early Breastfeeding Practices Contribute to Exclusive Breastfeeding in Bangladesh, Vietnam and Ethiopia," *Maternal & Child Nutrition* 16, no. 4 (April 22, 2020): e13012, https://doi.org/10.1111/mcn.13012.

Desirée Mena-Tudela et al., "Is Early Initiation of Maternal Lactation a Significant Determinant for Continuing Exclusive Breastfeeding up to 6 Months?," *International Journal of Environmental Research and Public Health* 20, no. 4 (February 11, 2023): 3184, https://doi.org/10.3390/ijerph20043184.

⁵⁴ Foyez Ahmmed et al., "The Trend in Exclusive Breastfeeding Practice and Its Association with Maternal Employment in Bangladesh: A Multilevel Analysis," *Frontiers in Public Health* 10 (November 25, 2022): 988016, https://doi.org/10.3389/fpubh.2022.988016.

⁵⁵ Sankar et al., "Optimal Breastfeeding Practices and Infant and Child Mortality."

- "The risk of all-cause mortality was higher in predominantly (RR 1.5), partially (RR 4.8) and nonbreastfed (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."
- 2. Kramer et al. (2001)⁵⁶ conducted a large randomized study (the "PROBIT trial") of a breastfeeding promotion intervention in Belarus that followed clinical outcomes, demonstrating a reduction in eczema and a small reduction in gastrointestinal infections in the first year of life.
 - Some have interpreted the PROBIT study as extremely supportive of the benefits of breastfeeding, since changes in clinical outcomes were detected even with the limited between-group differences produced by a promotional intervention.
 Others have been underwhelmed by the seemingly minor importance of the differences in clinical outcomes.
- 3. Long-term follow-up on the PROBIT trial suggested increased measures of intelligence at 6.5 years in the intervention arm (Kramer et al., 2008⁵⁷), though this was no longer seen at 16 years (Yang et al., 2018⁵⁸).
 - "Term infants randomized to the intervention had 7.5 points higher (95% CI 0.8–14.3) verbal IQ at age 6.5 years; 2.9 (95% CI –3.3–9.1) points higher performance IQ; and 5.9 (95% CI –1.0–12.8) points higher full-scale IQ. However, this finding was limited by high within-site clustering (intraclass correlation coefficient [ICC] = 0.31) of cognitive scores, leading to imprecision with wide confidence intervals in the effect estimates, and by potential bias due to nonblinding of study pediatricians who administered the cognitive test."
 - "We observed no benefit of a breastfeeding promotion intervention on overall neurocognitive function. The only beneficial effect was on verbal function at age 16. The higher verbal ability is consistent with results observed at early school age; however, the effect size was substantially smaller in adolescence."
- 4. Bhandari et al. (2003)⁵⁹ conducted a cluster RCT in India of a promotional breastfeeding intervention.
 - "At 3 months, exclusive breastfeeding rates were 79% (381) in the intervention and 48% (197) in the control communities."

⁵⁶ M. S. Kramer et al., "Promotion of Breastfeeding Intervention Trial (PROBIT): A Randomized Trial in the Republic of Belarus," *JAMA* 285, no. 4 (January 24, 2001): 413–20, https://doi.org/10.1001/jama.285.4.413.

⁵⁷ Michael S. Kramer et al., "Breastfeeding and Child Cognitive Development: New Evidence from a Large Randomized Trial," *Archives of General Psychiatry* 65, no. 5 (May 2008): 578–84, https://doi.org/10.1001/archpsyc.65.5.578.

⁵⁸ Seungmi Yang et al., "Breastfeeding during Infancy and Neurocognitive Function in Adolescence: 16-Year Follow-up of the PROBIT Cluster-Randomized Trial," *PLoS Medicine* 15, no. 4 (April 20, 2018): e1002554, https://doi.org/10.1371/journal.pmed.1002554.

⁵⁹ Nita Bhandari et al., "Effect of Community-Based Promotion of Exclusive Breastfeeding on Diarrhoeal Illness and Growth: A Cluster Randomised Controlled Trial," *Lancet (London, England)* 361, no. 9367 (April 26, 2003): 1418–23, https://doi.org/10.1016/S0140-6736(03)13134-0.

- o "The 7-day diarrhoea prevalence was lower in the intervention than in the control communities at 3 months (0·64, 0·44–0·95, p=0·028) and 6 months (0·85, 0·72–0·99, p=0·04)."
- Growth outcomes did not differ substantially
- This study largely replicates the findings of the PROBIT trial, but in a low-income setting with high baseline breastfeeding rates.
- 5. Dib et al. (2023)⁶⁰, in a meta-analysis of RCTs and cluster RCTs, find relatively thin experimental evidence for health outcomes after interventions promoting exclusive breastfeeding (EBF).
 - Breastfeeding promotion strongly increased rates of EBF, reduced respiratory infections (only in the first 3 months) and possibly reduced GI infections, but no effects were seen on growth, hospitalizations, or mortality.
 - Again, it's worth noting how randomized promotion trials are likely underpowered for all but the most frequent outcomes.

III. Reduction in prelacteal feeding

Summary

Prelacteal feeding is variably defined as either feeding a newborn anything prior to first breastfeeding or as feeding anything other than breastmilk within the first 3 days (including infant formula). Prelacteal feeding is associated with cessation of breastfeeding and discarding of colostrum (the benefits of which are discussed later), and has potential direct negative effects on gut permeability and the microbiome. It has been associated by observational evidence with adverse health outcomes and increased neonatal mortality in low-birthweight babies (reverse causation and confounding factors are possible, giving some caution to these findings). Regardless, as the pathway from EIBF to reduction in prelacteal feeding is clear, and there are plausible direct biological effects of prelacteal feeding, I would consider non-prelacteal feeding to be a potential direct mechanism of EIBF's benefits. However, the effects of prelacteal feeding seem likely to be primarily mediated via other associated factors we discuss here (namely, EBF and/or colostrum).

Evidence considered

1. Neves et al. (2022)⁶¹ reviewed data from Demographic Health Surveys and Multiple Indicator Cluster Surveys (2010–2019) in 76 low- and middle-income countries.

⁶⁰ Sarah Dib et al., "Effects of Exclusive Breastfeeding Promotion Interventions on Child Outcomes: A Systematic Review and Meta-Analysis," *Annals of Nutrition & Metabolism* 80, no. 2 (2024): 57–73, https://doi.org/10.1159/000535564.

⁶¹ Paulo Augusto Ribeiro Neves et al., "Disparities in Early Initiation of Breast Feeding and Prelacteal Feeding: A Study of Low- and Middle-Income Countries," *Paediatric and Perinatal Epidemiology* 36, no. 5 (September 2022): 741–49, https://doi.org/10.1111/ppe.12871.

