

SYSTEMATIC REVIEW / META-ANALYSIS

Oropharyngeal Colostrum Administration for the Prevention of Necrotising Enterocolitis in Preterm Infants: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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ARTICLE INFO	ABSTRACT
ARTICLE TYPE Systematic Review / Meta-Analysis ARTICLE HISTORY Received: September 12, 2026 Revised: September 20, 2026 Accepted: September 30, 2026 Available online: October 8, 2026 Published: October 9, 2026 KEYWORDS Colostrum; Enterocolitis, necrotising; Infant, preterm; Meta-analysis; Oropharynx; Sepsis CORRESPONDING AUTHOR I Wayan Windi Artha E-mail: windi.artha32@gmail.com DOI https://doi.org/10.59345/sjped.v4i2.344 LICENSE CC BY-NC-SA 4.0 COPYRIGHT © 2026 The Author(s). Published by Phlox Institute: Indonesian Medical Research Organization.	Background: Necrotising enterocolitis is a major gastrointestinal emergency of prematurity. Oropharyngeal colostrum may provide mucosal immune protection when enteral feeding is delayed, but its clinical effect remains uncertain. Objective: To determine whether oropharyngeal colostrum reduces necrotising enterocolitis at Bell stage 2 or above and whether the effect varies by administration regimen. Methods: PubMed/MEDLINE, Europe PMC, CENTRAL, and ClinicalTrials.gov were searched through September 9 2026, with citation searching, for randomised trials in infants born before 37 weeks. Two reviewers independently screened records, extracted data, and assessed risk of bias using RoB 2. Random-effects models with Hartung–Knapp intervals were used. Results: Nineteen trials were included; fifteen trials involving 1,541 infants entered the primary analysis. Colostrum reduced necrotising enterocolitis (36/786 vs 73/755; risk ratio 0.50, 95% confidence interval 0.33–0.76; p=0.003; I²=0.0%), with a number needed to treat of 21 (15–43). Late-onset sepsis, mortality, and ventilator-associated pneumonia were also reduced. Estimates did not differ significantly between administration protocols, and no intervention-related adverse events were reported. Conclusion: Oropharyngeal colostrum approximately halved necrotising enterocolitis without evidence of harm. Its low cost and feasibility support use in preterm infants who cannot yet be fed enterally, while adequately powered trials define the optimal regimen.

1. Introduction

Preterm birth remained the single largest contributor to neonatal morbidity worldwide, with an estimated 13.4 million infants born before 37 completed weeks of gestation in 2020 and little evidence of decline over the preceding decade.^{1,2} The burden fell disproportionately on low- and middle-income settings, where survival gains have not been matched by reductions in the complications of prematurity.³ Among infants born at the extremes of gestation, in-hospital morbidity remained common despite substantial improvements in intensive care, and rates of the major neonatal morbidities varied several-fold between centres in ways that could not be explained by case mix alone.^{4,5} That variation implied that modifiable elements of care, rather than immutable biology, accounted for a meaningful share of the residual risk.

Necrotising enterocolitis was the most consequential of those complications. It affected between 2% and 7% of infants born before 32 weeks and up to a fifth of those weighing less than 1,000 g at birth, and it carried a case fatality that approached one in three once surgical intervention became necessary.^{6,7} Infants who survived surgical disease faced prolonged parenteral nutrition, intestinal failure and measurable deficits in neurodevelopment at school age, so that the consequences of a single episode extended far beyond the neonatal admission.^{8,9} The condition has also proved stubbornly difficult to distinguish from spontaneous intestinal perforation at the

bedside, which complicates both clinical decision-making and trial ascertainment.¹⁰ Management remains largely supportive once disease is established, and even contemporary surgical trials have not identified an approach that materially alters outcome, which places the emphasis firmly on prevention.^{11,12}

The pathogenesis of necrotising enterocolitis is now understood as the convergence of an immature intestinal epithelium, an exaggerated inflammatory response and a disordered microbial community. Longitudinal profiling of preterm stool has shown that infants who later develop the disease follow a distinct trajectory of microbial assembly, with delayed acquisition of commensal anaerobes and expansion of potentially pathogenic Gammaproteobacteria.^{13,14} Specific human milk oligosaccharides, most notably disialyllacto-N-tetraose, have been linked prospectively to that trajectory and to disease risk, providing a direct mechanistic bridge between what an infant receives and what colonises the gut.¹⁵ Metabolomic and amniotic-fluid studies have converged on the same conclusion, and machine-learning models built on early microbial features have achieved useful discrimination well before clinical presentation.^{16–18} Interventions that shift the microbial trajectory, including specific probiotic strains, have reduced disease incidence in both experimental and clinical work, which establishes the principle that the trajectory is modifiable.^{19,20}

Mother's own milk is the most powerful modifier available. It delivers secretory immunoglobulin A, lactoferrin, cytokines,

growth factors and oligosaccharides that together shape mucosal immunity and microbial colonisation, and cohort and trial evidence has consistently linked exclusive human milk feeding to lower rates of necrotising enterocolitis and better cognitive outcome.²¹⁻²³ Quality-improvement programmes built around increasing the proportion of mother's own milk have reduced disease incidence at unit level, and the economic case for doing so is favourable.²⁴ Yet the infants at highest risk are precisely those who cannot be fed for the first days of life. Haemodynamic instability, respiratory failure and the practicalities of gastric tube feeding mean that colostrum, when it reaches these infants at all, bypasses the mouth and pharynx entirely. The oropharyngeal-associated lymphoid tissue, which in utero is bathed continuously in immunologically active amniotic fluid, is therefore left unstimulated during the very window in which it is most responsive.^{25,26}

Oropharyngeal colostrum administration was devised to close that gap. A volume of 0.1 to 0.4 mL of the mother's own colostrum is placed directly on the buccal and oropharyngeal mucosa, where its bioactive constituents contact mucosal immune cells without requiring gastrointestinal absorption or swallowing. Randomised trials have shown that the procedure raises salivary and urinary secretory immunoglobulin A and lactoferrin, alters the oral microbiome, and is well tolerated even in ventilated infants weighing less than 1,000 g at birth.²⁷⁻³¹ Parallel work with enteral bovine lactoferrin has confirmed that delivering such constituents to the mucosa produces measurable immunological change.^{32,33} The clinical question, however, has remained unsettled. Individual trials have been small and powered for immunological rather than clinical endpoints, and their estimates for necrotising enterocolitis have ranged from marked benefit to no effect.³⁴⁻³⁷ Published syntheses have reached correspondingly divergent conclusions, some reporting a significant reduction and others confidence intervals that comfortably included unity.³⁸⁻⁴¹

Three specific gaps motivated the present work. First, several randomised trials have appeared since the most recent syntheses were completed, and none of the published pooled estimates incorporates them.^{37,42-44} Second, administration protocols differ substantially between trials in dose, frequency and duration, yet no synthesis has formally tested whether those differences are associated with differing effect estimates. Third, existing analyses have generally pooled clinically suspected and culture-confirmed sepsis together, conflating a subjective judgement with an objective one and obscuring which of the two, if either, is affected. The second of these gaps is one this review can pose but, as the results below show, cannot resolve: no combination of the available trials yields enough trials per protocol stratum to test an interaction with useful power, and it is therefore presented as a research priority rather than as a contribution.

The novelty of this study lies in the combination of an evidence base extended to 2025 and larger in event count than any previous synthesis, a deliberate separation of culture-confirmed from clinically diagnosed sepsis, and a pre-specified comparison of administration regimens. The aim of this study was to determine whether oropharyngeal colostrum administration reduces the incidence of necrotising enterocolitis at Bell stage 2 or above in preterm infants, and to establish whether the magnitude of any effect depends upon the dose, frequency and duration of administration.

