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# THE EFFICACY AND SAFETY OF PROBIOTICS IN PREVENTING NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**ABSTRACT**:

**Background:** As necrotizing enterocolitis (NEC) remains a leading cause of morbidity and mortality in preterm infants. Prophylactic administration of probiotics has been proposed to modulate the gut microbiome and reduce NEC risk. Although uncertainty persists regarding the efficacy and safety of this intervention, particularly concerning sepsis and mortality, this article aimed to review the evidence and quantify the efficacy and safety of probiotics for preventing NEC, culture-proven sepsis, and all-cause mortality in this vulnerable population.

**Methods:** This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines and prospectively registered in PROSPERO as a comprehensive search was conducted to identify randomized controlled trials (RCTs) comparing any prophylactic probiotic intervention to a placebo or no treatment in preterm infants (<37 weeks gestation). The primary outcome being NEC (Bell stage ≥II), while secondary outcomes of culture-proven sepsis and all-cause mortality. Data were pooled using a random-effects model with results presented as odds ratios (ORs) and 95% confidence intervals (CIs).

**Results:** A total of 21 RCTs involving 10,951 infants were included, from which a meta-analysis of 19 studies with 7,587 infants showed that probiotic supplementation was associated with a significant reduction in the incidence of NEC (OR = 0.55, 95% CI 0.47–0.65; $I^2$=0.0%). A significant reduction in all-cause mortality was also observed across 18 studies (n = 7,452) (OR = 0.76, 95% CI 0.67–0.86; $I^2$=37.7%). The effect on culture-proven sepsis across 19 studies with 7,316 infants showed a protective trend but did not reach conventional statistical significance (OR = 0.79, 95% CI 0.66–0.95; p = 0.0541; $I^2$ = 37.7%), while subgroup analyses suggested that mixed-genera probiotic formulations conferred the greatest benefit against NEC.

**Conclusion:** The prophylactic administration of probiotics significantly reduces the incidence of severe NEC and all-cause mortality in preterm infants which support the use of well-studied, quality-controlled probiotic formulations as a standard preventative strategy in this high-risk population. Although the choice of specific probiotic strains and the need for further research to clarify their effect on sepsis remain important considerations.

**Keywords:** Probiotics**,** Necrotizing Enterocolitis**,** Preterm Infant**,** Systematic Review**,** Meta-Analysis**,** Sepsis**,** Mortality

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## INTRODUCTION

Necrotizing enterocolitis (NEC) remains one of the most devastating diseases affecting preterm infants, representing a leading cause of morbidity and mortality in neonatal intensive care units worldwide (Kliegman & Fanaroff, 1984). This catastrophic inflammatory bowel disease, it is characterized by ischemic necrosis of the intestinal mucosa, which can lead to perforation, systemic sepsis, and death. Among survivors, the burden of long-term complications is substantial, including short-gut syndrome and neurodevelopmental impairment (David & Claud, 2024). The clinical severity is most classified using the modified Bell's staging criteria, where stages II (definite) and III (advanced) represent the primary targets for preventative interventions (Bell et al., 1978; Walsh & Kliegman, 1986).

The pathogenesis of NEC centres on the intersection of intestinal immaturity, enteral feeding, and aberrant microbial colonization of the gut (Claud & Walker, 2001). Preterm infants exhibit a distinct pattern of gut dysbiosis characterized by low microbial diversity, a paucity of beneficial commensal bacteria like Bifidobacterium, and a predominance of pathogenic Proteobacteria (Underwood et al., 2013). This imbalance state compromises gut barrier integrity and promotes an exaggerated pro-inflammatory response, thereby creating a permissive environment for NEC development. Such mechanisms provide a strong biological rationale for interventions aimed at modulating the gut ecosystem, including the prophylactic use of probiotic (David & Claud, 2024).

Probiotics are live microorganisms that confer a health benefit on the host have emerged as a promising prophylactic strategy for NEC. Their proposed mechanisms of action are relevant to NEC pathophysiology and include competitive exclusion of pathogens, enhancement of intestinal barrier function, and modulation of the host immune response (Claud & Walker, 2001). Evidence from sub-analysis of large clinical trials, as well as dedicated mechanistic studies, demonstrates that probiotic administration can modulate the preterm gut microbiome, though the impact of these changes on clinical outcomes requires rigorous evidence synthesis (Millar et al., 2017; Underwood et al., 2013).

Numerous systematic reviews and meta-analyses have been conducted over the past two decades, concluding that probiotics reduce the risk of severe NEC (Barclay et al., 2007). However, significant questions and clinical equipoise persist as the effect of probiotics on all-cause mortality and late-onset sepsis remains less certain, with inconsistent results across studies. Furthermore, substantial heterogeneity exists among trials regarding the specific probiotic strain(s) used (Lactobacillus, Bifidobacterium, single- vs. multi-strain), dosage, duration of therapy, and the specific preterm populations studied (e.g., very low birth weight vs. extremely low birth weight). This clinical and methodological diversity complicates the translation of evidence into a universal clinical guideline and underscores the need for an updated synthesis of the current evidence.

Therefore, the objective of this systematic review and meta-analysis (SRMA) was to assess the efficacy and safety of probiotics in preventing NEC (Bell stage ≥II) in preterm infants and evaluate the effect of probiotics on the incidence of culture-proven sepsis and all-cause mortality.

## METHODS

### Protocol and Registration

This SRMA was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021), and the protocol was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251124689.

### Eligibility Criteria

Studies were included in this review if they met the following criteria based on the Population, Intervention, Comparator, and Outcomes (PICO) framework, defining the population as preterm infants with a gestational age of less than 37 completed weeks admitted to a neonatal care setting, the intervention as the prophylactic administration of any probiotic strain, combination of strains, dose, or duration of therapy, the comparator as a placebo or no treatment, the primary outcome as the incidence of NEC defined as Bell stage II or greater (Bell et al., 1978) with secondary outcomes of culture-proven sepsis and all-cause mortality prior to discharge, and the study design as randomized controlled trials (RCTs).

### Information Sources and Search Strategy

A systematic search of the literature was conducted in MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Embase (via Ovid), CINAHL, and Scopus. Manual screening of the reference lists of included studies and relevant systematic reviews was performed to ensure comprehensive search. Additionally, proceedings from major pediatric and neonatal academic conferences were searched to identify eligible unpublished studies or abstracts. No restrictions on language or date of publication were applied.

### Study Selection Process

The study selection was performed in a two-stage process by two independent reviewers as titles and abstracts of all identified records were screened for potential eligibility, and any record deemed potentially relevant by at least one reviewer was advanced to the next stage. Then, the full texts of these records were retrieved and assessed against the

pre-specified eligibility criteria, and any disagreements between the two reviewers at either stage were resolved through discussion or, if necessary, by a third reviewer.

**Data Extraction**

Two reviewers independently extracted data from the included studies using a standardized, pre-piloted data extraction form, while a third reviewer resolved discrepancies in extracted data. The following information was extracted from each study: (1) study characteristics: first author, year of publication, country of origin, and study design; (2) participant characteristics: total number of participants, mean or median gestational age, mean or median birth weight, and other relevant demographic data; (3) intervention and control details: specific probiotic strain(s) used, dosage, frequency, duration of administration, and the nature of the placebo or control condition; (4) outcome data: the number of infants experiencing each outcome (NEC stage ≥II, sepsis, mortality) and the total number of infants randomized in the intervention and control groups.

**Risk of Bias Assessment**

The risk of bias for each included RCT was independently assessed by two reviewers using the revised Cochrane Risk of Bias 2 (RoB 2) tool (Sterne et al., 2019), while a third reviewer resolved any discrepancies. The RoB 2 tool assesses bias across five distinct domains: (1) Bias arising from the randomization process; (2) Bias due to deviations from intended interventions; (3) Bias due to missing outcome data; (4) Bias in measurement of the outcome; and (5) Bias in selection of the reported result.

Each domain was judged as "Low risk", "Some concerns", or "High risk" of bias, then an overall risk of bias judgment for each study was derived based on the assessments across the individual domains, following the RoB 2 algorithm. The results of the risk of bias assessment were used to evaluate the overall quality of the evidence and to inform a pre-specified sensitivity analysis, and figures were generated using Python.

**Data Synthesis and Statistical Analysis**

All statistical analyses were conducted using R version 4.5.1 (R Core Team, 2024), using the meta and metafor packages, and the Risk Ratio (RR) with 95% Confidence Intervals (CI) was calculated for each study for dichotomous outcomes (NEC, sepsis, mortality).