- They found an inverse relationship between EIBF and prelacteal feeding (helping to confirm this common-sense intuition).
- 2. Pérez-Escamilla et al. (2022)⁶² conducted a systematic review and meta-analysis of prospective trials to assess differences in breastfeeding as a result of prelacteals.
 - "Findings from the meta-analysis showed a relationship between prelacteals and exclusive BF cessation (RR 1.44; 1.29-1.60) and any BF cessation (2.23; 1.63-3.06) among infants under 6 months old."
- 3. Gashaw and Mitku (2024)⁶³ performed a community-based cross-sectional study in Ethiopia (n=372) demonstrating a clear association between prelacteal feeding and colostrum avoidance (adjusted OR = 3.16, 95% CI: 1.93–5.15).
- 4. Nguyen et al. (2020b)⁶⁴ conducted a prospective cohort study following almost 2,000 infants in Vietnam to assess the effects of prelacteal feeding and formula feeding on morbidity in the first year of life.
 - At one year, prelacteal feeding was associated with increased odds of hospitalization (adjusted OR 1.43, 95% CI: 1.09 to 1.88), diarrhea (adjusted OR 1.56, 95% CI: 1.19 to 2.05), and lower respiratory tract infections (adjusted OR 1.50, 95% CI: 1.18 to 1.90)
- 5. Edmond et al. (2007)⁶⁵, in secondary analysis of data from a vitamin A supplementation trial in rural Ghana (previously reported in Edmond et al., 2006⁶⁶), examined the impact of early feeding practices on infection-specific mortality.
 - Prelacteal feeding was not associated with either infection-specific or noninfectious causes of mortality, after adjusting for timing of initiation of breastfeeding and established neonatal breastfeeding pattern.
- 6. Edmond et al. (2008)⁶⁷ examined early feeding practices for low-birthweight babies in the same cohort.
 - Prelacteal feeding was associated with a threefold significantly increased mortality risk (adjOR 3.12, 95% CI: 1.19–8.22) in infants aged 2 to 28 days.
 - "However, when timing of breastfeeding initiation and type of neonatal breastfeeding were included in model 2, the effect of prelacteal feeding was no longer statistically significant." (adjOR: 3.21, 95% CI: 0.91–11.34).

⁶² Rafael Pérez-Escamilla et al., "Impact of Prelacteal Feeds and Neonatal Introduction of Breast Milk Substitutes on Breastfeeding Outcomes: A Systematic Review and Meta-Analysis," *Maternal & Child Nutrition* 18 Suppl 3, no. Suppl 3 (May 2022): e13368, https://doi.org/10.1111/mcn.13368.

⁶³ Anteneh Gashaw et al., "Colostrum Avoidance and Associated Factors among Mothers of Less than 6-Month-Old Children in Dilla Town, Southern Ethiopia," *Frontiers in Pediatrics* 12 (July 11, 2024): 1399004, https://doi.org/10.3389/fped.2024.1399004.

⁶⁴ Phung Nguyen et al., "Prelacteal and Early Formula Feeding Increase Risk of Infant Hospitalisation: A Prospective Cohort Study," *Archives of Disease in Childhood* 105, no. 2 (February 2020): 122–26, https://doi.org/10.1136/archdischild-2019-316937.

⁶⁵ Edmond et al., "Effect of Early Infant Feeding Practices on Infection-Specific Neonatal Mortality."

⁶⁶ Edmond et al., "Delayed Breastfeeding Initiation Increases Risk of Neonatal Mortality."

⁶⁷ K. M. Edmond et al., "Impact of Early Infant Feeding Practices on Mortality in Low Birth Weight Infants from Rural Ghana," *Journal of Perinatology: Official Journal of the California Perinatal Association* 28, no. 6 (June 2008): 438–44, https://doi.org/10.1038/jp.2008.19.

Summary

Colostrum (the low-volume, thick, yellowish breast milk produced from birth up to approximately 3 days) is different in many important ways from "transitional" or mature breast milk (which develop further into lactation). Importantly, colostrum has concentrated amounts of components affecting immunity and gut development, such as immunoglobulins and cytokines. Animal studies demonstrate clinically significant benefits from feeding colostrum, including reductions in diarrhea and a life-threatening condition known as necrotizing enterocolitis. A large proportion of neonatal deaths occur within the first few days after birth and are related to infection. Since successful EIBF essentially guarantees that infants receive early colostrum, late-onset breastfeeding is associated with discarding colostrum, and colostrum appears to confer protection against infections, it seems likely that colostrum mediates some of the benefits of EIBF. However, direct evidence for this hypothesis in humans is scant.

Evidence Considered

- 1. Radillo et al. (2013)⁶⁸ demonstrate some of the differences between colostrum and mature breast milk, particularly cytokines relevant to gut and nervous system development.
- 2. Differences between colostrum and mature breast milk are further reviewed by Ballard & Morrow (2013)⁶⁹.
- 3. As previously mentioned, Gashaw and Mitku (2024)⁷⁰ performed a community-based cross-sectional study in Ethiopia (n=372) demonstrating a clear association between colostrum avoidance and delayed breastfeeding (adjusted OR 4.15, 95% CI: 2.51-6.84 as well as prelacteal feeding (adjusted OR = 3.16, 95% CI: 1.93–5.15).
- 4. Rasmussen et al. (2016)⁷¹ performed an animal study on piglets (n=14-18 per group) comparing the effects of bovine (cow) colostrum, human donor breast milk, and infant formula on gut development.
 - Relative to piglets fed infant formula, piglets fed bovine colostrum showed statistically significant benefits on a host of markers of gut health and immunity, including reductions in diarrhea and gut permeability and increases in mucosal mass and microbiome diversity.

⁶⁸ Oriano Radillo et al., "Presence of CTAK/CCL27, MCP-3/CCL7 and LIF in Human Colostrum and Breast Milk," *Cytokine* 61, no. 1 (January 2013): 26–28, https://doi.org/10.1016/j.cyto.2012.09.001.
⁶⁹ Olivia Ballard and Ardythe L. Morrow, "Human Milk Composition: Nutrients and Bioactive Factors," *Pediatric Clinics of North America* 60, no. 1 (February 2013): 49–74, https://doi.org/10.1016/j.pcl.2012.10.002.

⁷⁰ Gashaw et al., "Colostrum Avoidance and Associated Factors among Mothers of Less than 6-Month-Old Children in Dilla Town, Southern Ethiopia."

⁷¹ Stine O. Rasmussen et al., "Bovine Colostrum Improves Neonatal Growth, Digestive Function, and Gut Immunity Relative to Donor Human Milk and Infant Formula in Preterm Pigs," *American Journal of Physiology. Gastrointestinal and Liver Physiology* 311, no. 3 (September 1, 2016): G480-491, https://doi.org/10.1152/ajpgi.00139.2016.

- Expression of several immune-related genes were altered.
- Piglets fed donor breast milk generally had intermediate values between the bovine colostrum and infant formula groups.
- 5. In humans, a Cochrane review of RCTs by Nasuf et al. (2018)⁷² did not find convincing evidence of clinical benefits of oropharyngeal administration of colostrum in preterm infants.
 - "We included six studies that compared early oropharyngeal colostrum versus water, saline, placebo, or donor, or versus no intervention, enrolling 335 preterm infants with gestational ages ranging from 25 to 32 weeks' gestation and birth weights of 410 to 2500 grams."
 - No significant effects were noted in primary outcomes, including incidence of necrotizing enterocolitis, late-onset infection, and death before hospital discharge.
 - Of note, studies only examined premature infants and were conducted in developed country NICU settings (where standards of care are likely higher and infection rates may be lower than in lower-resource settings).