2. Methods

Study design and reporting

This systematic review and meta-analysis was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question was framed as a population, intervention, comparator, outcome and study design structure: preterm infants born before 37 weeks of gestation (population), oropharyngeal administration of colostrum or own mother's milk (intervention), placebo or standard care without oropharyngeal instillation (comparator), necrotising enterocolitis at Bell stage 2 or above as the primary outcome, and randomised controlled trials as the only admissible design. No individual patient data were sought and no primary data were collected, so ethical approval and informed consent were not required.

The review was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261369170.

Search strategy

Four sources were searched from inception to 9 September 2026 with no start-date restriction: PubMed/MEDLINE through the National Center for Biotechnology Information E-utilities interface; Europe PMC through its representational state transfer application programming interface; the Cochrane Central Register of Controlled Trials (CENTRAL) through the Cochrane Library trials interface; and ClinicalTrials.gov through its version two application programming interface. The strategy combined Medical Subject Headings with free-text terms across three concept blocks, joined by the Boolean operator AND, with synonyms within each block joined by OR.

The PubMed strategy was: ("Infant, Premature"[Mesh] OR preterm infant*[tiab] OR premature infant*[tiab] OR "very low birth weight"[tiab] OR VLBW[tiab] OR "extremely low birth weight"[tiab] OR ELBW[tiab]) AND ("Colostrum"[Mesh] OR colostrum[tiab] OR "human milk"[tiab] OR "breast milk"[tiab] OR "own mother's milk"[tiab] OR "mother's own milk"[tiab]) AND (oropharyngeal[tiab] OR oropharynx[tiab] OR buccal[tiab] OR "oral care"[tiab] OR "oral immune therapy"[tiab] OR "oral immunotherapy"[tiab] OR "oral application"[tiab] OR "oral administration"[tiab] OR "oral colostrum"[tiab] OR "oropharyngeal administration"[tiab] OR "oral priming"[tiab] OR "colostrum priming"[tiab] OR swab*[tiab]) AND (randomi*[tiab] OR trial[tiab] OR "randomized controlled trial"[pt]). This returned 74 records.

The third block deliberately extends beyond the word "oropharyngeal", because several trials describe the identical intervention as oral colostrum administration, oral colostrum priming or oral immunotherapy. The equivalent free-text strategy in Europe PMC returned 445 MEDLINE records and 4 preprints. The CENTRAL search, combining the same three concept blocks in title, abstract and keyword fields, returned 89 trial records, of which roughly a third were trial-registry entries rather than journal articles. ClinicalTrials.gov returned 11 registered studies. Reference lists of twelve previously published systematic reviews were screened and forward citation searching was performed on the trials already identified, together yielding 11 further records. Searches were restricted to reports published in English with full text available.

The registry search identified no completed trial whose results had not been published. Two included trials carry registry

identifiers, ChiCTR1900023697
IRCT20230312057698N1,^{34,43}

and **Eligibility criteria**

Eligibility was defined prospectively across six domains, as detailed in Table 1.

Table 1. Eligibility criteria applied at screening and full-text assessment.

Domain	Included	Excluded
Design	Parallel-group randomised controlled trial	Quasi-randomised, non-randomised, observational, single-arm or crossover designs; protocols without results; reviews, editorials and conference abstracts
Population	Preterm infants, gestational age <37 weeks, cared for in a neonatal unit	Term infants; populations not restricted to preterm infants
Intervention	Oropharyngeal or buccal administration of colostrum or own mother's milk	Enteral or gastric administration without an oropharyngeal component; donor milk given by the enteral route alone; formula-based oral care
Comparator	Placebo (sterile water, distilled water or 0.9% sodium chloride) delivered by the identical route, or standard care without oropharyngeal instillation	Active comparators such as probiotics or bovine lactoferrin
Outcomes	At least one of: necrotising enterocolitis; late-onset sepsis; culture-positive sepsis; all-cause mortality; ventilator-associated pneumonia; bronchopulmonary dysplasia; time to full enteral feeding; length of hospital stay	Trials reporting only immunological or microbiological endpoints with no clinical outcome
Report	Full text in English	Duplicate reports of an already included trial

Titles and abstracts were screened independently by two reviewers against these criteria. Reports passing screening were retrieved in full and assessed against the same criteria, with reasons for exclusion recorded. Disagreements were resolved by discussion and, where necessary, by a third reviewer. Records retrieved by more than one source were de-duplicated on digital object identifier and PubMed identifier.

Data extraction and verification

Two reviewers extracted data independently into a standardised form covering study identifiers, country, design, sample size by arm, gestational age, birth weight, the dose, frequency, timing and duration of colostrum administration, the nature of the comparator, and every outcome of interest with its arm-level event counts or means and standard deviations. Where a value was not reported it was recorded as not reported and left empty; no value was imputed, estimated from a graph, or converted from a median and interquartile range. Where a reported percentage was inconsistent with its own numerator and denominator, the counts were used and the discrepancy was flagged.

Risk of bias assessment

Risk of bias was assessed independently by two reviewers with the Cochrane risk-of-bias tool for randomised trials, version 2. Five domains were judged: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each domain was rated as low risk, some concerns or high risk, and an overall judgement was assigned by the algorithm specified in the tool, so that a single high-risk domain produced an overall high-risk judgement. Particular attention was paid to the second and fourth domains, because trials in which the control arm received no oropharyngeal placebo could not blind bedside caregivers, and because necrotising enterocolitis is adjudicated clinically and radiologically rather than by an automated assay. The risk-of-bias tool is outcome-specific by design; the judgements

reported here refer to the primary outcome of necrotising enterocolitis, and they should not be transferred without qualification to the continuous outcomes, for which the relevant threats differ. Disagreements were resolved by discussion.

Statistical analysis

All analyses were performed in R version 4.5.3 using the meta package version 8.2–1 and the metafor package version 4.8–0. Analyses followed the analysis populations reported by each trial; one trial reported a per-protocol analysis and the remainder analysed all randomised infants with complete outcome data.²⁷ Dichotomous outcomes were pooled as risk ratios with 95% confidence intervals, and continuous outcomes as mean differences in days, both estimated by the inverse-variance method under a random-effects model with the DerSimonian-Laird estimator for the between-study variance. Because the number of trials was small and the between-study variance was expected to be poorly estimated, the Hartung-Knapp adjustment was applied to the confidence interval of the primary outcome and is the specification reported throughout; the unadjusted interval is given alongside it as a sensitivity analysis. A random-effects model was chosen a priori rather than selected on the basis of the observed heterogeneity, because clinical and methodological diversity in gestational age, colostrum dose, frequency, timing and duration, and in the nature of the comparator, made a common underlying effect implausible on substantive grounds. Where a trial reported zero events in one arm, a continuity correction of 0.5 was applied to that trial alone; trials reporting zero events in both arms contribute no information to a ratio measure and were therefore excluded from the corresponding pooled estimate while remaining in the descriptive totals. Because a constant continuity correction is known to be biased with sparse data, the primary outcome was recomputed under five alternative handlings of the single zero cell.