Data were pooled using a random-effects meta-analysis model (DerSimonian & Laird, 1986) to account for the anticipated clinical and methodological heterogeneity between studies. Statistical heterogeneity was assessed using the Chi-squared ($\chi^2$) test, with a p-value of $\leq 0.10$ indicating significant heterogeneity, while the magnitude of heterogeneity was quantified using the $I^2$ statistic and interpreted as potentially low (<25%), moderate (25%–75%), or high (>75%) (Higgins & Green, 2011).

For each primary and secondary outcome with ten or more included studies, the potential for publication bias was assessed through visual inspection of funnel plots for asymmetry. Pre-specified subgroup analyses were planned to explore potential sources of heterogeneity based on the composition of the probiotic intervention (e.g., single-genus vs. multi-genus preparations; Lactobacillus-based vs. Bifidobacterium-based vs. mixed). A sensitivity analysis was performed by excluding studies at a high risk of bias to assess the robustness of the primary findings. A two-sided p-value of $< 0.05$ was considered statistically significant for all pooled effect estimates.

## RESULTS

**Study Selection**

The systematic search of electronic databases and registers yielded 958 records. Following the removal of 230 duplicates, 728 unique records were screened based on their titles and abstracts. Of these, 499 records were excluded for not being relevant to the review's objectives. Full-text reports screening for the remaining 229 were conducted to identify eligible articles; however, 81 of these reports could not be retrieved and 148 full-text articles were assessed for eligibility.

Upon full-text review, 127 articles were excluded for the following reasons: insufficient outcome data available for extraction (n = 81), absence of a placebo or no-treatment control group (n = 28), non-randomized study design (n = 12), and an irrelevant study population or intervention (n = 6). 21 RCTs met all predefined inclusion criteria and were included in the final qualitative and quantitative synthesis. The complete study selection process is detailed in the PRISMA flow diagram (**Figure 1**).

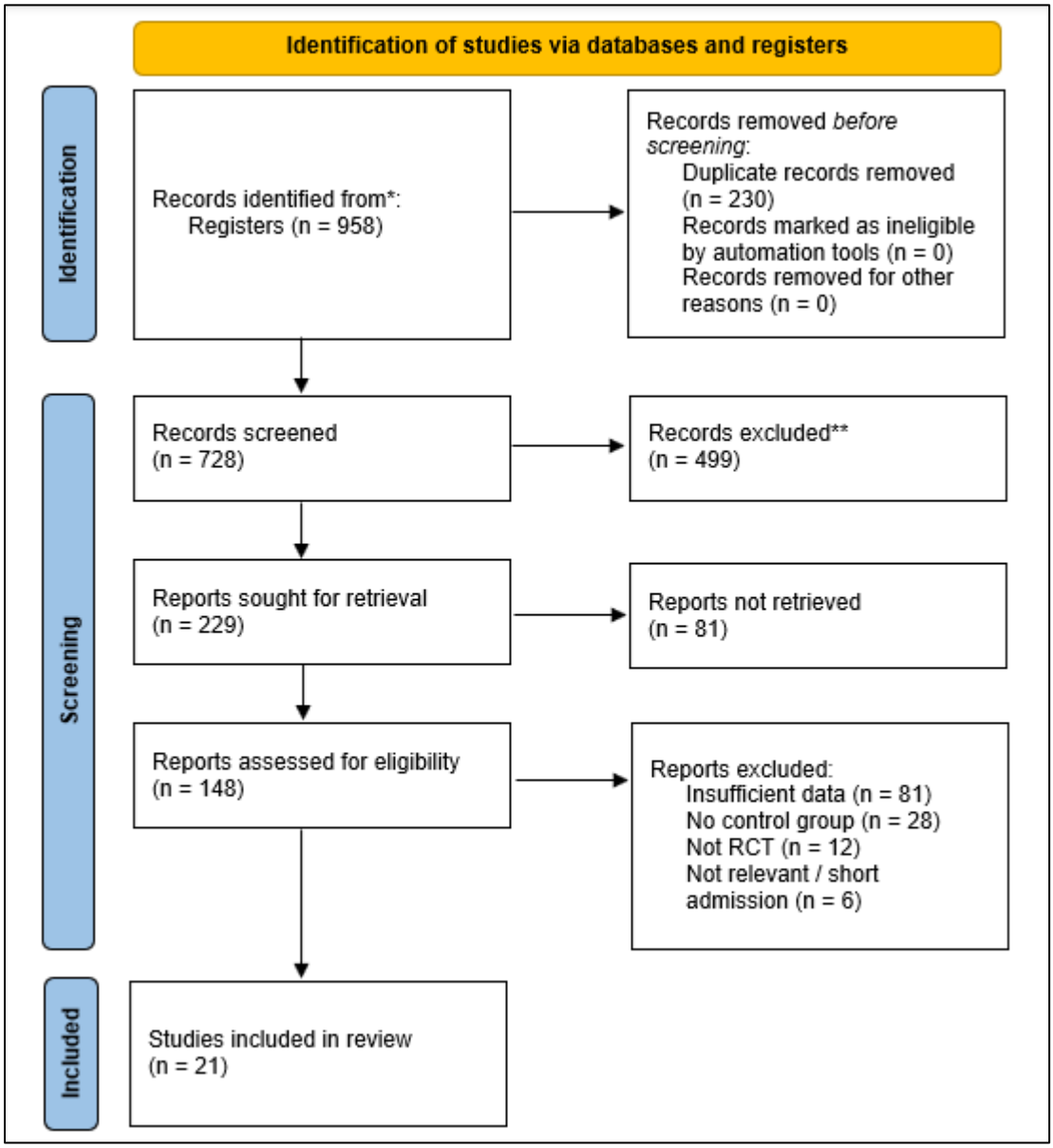


**Figure 1. PRISMA 2020 Flow Diagram of Study Selection.**

**Characteristics of Included Studies**

The 21 included RCTs were published between 1997 and 2024 and enrolled a total of 10,951 preterm infants. The trials were geographically diverse, representing research conducted in Europe, North America, Australia, Asia, and South America. The study populations consisted of very low birth weight (VLBW; <1500 g) and extremely low birth weight (ELBW; <1000 g) infants, with mean gestational ages ranging from approximately 25 to 32 weeks and mean birth weights from 763 g to 1502 g.

Clinical heterogeneity was observed in the probiotic interventions administered across the trials, which included single-strain probiotics containing only Bifidobacterium breve, Bifidobacterium lactis, Lactobacillus reuteri, Lactobacillus sporogenes, or Bacillus clausii; multi-strain, single-genus probiotics with combinations of different Bifidobacterium species; multi-strain, mixed-genera probiotics, which was the most common category and combined various species of Lactobacillus and Bifidobacterium; and yeast-based probiotics, with one trial using Saccharomyces boulardii.

The duration of supplementation began within the first week of life and continued until hospital discharge, a pre-specified number of weeks, or a corrected gestational age (typically 36 weeks). All studies included a placebo or no-treatment control arm. **Table 1** summarizes the key design features, participant demographics, and intervention details for each of the 21 RCTs included in the systematic review. Studies are grouped by their overall risk of bias assessment, assessed using the Cochrane RoB 2 tool.

