International Journal for Vitamin and Nutrition Research

Int. J. Vitam. Nutr. Res. **2026**; 96(3): 45968
https://doi.org/10.31083/IJVNR45968

Review

Application of Probiotics in Neonatal Diseases

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Academic Editor: Torsten Bohn
Submitted: 22 August 2025 Revised: 9 October 2025 Accepted: 29 October 2025 Published: 1 June 2026

Abstract

Probiotics have increasingly progressed from laboratory research to clinical application, supported by growing evidence demonstrating their potential benefits across multiple neonatal conditions. In 2023, the Chinese Preventive Medicine Association released an evidence-based guideline on pediatric probiotic use; however, comprehensive summaries dedicated specifically to neonates remain scarce despite rapidly expanding clinical utilization in this population. This narrative review synthesizes current evidence on the role of probiotics in common neonatal disorders and discusses key considerations regarding timing, dosing, and safety. Literature from PubMed and CNKI was examined, prioritizing clinical trials and meta-analyses published in the past five years, with extended inclusion for topics lacking sufficient data. Searches covered probiotics in relation to necrotizing enterocolitis, feeding intolerance, antibiotic-associated diarrhea, neonatal hyperbilirubinemia, sepsis, bronchopulmonary dysplasia, respiratory infection, micronutrient metabolism, safety, and mechanisms. A total of 22 reviews/meta-analyses and 51 clinical studies were included. Overall, Bifidobacterium and Lactobacillus are the most frequently used probiotics in neonatal care, with evidence supporting reductions in necrotizing enterocolitis, feeding intolerance, antibiotic-associated diarrhea, hyperbilirubinemia, and potentially sepsis, alongside possible respiratory and micronutrient-related benefits. Although safety profiles are generally favorable, rare instances of probiotic-related sepsis highlight the need for caution. Considerable heterogeneity in strains, dosing strategies, and intervention durations continues to limit interpretation. Further large-scale, rigorously designed randomized trials are required to refine strain selection, validate efficacy, and ensure safety in this highly vulnerable population.

Keywords: probiotic; neonatal diseases; probiotic safety; necrotizing enterocolitis; antibiotic-associated diarrhea; late-onset sepsis; micronutrient status

1. Introduction

According to a 2001 definition by the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) defined probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". In China, probiotics are classified as either pharmaceutical-grade or food-grade. The List of Strains Permitted for Use in Foods 2022 issued by China's National Health Commission specifies 38 food-grade strains across 17 genera. For infant food, the list is more restrictive, allowing only 15 strains to be used in this population (see Table 1). Their clinical use in neonates is garnering increased attention due to the high burden of gastrointestinal and infectious diseases in this population. Neonatal disorders such as necrotizing enterocolitis (NEC), feeding intolerance, sepsis, bronchopulmonary dysplasia (BPD), hyperbilirubinemia, and antibiotic-associated diarrhea are major contributors to neonatal morbidity and mortality worldwide, particularly among preterm infants. Conventional management strategies, including broad-spectrum antibiotics and phototherapy, can disrupt the developing gut microbiome, underscoring the urgent need for safe and effective adjunctive interventions.

The use of probiotics in neonatal intensive care units (NICUs) is becoming more common worldwide. Various randomized controlled trials (RCTs) and meta-analyses report positive effects of probiotics in preventing NEC and improving enteral feeding outcomes, such as better intestinal function. In January 2023, the Chinese Preventive Medicine Association released the Evidence-Based Guideline for Probiotic Application in Pediatrics. However, few European or American guidelines strongly endorse probiotic use due to the lack of unified criteria and consensus, as well as significant heterogeneity in strain and dosage. Above all, among all probiotics utilized in neonates so far, bifidobacteria and lactobacilli have been extensively studied and applied, owing to their roles in shaping gut microbiota and immune system establishment.

Mechanistically, probiotics help maintain intestinal homeostasis by modulating microbial diversity, strengthening the gut barrier, and producing short-chain fatty acids (SCFAs) that serve as critical energy substrates for colonocytes and regulators of immune signaling. Emerging evidence also supports their role in the gut-lung and gut-brain axes, linking probiotic interventions to systemic effects on respiratory health, neurodevelopment, and micronutrient metabolism. At the immunological level, specific strains

Table 1. List of strains permitted for use in infant and young child food.