Heterogeneity was quantified by the Q statistic with its degrees of freedom and p value, by the between-study variance τ^2 , and by I^2 with its 95% confidence interval. I^2 was

interpreted alongside the magnitude and direction of the individual estimates and the clinical characteristics of the trials, rather than as a stand-alone threshold. Subgroup analysis by administration protocol was specified after the intervention descriptions had been extracted but before any outcome data were examined, since the boundaries of the strata could only be drawn once the range of regimens in the literature was known; the strata were fixed and recorded before the first pooled estimate was computed. Trials were assigned to one of four mutually exclusive strata defined jointly by dose, frequency and duration, and differences between strata were tested by the random-effects Q statistic for subgroup differences. Because that test is weak with few trials per stratum, a random-effects meta-regression using dose in millilitres as a continuous moderator was run as a more efficient use of the same information. Robustness was examined by leave-one-out analysis, by excluding trials at overall high risk of bias, by substituting a restricted maximum-likelihood estimator for the between-study variance, and by applying the Hartung-Knapp adjustment to the confidence interval. Small-study effects were assessed by Egger regression and by the Peters test, both pre-specified to be

reported only when at least ten trials contributed, and by the trim-and-fill procedure. Statistical significance was taken as a two-sided p value below 0.05.

3. Results

Study selection

The searches returned 623 records from the four databases (PubMed/MEDLINE 74, Europe PMC 449, CENTRAL 89, ClinicalTrials.gov 11) and 11 from citation searching. After 197 duplicates were removed, 437 records were screened by title and abstract and 379 were excluded as irrelevant to the review question. Fifty-eight full-text reports were sought for retrieval and all 58 were obtained; 39 were excluded, comprising 12 review articles, 14 reports that were not randomised trials, 7 protocols without results, 5 that reported no extractable outcome data, and 1 that was not peer reviewed. Nineteen randomised controlled trials met every eligibility criterion and were included, as illustrated in Figure 1. Fifteen of these reported necrotising enterocolitis at Bell stage 2 or above and formed the primary quantitative synthesis.

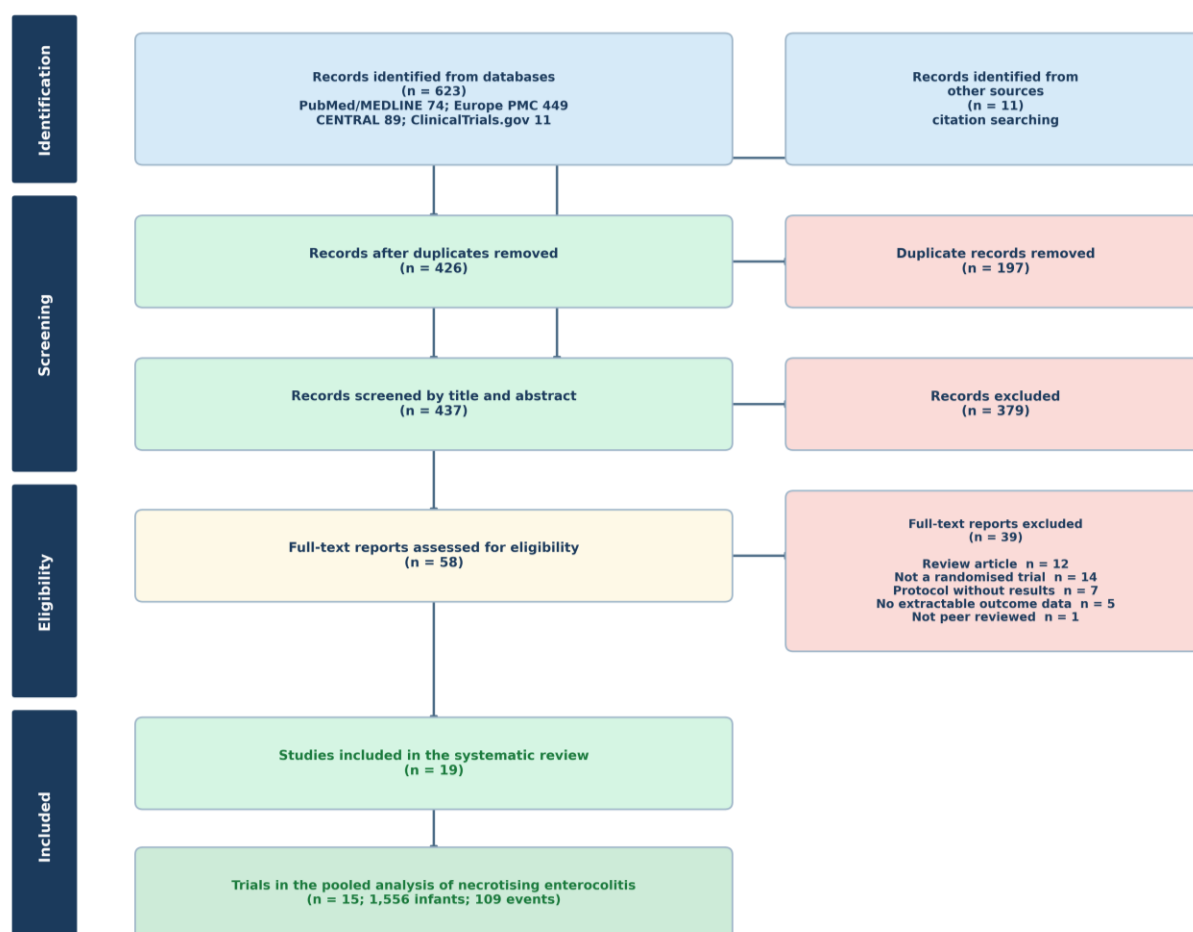


Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility assessment and inclusion.

Characteristics of the included trials

The nineteen trials enrolled 1,817 preterm infants; the difference reflects withdrawal, discharge against medical advice and incomplete outcome data, and all figures reported

here are the numbers analysed. The trials were conducted in nine countries: Iran (five trials), China (three), the United States (three), Egypt (two), India (two), and Brazil, South Korea, Turkey and Thailand (one each). Trial size ranged from 12 to 252 infants. Populations were uniformly high-risk: every trial restricted enrolment to infants below 34 weeks of

gestation or 1,500 g at birth, and several confined recruitment to infants below 28 to 30 weeks or below 1,000 to 1,250 g. The intervention was own mother's colostrum in every trial. Where the dose was reported it was 0.2 mL in most trials, with 0.3 mL in two and 0.4 mL in two; the interval ranged from every two hours to every six hours; and the duration ranged

from 46 hours to 21 days, or until full oral feeding was achieved. Administration began between birth and 96 hours of life. Eleven trials used a placebo of sterile water, distilled water or 0.9% sodium chloride delivered by the identical route, while eight used standard care without oropharyngeal instillation. Full characteristics are detailed in Table 2.

Table 2. Characteristics of the nineteen included randomised controlled trials.