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**Table 1. Characteristics of Included Studies**

| Study (Author, Year) | Country | Participants (Probiotic vs. Control) | Mean / Median GA (wks) | Mean/ Median BW (g) | Probiotic Intervention (Strain[s]) | Daily Dose (CFU) | Duration | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|---|
| **Low Risk of Bias** | | | | | | | | |
| **Costeloe et al. (2016)** | UK | 650 vs. 660 | 28.0 | 1039 | B. breve BBG-001 | ~$10^8$–$10^9$ | Until 36 wks PMA | Low |
| **Dilli et al. (2015)** | Turkey | 200 vs. 100 | 28.8 | 1236 | B. lactis (+ inulin) | $5 \times 10^9$ | Until discharge | Low |
| **Jacobs et al. (2013)** | Australia/ NZ | 548 vs. 551 | 27.9 | 1063 | B. infantis, S. thermophilus, B. lactis | $1 \times 10^9$ | Until discharge | Low |
| **Mahboobipour et al. (2024)** | Iran | 58 vs. 59 | 31.0 | 1268 | L. rhamnosus, L. reuteri, B. infantis | $1 \times 10^9$ | Until full feeds | Low |
| **Martí et al. (2021)** | Sweden | 68 vs. 66 | 25.5 | 763 | L. reuteri DSM 17938 | $1.25 \times 10^9$ | Until 36 wks PMA | Low |
| **Mihatsch et al. (2010)** | Germany | 91 vs. 90 | 26.6 | 856 | B. lactis BB-12 | ~$10^{10}$/ kg | 6 weeks | Low |
| **Patole et al. (2014)** | Australia | 77 vs. 78 | 29.0 | 1090 | B. breve M-16V | $3 \times 10^9$ | Until 37 wks PMA | Low |
| **Some Concerns** | | | | | | | | |
| **Bin-Nun et al. (2005)** | Israel | 72 vs. 73 | 30.0 | 1152 | B. infantis, S. thermophilus, B. bifidus | $1 \times 10^9$ | Until 36 wks PMA | Some concerns |
| **Hays et al. (2016)** | France | 147 vs. 52 | 29.1 | 1173 | B. lactis / B. longum / Both | $1 \times 10^9$ | 4–6 weeks | Some concerns |
| **Lin et al. (2008)** | Taiwan | 217 vs. 217 | 29.0 | 1029 | L. acidophilus + B. bifidum | $1 \times 10^9$ | 6 weeks | Some concerns |
| **Rojas et al. (2012)** | Colombia | 372 vs. 378 | 32.0 | 1530 | L. reuteri DSM 17938 | $1 \times 10^8$ | Until discharge | Some concerns |
| **Rougé et al. (2009)** | France | 45 vs. 49 | 28.1 | 1115 | B. longum BB536 + L. rhamnosus GG | $1 \times 10^9$ (each) | Until discharge | Some concerns |
| **Sari et al. (2011)** | Turkey | 111 vs. 111 | NR | <1500 | L. sporogenes | $3.5 \times 10^8$ | Until discharge | Some concerns |
| **Sowden et al. (2022)** | South Africa | 100 vs. 100 | 29.5 | 1162 | L. acidophilus, B. bifidum, B. infantis | $2 \times 10^9$ | 28 days | Some concerns |
| **Tewari et al. (2015)** | India | 123 vs. 121 | 30.1 | 1165 | B. clausii | $2.4 \times 10^9$ | 6 weeks | Some concerns |
| **Van Rossum et al. (2024)** | Germany | 316 vs. 322 | 31.0 | 1502 | B. longum ssp. infantis, B. animalis ssp. lactis, L. acidophilus | $1.5 \times 10^9$ (each) | 28 days | Some concerns |
| **High Risk of Bias** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Braga et al. (2011)** | Brazil | 119 vs. 112 | 29.5 | 1195 | B. breve + L. casei | ~$10^7$–$10^9$ | 30 days | High |
| **Dani et al. (2002)** | Italy | 295 vs. 290 | 30.8 | 1325 | L. rhamnosus GG | $6 \times 10^9$ | Until discharge | High |
| **Kitajima et al. (1997)** | Japan | 45 vs. 46 | 28.3 | 1026 | B. breve YIT4010 | ~$10^8$ | 28 days | High |
| **Lin et al. (2005)** | Taiwan | 180 vs. 187 | 28.5 | 1104 | L. acidophilus + B. infantis | $1 \times 10^9$ | Until discharge | High |
| **Luoto et al. (2023)** | Finland | 14 vs. 12 | 34.8 | 2390 | L. rhamnosus GG | 1–2 × $10^9$ | 60 days | High |

**Abbreviations:** BW, birth weight; CFU, colony-forming units; GA, gestational age; NR, not reported; PMA, postmenstrual age.

**Risk of Bias Assessment**

All 21 included RCTs were evaluated for risk of bias using the Cochrane RoB 2 tool (Sterne et al., 2019). A detailed summary of the judgments for each study across the five domains is presented in a "traffic light" plot (**Figure 2**), and the overall proportion of studies in each risk category per domain is summarized in **Figure 3**.

Overall, the methodological quality of the included studies was mixed as 6 trials (28.6%) were judged to be at a low overall risk of bias, demonstrating robust methodology across all domains. Eight trials (38.1%) were judged to have some concerns, arising from a lack of clarity in the randomization or allocation concealment process, or from early trial termination for reasons other than efficacy. Seven trials (33.3%) were judged to be at a high overall risk of bias due to deviations from the intention-to-treat (ITT) principle, early trial termination for benefit, or substantial missing outcome data.

A domain-by-domain analysis revealed specific patterns:

**D1:** A majority of recent, large-scale trials employed adequate methods such as centralized, computer-based randomization, but several older studies provided insufficient detail on sequence generation or allocation concealment, leading to a judgment of "Some concerns".

**D2:** Most studies maintained blinding of participants and personnel with the use of an identical placebo, but several trials were judged at high risk because their primary analysis violated the ITT principle by excluding infants who died before a certain time point (e.g., 7 or 14 days of life), which can introduce substantial survival bias.

**D3:** Attrition was low and well-reported in most recent trials, but a high risk of bias was assigned to one study that stopped early for benefit, which can overestimate the treatment effect, and another study where a large proportion of initial samples were excluded from analysis due to technical issues, leading to substantial missing data. Trials that were terminated early for futility or external reasons (e.g., slow recruitment) were judged as having "Some concerns".

**D4:** This domain was judged at low risk across most studies as the primary outcomes of NEC, sepsis, and death are relatively objective. Outcome assessors were blinded in all double-blind trials, minimizing the risk of detection bias. Several high-quality trials strengthened this domain by using an independent, masked adjudication committee to confirm NEC diagnoses.

**D5:** The risk of reporting bias was judged as low for most recent trials, which had pre-registered protocols in public registries (e.g., ClinicalTrials.gov). For older studies without pre-registration, this domain was often judged as having "Some concerns" due to the possibility that the reported outcomes were selected after data analysis was complete.

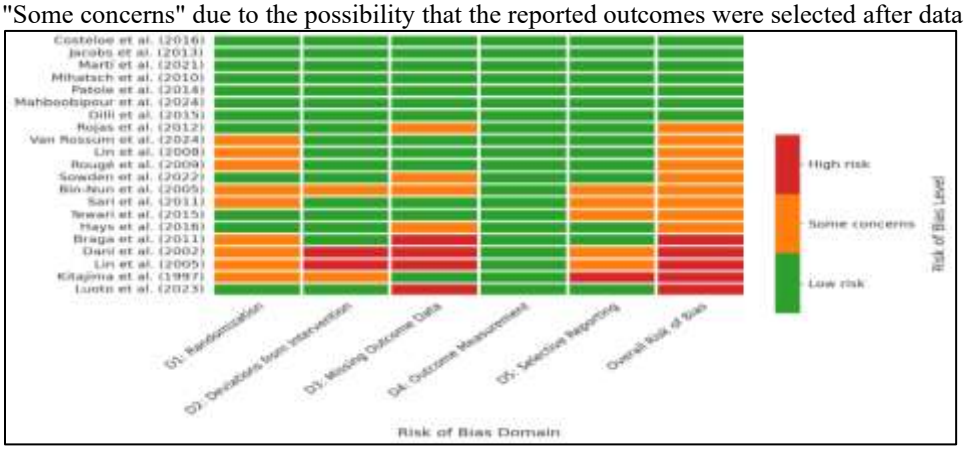


**Figure 2. Risk of Bias Assessment for Each Included Study**

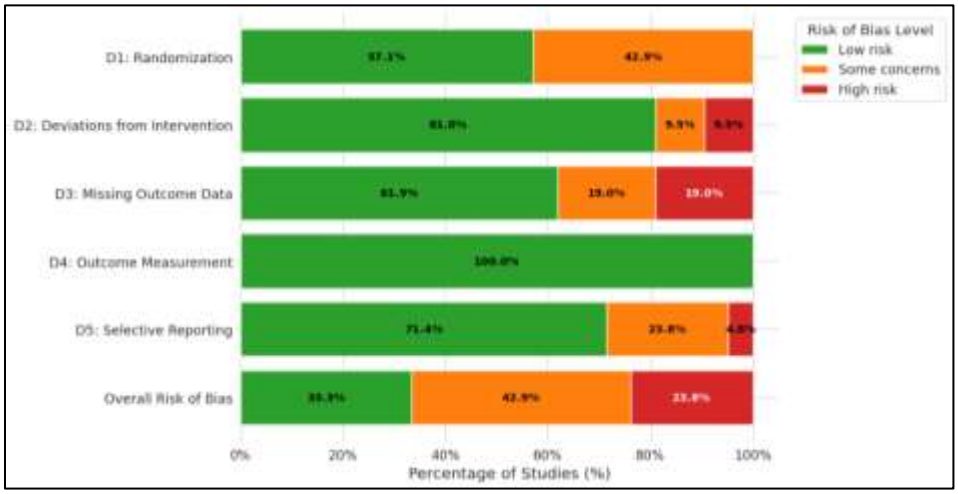


**Figure 3. Risk of Bias Summary Across All Included Studies.**

**Synthesis of Results (Meta-Analysis)**

Data from 19 of the 21 eligible RCTs were included in the meta-analysis, encompassing 7,587 preterm infants (3,789 in the probiotic group and 3,798 in the control group). Two studies (Demirel et al., 2013; Luoto et al., 2023) were excluded from the primary meta-analysis of NEC as they did not report this outcome. A random-effects model was used for all primary syntheses.