V. Effects of skin-to-skin contact

Summary

Substantial evidence (more extensive and of higher quality than for other potential mechanisms discussed above) supports the benefits of early skin-to-skin contact (SSC) between infant and mother after birth. SSC is typically categorized as "immediate" if occurring within 10 minutes and "early" if occurring within the first 24 hours (though some studies seemed to classify only the first 2 hours as "early").

The most clearly-established benefits of immediate and/or early SSC include decreased rates of neonatal hypoglycemia (low blood sugar), improved temperature regulation (reductions in both hyperthermia and hypothermia), increased rates of exclusive breastfeeding (extending to 6 months), and greater success and longer duration of initial breastfeeding episodes. *Immediate* SSC appears to moderately reduce the duration from birth to expulsion of the placenta as well as the likelihood of incomplete delivery of the placenta and uterine atony (which are all implicated in postpartum hemorrhage).⁷³ Limited and conflicting evidence (not cited) suggests that immediate and/or early SSC could slightly reduce postpartum depression.

⁷² Amna Widad A. Nasuf, Shalini Ojha, and Jon Dorling, "Oropharyngeal Colostrum in Preventing Mortality and Morbidity in Preterm Infants," *Cochrane Database of Systematic Reviews*, no. 9 (2018), https://doi.org/10.1002/14651858.CD011921.pub2.

⁷³ This could be particularly important when uterotonic medications such as oxytocin are delayed or not administered and/or where there is inadequate ability to respond to hemorrhage (such as in non-facility deliveries).

EIBF is known to be promoted by SSC and requires at least some SSC, and the benefits of early SSC are robustly established by high-quality evidence. Therefore it seems clear that early SSC is a contributor to the benefit of EIBF.

Evidence considered

- 1. Lord et al. $(2023)^{74}$ conducted a systematic review and meta-analysis of trials including multiple study designs to evaluate the effect of early SSC (either <10 minutes, 10 mins to 24 hours, or 24 hours to discharge) on neonatal hypoglycemia.
 - "This review included 84,900 participants in 108 studies, comprising 65 RCTs, 16 quasi-RCTs, seven non-randomised studies of intervention, eight prospective cohort studies, nine retrospective cohort studies and three case–control studies"
 - The primary outcome was neonatal hypoglycemia; additional prespecified outcomes included thermoregulation (both hyperthermia and hypothermia) and duration of hospital stay, among others. Non-prespecified outcomes included exclusive breastfeeding up to 6 months duration.
 - There was a large decrease in rates of neonatal hypoglycemia with early SSC (RR 0.29, 95% CI: 0.13, 0.66) based on 7 RCTs/quasi-RCTs including 922 infants. Thermoregulation was improved with early SSC (both hypo and hyperthermia). Additionally, the duration of hospital stays was reduced by more than 2 days [31 RCTs, 3,437 infants, mean difference -2.37 (-3.66, -1.08) days].
 - Subgroup analysis evaluated the timing of SSC (<10 mins, 10 mins to 24 hours, and 24 hours to discharge) and duration (<60 mins vs. >60 mins). Effects on glucose were most prominent for immediate SSC, without much impact of the duration of SSC. In contrast, thermoregulation seemed more sensitive to duration than timing.
 - Exclusive breastfeeding rates from birth to 6 months favored early SSC, though exact timing and duration didn't seem to matter much (keeping in mind the reductions in power for subgroup analysis).
- A Cochrane review of early SSC for full-term, healthy infants by Moore et al. (2016)⁷⁵ found that immediate or early SSC likely results in higher rates of breastfeeding up to 4 months. No differences were noted between immediate (<10 mins) or early (>10 mins) SSC, nor duration (<60 mins vs. >60 mins).
 - "SSC women were probably more likely to exclusively breast feed from hospital discharge to one month post birth and from six weeks to six months post birth, though both analyses had substantial heterogeneity (from discharge average RR 1.30, 95% CI 1.12 to 1.49; participants = 711; studies = six; I² = 44%; GRADE:

⁷⁴ Libby G. Lord et al., "Skin-to-Skin Contact for the Prevention of Neonatal Hypoglycaemia: A Systematic Review and Meta-Analysis," *BMC Pregnancy and Childbirth* 23, no. 1 (October 21, 2023): 744, https://doi.org/10.1186/s12884-023-06057-8.

⁷⁵ Elizabeth R. Moore et al., "Early Skin-to-Skin Contact for Mothers and Their Healthy Newborn Infants," *The Cochrane Database of Systematic Reviews* 11, no. 11 (November 25, 2016): CD003519, https://doi.org/10.1002/14651858.CD003519.pub4.

- moderate quality; from six weeks average RR 1.50, 95% CI 1.18 to 1.90; participants = 640; studies = seven; $I^2 = 62\%$; GRADE: moderate quality)."
- 3. Supporting the hypothesis that the exact timing of early SSC may not matter for EBF rates, Agudelo et al. (2021)⁷⁶ conducted a randomized trial of immediate (1 minute) versus early (1 hour) SSC on rates and duration of breastfeeding in Colombia (n=297), finding no difference between groups in breastfeeding exclusivity or duration at 6 months.
- 4. Karimi et al. (2020)⁷⁷ conducted a systematic review and meta-analysis of RCTs studying the effects of immediate SSC on exclusive breastfeeding up to 6 months.
 - "The effects of mother-infant SSC on exclusive breastfeeding was statistically significant [odds raito (OR)=2.19; 95% confidence interval (CI): (1.66-2); p<0.001]. The subgroup analysis results in the normal vaginal delivery group included OR=2.45 [95% CI: (1.76-3.35); p<0.001], for the cesarean delivery group the results were OR=1.44 [95% CI: (0.78-2.65); p=0.24], the results for the duration of exclusive breastfeeding as of the discharge time up to 3 months were OR=2.47 [95% CI: (1.76-3.48); p<0.001], and the results for the 3 to 6 months of exclusive breastfeeding were OR=1.71 [95% CI: (1.05-2.78); p=0.030]."</p>
- 5. Karimi et al. (2019)⁷⁸ conducted a systematic review and meta-analysis of RCTs studying the effects of immediate skin-to-skin contact (<10 minutes) versus routine care on the success and duration of the initial breast feed in full-term, healthy infants.
 - Nine studies were identified, with 597 intervention participants and 553 controls.
 Studies were conducted in high, middle, and low income countries. All nine evaluated "success" with a standardized scoring tool. Six studies reported breastfeeding duration, based on observation.
 - The success (OR 2.771, 95% CI: 1.587-4.838) and duration of initial breastfeeding was higher in the SSC group.
- 6. Martínez-Rodríguez et al. (2024)⁷⁹ conducted a systematic review with meta-analysis of randomised controlled trials and prospective quasi-experimental studies, including 25 trials, to examine the effects of immediate SSC on the length of the third stage of labor (i.e., time from delivery of the infant until delivery of the placenta).
 - "Skin-to-skin contact significantly reduced the duration of the third stage of labour (MD: -4.26 [minutes]; 95 %; CI: -5.70, -2.81), increased the likelihood of complete

⁷⁶ Sergio I. Agudelo et al., "Randomized Clinical Trial of the Effect of the Onset Time of Skin-to-Skin Contact at Birth, Immediate Compared to Early, on the Duration of Breastfeeding in Full Term Newborns," *International Breastfeeding Journal* 16, no. 1 (April 13, 2021): 33, https://doi.org/10.1186/s13006-021-00379-z.