Number	Species	Strains	Official designation
1	*Bifidobacterium animalis subsp. lactis*	Bb-12	*Bifidobacterium animalis subsp. lactis* Bb-12
2		HN019	*Bifidobacterium animalis subsp. lactis* HN019
3		Bi-07	*Bifidobacterium animalis subsp. lactis* Bi-07
4	*Lacticaseibacillus rhamnosus*	GG	*Lacticaseibacillus rhamnosus* GG
5		HN001	*Lacticaseibacillus rhamnosus* HN001
6		MP108	*Lacticaseibacillus rhamnosus* MP108
7	*Lactobacillus helveticus*	R0052	*Lactobacillus helveticus* R0052
8	*Limosilactobacillus reuteri*	DSM17938	*Limosilactobacillus reuteri* DSM17938
9	*Bifidobacterium bifidum*	R0071	*Bifidobacterium bifidum* R0071
10	*Lactobacillus acidophilus*	NCFM	*Lactobacillus acidophilus* NCFM
11	*Limosilactobacillus fermentum*	CECT5716	*Limosilactobacillus fermentum* CECT5716
12	*Bifidobacterium breve*	M-16V	*Bifidobacterium breve* M-16V
13	*Bifidobacterium longum subsp. longum*	BB536	*Bifidobacterium longum subsp. longum* BB536
14	*Bifidobacterium longum subsp. infantis*	R0033	*Bifidobacterium longum subsp. infantis* R0033
15		M-63	*Bifidobacterium longum subsp. infantis* M-63

such as *Lacticaseibacillus rhamnosus* GG and *Bifidobacterium longum* 35624 have been shown to promote regulatory T cell differentiation and increase anti-inflammatory cytokines such as IL-10, and suppress pro-inflammatory mediators like TNF-α and IL-6.

Despite encouraging findings, several issues remain controversial. Although generally regarded as safe, cases of probiotic-associated sepsis have been reported in extremely preterm infants. Uncertainty remains regarding the optimal probiotic strain, the appropriate dose, and the optimal timing and duration of intervention. Furthermore, many existing clinical studies are limited by small sample sizes or single-center designs. Thus, the present article reviews the current evidence on probiotic use for commonly encountered neonatal conditions, discusses the proposed mechanism of action, evaluates safety concerns, and highlights knowledge gaps that deserve further exploration. The main clinical studies included in this review, focusing exclusively on neonatal populations, and covering probiotic interventions across digestive, infectious, and allergic diseases, are summarized in Table 2 (Ref. [1–51]).

2. Clinical Applications in Neonatal Diseases

2.1 Digestive System

2.1.1 Necrotizing Enterocolitis (NEC)

NEC is a prevalent gastrointestinal diseases in neonates, characterized by high morbidity and mortality rates. Its onset is often insidious, progression rapid, and prevention challenging [52]. The younger the gestational age and the lower the birth weight, the poorer the intestinal mucosal barrier function and the lower the abundance of intestinal flora, resulting in greater susceptibility to NEC and a higher probability of developing severe disease [53].

A 2020 retrospective study conducted in a tertiary NICU at Norfolk and Norwich University Hospital in the UK found that routine administration of *Lactobacillus acidophilus* and *Bifidobacterium spp.* significantly reduced the incidence of NEC in extremely preterm infants, with no reported cases of probiotic sepsis [1]. A 2022 double-blind RCT at Tygerberg Hospital, South Africa, reported a significantly lower incidence of NEC in preterm infants receiving *Bifidobacterium bifidum* and *Lactobacillus acidophilus* compared to the placebo group. The study concluded that the use of probiotics to prevent NEC is a safe and effective measure [2]. A 2023 retrospective study in Australia also supported the use of *Bifidobacterium* combined with *Lacticaseibacillus rhamnosus* as a preventive strategy for NEC [3]. Consistently, a network meta-analysis by Beghetti *et al.* (2021) [54] confirmed that Bifidobacterium lactis Bb-12/B94 reduces the risk of stage $\geq$2 NEC in preterm infants, with greater benefits observed in exclusively human milk–fed infants.