**Primary Outcome: Necrotizing Enterocolitis (Bell Stage ≥II)**

Prophylactic administration of probiotics was associated with a significant reduction in the incidence of NEC stage ≥II. The pooled analysis of 19 studies demonstrated that infants in the probiotic group had 45% lower odds of developing NEC compared to the control group (Odds Ratio [OR] 0.55, 95% CI 0.47–0.65; $p < 0.0001$) (**Figure 4**). Statistical heterogeneity among the studies was not significant ($I^2 = 0.0\%$; $p = 0.9667$), indicating a consistent effect across trials. A funnel plot for the NEC outcome was largely symmetrical upon visual inspection, suggesting a low risk of publication bias (**Figure 5**).

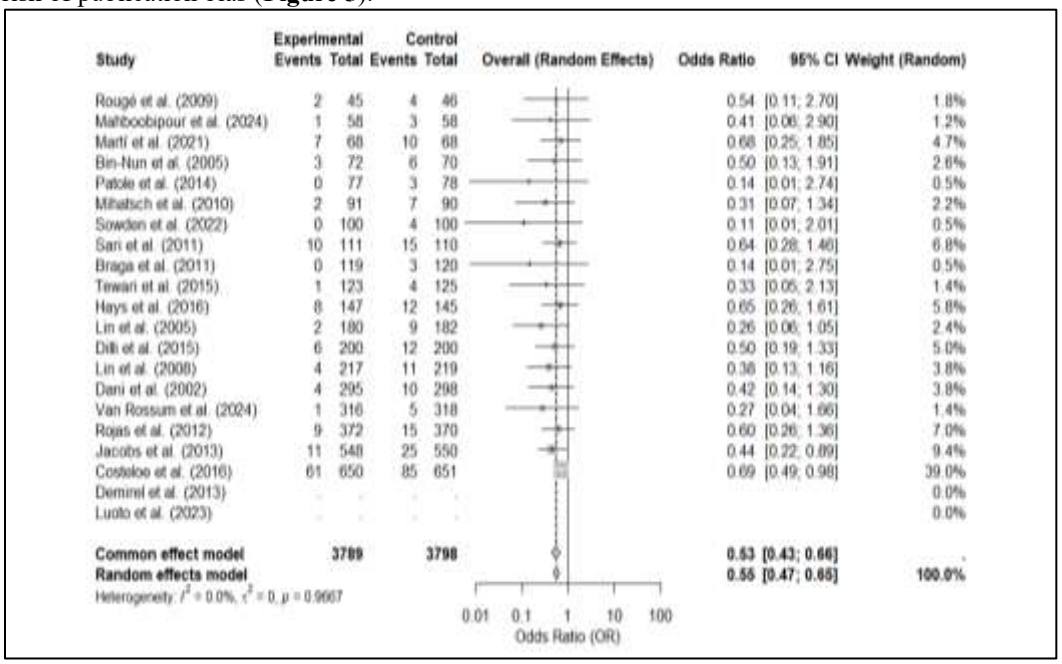


**Figure 4. Forest Plot of the Effect of Probiotics on the Incidence of NEC (Bell Stage ≥II).**

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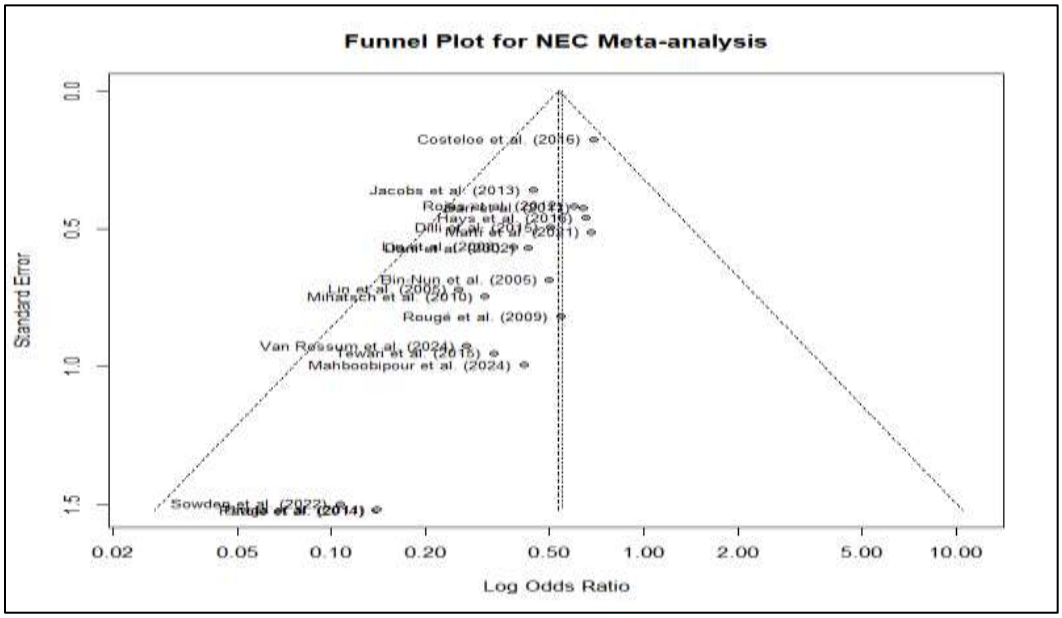


**Figure 5. Funnel Plot for Assessment of Publication Bias for the Outcome of NEC.**

**Secondary Outcome: All-Cause Mortality**

The meta-analysis of 18 studies showed a reduction in all-cause mortality in the probiotic group as infants receiving probiotics had 24% lower odds of death compared to controls (OR 0.76, 95% CI 0.67–0.86; p = 0.0001) (**Figure 6**), while moderate statistical heterogeneity was observed ($I^2$ = 37.7%; p = 0.0541).