⁷⁷ Fatemeh Zahra Karimi et al., "The Effect of Mother-Infant Skin-to-Skin Contact Immediately after Birth on Exclusive Breastfeeding: A Systematic Review and Meta-Analysis," *Journal of the Turkish German Gynecological Association* 21, no. 1 (March 6, 2020): 46–56, https://doi.org/10.4274/jtgga.galenos.2019.2018.0138.

⁷⁸ Fatemeh Zahra Karimi et al., "The Effect of Mother-Infant Skin to Skin Contact on Success and Duration of First Breastfeeding: A Systematic Review and Meta-Analysis," *Taiwanese Journal of Obstetrics & Gynecology* 58, no. 1 (January 2019): 1–9, https://doi.org/10.1016/j.tjog.2018.11.002. ⁷⁹ Sandra Martínez-Rodríguez et al., "Efficacy of Skin-to-Skin Contact between Mother and Infant on Maternal Outcomes during the Third Stage of Labour: A Systematic Review and Meta-Analysis," *International Journal of Nursing Studies* 162 (February 2025): 104981, https://doi.org/10.1016/j.ijnurstu.2024.104981.

placental integrity (RR: 1.09; 95 % CI: 1.02, 1.16), and significantly reduced both the likelihood of a supraumbilical position of the uterine fundus (RR: 0.39; 95 % CI: 0.20, 0.76) and the need for uterotonic administration (RR: 0.24; 95 % CI: 0.12, 0.48)."

7. In a scoping review, Ruiz et al. (2023)⁸⁰ find similar effects on placental delivery and uterine contraction, and find lower drops in hemoglobin levels (suggesting less bleeding).

<u>F. What risks are associated with EIBF, its associated practices, and/or promotion of these practices?</u>

Summary

SSC and EIBF are very safe practices. In their Cochrane meta-analysis, Moore et al. (2016)⁸¹ state that "we found no evidence of harm in any included studies."

A very rare risk associated with EIBF and early skin-to-skin contact is the sudden unexpected postnatal collapse of an apparently-healthy neonate within the first few hours after birth, which is often fatal or results in neurological injury. This sometimes reflects undiagnosed pathology, but in many cases it is attributed to asphyxiation due to airway obstruction with the infant in the prone position. Immediate breastfeeding or SSC could also theoretically interfere with medical monitoring and intervention in unwell babies (though I did not find evidence specifically examining this).

For mothers, breastfeeding can result in mastitis (breast inflammation commonly due to infection), nipple and/or breast pain, disrupted sleep, and negative effects on employment in unsupportive workplaces (evidence not cited).

Based on personal reflection, I believe the act of actively promoting EIBF and/or associated practices could have a few potential harms, though none seem disqualifying.

- Mothers who are unable to do EIBF, SSC, or associated practices may feel guilt, and may also feel shamed by healthcare providers or others promoting these practices. This could cause psychological distress and concern about their child's future.
- Health workers are typically over-burdened. Training health workers in promoting SSC, EIBF, or related practices could distract attention and resources from other priorities, potentially causing unseen harms.

⁸⁰ Mariana Torreglosa Ruiz et al., "Skin-to-Skin Contact in the Third Stage of Labor and Postpartum Hemorrhage Prevention: A Scoping Review," *Maternal and Child Health Journal* 27, no. 4 (April 2023): 582–96, https://doi.org/10.1007/s10995-022-03582-4.

⁸¹ Moore et al., "Early Skin-to-Skin Contact for Mothers and Their Healthy Newborn Infants."

- Many studies I reviewed had near-100% participation rates, suggesting that pregnant
 women in study locations may not feel empowered to decline recommendations from
 study or medical staff (who are likely of higher socioeconomic status). Promoting EIBF
 and/or associated practices in this type of setting could be viewed as paternalistic or
 even coercive.
- EIBF and/or associated practices, while likely consistent with most cultural norms, may in some cases conflict with other values or nonscientific sources of knowledge (e.g., a belief that colostrum is harmful).

Evidence considered

- 1. Becher et al. (2012)⁸² reported on 45 fatal cases of sudden unexpected postnatal collapse in the UK. In two-thirds of cases no underlying disease was suspected or diagnosed, and the majority of these deaths were attributed to asphyxiation in the prone position while breastfeeding or in skin-to-skin contact (often without medical staff present and with primiparous mothers).
- 2. Fleming (2012)⁸³ summarized findings from six studies (all in Europe) of sudden unexpected postnatal collapse. Events seem to occur largely during unsupervised skin-to-skin contact. The incidence in population-based studies from France, Germany and the UK ranged from 2.6 to five cases per 100,000 births and death rates from 0 to 1.1 deaths per 100,000 live births.

G. What specific practices / factors have been shown to promote EIBF and/or SSC? In particular, what are the behavioral determinants of EIBF and/or SSC?

Summary

Several experimental studies report on interventions to promote EIBF.

- Educational / promotional breastfeeding interventions generally seemed effective, though the details of the interventions and effectiveness varied.
- Peer counseling for breastfeeding promotion seems to have a positive effect on EIBF rates, based on a few cluster randomized trials.
- A multi-pronged intervention with interpersonal counseling plus mass media / community / policy components showed sustained improvements in EIBF rates.

⁸² Julie-Clare Becher, Shetty S. Bhushan, and Andrew J. Lyon, "Unexpected Collapse in Apparently Healthy Newborns--a Prospective National Study of a Missing Cohort of Neonatal Deaths and near-Death Events," *Archives of Disease in Childhood. Fetal and Neonatal Edition* 97, no. 1 (January 2012): F30-34, https://doi.org/10.1136/adc.2010.208736.

⁸³ Peter J. Fleming, "Unexpected Collapse of Apparently Healthy Newborn Infants: The Benefits and Potential Risks of Skin-to-Skin Contact," *Archives of Disease in Childhood. Fetal and Neonatal Edition* 97, no. 1 (January 2012): F2-3, https://doi.org/10.1136/archdischild-2011-300786.

• Limited evidence suggests health worker training can improve EIBF rates, particularly after Cesarean section.

Observational evidence indicates several characteristics that predict EIBF rates.

- Potentially modifiable factors include facility-based delivery (strongly associated in many studies), skin-to-skin contact, and (in one study) maintaining visual privacy.
- Difficult-to-modify factors include Cesarean delivery (strongly linked to later initiation of breastfeeding in multiple observational studies), complications during birth, and certain characteristics such as education level (generally, EIBF rates seem slightly higher with more education).

A few quality improvement interventions (quasi-experimental, before-and-after study designs) report large increases in skin-to-skin contact after birth in hospitals.

- Two facility-based quality improvement interventions in India promoting early SSC resulted in dramatic increases in SSC.
- A brief educational intervention to health workers at a hospital in Uganda dramatically increased rates of uninterrupted SSC for the first hour after birth.