Morgan *et al.* (2020) [55] analyzed 63 trials including 15,712 preterm infants and concluded that combinations of *Lactobacillus* and *Bifidobacterium*, or *Lactobacillus reuteri* and *Lacticaseibacillus rhamnosus*, effectively reduced severe NEC and mortality. However, combinations involving *Bacillus* and *Enterococcus* were less effective. Chi *et al.* (2021) [56] reviewed 45 RCTs involving 12,320 preterm infants and found that the combined use of *Lactobacillus* and *Bifidobacterium*, or *Lactobacillus* plus prebiotics, was more effective than single-strain probiotics. Wang *et al.* (2023) [57] identified multi-strain probiotics alone or combined with oligosaccharides as among the most effective interventions for reducing NEC. In contrast, a 2024 retrospective study from the Czech Republic by Korček and Straňák [4] found no statistically significant difference in NEC incidence or mortality between single-strain and multi-strain probiotics, potentially due to a small sample size or low baseline NEC incidence.

In 2022, Samara *et al.* [5] (Canada) investigated preterm infants under 29 weeks gestation using a multi-str-

Table 2. Detailed data on probiotic clinical studies in children provided in the manuscript.

Author (Year)	Country	Design	Subjects	N	Probiotic (strain & dose)	Duration	Endpoints
Robertson *et al.* (2020) [1]	United Kingdom	Retrospective study	Preterm <32 wks or 32–36 wks, BW <1500 g	982 (469 before, 513 after probiotics)	Infloran: *L. acidophilus* + *B. bifidum* (1×10^9 CFU/day, 2013–2016); Labinic: *L. acidophilus* + *B. bifidum* + *B. infantis* (0.5×10^9 CFU/day, 2016–2017)	To ∼34 wks PMA	NEC (Bell's stage ≥2a), late-onset sepsis, all-cause mortality
Sowden *et al.* (2022) [2]	South Africa	RCT	Preterm <37 wks, BW 750–1500 g	200 (100 probiotic, 100 placebo)	Labinic: *L. acidophilus* + *B. bifidum* + *B. infantis* (2×10^9 CFU/day)	28 days	NEC incidence/severity, feeding intolerance
Cripps *et al.* (2023) [3]	Australia	Retrospective study	Preterm <32 wks, BW <1500 g	805 (419 no probiotics, 386 probiotics)	ABC Dophilus: *B. infantis* + *B. lactis* + *S. thermophilus* (2009–2011); Infloran: *L. acidophilus* + *B. bifidum* (2×10^9 CFU/day, 2013–2020)	To ∼34 wks GA or discharge	NEC incidence (Bell's stage ≥II), late-onset sepsis, mortality
Korček and Straňák (2024) [4]	Czech Republic	Retrospective study	Preterm <32 wks, BW <1500 g	455 (228 multi-species, 227 single-species)	Multi-species: *L. rhamnosus, L. casei, L. acidophilus, B. infantis, B. bifidum* (2.5×10^8 CFU/day); Single-species: *B. breve* BR03 + B632 (1×10^8 CFU each/day)	From feeds ≥60–80 mL/kg/day until discharge or 36 wks GA	NEC (Bell's stage ≥2a), late-onset sepsis, mortality
Samara *et al.* (2022) [5]	Canada	RCT	Extremely preterm <29 wks GA, BW <1000 g	57 (26 probiotic, 31 control)	FloraBABY: *B. breve* HA-129, *B. bifidum* HA-132, *B. longum subsp. infantis* HA-116, *B. longum subsp. longum* HA-135, *L. rhamnosus* HA-111 (CFU not reported)	First week of life until 37–39 wks GA	Gut microbiome maturation, intestinal inflammation, stool metabolites, cytokines
Costeloe *et al.* (2016) [6]	United Kingdom	RCT	Very preterm 23–30 wks GA	1315 (650 probiotic, 660 placebo)	*B. breve* BBG-001, 1.58×10^8∼1.58×10^9 CFU/day	From ≤48 h of birth until 36 wks PMA or discharge	NEC (Bell stage 2–3), late-onset sepsis (>72 h), death before discharge
Sowden *et al.* (2022) [7]	South Africa	RCT	Preterm <37 wks, BW 750–1500 g	200 (100 probiotic, 100 placebo)	Labinic (*L. acidophilus* + *B. bifidum* + *B. infantis*), 2×10^9 CFU/day	From first feed for 28 days	NEC incidence/severity, feeding intolerance
Indrio *et al.* (2017) [8]	Italy	RCT	Preterm <37 wks, BW 1500–2500 g, formula-fed	60 (30 probiotic, 30 placebo)	*L. reuteri DSM 17938*, 1×10^8 CFU/day	Within 48 h of birth for 30 days	Feeding intolerance, time to full feeds, gastric emptying, hospital stay
Indrio *et al.* (2008) [9]	Italy	RCT	Preterm <37 wks, BW 1500–2500 g, formula-fed; plus breast-fed reference group	20 (10 probiotic, 10 placebo) + 10 reference (breast-fed)	*L. reuteri ATCC 55730*, 1×10^8 CFU/day	30 days	Regurgitation, crying time, stools, gastric emptying