Trial	Country	n (I/C)	Gestational age / birth weight	Dose	Interval	Duration	Comparator	Protocol group	Overall risk of bias
Abd-Elgawad 2020 ⁴⁵	Egypt	100/100	<32 wk; <1500 g	0.2 mL	2–4 h	Until full oral feeding	Routine care	C	High
Behrooj 2025 ⁴³	Iran	34/34	28–32 wk	0.4 mL	3 h	7 days	Standard care	-	Some concerns
Chen 2022 ²⁹	China	56/55	≤32 wk; ≤1500 g	0.3 mL	3 h	14 days	Normal saline	D	Some concerns
Ferreira 2019 ³⁶	Brazil	47/66	<34 wk; <1500 g	0.2 mL	2 h	48 hours	Sterile water	A	Some concerns
Glass 2017 ²⁷	USA	17/13	23–32 wk; <1500 g	0.2 mL	3 h	Day 2 to day 7	Sterile water	A	High
Kelich 2024 ⁴⁶	Iran	40/40	25–30 wk	0.2 mL	2 h	Until 1 mL taken orally	Sterile water	-	Some concerns
Lamsehchi 2025 ⁴²	Iran	63/63	<32 wk; <1500 g	0.2 mL	6 h	3 days	Distilled water	B	Low
Lee 2015 ²⁸	South Korea	24/24	<28 wk	0.2 mL	3 h	72 hours	Sterile water	A	Low
Liu 2024 ⁴⁴	China	53/51	≤1500 g	0.3 mL	3 h	21 days	Normal saline	D	Some concerns
Mohammadizadeh 2024 ³⁷	Iran	30/30	≤30 wk; ≤1500 g	0.2 mL	3 h	72 hours	Distilled water	A	Low
Oruc 2025 ⁴⁷	Turkey	92/46	<32 wk	0.2 mL	3 h	3 or 10 days	No colostrum	-	Some concerns
OuYang 2021 ³⁴	China	127/125	≤32 wk	0.4 mL	3 h	10 days	Normal saline	D	Some concerns
Romano-Keeler 2016 ⁴⁸	USA	48/51	<32 wk	0.2 mL	6 h	5 days	Routine care	A	High
Sharma 2019 ³⁵	India	59/58	≤30 wk; ≤1250 g	0.2 mL	2 h	72 hours	Routine care	A	High
Sohn 2016 ⁴⁹	USA	6/6	<1500 g	0.2 mL	2 h	46 hours	Routine care	A	High
Taha 2025 ⁵⁰	Egypt	32/33	VLBW	0.2 mL	6 h	5 days	Sterile water	-	Some concerns
Tehranchi 2024 ⁵¹	Iran	37/39	VLBW	0.2 mL	3 h	Until oral feeding	No colostrum	-	High
Thatrimontrichai 2023 ⁵²	Thailand	30/33	VLBW	0.2 mL	3 h	Until oral feeding	Sterile water	-	Some concerns
Zhang 2017 ⁵³	China	27/28	≤1500 g	0.2 mL	4 h	7 days	Normal saline	B	Some concerns

I, intervention; C, control. Sample sizes are the numbers analysed. Protocol groups: A, 0.2 mL every 2–3 h for 2–5 days; B, 0.2 mL every 4–6 h for 3–7 days; C, 0.2 mL every 3 h until full oral feeding; D, 0.3–0.4 mL every 3 h for 10–21 days. A dash indicates a trial that did not report necrotising enterocolitis and was therefore not assigned to a protocol group. Overall risk of bias is the Cochrane RoB 2 overall judgement.

Risk of bias

Of the nineteen trials, three (15.8%) were judged at overall low risk of bias, ten (52.6%) raised some concerns and six (31.6%) were at overall high risk, as illustrated in Figure 2. The randomisation process was the strongest domain, with 17 trials (89.5%) at low risk. Deviations from intended interventions was much the weakest: 5 trials (26.3%) at low

risk, 7 (36.8%) with some concerns and 7 (36.8%) at high risk, in every high-risk case because the control arm received nothing by the oropharyngeal route and bedside caregivers could therefore not be blinded. Missing outcome data were well handled, with 16 trials (84.2%) at low risk. Measurement of the outcome was at low risk in 9 trials (47.4%) and at high risk in 5 (26.3%), reflecting unblinded adjudication of clinically diagnosed endpoints. Selection of the reported result was at low risk in 16 trials (84.2%).



Figure 2. Risk of bias in the nineteen included trials, assessed with the Cochrane risk-of-bias tool for randomised trials, version 2. Green denotes low risk, amber some concerns and red high risk. The rightmost column, separated by a rule, is the overall judgement.

Primary outcome: necrotising enterocolitis

Fifteen trials enrolling 1,541 preterm infants (786 assigned to colostrum and 755 to control) contributed arm-level counts for necrotising enterocolitis at Bell stage 2 or above. The condition occurred in 36 of 786 infants (4.58%) receiving colostrum and in 73 of 755 (9.67%) receiving placebo or standard care. The pooled random-effects risk ratio was 0.50 (95% Hartung-Knapp confidence interval 0.33 to 0.76; $t=-3.57$ on 14 degrees of freedom; $p=0.003$), an absolute risk reduction

of 5.09 percentage points and a number needed to treat of 21 (95% confidence interval 15 to 43), as summarised in Table 3 and illustrated in Figure 3. The number needed to treat is illustrative and holds only at the control-arm risk of 9.67% observed here; it will be larger in units with a lower baseline incidence. The unadjusted DerSimonian-Laird interval was narrower, at 0.34 to 0.75 ($p=0.0006$). Heterogeneity was absent ($\tau^2=0$; $Q=12.75$, $df=14$, $p=0.55$; $I^2=0.0\%$, 95% confidence interval 0.0% to 53.6%). Eleven of the fifteen point estimates lay below unity, and the four that did not came from trials contributing few events.

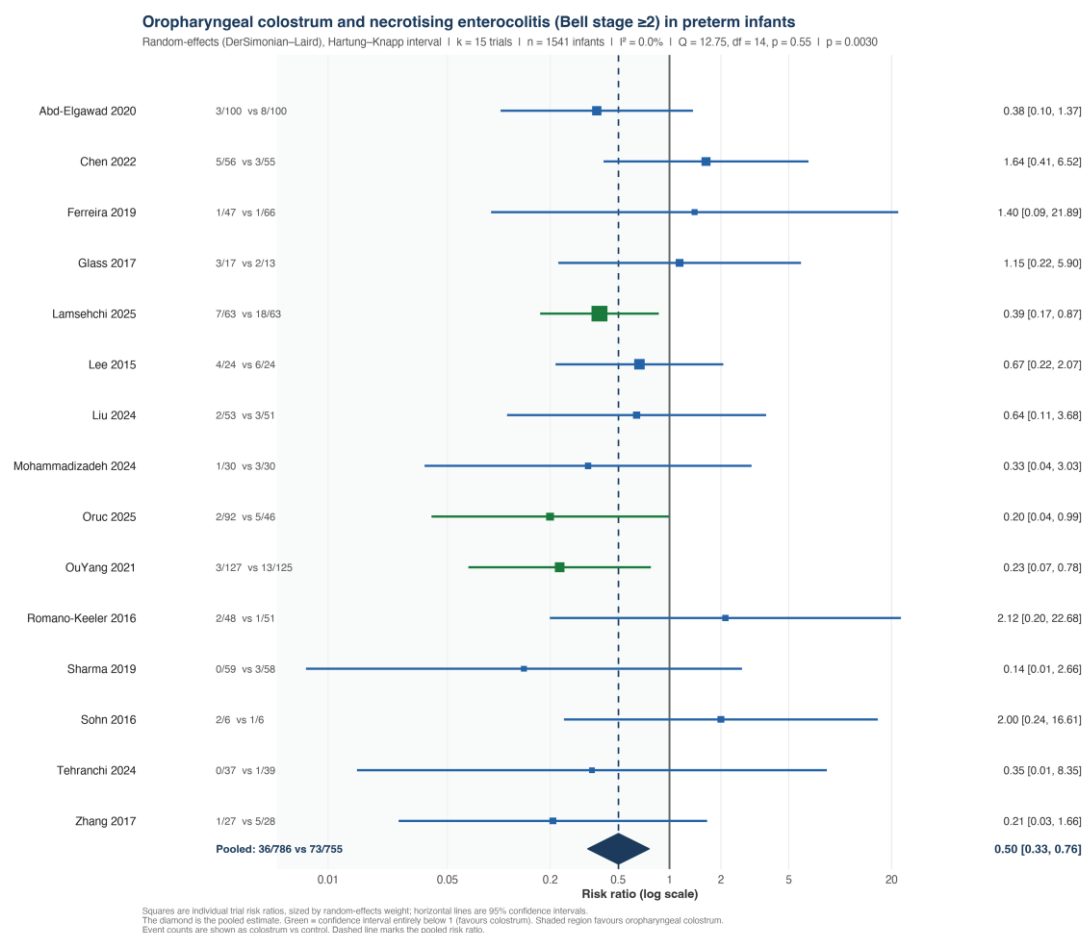


Figure 3. Forest plot of the effect of oropharyngeal colostrum on necrotising enterocolitis at Bell stage 2 or above, random-effects model. Squares are trial-level risk ratios scaled by weight, horizontal lines are 95% confidence intervals, and the diamond is the pooled estimate. Event counts are shown as colostrum versus control.