Evidence considered

(Experimental trials of EIBF promotion)

- 1. Balogun et al. (2016)⁸⁴ performed a systematic review and meta-analysis of randomized trials for the Cochrane Library on interventions for promoting the initiation of breastfeeding.
 - Only 3 studies assessed promotional interventions that reported the outcome of early initiation of breastfeeding. All were delivered by non-healthcare professionals (counsellors and support groups).
 - No significant effects of the interventions were noted.
 - This is in contrast to the later study by Abdulahi et al. (2021), previously discussed, where an enhanced breastfeeding education and support program, delivered by trained peer supporters, raised EIBF rates by 25 percentage points.
 - Another subsequent study by Adamasu et al. (2022) with contrary findings to the Cochrane review is reported directly below.
- 2. Adamasu et al. (2022)⁸⁵ conducted a cluster RCT in Ethiopia (n=310) examining the effects of breastfeeding education on EIBF and EBF.
 - The intervention consisted of "nutrition education using lectures given once every week for 3 weeks to the women in the intervention group using the local

⁸⁴ Olukunmi O. Balogun et al., "Interventions for Promoting the Initiation of Breastfeeding," *The Cochrane Database of Systematic Reviews* 11, no. 11 (November 9, 2016): CD001688, https://doi.org/10.1002/14651858.CD001688.pub3.

⁸⁵ Jatani Admasu et al., "Effect of Maternal Nutrition Education on Early Initiation and Exclusive Breast-Feeding Practices in South Ethiopia: A Cluster Randomised Control Trial," *Journal of Nutritional Science* 11 (May 30, 2022): e37, https://doi.org/10.1017/jns.2022.36.

language, poster, manual and discussion on topics relevant to the study. Additionally, one session of education was given to the women in the intervention group at third post-partum month. A health professional (BSc Nurse) who can speak the local language was selected to give nutrition education and was given detailed information on the content of each session."

- EIBF rates were higher in the intervention group (72.7% vs. 59.9%).
- "Breast-feeding education [AORs 1·55, 95 % CI (1·02, 2·36)], institutional delivery [AOR 2·29, 95 % CI (1·21, 4·35)], vaginal delivery [AOR 2·85, 95 % CI (1·61, 5·41)] and pre-lacteal feeding [AOR 0·47, 95 % CI (0·25, 0·85)] were predictors of early initiation of breast-feeding."
- 3. Reported in a preprint manuscript (i.e., not yet peer-reviewed or published), Rifat et al. (2024)⁸⁶ conducted a systematic review and meta-analysis of RCTs in South Asia involving promotion interventions and reporting EIBF as an outcome.
 - "The interventions identified were categorized into behavioral, mHealth, health system strengthening, and nutritional interventions."
 - "The pooled relative risk (RR) of EIBF among mothers in the intervention groups, as compared to their counterparts, was 1.55 (95% CI: 1.24, 1.95; I2 = 99.56; p < 0.001). Interventions targeted health system strengthening represented stronger effect than other types of interventions."
- 4. The PROMISE-EBF trial, as reported by Tylleskär et al. (2011)⁸⁷, was a cluster randomised behaviour change intervention trial of exclusive breastfeeding (EBF) promotion by peer counsellors in Burkina Faso, Uganda and South Africa implemented during 2006-2008 among 2579 mother-infant pairs. Counselling started in the last pregnancy trimester.
 - "In the intervention group, we scheduled one antenatal breastfeeding peer counselling visit and four post-delivery visits by trained peers".
 - Large increases in EBF rates were achieved, though the clinical outcome of interest (diarrhea rates) was not statistically improved.
 - Authors conclude that "Low-intensity individual breastfeeding peer counselling is achievable and, although it does not affect the diarrhoea prevalence, can be used to effectively increase EBF prevalence in many sub-Saharan African settings."
- 5. A subsequent publication by Engebretsen et al. (2014)⁸⁸ reports on early feeding practices in the PROMISE-EBF trial.

⁸⁷ Thorkild Tylleskär et al., "Exclusive Breastfeeding Promotion by Peer Counsellors in Sub-Saharan Africa (PROMISE-EBF): A Cluster-Randomised Trial," *Lancet (London, England)* 378, no. 9789 (July 30, 2011): 420–27, https://doi.org/10.1016/S0140-6736(11)60738-1.

⁸⁶ M. A. Rifat et al., "Effectiveness of Interventions on Early Initiation of Breastfeeding in South Asia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" (Research Square, October 7, 2024), https://doi.org/10.21203/rs.3.rs-4836046/v1.

⁸⁸ Ingunn Marie S. Engebretsen et al., "Early Infant Feeding Practices in Three African Countries: The PROMISE-EBF Trial Promoting Exclusive Breastfeeding by Peer Counsellors," *International Breastfeeding Journal* 9 (2014): 19, https://doi.org/10.1186/1746-4358-9-19.

- Early infant feeding practices were defined as use of prelacteal feeds (any foods or drinks other than breast milk given within the first 3 days), expressing and discarding colostrum, and timing of initiation of breastfeeding.
- Results varied by study site (Burkina Faso, Uganda, and South Africa).
- For EIBF, "only a minority in Burkina Faso (<4%) and roughly half in South Africa initiated breastfeeding within the first hour with no large or statistically significant differences between the trial arms, whilst in Uganda the proportion of early initiation of breastfeeding in the intervention and control arms were: 55% and 41%, PR 0.8 (95% CI 0.7, 0.9)."
- 6. Ara et al. (2018)⁸⁹ conducted a cluster RCT in Bangladesh of a peer counseling intervention. "EIBF rate was higher in the intervention group than in the control group (89.1% vs. 77.4%, p = .005)"
- 7. Menon et al. (2016)⁹⁰ report on a cluster randomized evaluation of the "Alive & Thrive" intervention, consisting of "intensified interpersonal counseling (IPC), mass media (MM), and community mobilization (CM) intervention components delivered at scale in the context of policy advocacy (PA) in Bangladesh and Viet Nam."
 - "In Bangladesh, improvements were significantly greater in the intensive compared to the non-intensive group for the proportion of women who reported ...engaging in early initiation of breastfeeding (EIBF) (16.7 pp, 95% CI 2.8–30.6, p = 0.021; 63.7% to 94.2%)."
 - \circ "In Viet Nam... EIBF declined (60.0% to 53.2%) in the intensive group, but less than in the non-intensive group (57.4% to 40.6%; DDE 10.0 pp, 95% CI –1.3 to 21.4, p = 0.072)."
- 8. Kim et al. (2018)⁹¹ report that improvements from the "Alive & Thrive" intervention persisted at 2 years: "Large differential improvements of 12-17 percentage points in intensive, compared with nonintensive areas, between baseline and follow-up remained for early initiation of and exclusive breastfeeding, timely introduction of foods, and consumption of iron-rich foods. "
- 9. Kim et al. (2016)⁹² report positive results of the "Alive & Thrive" intervention in Ethiopia in a pre-post design, with a 13.7 percentage point improvement in EIBF.

⁹⁰ Purnima Menon et al., "Impacts on Breastfeeding Practices of At-Scale Strategies That Combine Intensive Interpersonal Counseling, Mass Media, and Community Mobilization: Results of Cluster-Randomized Program Evaluations in Bangladesh and Viet Nam," *PLoS Medicine* 13, no. 10 (October 2016): e1002159, https://doi.org/10.1371/journal.pmed.1002159.

⁸⁹ Gulshan Ara et al., "Peer Counselling Improves Breastfeeding Practices: A Cluster Randomized Controlled Trial in Urban Bangladesh," *Maternal & Child Nutrition* 14, no. 3 (July 2018): e12605, https://doi.org/10.1111/mcn.12605.