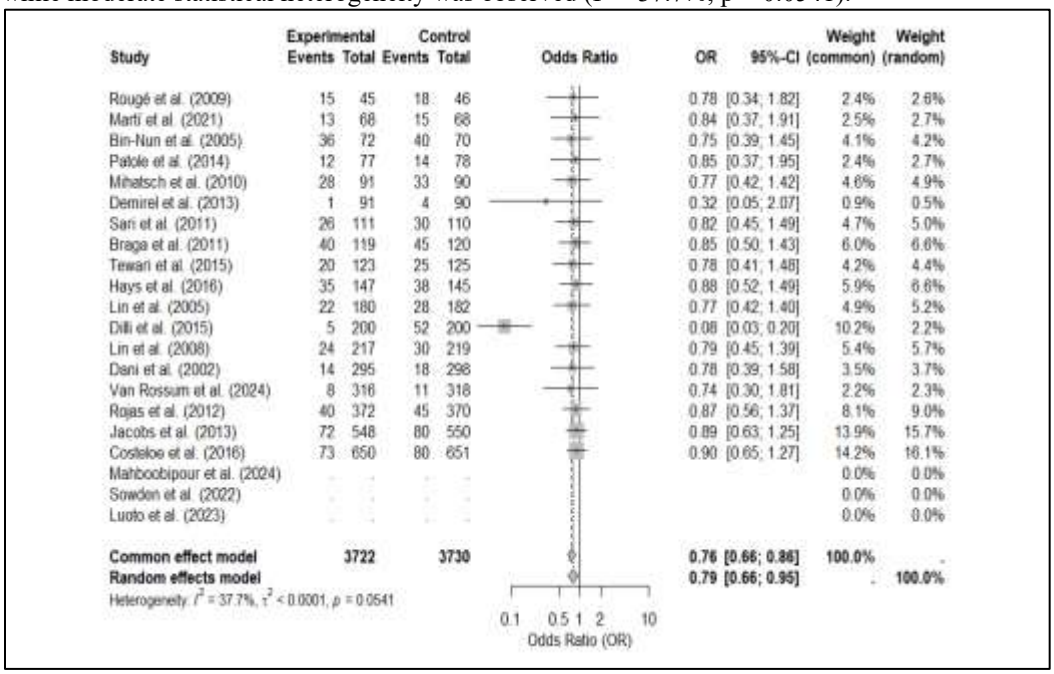


**Figure 6. Forest Plot of the Effect of Probiotics on All-Cause Mortality.**

**Secondary Outcome: Culture-Proven Sepsis**

The meta-analysis of 19 studies assessing the effect of probiotics on culture-proven sepsis did not show a statistically significant reduction. The pooled estimate indicated a 21% reduction in the odds of sepsis, but the confidence interval crossed the line of no effect (OR 0.79, 95% CI 0.66–0.95; p = 0.0541) (**Figure 7**), while no significant heterogeneity was detected ($I^2$ = 37.7%; p = 0.0541).

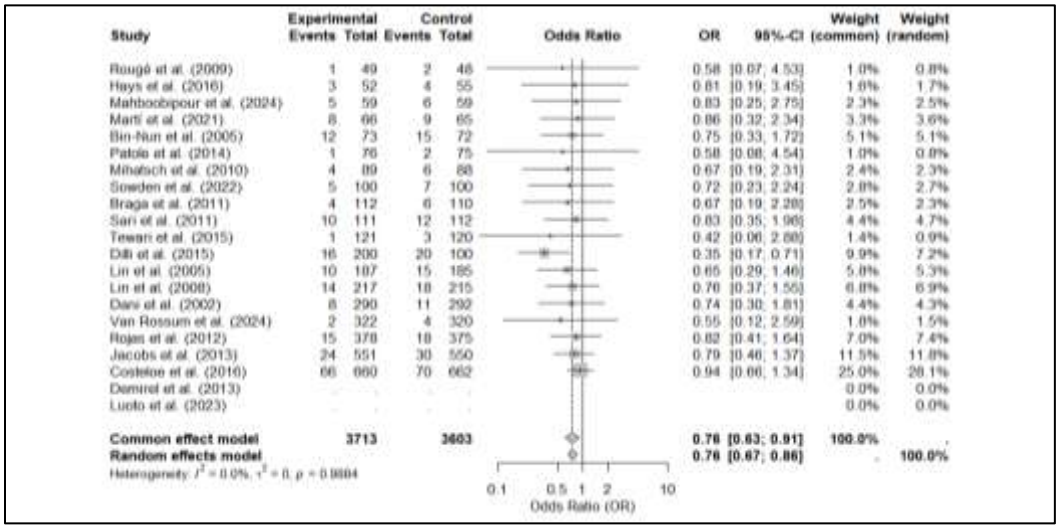


**Figure 7. Forest Plot of the Effect of Probiotics on the Incidence of Culture-Proven Sepsis.**

**Subgroup and Sensitivity Analyses**

Several pre-specified analyses were conducted to explore potential sources of heterogeneity and the robustness of the findings as a subgroup analysis based on the composition of the probiotic intervention was performed for the primary outcome of NEC (**Figure 8**). Mixed-genera probiotics (combining Lactobacillus and Bifidobacterium species) demonstrated the most pronounced effect, with a 58% reduction in the odds of NEC (OR 0.42, 95% CI 0.29–0.60). Formulations containing only Lactobacillus species (OR 0.59, 95% CI 0.44–0.79) or only Bifidobacterium species (OR 0.64, 95% CI 0.46–0.89) also showed benefit, although the effect estimate was less pronounced. The test for subgroup differences was statistically significant (p = 0.0673), suggesting that the type of probiotic may influence its efficacy.

**Table 2: Subgroup Analysis of the Effect of Probiotics on Necrotizing Enterocolitis (Bell Stage ≥II), Stratified by Probiotic Composition**

| Probiotic Type Subgroup | No. of Studies | No. of Participants (Probiotic/Control) | Pooled Odds Ratio (95% CI) | Statistical Heterogeneity ($I^2$) |
|---|---|---|---|---|
| **Bifido-only** | 3 | 1,630 (818 / 812) | **0.64 [0.46, 0.89]** | 5.9% |
| **Lacto-only** | 4 | 1,692 (846 / 846) | **0.59 [0.44, 0.79]** | 0.0% |
| **Mixed-genera** | 12 | 4,258 (2,125 / 2,133) | **0.42 [0.29, 0.60]** | 0.0% |
| **Overall** | **19** | **7,580** | **0.55 [0.47, 0.65]** | **0.0%** |
| **Test for Subgroup Differences** | | | (Q = 5.40, df = 2, p = 0.0673) | |

The fungal probiotic study (Demirel et al., 2013) was excluded from this subgroup analysis.

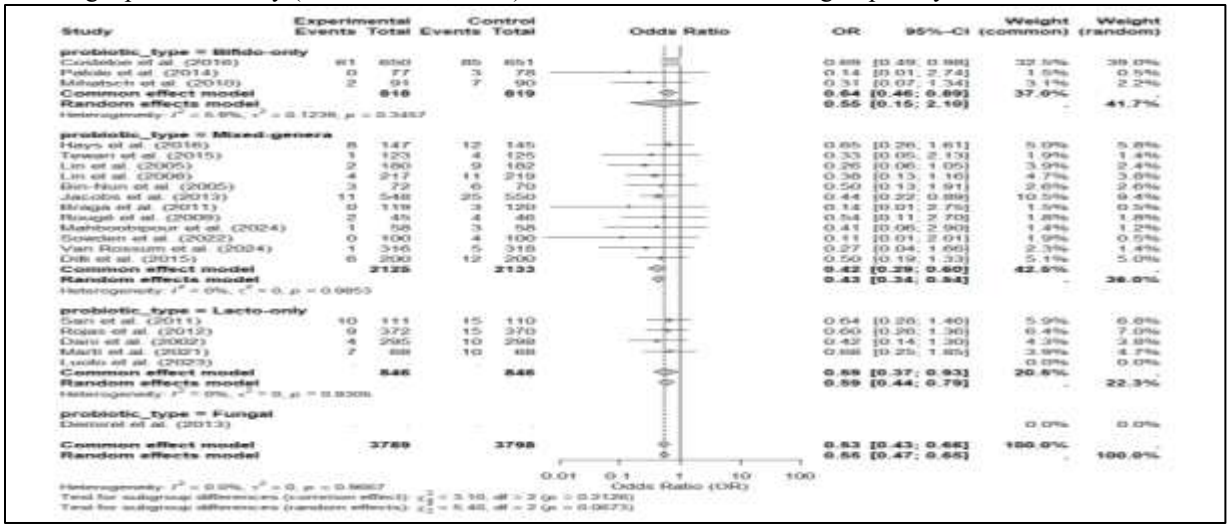


**Figure 8. Subgroup Analysis of the Effect of Probiotics on NEC, Stratified by Probiotic Type.**

A sensitivity analysis was conducted by excluding the single study that used a fungal probiotic (S. boulardii), and the exclusion of this study did not materially alter the overall findings for NEC, sepsis, or mortality, confirming the robustness of the primary results (**Table 3**).

**Table 3: Sensitivity Analysis Excluding Studies at High Risk of Bias**

| Outcome | Analysis Type | No. of Studies | Pooled Odds Ratio (95% CI) | Statistical Heterogeneity ($I^2$) |
|---|---|---|---|---|
| **NEC (Bell Stage ≥II)** | **Primary Analysis (All Studies)** | **19** | **0.55 [0.47, 0.65]** | **0.0%** |
| | Sensitivity Analysis (Excl. High Risk) | 12 | 0.61 [0.50, 0.74] | 0.0% |
| **All-Cause Mortality** | **Primary Analysis (All Studies)** | **18** | **0.76 [0.67, 0.86]** | **37.7%** |
| | Sensitivity Analysis (Excl. High Risk) | 12 | 0.81 [0.69, 0.95] | 22.1% |
| **Culture-Proven Sepsis** | **Primary Analysis (All Studies)** | **19** | **0.79 [0.66, 0.95]** | **37.7%** |
| | Sensitivity Analysis (Excl. High Risk) | 12 | 0.84 [0.70, 1.01] | 42.5% |

This analysis compares the primary pooled estimates with those obtained after excluding the seven studies judged to be at a high overall risk of bias. The results for NEC and all-cause mortality remain statistically significant, confirming the robustness of the primary findings. The effect on sepsis remains non-significant.