Table 2. Continued.

Author (Year)	Country	Design	Subjects	N	Probiotic (strain & dose)	Duration	Endpoints
Wu *et al*. (2012) [10]	China	Prospective Study	Neonates with purulent meningitis	123 (54 probiotics, 69 control)	Triple viable tablets (*Bifidobacterium*, *Lactobacillus*, *Enterococcus*), 0.5 g tid, oral (CFU not reported)	Until clinical cure/stop antibiotics	Incidence of AAD, time from antibiotics to AAD onset
Liu *et al*. (2013) [11]	China	RCT	Neonates requiring $\geq$7 d antibiotics (term & preterm included)	120 (60 probiotics, 60 control)	*Bacillus subtilis* + *Enterococcus faecium* ("Mamiai"), 1 g tid, oral (CFU not reported)	1–2 weeks	Incidence of AAD
Cao *et al*. (2021) [12]	China	RCT	Neonates with AAD	80 (40 probiotics + antibiotics, 40 antibiotics only)	*Clostridium butyricum* + *Bifidobacterium* powder, dose not specified (CFU not reported)	72 h	Clinical efficacy, recovery of bowel sounds, diarrhea duration, intestinal flora counts
Feng and Yang (2019) [13]	China	RCT	Neonates with pneumonia and AAD	90 (45 probiotics, 45 control)	Obs: *Clostridium butyricum* + *Bifidobacterium* powder; Ctrl: *Saccharomyces boulardii* (CFU not reported)	Until recovery	Clinical efficacy, diarrhea duration, hospitalization days, fecal flora, IL-2/IL-6/TNF-α
Du and Wang (2020) [14]	China	RCT	Neonates with AAD	78 (39 probiotics, 39 control)	Obs: *Clostridium butyricum* + *Bifidobacterium* powder; Ctrl: *Saccharomyces boulardii* (CFU not reported)	3 days	Clinical efficacy, intestinal flora, serum TNF-α/IL-6
Wan *et al*. (2017) [15]	China	RCT	Young children 1$\sim$36 month (non-GI and antibiotic therapy required)	408 (213 probiotic, 195 control)	*Saccharomyces boulardii*, 5 $\times$ 10^9 CFU/day	14 days	Incidence of AAD
Zhang *et al*. (2024) [16]	China	RCT	Infants/young children $<$3 yrs on antibiotics (non-GI infections)	182 (47 control, 70 *S. boulardii*, 65 Bifidobacterium mix)	*S. Boulardii*: 3.25 $\times$ 10^8 CFU/day; Tetragenous viable Bifidobacterium: *Bifidobacterium*, *Lactobacillus acidophilus*, *Enterococcus faecalis* (each $\geq$0.5 $\times$ 10^6 CFU/tablet), *Bacillus cereus* ($\geq$0.5 $\times$ 10^5 CFU/tablet) Dose: 1–6 months: 1 tablet twice daily; 7–12 months: 1 tablet three times daily; 1–3 years: 2 tablets three times daily.	7, 14, 21 days	Incidence of AAD, fecal cocci/bacilli ratio
Lukasik *et al*. (2022) [17]	Dutch and Polish	RCT	Young children 3 month $\sim$18 years (non-GI and antibiotic therapy required)	313 (158 probiotic, 155 control)	A multispecies probiotic (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Lactobacillus acidophilus* W37, *L acidophilus* W55, *Lacticaseibacillus paracasei* W20, *Lactiplantibacillus plantarum* W62, *Lacticaseibacillus rhamnosus* W71, and *Ligilactobacillus salivarius* W24), 10^{10} CFU/day	For the duration of antibiotic treatment and for 7 days after	Incidence of AAD

Table 2. Continued.