⁹¹ Sunny S Kim et al., "Large-Scale Social and Behavior Change Communication Interventions Have Sustained Impacts on Infant and Young Child Feeding Knowledge and Practices: Results of a 2-Year Follow-Up Study in Bangladesh," *The Journal of Nutrition* 148, no. 10 (October 2018): 1605–14, https://doi.org/10.1093/jn/nxy147.

⁹² Sunny S. Kim et al., "Exposure to Large-Scale Social and Behavior Change Communication Interventions Is Associated with Improvements in Infant and Young Child Feeding Practices in Ethiopia," *PloS One* 11, no. 10 (2016): e0164800, https://doi.org/10.1371/journal.pone.0164800.

- 10. Tongun et al. (2019)⁹³ report results from a before-and-after study of a Baby-Friendly Hospital Initiative training in South Sudan.
 - "A paediatrician with specific training and practice in supporting lactation and breastfeeding conducted a 4-day training for 30 health workers including gynaecologists, doctors, midwives and nurses at the maternity unit of JTH in December 2017. All the health workers were enthusiastic and completed the 4-day training. The training was based on the UNICEF/WHO BFHI—a 20 hour course for maternity staff [13]. The training course consisted of 15.5 hours of theory and 4.5 hours of demonstrations, role-plays and hands-on practice. Four to six months after the training, we carried out the "after" survey to assess breastfeeding practices in the same hospital. Between the "before" and "after" surveys, there was no change either in hospital leadership or in the maternity ward. No significant political or policy changes had taken place in the country in this field, nor had any interventions, such as breastfeeding awareness campaigns.
 - EIBF rates improved from 48% (388/806) before to 91% (732/806) after training.
 In women who delivered by Caesarian section, EIBF improved from 3% (3/97) before to 60% (12/20) after training.

(Observational studies on EIBF)

- 11. Takahashi et al. (2017)⁹⁴ performed a secondary analysis of data from the WHO Global Survey on Maternal and Perinatal Health, covering 244,569 facility-based births in 24 countries across Africa, Asia, and South America, to identify factors associated with EIBF.
 - "EIBF was significantly lower among women who had complications during pregnancy (AOR 0.76; 95% CI 0.65–0.88) and those who delivered by caesarean section (AOR 0.28; 95% CI 0.22–0.37). Deliveries at facilities with available postnatal and/or neonatal guidelines/protocols were more likely to be associated with EIBF (AOR 2.05; 95% CI 1.07–3.92) than those at facilities with no guidelines."
- 12. Mohammed et al. (2023)⁹⁵ conducted a prospective cohort trial covering 2,660 mother-infant pairs in Ethiopia studying the impact of birth complications and newborn care practices on EIBF.

⁹³ Justin Bruno Tongun et al., "The Effect of Health Worker Training on Early Initiation of Breastfeeding in South Sudan: A Hospital-Based before and after Study," *International Journal of Environmental Research and Public Health* 16, no. 20 (October 2019): 3917, https://doi.org/10.3390/ijerph16203917.

⁹⁴ Kenzo Takahashi et al., "Prevalence of Early Initiation of Breastfeeding and Determinants of Delayed Initiation of Breastfeeding: Secondary Analysis of the WHO Global Survey," *Scientific Reports* 7, no. 1 (March 21, 2017): 44868, https://doi.org/10.1038/srep44868.

⁹⁵ Shamsudeen Mohammed, Alhassan S. Abukari, and Agani Afaya, "The Impact of Intrapartum and Immediate Post-Partum Complications and Newborn Care Practices on Breastfeeding Initiation in Ethiopia: A Prospective Cohort Study," *Maternal & Child Nutrition* 19, no. 1 (January 2023): e13449, https://doi.org/10.1111/mcn.13449.

- "After adjustment, EIBF was less likely among women who experienced intrapartum haemorrhage (adjusted odds ratio [AOR]: 0.76, 95% confidence interval [CI]: 0.59–0.97), malpresentation (AOR: 0.46, 95% CI: 0.30–0.72) and convulsions (AOR: 0.48, 95% CI: 0.34–0.66) during childbirth. Mother–newborn skin-to-skin contact increased the likelihood of EIBF (AOR: 1.47, 95% CI: 1.11–1.94). Women who experienced post-partum haemorrhage (AOR: 0.63, 95% CI: 0.47–0.84), retained placenta for more than 30 min (AOR: 0.36, 95% CI: 0.24–0.52) and convulsions after delivery (AOR: 0.57, 95% CI: 0.41–0.79) were less likely to initiate breastfeeding early. Also, women who had a caesarean birth (AOR: 0.28, 95% CI: 0.18–0.41), delivered outside of a healthcare facility (AOR: 0.70, 95% CI: 0.50–0.99) or had twin birth (AOR: 0.43, 95% CI: 0.22–0.85) were less likely to initiate breastfeeding early."
- 13. Karim et al. (2018)⁹⁶ report on direct observations of 249 deliveries in Bangladesh.
 - "Odds of initiating breastfeeding within one hour of birth was significantly higher if mothers gave birth in district hospitals (AOR 3.5: 95% CI 1.5, 6.4), visual privacy was well-maintained in delivery room (AOR 2.6: 95% CI 1.2, 4.8), newborns cried spontaneously (AOR 4.9: 95% CI 3.4, 17.2), were put to skin-to-skin contact with mothers (AOR 3.4: 95% CI 1.9, 10.4) or were examined by health care providers in the facilities (AOR 2.4: 95% CI 1.3, 12.9)."

(Qualitative and quasi-experimental studies on SSC)

- 14. Callaghan-Koru et. al (2016)⁹⁷ conducted a quasi-experimental pre-post study in Ethiopia of a multilevel community and facility intervention promoting immediate SSC and exclusive breastfeeding for all babies born at home or facility.
 - "Overall practice of SSC at any time following delivery increased significantly from 13.1% to 44.1% of mothers. Coverage of immediate SSC also increased significantly from 8.4% to 24.1%. Breastfeeding within the first hour increased from 51.4% to 67.9% and exclusive breastfeeding within the first three days increased from 86% to 95.8%. At endline, SSC was significantly higher among facility births than home births—community health workers had limited contact with mothers."
- 15. A qualitative study by Mbalinda et al. (2018)⁹⁸ examined the receptiveness of health workers in Uganda to a brief intervention to promote immediate skin-to-skin contact.

⁹⁶ Farhana Karim et al., "Initiation of Breastfeeding within One Hour of Birth and Its Determinants among Normal Vaginal Deliveries at Primary and Secondary Health Facilities in Bangladesh: A Case-Observation Study," *PLoS ONE* 13, no. 8 (August 16, 2018): e0202508, https://doi.org/10.1371/journal.pone.0202508.
 ⁹⁷ Jennifer A. Callaghan-Koru et al., "Practice of Skin-to-Skin Contact, Exclusive Breastfeeding and Other Newborn Care Interventions in Ethiopia Following Promotion by Facility and Community Health Workers: Results from a Prospective Outcome Evaluation," *Acta Paediatrica* 105, no. 12 (2016): e568–76, https://doi.org/10.1111/apa.13597.

⁹⁸ Scovia Mbalinda et al., "Experience of Perceived Barriers and Enablers of Safe Uninterrupted Skin-to-Skin Contact during the First Hour after Birth in Uganda," *Midwifery* 67 (December 1, 2018): 95–102, https://doi.org/10.1016/j.midw.2018.09.009.