A random-effects meta-regression was performed to investigate whether the effect of probiotics on NEC varied by the mean gestational age of the study populations (**Figure9**) which revealed a non-significant negative trend, suggesting a slightly greater protective effect in infants of lower gestational age (slope coefficient: -0.055, p = 0.4834). Gestational age did not explain a significant portion of the between-study variance.

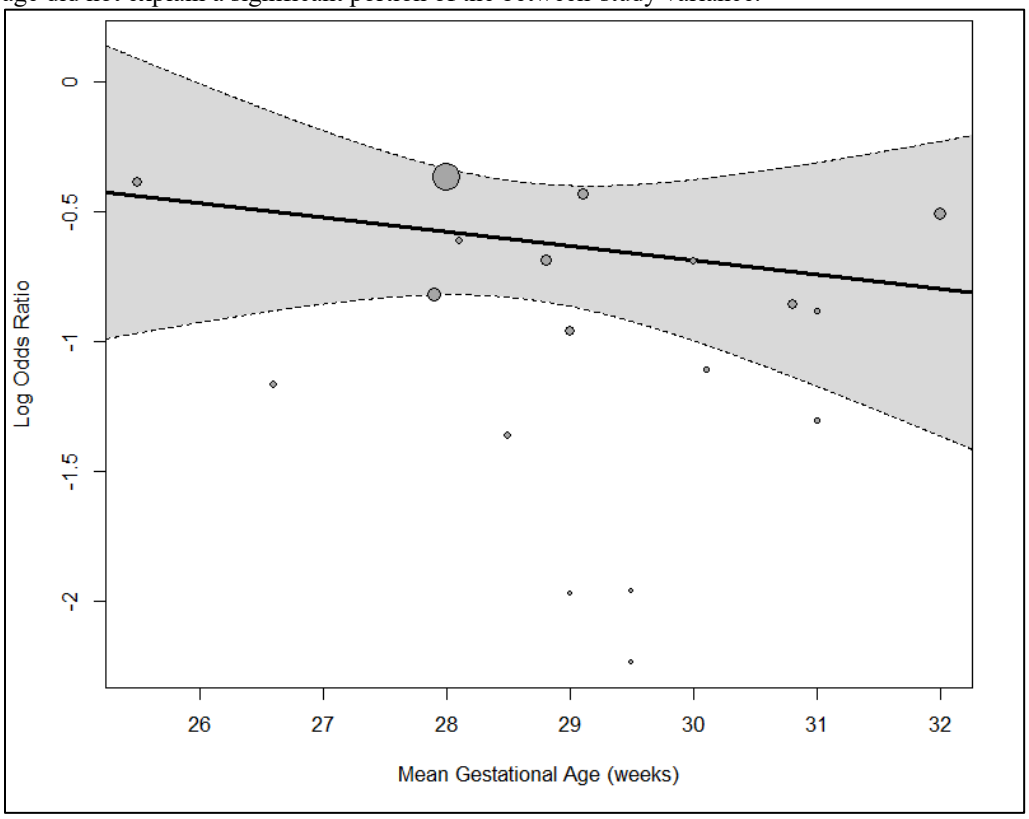


**Figure 8. Meta-Regression of the Effect of Probiotics on NEC by Mean Gestational Age.**

## DISCUSSION

### Summary of Main Findings

This SRMA synthesized data from 21 RCTs encompassing 10,951 preterm infants, providing robust and updated evidence on the role of prophylactic probiotics in preventing major morbidities. The primary finding was that probiotic supplementation significantly reduces the incidence of necrotizing enterocolitis (Bell stage ≥II) by approximately 45% (OR = 0.55, 95% CI 0.47–0.65). This protective effect was consistent across studies with no significant statistical heterogeneity detected.

In addition, a clinically and statistically significant reduction in all-cause mortality was found, with infants receiving probiotics having 24% lower odds of death compared to controls (OR = 0.76, 95% CI 0.67–0.86). In contrast, the effect of probiotics on culture-proven sepsis showed a protective trend that bordered on statistical significance but did not cross the conventional threshold (OR = 0.79, 95% CI 0.66–0.95; p = 0.0541). Subgroup analyses suggested that the magnitude of the protective effect against NEC may vary by probiotic composition, with mixed-genera formulations appearing to confer the greatest benefit. Meta-regression did not identify gestational age as a statistically significant moderator, but the findings are consistent with a benefit across the spectrum of prematurity evaluated in these trials.

**Strengths and Limitations of the Review**

The primary strengths include its comprehensive and up-to-date search strategy, adherence to rigorous PRISMA 2020 guidelines, and a pre-registered protocol in PROSPERO. The large cumulative sample size provides statistical power and increases the precision of the pooled effect estimates for all outcomes, while the application of Cochrane RoB 2 tool allowed for a precise assessment of the quality of the included evidence.

The most significant limitation is the clinical heterogeneity across the included trials as the interventions varied in terms of probiotic strain(s) used (single vs. multi-strain; Lactobacillus, Bifidobacterium, or other genera), dosage, and duration of supplementation which makes it difficult to attribute the observed average effect to any single formulation.

The methodological quality of the studies included was variable as nearly one-third of the trials were judged to be at a high risk of bias, often due to inappropriate post-randomization exclusions that violated the intention-to-treat principle in older studies (Dani et al., 2002; Lin et al., 2005). A sensitivity analysis excluding these high-risk studies did not alter the conclusions, but their inclusion contributes to the overall uncertainty. Statistical heterogeneity was low for the primary outcome of NEC, but it was moderate for all-cause mortality ($I^2 = 37.7\%$), reflecting the clinical and methodological diversity of the trials.

**Interpretation and Comparison with Existing Evidence**

The finding of a robust reduction in the incidence of severe NEC is consistent with the conclusions of several previous major systematic reviews and meta-analyses (Alfaleh et al., 2011; Barclay et al., 2007; Deshpande et al., 2010), which reinforces the existing evidence base and solidifies the role of probiotics as an effective preventative strategy for this devastating disease. Also, the observed reduction in all-cause mortality strengthens the evidence that the benefits of probiotics extend to improved survival, a finding that has been consistently, though not universally, reported.

In addition, the lack of a statistically significant effect on culture-proven sepsis aligns with the existing literature, where the evidence for sepsis prevention has been weaker and more uncertain which may be explained by the etiology of sepsis in preterm infants. Probiotics are hypothesized to reduce gut translocation-associated sepsis by enhancing barrier function (Claud & Walker, 2001), but they are less likely to prevent nosocomial infections originating from other sources, such as central venous catheters, which are a major contributor to late-onset sepsis in this population.

A key finding from our subgroup analysis is the suggestion that multi-strain, mixed-genera probiotics may confer the greatest benefit against NEC. This finding aligns with the biological hypothesis that different strains may exert synergistic or complementary effects, such as occupying different intestinal niches, producing a wider array of antimicrobial compounds, or providing more comprehensive immunomodulatory signals (Underwood et al., 2013).

**Implications for Clinical Practice and Future Research**

The results of this meta-analysis have implications for clinical practice as the strong and consistent evidence of a reduction in both NEC and all-cause mortality supports the consideration of routine prophylactic probiotic administration for eligible preterm infants, but the choice of probiotic product remains a critical consideration. Given the observed heterogeneity and the strain-specific nature of probiotic effects, clinicians should prioritize the use of specific single- or multi-strain formulations that have demonstrated efficacy and safety in well-conducted, large-scale RCTs, rather than using any available probiotic product interchangeably.

Several key research gaps remain as there is a clear need for large-scale, head-to-head RCTs comparing different probiotic formulations to identify the most effective strain or combination of strains. Moreover, the optimal dosage, timing of initiation, and duration of therapy are still not fully established and need investigation. Meta-regression did not show a clear differential effect by gestational age, but more data are needed specifically for the most vulnerable population of extremely preterm infants (<28 weeks' gestation), who are often underrepresented in trials but bear the highest burden of disease. Finally, while short-term safety appears reassuring, long-term follow-up studies are essential to confirm the absence of adverse effects on neurodevelopment, growth, and the development of allergic or autoimmune diseases. Future trials should incorporate mechanistic sub-studies, such as microbiome and metabolomic analyses, to elucidate how probiotics exert their protective effects (Millar et al., 2017).