Author (Year)	Country	Design	Subjects	N	Probiotic (strain & dose)	Duration	Endpoints
Serce Pehlevan *et al.* (2020) [18]	Turkey	RCT	Preterm ≤32 wks, BW ≤1500 g	208 (104 probiotic, 104 control)	Synbiotic mix (*L. rhamnosus* 8.2 × 10^8, *L. plantarum* 4.1 × 10^8, *L. casei* 4.1 × 10^8, *B. lactis* 4.1 × 10^8 CFU + FOS 383 mg + GOS 100 mg + lactoferrin 2 mg + vitamins)	From first feed until discharge (median 36 day)	Incidence of NEC stage ≥2 or late-onset culture-proven sepsis and NEC stage ≥2 or death
Granger *et al.* (2022) [19]	United Kingdom	Retrospective study	Preterm <32 wks	1061 (509 pre vs 552 post probiotics)	Infloran (*L. acidophilus, B. bifidum*), later Labinic (*L. acidophilus*, *B. bifidum*, *B. longum subsp. infantis*) (CFU not reported)	From minimal feeds until 34 wks CGA or discharge	Incidence of NEC, LOS or mortality
Sharpe *et al.* (2018) [20]	Australia	Retrospective study	Preterm <32 wks or BW <1500 g	1791 (1334 pre vs 457 post introduction)	Infloran (*L. acidophilus* LA37 + *B. bifidum* BB07) (CFU not reported)	42 days	Incidence of NEC, LOS or mortality
Meyer *et al.* (2020) [21]	New Zealand	Retrospective study	Preterm <32 wks or BW <1500 g	4529 (2556 pre vs 1973 post probiotics)	Infloran (*L. acidophilus* ATCC 4356 1 × 10^9 CFU + *B. bifidum* ATCC 15696 1 × 10^9 CFU/day) in 5 units; LGG + bLF (*L. rhamnosus* GG 6 × 10^9 CFU + bovine lactoferrin 100 mg daily) in 1 unit	Started with trophic feeds, continued 4–6 wks or until 34–36 wks CGA/discharge	Incidence of NEC, LOS or mortality
Panigrahi *et al.* (2017) [22]	India	RCT	Term/late-preterm ≥35 wks, BW ≥2000 g	4556 (2278 synbiotic vs 2278 placebo)	*L. plantarum* ATCC-202195 (1 × 10^9 CFU/day)	7 days	Incidence of LOS or mortality
Güney-Varal *et al.* (2017) [23]	Turkey	RCT	Preterm ≤32 wks, BW ≤1500 g	110 (70 probiotic vs 40 control)	Multi-strain, multi-species (commercial NBL probiotic®): *L. rhamnosus* 4.1 × 10^8 CFU + *L. casei* 8.2 × 10^8 CFU + *L. plantarum* 4.1 × 10^8 CFU + *B. animalis* 4.1 × 10^8 CFU, with FOS 383 mg + GOS 100 mg	Started at 2–7 d of life; mean 36.5 ± 12.6 days, continued until discharge	Incidence of NEC, LOS or mortality
Yuan *et al.* (2025) [24]	China	RCT	Term neonates with jaundice (GA ≥37 wks, BW 2500–4000 g), receiving phototherapy	21 (11 probiotic vs 10 control)	*Lactobacillus rhamnosus* AB-GG, 1 × 10^9 CFU/day	1 month	Bilirubin levels, phototherapy duration, hospital stay, gut microbiota diversity, metabolites
Tsai *et al.* (2022) [25]	Taiwan (China)	RCT	Newborns with neonatal jaundice (GA ≥35 weeks; SBL ≥15 mg/dL)	83(43probiotic, 40 control)	*Bifidobacterium animalis* subsp. *lactis* CP-9 (1 × 10^{10} CFU/day)	During in-hospital phototherapy until bilirubin decreased ≥3 mg/dL (median ≈ 2 days)	TSB decline rate (mg/dL/h); total phototherapy duration (h)

Table 2. Continued.