- "The intervention package including above all, watching a DVD on practical advice about how to implement safe uninterrupted SSC following birth and discussions with health professionals, was shown to be applicable and accepted. The involvement of health professionals and the observation of the benefits of SSC resulted in a change both in attitudes and in care practices."
- 16. Following up on this intervention with a quasi-experimental (before and after) study, Nissen et al. (2019)⁹⁹ report an increase in infants who received SSC for the first full hour after birth from 0% pre-intervention to 54% post-intervention.
 - The intervention had six parts:
 - i. "To gain support from the hospital management to conduct the project aimed at implementing skin-to-skin contact
 - ii. To show a DVD entitled, Skin to skin in the first hour after birth: Practical advice after vaginal and caesarean birth (Brimdyr et al, 2011) to staff, who were also informed in a lecture about the health benefits of skin-to-skin contact and breastfeeding
 - iii. To distribute pamphlets produced for the project to health professionals, with details of how to practice skin-to-skin contact
 - iv. To hang a poster describing the nine stages of starting breastfeeding in the first hour after birth (Widström et al, 2011) on the walls of the maternal unit
 - To conduct focus group and individual interviews with the staff to explore what they perceived as factors that encouraged or hindered skin-to-skin contact
 - vi. To distribute 'skin-to-skin contact ambassador cards' to those who participated in interviews."
 - "In the pre-intervention group, all (100%) of the mothers were separated from their babies after birth. In the post-intervention group, 46.2% of the mother–baby dyads were separated. In both groups, the reasons for separating the mothers and their infants were infant examination and weighing, injection of vitamin K and application of tetracycline ointment. The separated infants were placed beside the examination bed or on a desk in the delivery ward."
 - The post-intervention data collection occurred in the 3 months following the intervention.
- 17. Vishnurajan et al. (2023)¹⁰⁰ report on a quality improvement initiative aimed at increasing immediate SSC rates for vaginally delivered healthy full-term infants in a tertiary care hospital in south India.
 - "Prior to this QI, baseline data showed that no babies received SSC for 30 min.
 During the first PDSA cycle, 16.6% (4/24) of babies received SSC and zero

⁹⁹ Eva Nissen et al., "A Low-Cost Intervention to Promote Immediate Skin-to-Skin Contact and Improve Temperature Regulation in Northern Uganda," *African Journal of Midwifery and Women's Health* 13 (June 19, 2019): 1–12, https://doi.org/10.12968/ajmw.2018.0037.

¹⁰⁰ Radhakrishnan Vishnurajan et al., "Immediate Skin to Skin Contact and Zero Separation of Mother Infant Dyads Among Healthy Term Infants Delivered Vaginally: A Quality Improvement Initiative in a Tertiary Care Institute in South India," *Journal of Neonatology* 38, no. 2 (June 1, 2024): 227–34, https://doi.org/10.1177/09732179231203084.

- separation for 30 min. During the II PDSA cycle, among 46 eligible neonates, 50% (23/46) received SSC >30 min. During the sustenance phase, among 262 eligible neonates, 75.2 % (197/262) received >30 min of SSC immediately after delivery."
- 18. Bhardwaj et al. (2024)¹⁰¹ report on a quality improvement initiative conducted over about 5 months, aimed at increasing immediate SSC rates for vaginally delivered infants at >35 weeks gestational age in a newly-established tertiary care hospital in northwest India.
 - "The duration of early SSC increased from 0 to 67 min without any additional resources. The practice of SSC got well established in the system as reflected by a sustained improvement of 63 min and 72 min, respectively, at the end of 2 months and 4 years after study completion."

H. How much room for improvement is there in rates of EIBF and/or SSC?

I. What geographies have the most room for improvement?

Summary

Reported rates of EIBF vary substantially between countries. "Official" data comes primarily from periodic large-scale surveys such as the Multiple Indicators Cluster Survey ("MICS") or Demographic and Health Survey ("DHS"). These survey data have the advantage of standardization and methodological rigor (e.g., avoiding risks of sampling bias), large numbers, and subnational-level data (allowing rates to be compared with high geographic resolution). However they also have substantial risks of recall bias (e.g., EIBF rates may be based on recall of births in the past 2 years) and social desirability bias, and there is some evidence that these are not just theoretical concerns. In addition, exact methods have changed slightly over time¹⁰², complicating the comparison of trends.

Some studies report directly-observed EIBF rates from particular hospitals or geographies. If these happen to be available in areas of interest, they may be more reliable than self-reported data, but suffer from other shortcomings such as selection bias (such as excluding births outside of healthcare facilities). The most comprehensive

Naveen Kumar Bhardwaj et al., "Implementing the Practice of Early Skin-to-Skin Contact among Infants ≥35 Weeks Gestation Born Vaginally: A Quality Improvement Study," BMJ Open Quality 13, no. Suppl 1 (April 8, 2024): e002408, https://doi.org/10.1136/bmjoq-2023-002408.

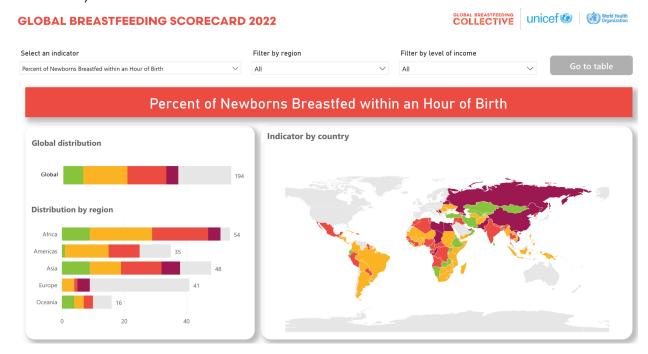
¹⁰² For the DHS survey "The early breastfeeding indicators have changed over time. For DHS-IV and DHS-V surveys, the early breastfeeding indicators were reported for all children born in the 5 years before the survey. For DHS-VI and DHS-7 surveys, the indicators were reported for last-born children born in the 2 years preceding the survey. For DHS-8, all early breastfeeding indicators are reported for all children born in the 2 years preceding the survey, both alive and dead. In earlier rounds of DHS, initiation of breastfeeding within one hour and within one day of birth were calculated among the children who were ever-breastfed, whereas for the DHS-VI and DHS-7 results were based on last-born children who were born in the 2 years preceding the survey. Hence, caution should be observed when comparing the figures in DHS-8 with the results published in the final reports for previous DHS surveys."

report I found on healthcare provider-reported EIBF timing across 24 countries showed EIBF rates varying from 18% to 98%, with substantial variation both within and between countries.

SSC and EIBF could be practiced by the vast majority of mothers and newborns. There are few theoretical limits, and observed percentages are very high in some countries. The percentage of newborns and/or mothers expected to need emergency medical interventions that would interfere with SSC and EIBF is probably in the single digits. Most standard newborn care procedures (such as ophthalmic ointments) can be safely deferred until after the first hour. Furthermore, routine interventions such as suturing vaginal tears and injections can be performed with the infant in SSC, and SSC may even improve both maternal and newborn pain during such procedures. It is feasible to achieve substantial SSC and EIBF rates even after cesarean section, and in many settings immediate SSC after cesarean is the standard practice.