Table 3. Pooled effect of oropharyngeal colostrum on necrotising enterocolitis (Bell stage ≥ 2).

Parameter	Value
Trials contributing (k)	15
Infants analysed	1,541 (786 colostrum; 755 control)
Events	36/786 (4.58%) colostrum; 73/755 (9.67%) control
Pooled risk ratio (95% CI), Hartung-Knapp	0.50 (0.33 to 0.76)
Pooled risk ratio (95% CI), unadjusted	0.50 (0.34 to 0.75)
t statistic (df)	-3.57 (14)
p value	0.003
Absolute risk reduction	5.09 percentage points
Number needed to treat (95% CI)	21 (15 to 43)
tau ²	0
Q (df); p	12.75 (14); 0.55
I ² (95% CI)	0.0% (0.0% to 53.6%)

Subgroup analysis by administration protocol

Thirteen of the fifteen contributing trials were assignable to one of four protocol strata defined jointly by dose, frequency and duration; the remaining two used regimens spanning more than one stratum. In group A (0.2 mL every 2–3 hours for 2–5 days; seven trials, 494 infants) the risk ratio was 0.83 (0.41 to 1.67; p=0.60; $I^2=0.0\%$). In group B (0.2 mL every 4–6 hours for 3–7 days; two trials, 181 infants) it was 0.36 (0.17 to 0.76; p=0.007; $I^2=0.0\%$). In group C (0.2 mL every 3 hours until full oral feeding; one trial, 200 infants) it was 0.38 (0.10 to

1.37; p=0.14). In group D (0.3–0.4 mL every 3 hours for 10–21 days; three trials, 467 infants) it was 0.60 (0.17 to 2.05; p=0.41; $I^2=54.6\%$). The test for subgroup differences was not significant (Q=2.88, df=3, p=0.41), as presented in Table 4 and illustrated in Figure 4. Random-effects meta-regression using dose as a continuous moderator likewise found no association with effect size (beta=-1.86 per mL, 95% confidence interval -7.94 to 4.23; p=0.55), and dose accounted for none of the between-study variance.

The apparent superiority of group B therefore rests on a formally negative test for interaction and on only two trials. It

should be read as the stratum in which the effect reached conventional significance rather than as evidence that this regimen outperforms the others, and it provides no support

for a dose-response relationship: the highest-dose, longest-duration stratum did not produce the largest effect.

Table 4. Necrotising enterocolitis by oropharyngeal colostrum administration protocol.

Protocol group	k	Events colostrum	Events control	Risk ratio (95% CI)	I ²	p
A: 0.2 mL every 2–3 h, 2–5 days	7	13/231	17/248	0.83 (0.41 to 1.67)	0.0%	0.60
B: 0.2 mL every 4–6 h, 3–7 days	2	8/90	23/91	0.36 (0.17 to 0.76)	0.0%	0.007
C: 0.2 mL every 3 h until full oral feeding	1	3/100	8/100	0.38 (0.10 to 1.37)	Not estimable	0.14
D: 0.3–0.4 mL every 3 h, 10–21 days	3	10/236	19/231	0.60 (0.17 to 2.05)	54.6%	0.41
Test for subgroup differences				Q=2.88, df=3		0.41

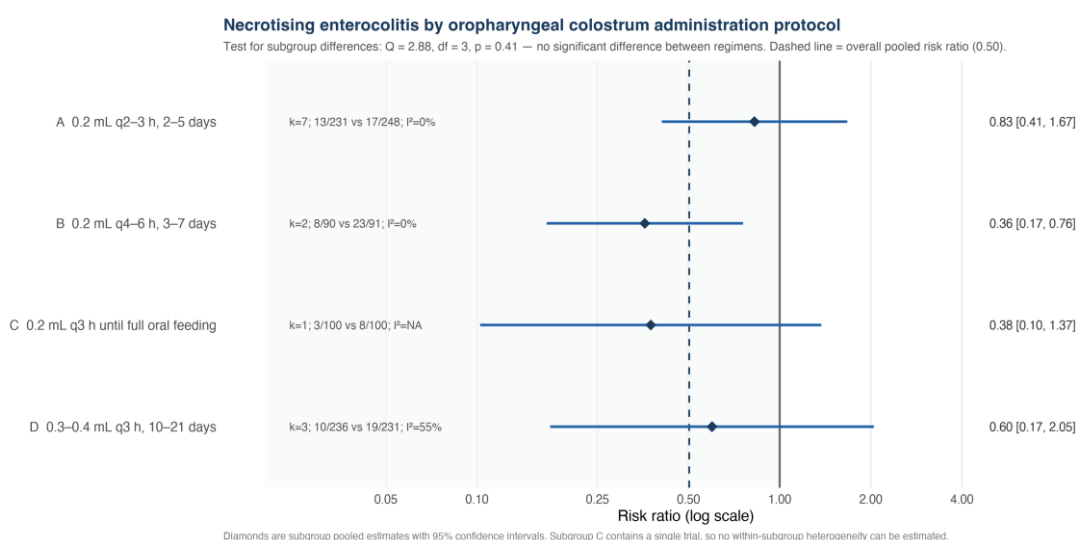


Figure 4. Subgroup forest plot of necrotising enterocolitis by administration protocol. Diamonds are subgroup pooled estimates with 95% confidence intervals; the dashed line marks the overall pooled risk ratio of 0.50.

Sensitivity analyses

The primary estimate was robust to every planned perturbation, as detailed in Table 5. Omitting each trial in turn produced pooled risk ratios between 0.45 and 0.55, a maximum absolute displacement of 0.050 from the primary estimate, and the confidence interval excluded unity in all fifteen iterations. Excluding the trials at overall high risk of bias left nine trials and a risk ratio of 0.45 (0.29 to 0.71;

p=0.0006). Substituting a restricted maximum-likelihood estimator for the between-study variance reproduced the primary estimate exactly, and the Hartung-Knapp adjustment widened the interval only marginally, to 0.50 (0.33 to 0.76; p=0.003). Handling of the zero cells was not load-bearing: five alternative treatments, including a treatment-arm correction, a Mantel-Haenszel analysis without correction, exclusion of those trials altogether and a Peto odds ratio, produced estimates between 0.44 and 0.52, all significant.

Table 5. Sensitivity analyses for necrotising enterocolitis.