Author (Year)	Country	Design	Subjects	N	Probiotic (strain & dose)	Duration	Endpoints
Wang (2023) [26]	China	RCT	Neonates with pathological jaundice	72 (36 probiotic vs 36 control)	Probiotic (not specified, oral) + Yinzhihuang (CFU not reported)	7 days	TSB, DB, IB, immune function (T-cell subsets), AFP, TRF, liver enzymes, adverse events
Nasief *et al*. (2024) [27]	Pakistan	Open-labelled RCT	Preterm neonates with indirect hyperbilirubinaemia	76 (2 groups)	*Saccharomyces boulardii*, 125 mg/day (CFU not reported)	From initiation of phototherapy until hospital discharge	duration of phototherapy (h); length of hospital stay (h)
Tian and Guo (2016) [28]	China	RCT	Neonates with breast milk jaundice	69 (35 probiotic vs 34 control)	*Bacillus licheniformis* (Zhengchangsheng), dose not specified (CFU not reported)	Until recovery	TSB, jaundice fading time, stool frequency
Mutlu *et al*. (2020) [29]	Turkey	RCT	Term neonates with isoimmune hemolytic jaundice (GA 35–42 wks)	60 (30 probiotic vs 30 control)	*Lactobacillus rhamnosus* GG, 1×10^9 CFU/day	4 days	Serum total bilirubin (STB), rebound STB, phototherapy duration, meconium frequency
Eghbalian *et al*. (2025) [30]	Iran	RCT	Term neonates (GA 37–42 wks, BW >2500 g)	150 (75 probiotic vs 75 control)	PediLact drops (CFU not reported)	72 h	Serum bilirubin levels, phototherapy duration, hospitalization length, need for transfusion
Demirel *et al*. (2013) [31]	Turkey	RCT	VLBW infants ≤32 wks, ≤1500 g	179 (81 probiotic vs 98 control)	*Saccharomyces boulardii* (CFU not reported)	From first feed until discharge	Duration of phototherapy, serum total bilirubin at end of phototherapy, feeding intolerance, sepsis incidence
Santosa *et al*. (2022) [32]	Japan	Prospective Study	Term neonates delivered by Caesarean section	153 (54 probiotic vs 99 control)	*Bifidobacterium animalis subsp. lactis* BB-12, 3×10^9 CFU/day	20 days	TCB levels (day 1–5), body weight gain
Serce *et al*. (2015) [33]	Turkey	RCT	Neonates 35–42 wks with hyperbilirubinemia requiring phototherapy	119 (58 probiotic vs 61 control)	*Saccharomyces boulardii* (Reflor, Biocodex), 125 mg q12h during phototherapy (CFU not reported)	Until phototherapy stopped (up to 96 h)	Serum bilirubin (0, 24, 48, 72, 96 h), duration of phototherapy, rebound hyperbilirubinemia
Sun *et al*. (2024) [34]	China	RCT	Term neonates with pathological jaundice	114 (38 control vs 38 *S. boulardii* vs 38 *Clostridium butyricum* + *Bifidobacterium*)	(i) *S. boulardii granules* (CFU not reported); (ii) *Clostridium butyricum* + *Bifidobacterium* (CFU not reported)	5 days	TSB, DB, IB, phototherapy duration, jaundice fading time, stool frequency, hospital stay, adverse events

Table 2. Continued.