Evidence considered

1. The Global Breastfeeding Collective publishes the Global Breastfeeding Scorecard, "a country scorecard to track progress on seven policy actions and on breastfeeding practices within countries". EIBF is one of the practices that is tracked; its underlying comes from UNICEF's Data Team (typically the MICS or DHS). Data on EIBF rates can be downloaded here. This interactive view of the 2022 Global Breastfeeding Scorecard shows global data on EIBF rates. Here is a screenshot of the map view (green represents high rates of EIBF, while shades of yellow and red indicate progressively lower rates):



- 2. As previously mentioned, Stewart et al. (2024)¹⁰³ find evidence for recall bias in EIBF and social desirability bias in EBF in a population that received an intervention that included promotion of breastfeeding practices.
- 3. In another study examined previously (Mullaney et al., 2008¹⁰⁴), the authors note that national Demographic and Health Survey data report much higher rates of early breastfeeding in Nepal (~35% within 1 hour and ~85% within 24 hours), compared to what they determined in their study with very short followup assessments after birth (~3% within 1 hour, ~55% within 24 hours).
- 4. Takahashi et al. (2017)¹⁰⁵, previously mentioned, performed a secondary analysis of data from the WHO Global Survey on Maternal and Perinatal Health, covering 244,569 births in 24 countries across Africa, Asia, and South America, to identify factors associated with EIBF.
 - "Overall, breastfeeding was initiated for 57.6% and 37.2% of neonates within the first hour after birth and from 1–24 hours after birth, respectively. The proportion of EIBF among all live births ranged from 17.7% to 98.4% with the lowest percentages found in Peru (17.7%), Ecuador (20.1%) and the Philippines (39.9%) and the highest in Angola (98.4%), Cuba (89.2%) and Sri Lanka (88.5%). We observed wide variation in EIBF both within and between countries."
- 5. As previously mentioned, Karim et al. (2018)¹⁰⁶ report on direct observations of 249 deliveries in Bangladesh, finding that 67% initiated breastfeeding within 1 hour.
- 6. The DHS Program "Guide to DHS Statistics DHS-8", https://dhsprogram.com/Data/Guide-to-DHS-Statistics/Early_Breastfeeding.htm

I. Are there any existing CEAs on EIBF interventions we can point to, especially those done in EA / GiveWell type frameworks?

Summary

I was unable to find any prior cost-effectiveness analyses (CEAs) specific to EIBF or skin-to-skin care (excluding kangaroo care). I specifically checked the <u>Tufts CEA registry</u> and <u>GiveWell</u> websites, in addition to Google searches. I also contacted a researcher at <u>Ambitious Impact</u> (since I know they do shallow reviews of hundreds of topics), and they were unaware of any prior work in this area.

¹⁰³ Christine P Stewart et al., "Social Desirability Bias in a Randomized Controlled Trial That Included Breastfeeding Promotion in Western Kenya," *Current Developments in Nutrition*, September 23, 2024, 103779, https://doi.org/10.1016/j.cdnut.2024.103779.

¹⁰⁴ Mullany et al., "Breast-Feeding Patterns, Time to Initiation, and Mortality Risk among Newborns in Southern Nepal,."

¹⁰⁵ Takahashi et al., "Prevalence of Early Initiation of Breastfeeding and Determinants of Delayed Initiation of Breastfeeding."

¹⁰⁶ Karim et al., "Initiation of Breastfeeding within One Hour of Birth and Its Determinants among Normal Vaginal Deliveries at Primary and Secondary Health Facilities in Bangladesh."

There are pre-existing CEAs for essential newborn care "packages" (which include EIBF and SSC), more general breastfeeding promotion, or promotion of EBF, including by GiveWell. GiveWell also reports on the Alive & Thrive program, previously mentioned here.

Evidence considered

Brief (~15 minute) online search.

J. What are existing organizations / actors doing? How neglected or not is this problem?

Summary

Breastfeeding, writ large, has many prominent promoters, and EIBF is among the standard practices that are promoted. The <u>Global Breastfeeding Collective</u>, an initiative of the WHO and UNICEF, is "a partnership of prominent international agencies calling on donors, policymakers, philanthropists and civil society to increase investment in breastfeeding worldwide." <u>Partners</u> include many prominent NGOs and bilateral/multilateral agencies (including the Gates Foundation, Catholic Relief Services, Helen Keller International, Save the Children, PATH, USAID, and the World Bank).

My impression is that breastfeeding interventions are typically promoted as a "package". In a brief search I was unable to find any organizations working exclusively on EIBF (or disproportionately on EIBF relative to other breastfeeding interventions).

Evidence considered

Brief (~15 minute) online search.

EVIDENCE GAPS & ADDITIONAL RESEARCH NEEDED

What is the estimated cost-effectiveness of interventions that promote immediate SSC and EIBF among health workers? A preliminary analysis by HealthLearn¹⁰⁷ suggests that its online health worker training, which promotes early SSC and EIBF along with other newborn care practices, is plausibly cost-effective. However, more research (including by independent evaluators) is needed to better understand the costs and likely impacts of different EIBF-promoting programs.

What is the best level for intervention? Immediate SSC and/or EIBF rates seem to respond to interventions among health workers, mothers, and broader communities, but we lack good evidence on comparative effectiveness. There may also be other cost-effective methods, such as mass media campaigns or policy changes to monitor SSC and EIBF among health facility reporting metrics.

Where is the "sweet spot" in terms of cost and effectiveness of promotional interventions for EIBF and SSC among health workers? It seems likely that resource-intensive efforts may improve rates further than "light-touch" interventions. However it isn't clear whether the optimal cost-effectiveness is found with intensive and costly (but highly effective) interventions or with more basic interventions (which may still have some effect at a much lower cost).

How does the effectiveness and cost of promoting a narrow set of interventions (immediate SSC and EIBF) compare to more comprehensive essential newborn care training interventions? An analysis from GiveWell¹⁰⁸ suggests that such programs are potentially cost-effective, but have "very heterogeneous training content." It may be that specific components (such as early SSC and EIBF promotion) contribute a substantial portion of the impact of these programs. A better mechanistic understanding of *how* these programs save lives could increase their consistency and effectiveness.

Can we better calibrate the mortality benefit of immediate SSC by incorporating observational evidence for mortality benefits associated with its other effects beyond EIBF? Our mortality estimates are drawn only from studies on EIBF, but observational studies have also found mortality associations with exclusive breastfeeding, hypoglycemia, body temperature, and cardiac stability.

How much of the benefit of SSC and EIBF is driven by premature and/or low birthweight infants? If the overall benefits are mostly driven by this subset, promoting SSC and EIBF may

¹⁰⁷

https://forum.effectivealtruism.org/posts/dA99mkei3mKrojDA9/healthlearn-impact-evaluation-and-next-ste

https://www.givewell.org/international/technical/programs/facility-based-maternal-and-neonatal-health-interventions

be less beneficial in areas where KC is standard practice for these high-risk newborns. While promotion of universal immediate SSC and EIBF seems to have few downsides, there is some risk it could be perceived as a substitute for full KC programs (which require more resources but have proven benefits). Conversely, it seems very likely that immediate SSC and EIBF will confer some protection to at-risk newborns in contexts where resource constraints prevent full implementation of KC programs.

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