Analysis	k	Risk ratio (95% CI)	I ²	p
Hartung-Knapp interval (primary specification)	15	0.50 (0.33 to 0.76)	0.0%	0.003
Unadjusted DerSimonian-Laird interval	15	0.50 (0.34 to 0.75)	0.0%	0.0006
Excluding trials at overall high risk of bias	9	0.45 (0.29 to 0.71)	0.0%	0.0006
Restricted maximum-likelihood estimator for tau ²	15	0.50 (0.34 to 0.75)	0.0%	0.0006
Leave-one-out, range across 15 iterations	14	0.45 to 0.55	0.0%	<0.05 throughout
Treatment-arm continuity correction	15	0.50 (0.34 to 0.75)	0.0%	0.0006
Constant continuity correction of 0.1	15	0.51 (0.34 to 0.76)	0.0%	0.0009
Mantel-Haenszel, no continuity correction	15	0.50 (0.34 to 0.75)	0.0%	0.0006
Trials with a zero cell excluded	13	0.52 (0.35 to 0.77)	0.0%	0.001
Peto odds ratio, fixed effect	15	0.44 (0.30 to 0.65)	0.0%	<0.0001

The first row is the primary specification reported throughout the manuscript. Every subsequent row is an unadjusted DerSimonian-Laird interval, so that the rows are comparable with one another. The leave-one-out row summarises eleven separate analyses of fourteen trials each

Publication bias

With fifteen trials contributing, the pre-specified threshold of ten was met and formal testing for small-study effects was undertaken. Egger regression gave $t=0.64$ on 13 degrees of freedom ($p=0.53$) and the Peters test gave $p=0.09$, neither indicating funnel asymmetry at conventional significance. The

trim-and-fill procedure imputed one missing trial, moving the adjusted estimate marginally to 0.48 (0.33 to 0.71), which does not alter the conclusion. The funnel plot was broadly symmetrical about the pooled estimate, as illustrated in Figure 5. These results do not exclude publication bias, since fifteen trials give limited power to detect asymmetry, but they provide no strong evidence of it.

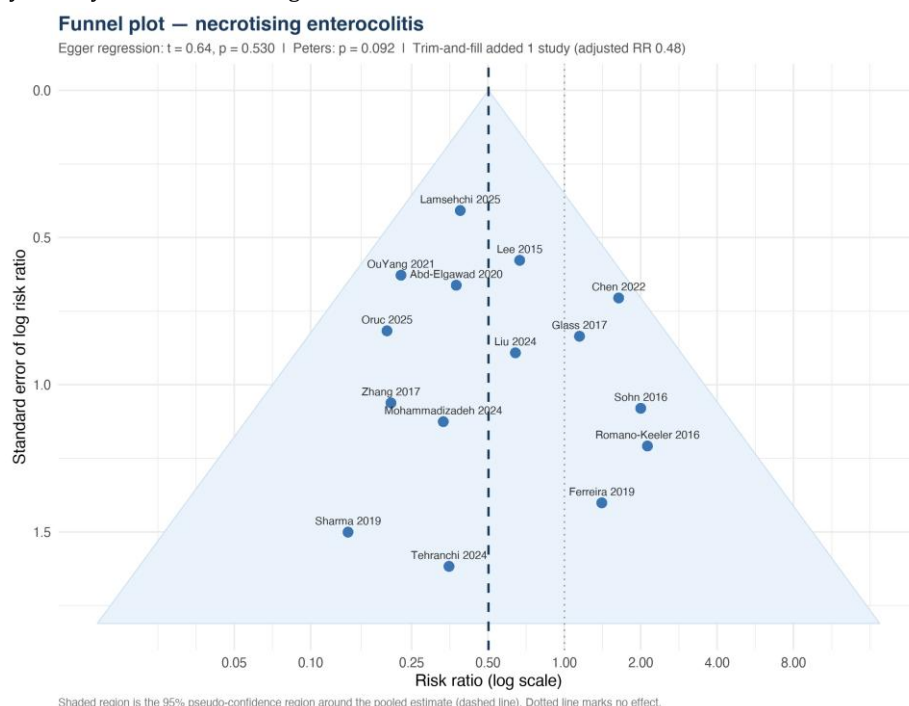


Figure 5. Funnel plot of trial-level risk ratios for necrotising enterocolitis against the standard error of the log risk ratio. The shaded region is the 95% pseudo-confidence region about the pooled estimate.

Secondary outcomes

Seventeen trials enrolling 1,599 infants reported late-onset sepsis by the definition used in each trial. Sepsis occurred in 130 of 790 infants receiving colostrum and 213 of 809 controls, giving a risk ratio of 0.67 (0.57 to 0.79; $Z=-4.91$; $p<0.001$) with no heterogeneity ($I^2=0.0\%$; $Q=11.96$, $df=16$, $p=0.75$). Restricting the analysis to the three trials that reported blood-culture-confirmed sepsis separately gave a risk ratio of 0.52 (0.27 to 1.00; $p=0.049$) across 578 infants. That last estimate rests on three trials and 39 events, with an upper confidence limit lying on unity, and should be treated as hypothesis-generating rather than as a finding.

Eleven trials reported all-cause mortality; two recorded no deaths in either arm and therefore contributed no information to a ratio measure, leaving nine informative trials enrolling 909 infants. Among those nine, death occurred in 41 of 445

infants receiving colostrum and 69 of 464 controls, a risk ratio of 0.62 (0.43 to 0.89; $p=0.010$; $I^2=0.0\%$). Ventilator-associated pneumonia was reported by four trials enrolling 406 infants and was also reduced (13/204 versus 27/202; risk ratio 0.48, 0.27 to 0.87; $p=0.016$; $I^2=0.0\%$). Nine trials enrolling 984 infants reported time to full enteral feeding, which was shorter with colostrum by a mean difference of 2.50 days (95% confidence interval 0.61 to 4.39 days shorter; $p=0.010$), although heterogeneity was substantial ($I^2=88.1\%$). Nine trials enrolling 942 infants reported length of hospital stay, which was shorter by 6.30 days (1.98 to 10.62 days shorter; $p=0.004$), again with substantial heterogeneity ($I^2=86.3\%$). Bronchopulmonary dysplasia was reported with extractable counts by only three trials and did not differ significantly (risk ratio 0.65, 0.28 to 1.50; $p=0.31$; $I^2=66.4\%$); that estimate is reported for completeness in Table 6 but should not be used to guide practice.

Table 6. Secondary outcomes.

Outcome	Measure	k	Colostrum	Control	Estimate (95% CI)	I^2	p
Late-onset sepsis (trial definition)	RR	17	130/790	213/809	0.67 (0.57 to 0.79)	0.0%	<0.001
Culture-positive sepsis (hypothesis-generating; 3 trials, 39 events)	RR	3	13/290	26/288	0.52 (0.27 to 1.00)	0.0%	0.049
All-cause mortality (informative trials only)	RR	9	41/445	69/464	0.62 (0.43 to 0.89)	0.0%	0.010
Ventilator-associated pneumonia	RR	4	13/204	27/202	0.48 (0.27 to 0.87)	0.0%	0.016
Bronchopulmonary dysplasia (3 trials only)	RR	3	25/130	37/132	0.65 (0.28 to 1.50)	66.4%	0.31
Time to full enteral feeding (days)	MD	9	n=494	n=490	-2.50 (-4.39 to -0.61)	88.1%	0.010
Length of hospital stay (days)	MD	9	n=472	n=470	-6.30 (-10.62 to -1.98)	86.3%	0.004

RR, risk ratio; MD, mean difference. For mortality, eleven trials enrolling 589 and 602 infants reported the outcome, but two recorded no deaths in either arm and contribute no information to a ratio measure; the row reports the nine informative trials and their denominators. Negative mean differences favour oropharyngeal colostrum. The culture-positive sepsis and bronchopulmonary dysplasia rows rest on three trials each and are not a basis for practice.