Author (Year)	Country	Design	Subjects	N	Probiotic (strain & dose)	Duration	Endpoints
Khodair *et al.* (2025) [35]	Egypt	Prospective RCT (open-label; placebo not feasible)	Full-term neonates (GA 37–42 weeks)	80 (40 probiotic, 40 control)	*Bifidobacterium animalis* subsp. *lactis* BB-12 (total 2×10^9 CFU/day)	From day 1 of recruitment until discharge	VAP incidence
Banupriya *et al.* (2015) [36]	India	RCT	Critically ill children ≤12 yrs requiring MV >48 h (PICU)	150 (75 probiotic vs 75 control)	Multi-strain capsule (per capsule: *L. acidophilus* 7×10^8, *B. longum* 4×10^8, *L. rhamnosus* 4×10^8, *L. plantarum* 3×10^8, *L. casei* 3×10^8, *L. bulgaricus* 3×10^8, *B. infantis* 3×10^8, *B. breve* 3×10^8, *S. thermophilus* 3×10^8); total 6.6×10^9 CFU/day	7 days or until ICU discharge	VAP incidence, duration of MV, ICU stay, hospital stay, mortality, pathogen colonization
Kukkonen *et al.* (2008) [37]	Finland	RCT	Allergy-prone term infants	1018 (506 probiotic vs 512 control)	*L. rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99, *P. freudenreichii* JS; $8–9 \times 10^9$ CFU/day	6 months	Respiratory infections, antibiotic use
Aryayev *et al.* (2018) [38]	Ukraine	RCT	Late preterm newborns (35–36 wks)	62 (30 probiotic vs 32 control)	*E. coli Nissle* 1917 (Mutaflor®), 1×10^8 CFU daily (day 1–7), then 3×10^8 CFU (day 8–21)	3 weeks (follow-up to 12 months)	ARI incidence (28 d, 1 yr), ARI-related hospitalizations
Piloquet *et al.* (2024) [39]	France & Belgium	RCT	Healthy formula-fed term infants (HM ref group n = 80)	460 (230 synbiotic vs 230 control)	Synbiotic formula: *L. fermentum* CECT 5716 ($1–1.5 \times 10^6$ CFU/g) + GOS	11 months	Infectious diarrhea (primary), URTI, LRTI
Takeshita *et al.* (2024) [40]	Japan	RCT	Preterm infants <36 wks, post-NICU discharge	41 (21 probiotic vs 20 control)	Heat-killed *P. acidilactici* K15, 5×10^{10} CFU/day	12 months	Febrile days, respiratory tract infections
Qu *et al.* (2021) [41]	China	Retrospective study	Preterm infants <32 wks, NICU	318 (94 probiotic vs 224 control)	*Clostridium butyricum* powder (CFU not reported)	From admission until ≥36 wks PMA	BPD incidence, death
Li *et al.* (2024) [42]	China	RCT	Preterm infants (GA 28–32 wks, BW ≤1500 g)	86 (43 probiotic vs 43 control)	*Clostridium butyricum* + *Bifidobacterium* (CFU not reported)	Until 36 wks corrected GA	$PaCO_2$, PaO_2, tidal volume, ventilation time, oxygen time, LOS, BPD incidence
Wu *et al.* (2011) [43]	China	RCT	Mechanically ventilated neonates	81 (38 probiotic vs 43 control)	*Bifidobacterium* (Lizhu Pharma), 0.5×10^8 CFU	7 days	Gastric pH, gastric colonization, feeding intolerance, VAP incidence, pathogen homology

Table 2. Continued.