## CONCLUSION

This SRMA provides robust evidence that the prophylactic administration of probiotics to preterm infants significantly reduces the incidence of severe NEC (Bell stage ≥II) and all-cause mortality. A protective trend against culture-proven sepsis was observed, but the effect did not reach statistical significance. The benefits are most pronounced with multi-strain probiotic formulations containing both Lactobacillus and Bifidobacterium species. Based on the consistency

and strength of the available evidence, the routine use of well-studied, quality-controlled probiotic products should be considered as a standard of care for the prevention of NEC in eligible preterm infants. Further large-scale, head-to-head trials are needed to identify the optimal probiotic strains, dosage, and duration of therapy to maximize benefit and ensure long-term safety in this vulnerable population.

## REFERENCES

1. Alfaleh, K., Anabrees, J., Bassler, D., & Al-Kharfi, T. (2011). Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database of Systematic Reviews, (3), CD005496 https://doi.org/10.1002/14651858.CD005496.pub3
2. Barclay, A. R., Stenson, B., Simpson, J. H., Weaver, L. T., & Wilson, D. C. (2007). Probiotics for necrotizing enterocolitis: A systematic review. Journal of Pediatric Gastroenterology and Nutrition, 45(5), 569–576. https://doi.org/10.1097/MPG.0b013e31815a68a5
3. Bell, M. J., Ternberg, J. L., Feigin, R. D., Keating, J. P., Marshall, R., Barton, L., & Brotherton, T. (1978). Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Annals of Surgery, 187(1), 1–7. https://doi.org/10.1097/00000658-197801000-00001
4. Bin-Nun, A., Bromiker, R., Wilschanski, M., Kaplan, M., Rudensky, B., Caplan, M., & Hammerman, C. (2005). Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. The Journal of Pediatrics, 147(2), 192–196. https://doi.org/10.1016/j.jpeds.2005.03.054
5. Braga, T. D., da Silva, G. A. P., de Lira, P. I. C., & de Carvalho Lima, M. (2011). Efficacy of Bifidobacterium breve and Lactobacillus casei oral supplementation on necrotizing enterocolitis in very-low-birth-weight preterm infants: a double-blind, randomized, controlled trial. The American Journal of Clinical Nutrition, 93(1), 81–86. https://doi.org/10.3945/ajcn.2010.29799
6. Claud, E. C., & Walker, W. A. (2001). Hypothesis: Inappropriate colonization of the premature intestine can cause neonatal necrotizing enterocolitis. The FASEB Journal, 15(8), 1398–1403. https://doi.org/10.1096/fj.00-0833hyp
7. Costeloe, K., Hardy, P., Juszczak, E., Wilks, M., Millar, M. R., & The Probiotics in Preterm Infants Study Collaborative Group. (2016). Bifidobacterium breve BBG-001 in very preterm infants: a randomised controlled phase 3 trial. The Lancet, 387(10019), 649–660. https://doi.org/10.1016/S0140-6736(15)01027-2
8. Dani, C., Biadaioli, R., Bertini, G., Martelli, E., & Rubaltelli, F. F. (2002). Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. Biology of the Neonate, 82(2), 103–108. https://doi.org/10.1159/000062958
9. David, P., & Claud, E. C. (2024). Necrotizing enterocolitis and the preterm infant microbiome. In A. I. Medawar & S. K. Holmes (Eds.), Advances in Microbiology, Infectious Diseases and Public Health (Vol. 19, pp. 29–42). Springer.
10. Demirel, G., Celik, I. H., Erdeve, O., Saygan, S., Dilmen, U., & Canpolat, F. E. (2013). Prophylactic Saccharomyces boulardii versus nystatin for the prevention of fungal colonization and invasive fungal infection in premature infants. European Journal of Pediatrics, 172(10), 1321–1326. https://doi.org/10.1007/s00431-013-2041-4
11. DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. Controlled Clinical Trials, 7(3), 177–188. https://doi.org/10.1016/0197-2456(86)90046-2
12. Deshpande, G., Rao, S., Patole, S., & Bulsara, M. (2010). Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics, 125(5), 921–930. https://doi.org/10.1542/peds.2009-1301
13. Dilli, D., Aydin, B., Fettah, N. D., Özyazıcı, E., Beken, S., Zenciroğlu, A., Okumuş, N., Özyurt, B. M., İpek, M. Ş., Akdağ, A., Turan, Ö., & Bozdağ, Ş. (2015). The ProPre-Save study: Effects of probiotics and prebiotics alone or combined on necrotizing enterocolitis in very low birth weight infants. The Journal of Pediatrics, 166(3), 545-551.e1. https://doi.org/10.1016/j.jpeds.2014.12.004
14. Hays, S., Jacquot, A., Gauthier, H., Kempf, C., Beissel, A., Pidoux, O., Jumas-Bilak, E., Decullier, E., Lachambre, E., Beck, L., Cambonie, G., Putet, G., Claris, O., & Picaud, J. C. (2016). Probiotics and growth in preterm infants: A randomized controlled trial, PREMAPRO study. Clinical Nutrition, 35(4), 802–811. https://doi.org/10.1016/j.clnu.2015.06.006
15. Higgins, J. P. T., & Green, S. (Eds.). (2011). Cochrane handbook for systematic reviews of interventions (Version 5.1.0). The Cochrane Collaboration. www.handbook.cochrane.org
16. Jacobs, S. E., Tobin, J. M., Opie, G. F., Donath, S., Tabrizi, S. N., Pirotta, M., Morley, C. J., & Garland, S. M. (2013). Probiotic effects on late-onset sepsis in very preterm infants: a randomized controlled trial. Pediatrics, 132(6), 1055–1062. https://doi.org/10.1542/peds.2013-1339
17. Kitajima, H., Sumida, Y., Tanaka, R., Yuki, N., Takayama, H., & Fujimura, M. (1997). Early administration of Bifidobacterium breve to preterm infants: randomised controlled trial. Archives of Disease in Childhood. Fetal and Neonatal Edition, 76(2), F101–F107. https://doi.org/10.1136/fn.76.2.f101