4. Discussion

Principal findings

Across fifteen randomised controlled trials enrolling 1,541 preterm infants, oropharyngeal or oral administration of the mother's own colostrum approximately halved the incidence of necrotising enterocolitis at Bell stage 2 or above, from 9.67% to 4.58%, with a pooled risk ratio of 0.50 (0.33 to 0.76). The finding was accompanied by complete statistical homogeneity, which is unusual in neonatal meta-analysis. The strength of that observation rests on the Q statistic, which at 12.75 on 14 degrees of freedom fell below its expectation under homogeneity. It does not rest on the I^2 point estimate, whose 95% confidence interval extended to 53.6%; that wide interval indicates that between-study variance was estimated imprecisely, and is a constraint on how confidently homogeneity can be asserted rather than support for it. It is also why the Hartung-Knapp interval, which is robust to poor estimation of the between-study variance, was adopted as the primary specification. Fifteen trials conducted on four continents, in units with different feeding protocols, different baseline disease rates and different colostrum regimens, produced estimates that were statistically indistinguishable from one another. The absolute risk reduction of 5.09 percentage points implies that 21 infants must receive the intervention to prevent one case, a figure that compares favourably with most preventive strategies in neonatal care given that the intervention costs almost nothing and requires no equipment.

The stability of the estimate was the second notable feature. No single trial drove the result: omitting each in turn moved the risk ratio by at most 0.050 and never abolished significance. Removing every trial at overall high risk of bias left the estimate slightly stronger at 0.45. Neither formal test for small-study effects reached significance, and trim-and-fill imputed a single trial, moving the estimate to 0.48. A finding small-study effects was significant and trim-and-fill imputed no missing trials. A finding that survives this range of challenges is unlikely to be an artefact of any single methodological choice.

Comparison with previous syntheses

Published meta-analyses of this intervention have disagreed. Earlier syntheses reported risk ratios for necrotising enterocolitis whose confidence intervals included unity, and concluded that the evidence was insufficient.³⁹ Later work incorporating additional trials found a significant reduction, and a subsequent synthesis focused on sepsis reached a similar conclusion for infection-related endpoints.^{38,40,41} The present analysis resolves that inconsistency in a specific way. The earlier null results were not produced by trials that contradicted the later ones; they were produced by pooling fewer trials and fewer events. The fifteen trials analysed here contributed 109 events, more than double the number available to the earliest syntheses, and the point estimate has remained in a narrow band while the confidence interval has narrowed until it excluded unity. The 2020 synthesis of nine trials reported 0.59 (0.33 to 1.06), the 2022 synthesis reported a significant reduction on a larger set, and the present fifteen-trial analysis gives 0.50 (0.33 to 0.76).^{38,39} The point estimate did not move materially as trials accumulated; the interval contracted around it. That pattern is more consistent with an underlying effect estimated with increasing precision than with a result generated by the addition of new data.

A second difference concerns the sepsis endpoint. Previous syntheses have generally pooled clinically suspected and culture-confirmed sepsis together, which mixes a physician's judgement with a microbiological result. Separating them here showed a significant reduction on the composite definition (risk ratio 0.67, 0.57 to 0.79) and a borderline reduction on the culture-confirmed definition alone (0.52, 0.27 to 1.00, $p=0.049$) across only three trials. The direction of effect was consistent, but the culture-confirmed estimate rests on 39 events in total and should be regarded as hypothesis-generating. This distinction plausibly explains part of the disagreement between earlier reviews, since a composite that includes clinically suspected sepsis is vulnerable to ascertainment bias precisely in the unblinded trials that also carry the highest risk of bias overall.

The finding for ventilator-associated pneumonia now agrees with an earlier synthesis that reported a significant reduction.⁵⁴ Four trials contributed extractable counts, giving 40 events, and the pooled risk ratio of 0.48 (0.27 to 0.87) is consistent with the mucosal mechanism proposed below. The estimate nonetheless rests on few events and, given that ventilator-associated pneumonia carries measurable attributable cost and mortality in neonatal units, the outcome deserves systematic reporting in future trials.^{55–58}

Biological plausibility

A halving of necrotising enterocolitis risk from a few millilitres of colostrum distributed over several days requires a plausible mechanism, and one is available. The oropharyngeal mucosa is densely populated with lymphoid tissue that in utero is bathed continuously in immunologically active amniotic fluid; gastric tube feeding bypasses this surface entirely at the moment it is most responsive.²⁵ Direct application of colostrum restores the exposure. Randomised trials of the intervention have demonstrated the expected proximal biological effects: salivary and urinary secretory immunoglobulin A and lactoferrin rise, pro-inflammatory cytokines fall, and the oral microbiome shifts.^{27–31} Secretory immunoglobulin A resists enzymatic degradation, is absorbed across the mucosa and appears in urine, so a locally applied dose can plausibly exert systemic effects.²⁶ Trials of enteral bovine lactoferrin have independently confirmed that supplying such constituents produces measurable immunological and clinical change.^{32,33}

The link from mucosal immunity to necrotising enterocolitis runs through microbial colonisation. Infants who develop the disease follow a distinct trajectory of gut microbial assembly, with delayed acquisition of commensal anaerobes and expansion of Gammaproteobacteria, and this trajectory is detectable well before clinical presentation.^{13,14,18} Specific human milk oligosaccharides shape that trajectory and predict disease risk, and interventions that alter colonisation alter incidence.^{15,19,20} It has been proposed that swallowed saliva carrying colostrum constituents reaches the upper gastrointestinal tract even when no enteral feed is given, so that oropharyngeal administration acts on both the mucosal immune compartment and the colonising community; no trial included in this review measured that transit directly, and the pathway remains a hypothesis rather than a demonstrated mechanism. The mechanism is therefore continuous with the established protective effect of enteral mother's own milk rather than separate from it.^{21–23}

Interpretation of heterogeneity

The heterogeneity pattern was as informative as the effect estimate. For necrotising enterocolitis, late-onset sepsis, culture-positive sepsis, mortality and ventilator-associated

pneumonia, I^2 was 0.0%. For the two continuous outcomes it exceeded 87%. This split is coherent rather than paradoxical. Necrotising enterocolitis at Bell stage 2 or above is anchored to a published staging system with radiological criteria, so it means much the same thing across every unit that applied it. Time to full enteral feeding and length of hospital stay are not anchored to anything comparable: the threshold defining full feeds varied between 100 and 160 mL/kg/day across these trials, feed advancement protocols differ between units, and discharge is governed by local criteria, family circumstances and health-system structure as much as by physiology.⁵⁹⁻⁶³ The mean hospital stay in the control arms of these trials ranged from 26 to 60 days, so a pooled difference of 6.30 days is being averaged across settings that are not commensurable. This explanation was tested as far as the data allowed: only two of the nine trials contributing to the feeding analysis stated an explicit threshold in mL/kg/day, at 140 and 160 respectively, which is too few to support meta-regression on that variable.^{27,34} The explanation therefore remains a conjecture that the available reporting cannot confirm, and it is a further argument for a standardised outcome definition in future trials. The direction of effect for both continuous outcomes was consistent, and both remained significant, but the magnitudes should be read as indicative rather than as quantities to be planned around.

The one stratum that showed appreciable heterogeneity for the primary outcome was group D, the highest-dose and longest-duration regimen ($I^2=54.6\%$). That stratum contained the trial with the largest single effect and two trials whose primary endpoints were immunological or microbiological rather than clinical, so necrotising enterocolitis was captured as a safety observation rather than as a powered outcome. Differential ascertainment is the most economical explanation.^{29,34,44}

Strengths

The review has three particular strengths. First, no value anywhere in the analysis was imputed, estimated from a figure, or converted from a median, so every pooled estimate rests on values as the trialists reported them; this is why the analyses carry differing denominators. Second, the primary outcome was anchored to a single staging system, which is what allows fifteen trials from nine countries to be combined without heterogeneity. Third, the robustness of the estimate was tested against leave-one-out omission, exclusion of every trial at high risk of bias, five treatments of the sparse-data cells, two estimators of the between-study variance, and two tests for small-study effects, and it survived all of them.