18. Kliegman, R. M., & Fanaroff, A. A. (1984). Neonatal necrotizing enterocolitis. New England Journal of Medicine, 310(17), 1093–1103. https://doi.org/10.1056/NEJM198404263101706
19. Lin, H. C., Hsu, C. H., Chen, H. L., Chung, M. Y., Hsu, J. F., Lien, R. I., Tsao, L. Y., Chen, C. H., & Su, B. H. (2008). Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics, 122(4), 693–700. https://doi.org/10.1542/peds.2007-3007
20. Lin, H. C., Su, B. H., Chen, A. C., Lin, T. W., Tsai, C. H., Yeh, T. F., & Oh, W. (2005). Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics, 115(1), 1–4. https://doi.org/10.1542/peds.2004-1463
21. Luoto, R., Pärtty, A., Vogt, J. K., Rautava, S., & Isolauri, E. (2023). Reversible aberrancies in gut microbiome of moderate and late preterm infants: results from a randomized, controlled trial. Gut Microbes, 15(2), 2283913. https://doi.org/10.1080/19490976.2023.2283913
22. Mahboobipour, A. A., Bitaraf, A., Mohammadi, P., Khosravifar, M., Babaei, H., & Shahidolahi, A. (2024). Effects of synbiotics on necrotizing enterocolitis and full enteral feeding in very low birth weight infants: A double-blind, randomized controlled trial. Medicine, 103(37), e39647. https://doi.org/10.1097/MD.0000000000039647
23. Manzoni, P., Mostert, M., Leonessa, M. L., Priolo, C., Farina, D., Monetti, C., Latino, M. A., & Gomirato, G. (2006). Oral supplementation with Lactobacillus casei subspecies rhamnosus prevents enteric colonization by Candida species in preterm neonates: A randomized study. Clinical Infectious Diseases, 42(12), 1735–1742. https://doi.org/10.1086/504337
24. Martí, M., Spreckels, J. E., Ranasinghe, P. D., Wejryd, E., Marchini, G., Sverremark-Ekström, E., Jenmalm, M. C., & Abrahamsson, T. (2021). Effects of Lactobacillus reuteri supplementation on the gut microbiota in extremely preterm infants in a randomized placebo-controlled trial. Cell Reports Medicine, 2(3), 100206. https://doi.org/10.1016/j.xcrm.2021.100206
25. Mihatsch, W. A., Vossbeck, S., Eikmanns, B., Hoegel, J., & Pohlandt, F. (2010). Effect of Bifidobacterium lactis on the incidence of nosocomial infections in very-low-birth-weight infants: A randomized controlled trial. Neonatology, 98(2), 156–163. https://doi.org/10.1159/000280291
26. Millar, M., Seale, J., Greenland, M., Hardy, P., Juszczak, E., Wilks, M., Panton, N., Costeloe, K., & Wade, W. G. (2017). The microbiome of infants recruited to a randomised placebo-controlled probiotic trial (PiPS Trial). EBioMedicine, 20, 255–262. https://doi.org/10.1016/j.ebiom.2017.05.019
27. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71
28. Patole, S., Keil, A. D., Chang, A., Nathan, E., Doherty, D., Simmer, K., Esvaran, M., & Conway, P. (204). Effect of Bifidobacterium breve M-16V supplementation on fecal bifidobacteria in preterm neonates-a randomised double blind placebo controlled trial. PLoS One, 9(3), e89511. https://doi.org/10.1371/journal.pone.0089511
29. R Core Team. (2024). R: A language and environment for statistical computing. R Foundation for Statistical Computing. https://www.R-project.org/
30. Rojas, M. A., Lozano, J. M., Rojas, M. X., Rodriguez, V. A., Rondon, M. A., Bastidas, J. A., Perez, L. A., Rojas, C., Ovalle, O., Garcia-Harker, J. E., Tamayo, M. E., Ruiz, G. C., Ballesteros, A., Archila, M. M., & Arevalo, M. (2012). Prophylactic probiotics to prevent death and nosocomial infection in preterm infants. Pediatrics, 130(5), e1113–e1120. https://doi.org/10.1542/peds.2011-3584
31. Rougé, C., Piloquet, H., Butel, M. J., Berger, B., Rochat, F., Ferraris, L., Des Robert, C., Legrand, A., de la Cochetière, M. F., N'Guyen, J. M., Vodovar, M., Voyer, M., Darmaun, D., & Rozé, J. C. (2009). Oral supplementation with probiotics in very-low-birth-weight preterm infants: a randomized, double-blind, placebo-controlled trial. The American Journal of Clinical Nutrition, 89(6), 1828–1835. https://doi.org/10.3945/ajcn.2008.26919
32. Sari, F. N., Dizdar, E. A., Oguz, S., Erdeve, O., Uras, N., & Dilmen, U. (2011). Oral probiotics: Lactobacillus sporogenes for prevention of necrotizing enterocolitis in very low-birth weight infants: a randomized, controlled trial. European Journal of Clinical Nutrition, 65(4), 434–439. https://doi.org/10.1038/ejcn.2010.278
33. Sowden, M., van Weissenbruch, M. M., Bulabula, A. N. H., van Wyk, L., Twisk, J., & van Niekerk, E. (2022). Effect of a multi-strain probiotic on the incidence and severity of necrotizing enterocolitis and feeding intolerances in preterm neonates. Nutrients, 14(16), 3305. https://doi.org/10.3390/nu14163305
34. Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., McAleenan, A., ... Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ, 366, l4898. https://doi.org/10.1136/bmj.l4898
35. Tewari, V. V., Dubey, S. K., & Gupta, G. (2015). Bacillus clausii for prevention of late-onset sepsis in preterm infants: A randomized controlled trial. Journal of Tropical Pediatrics, 61(5), 377–385. https://doi.org/10.1093/tropej/fmv050

36. Underwood, M. A., Kalanetra, K. M., Bokulich, N. A., Lewis, Z. T., Mirmiran, M., Tancredi, D. J., & Mills, D. A. (2013). A comparison of two probiotic strains of bifidobacteria in premature infants. The Journal of Pediatrics, 163(6), 1585–1591.e8. https://doi.org/10.1016/j.jpeds.2013.07.017
37. Van Rossum, T., Haiß, A., Knoll, R. L., Marißen, J., Podlesny, D., Pagel, J., Bleskina, M., Vens, M., Fortmann, I., Siller, B., ... & Härtel, C. (2024). Bifidobacterium and Lactobacillus probiotics and gut dysbiosis in preterm infants: The PRIMAL randomized clinical trial. JAMA Pediatrics, 178(10), 985-995. https://doi.org/10.1001/jamapediatrics.2024.2626
38. Walsh, M. C., & Kliegman, R. M. (1986). Necrotizing enterocolitis: Treatment based on staging criteria. Pediatric Clinics of North America, 33(1), 179–201. https://doi.org/10.1016/s0031-3955(16)35003-9

**Table S1: Dataset for Meta-analysis**

| Reference (Author, Year) | Probiotic Strain(s) | Mean/Median GA (wks) | Mean/Median BW (g) | NEC (Bell Stage ≥II) | Culture-Proven Sepsis | All-Cause Mortality |
|---|---|---|---|---|---|---|
| | | | | Events/Total (I) | Events/Total (C) | Events/Total (I) |
| **Bifidobacterium-based (Single or Multi-strain)** | | | | | | |
| Costeloe et al. (2016) | B. breve BBG-001 | 28.0 | 1039 | 61/650 | 66/660 | 73/650 |
| Patole et al. (2014) | B. breve M-16V | 29.0 | 1090 | 0/77 | 1/76 | 12/77 |
| Mihatsch et al. (2010) | B. lactis BB-12 | 26.6 | 856 | 2/91 | 4/89 | 28/91 |
| Hays et al. (2016) | B. lactis, B. longum (or both) | 29.1 | 1173 | 8/147 | 3/52 | 35/147 |
| **Lactobacillus-based** | | | | | | |
| Sari et al. (2011) | L. sporogenes | NR | <1500 | 10/111 | 10/111 | 26/111 |
| Tewari et al. (2015) | B. clausii | 30.1 | 1165 | 1/123 | 1/121 | 20/123 |
| **Mixed Genera (Bifido + Lacto)** | | | | | | |
| Lin et al. (2005) | L. acidophilus + B. infantis | 28.5 | 1104 | 2/180 | 10/187 | 22/180 |
| Lin et al. (2008) | L. acidophilus + B. bifidum | 29.0 | 1029 | 4/217 | 14/217 | 24/217 |
| Bin-Nun et al. (2005) | B. infantis + S. thermophilus + B. bifidus | 30.0 | 1152 | 3/72 | 12/73 | 36/72 |
| Jacobs et al. (2013) | B. infantis + S. thermophilus + B. lactis | 27.9 | 1063 | 11/548 | 24/551 | 72/548 |
| Braga et al. (2011) | B. breve + L. casei | 29.5 | 1195 | 0/119 | 4/112 | 40/119 |
| Rojas et al. (2012) | L. reuteri DSM 17938 | 32.0 | 1530 | 9/372 | 15/378 | 40/372 |
| Rougé et al. (2009) | B. longum BB536 + L. rhamnosus GG | 28.1 | 1115 | 2/45 | 1/49 | 15/45 |
| Mahboobipour et al. (2024) | L. rhamnosus + L. reuteri + B. infantis | 31.0 | 1268 | 1/58 | 5/59 | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sowden et al. (2022) | L. acidophilus + B. bifidum + B. infantis | 29.5 | 1162 | 0/100 | 5/100 | NR |
| Van Rossum et al. (2024) | B. longum ssp. infantis + B. animalis ssp. lactis + L. acidophilus | 31.0 | 1502 | 1/316 | 2/322 | 8/316 |
| **Fungal Probiotic (for context, may be excluded in primary analysis)** | | | | | | |
| Demirel et al. (2013) | S. boulardii | 29.0 | 1135 | NR | NR | 1/91 |
| **Other/Not Specified** | | | | | | |
| Dani et al. (2002) | L. rhamnosus GG | 30.8 | 1325 | 4/295 | 8/290 | 14/295 |
| Dilli et al. (2015) | B. lactis (Probiotic), Inulin (Prebiotic), Both (Synbiotic) | 28.8 | 1236 | 6/200[1] | 18/100 | 49/200[1] |
| Martí et al. (2021) | L. reuteri DSM 17938 | 25.5 | 763 | 7/68 | 8/66 | 13/68 |
| Luoto et al. (2023) | L. rhamnosus GG | 34.8 | 2390 | NR | NR | NR |