Limitations

Several limitations qualify these findings. First, and most important, blinding was inadequate in a substantial minority of trials. Eight of the nineteen used no oropharyngeal placebo at all, so bedside caregivers necessarily knew the allocation, and necrotising enterocolitis is adjudicated by clinicians who also make feeding decisions. This is the single largest threat to validity. It is mitigated by the observation that excluding every trial at overall high risk of bias left the estimate slightly stronger at 0.45, but it is not eliminated.

Second, the evidence base is small in absolute terms. A hundred and nine events across fifteen trials is modest for an outcome of this importance, several trials contributed fewer than five events, and two contributed none in the colostrum arm and therefore required a continuity correction. Confidence intervals for the subgroup and secondary analyses are correspondingly wide, and the analyses of

bronchopulmonary dysplasia and culture-positive sepsis rest on three trials each and that of ventilator-associated pneumonia on four. Third, the subgroup analysis was underpowered by construction: with one to seven trials per stratum, the test for subgroup differences had little ability to detect a genuine interaction, and its null result should not be read as establishing that regimen does not matter. Fourth, no trial reported outcomes beyond hospital discharge. Given that the consequences of necrotising enterocolitis extend into childhood, the absence of neurodevelopmental follow-up is a substantive gap.^{8,64} Fifth, the sepsis analysis pooled definitions that ranged from clinical suspicion to blood culture confirmation, and the trials were conducted in units with differing baseline infection rates and antimicrobial practice.⁶⁵⁻⁶⁷ Finally, the search was restricted to English-language full-text reports, which may have excluded trials published in Chinese or Persian, the two languages most represented among the included trials' host countries.

Implications for practice and research

For clinical practice, the reasoning that follows should be stated explicitly rather than asserted. Three quantities govern the decision. The expected benefit is a number needed to treat of 21 (15 to 43) at the control-arm risk observed here, for a condition with substantial case fatality and lasting neurodevelopmental consequences among survivors. The expected harm is, on present evidence, zero: no adverse event attributable to the intervention was reported in any of the nineteen trials, including in ventilated infants below 1,000 g. The cost is close to zero, since the intervention uses a substance already being expressed for the infant, requires nothing beyond a syringe and takes under two minutes. Where expected benefit is appreciable, identified harm is absent and cost is negligible, the evidential threshold for offering an intervention is lower than it would be for one carrying risk or expense. On that reasoning it is reasonable to offer oropharyngeal colostrum to preterm infants who cannot be fed enterally in the first days of life, while recognising that no trial to date has been powered to confirm the effect and that a definitive trial remains necessary.⁶⁻⁸ Units introducing it should recognise that it complements rather than replaces efforts to increase enteral mother's own milk, and that both are most effective when embedded in a structured lactation support programme.^{23,24,68,69}

Adoption is nonetheless conditional on something the trials largely take for granted: that colostrum is available in the first hours after a preterm delivery. Several of the included trials began administration only once colostrum could be obtained, and the interval between birth and first dose ranged from immediately after delivery to 96 hours. Availability in that window is determined by maternal illness, operative delivery, mother-infant separation and, above all, by whether expression is initiated and supported within the first hours. A unit adopting oropharyngeal colostrum without simultaneously strengthening early expression will find the intervention undeliverable for precisely the infants at highest risk, whose mothers are most often unwell or separated. The practical prerequisites are therefore a protocol for initiating expression within six hours of preterm delivery, cold-chain transport of small volumes from the postnatal ward, and a nursing procedure that specifies the dose, the interval and the technique.^{23,24,61}

For research, four priorities follow. The first is an adequately powered multicentre trial with a genuine oropharyngeal placebo and blinded outcome adjudication; on the control-arm risk of 9.67% observed here, and assuming a risk ratio of 0.50, approximately 560 infants per arm would be required to

detect the effect with 90% power at a two-sided alpha of 0.05, before any allowance for attrition; a 10% loss would take the requirement above 620 per arm, which is larger than any trial conducted to date. The second is a factorial or dose-ranging design capable of resolving the protocol question that the present subgroup analysis could only pose. The third is systematic reporting of a standard outcome set, since the analyses of ventilator-associated pneumonia, bronchopulmonary dysplasia and culture-confirmed sepsis were limited by reporting rather than by the number of trials conducted.⁷⁰⁻⁷² The fourth is follow-up to at least 24 months, both because necrotising enterocolitis has lasting neurodevelopmental consequences and because the mechanism proposed here operates through microbial colonisation, whose effects extend well beyond discharge.⁷³⁻⁷⁶

5. Conclusion

In this systematic review and meta-analysis of nineteen randomised controlled trials, fifteen of which enrolling 1,541 preterm infants contributed to the primary quantitative synthesis, oropharyngeal or oral administration of the mother's own colostrum reduced the incidence of necrotising enterocolitis at Bell stage 2 or above by approximately half (risk ratio 0.50, 95% confidence interval 0.33 to 0.76; $p=0.003$). The estimate was statistically homogeneous across trials conducted on four continents, was displaced by no more than 0.050 by the omission of any single trial, persisted when all trials at high risk of bias were excluded and under every alternative handling of the sparse-data cells, and showed no evidence of small-study effects. Approximately 21 infants (15 to 43) would need to receive the intervention to prevent one case at the baseline risk observed here.

Late-onset sepsis (risk ratio 0.67, 0.57 to 0.79), all-cause mortality (0.62, 0.43 to 0.89) and ventilator-associated pneumonia (0.48, 0.27 to 0.87) were also reduced, and time to full enteral feeding and length of hospital stay were shorter by approximately two and a half and six days respectively, although substantial heterogeneity in those two outcomes reflects genuine differences in how full feeding and discharge readiness are defined between units and means the magnitudes should be treated as indicative. Bronchopulmonary dysplasia did not differ significantly, on limited data rather than on evidence of absence of effect. Effect estimates did not differ significantly between administration protocols, and the data provided no support for a dose-response relationship, either between strata ($p=0.41$) or in a meta-regression using dose as a continuous moderator ($p=0.55$); the regimen delivering 0.2 mL every four to six hours for three to seven days produced the largest effect, but on two trials and against a formally negative test for interaction.

Oropharyngeal colostrum is inexpensive, uses a substance already being expressed for the infant, takes a nurse under two minutes to deliver, and caused no adverse events in any of the nineteen trials. Set against a condition that remains a leading cause of death and long-term disability among infants born very preterm, and given an expected benefit that is appreciable, an identified harm that is absent and a cost that is negligible, it is reasonable to offer the intervention as an adjunct to established feeding practice, particularly for infants who cannot be fed enterally in the first days of life. Doing so requires a unit-level commitment to initiating and supporting early maternal expression, without which the intervention cannot reach the infants who stand to gain most. It is not yet sufficient to specify the optimal regimen. An adequately powered multicentre trial with a genuine oropharyngeal placebo, blinded outcome adjudication, a standardised outcome set and follow-up to at least two years of corrected

age is the necessary next step, and should be designed to resolve the dose, frequency and duration question that the present evidence can only raise.

Declarations

Review registration

This systematic review was prospectively registered with PROSPERO (CRD420261369170).

Ethics approval

This study synthesised aggregate data from previously published randomised controlled trials and did not involve individual-level or restricted data; therefore, ethics committee approval and informed consent were not required.

PRISMA guideline statement

This systematic review and meta-analysis was prepared and reported in accordance with the PRISMA 2020 statement.

Data availability

All data supporting the findings are provided in the article and its tables. The extracted dataset, analysis scripts, and complete statistical output are available from the corresponding author on reasonable request.

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Conflict of interest

The authors declare no financial or non-financial conflicts of interest related to this manuscript.

Author contributions

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Use of artificial intelligence

No artificial intelligence (AI) tools were used in the preparation of this manuscript.

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