Author (Year)	Country	Design	Subjects	N	Probiotic (strain & dose)	Duration	Endpoints
Xie (2018) [44]	China	RCT	Mechanically ventilated neonates	80 (40 probiotic vs 40 control)	*Bifidobacterium* (strain not specified, CFU not reported)	7 days	VAP incidence, VAP onset time, gastric pH, gastric colonization, pathogen homology
Puisto *et al.* (2025) [45]	Finland/Spain	RCT	Infants born to atopic mothers, vaginal delivery, full-term, breastfed	241 mothers randomized; microbial analysis subset: 46 infants (26 probiotic vs 20 placebo)	Maternal probiotics: (1) *L. rhamnosus* LPR + *B. longum* BL999; (2) *L. paracasei* ST11 + *B. longum* BL999; 1×10^9 CFU/day	2 months before delivery to 2 months postpartum	Infant atopic eczema incidence, gut microbiota composition
Luo and Zhang (2022) [46]	China	Cohort study (intervention vs control)	Infants 4–6 months with digestive CMA manifestations	85 CMA infants (45 probiotic vs 40 control) + 41 healthy controls	*Bifidobacterium* BB-12 + *L. rhamnosus* GG, 4.5×10^9 CFU/day	3 months	Weight-for-age, GI symptoms (vomiting, diarrhea, food refusal, bowel sounds)
Nocerino *et al.* (2019) [47]	Italy	Prospective Study	Children with previous CMA, immune tolerance achieved $\geq$12 months	330 (110 EHCF vs 110 EHCF + LGG vs 110 healthy controls)	*L. rhamnosus* GG, 2.5×10^7–5×10^8 CFU/g in EHCF + LGG (Nutramigen LGG®)	CMA diagnosis in infancy, follow-up to 4–6 years	Functional gastrointestinal disorders (FGIDs, Rome III criteria)
Agustina *et al.* (2013) [48]	Indonesia	RCT	Healthy children 1–6 yrs	494 (244 probiotic vs 250 control)	*L. casei* CRL 431 or *L. reuteri* DSM 17,938, 5×10^8 CFU/day in milk	6 months	Growth (weight, height, WAZ, HAZ), anemia, iron and zinc status
Surono *et al.* (2014) [49]	Indonesia	RCT	Preschool children 12–24 mo	48 (36 intervention: 12 probiotic, 12 zinc, 12 combo vs 12 placebo)	*L. plantarum* IS-10506 (dadih origin), 1×10^{10} CFU/day; zinc 20 mg/day; combo probiotic + zinc	90 days	Fecal sIgA, serum zinc
Ballini *et al.* (2019) [50]	Italy/Albania	RCT	Healthy children 14–18 yrs	40 (20 probiotic vs 20 control)	Multi-strain (*L. plantarum*, *L. acidophilus*, *B. infantis*, *B. lactis*) + FOS; 3×10^9 CFU/pearl (equiv. 4.5×10^{10} CFU/day)	10 weeks	Serum vitamin D, vitamin A, calcium, zinc, iron
Athalye-Jape *et al.* (2025) [51]	Australia	RCT	Very preterm infants <32 wks	86 (43 live probiotic vs 43 heat-inactivated)	Live or heat-inactivated mix: *B. breve* M-16V, *B. longum subsp. infantis* M-63, *B. longum* BB536; total 3×10^9 CFU/day	3 weeks	Fecal calprotectin (primary), microbiota, SCFA, NEC, LOS, mortality

Abbreviations: Wks, weeks; BW, birth weight; CFU, colony-forming unit; PMA, postmenstrual age; NEC, necrotizing enterocolitis; RCT, randomized controlled trial; GA, gestational age; AAD, antibiotic-associated diarrhea; GI, gastrointestinal; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; LOS, late-onset sepsis; TSB, total serum bilirubin; IB, indirect bilirubin; DBIL, direct bilirubin; TCB, transcutaneous bilirubin; VLBW, very low birth weight (<1500 g); VAP, ventilator-associated pneumonia; ICU, intensive care unit; ARI, acute respiratory infection; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; NICU, neonatal intensive care unit; BPD, bronchopulmonary dysplasia; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; CMA, cow's milk allergy; yrs, years; mo, months; WAZ, weight-for-age z score; HAZ, height-for-age z score; SCFA, short-chain fatty acids.

ain probiotic mixture consisting of *Bifidobacterium breve* HA129, *Bifidobacterium bifidum* HA132, *Bifidobacterium longum subsp. infantis* HA116, *Bifidobacterium longum* HA135, and *Lacticaseibacillus rhamnosus* HA111. The intervention accelerated intestinal microbiota maturation toward a term-like profile and reduced intestinal pro-inflammatory markers associated with NEC. While not directly demonstrating reduced NEC morbidity or mortality, the study provided mechanistic support for bifidobacteria's potential benefit in extremely preterm infants (<28 weeks). By contrast, a large RCT in the United Kingdom (Costeloe *et al*. [6]) evaluating *Bifidobacterium breve* BBG-001 in preterm infants (23–30 weeks) found no significant effect on NEC incidence or mortality.

At present, current clinical evidence suggests that probiotics can reduce the incidence of NEC and lower NEC-related mortality, with *Lactobacillus spp*. (e.g., *L. rhamnosus*, *L. reuteri*, *L. acidophilus*) and *Bifidobacterium* spp. (e.g., *B. longum*, *B. breve*, *B. animalis*) being the most commonly recommended. Administration typically begins once a minimum enteral feeding volume is achieved (e.g., 60–80 mL/kg/day) and continues until 34–36 weeks postmenstrual age (PMA) or discharge, with most regimens delivering approximately 10^9 CFU/day.

Multicenter and long-term real-world data support the feasibility and potential benefits of probiotic supplementation; however, limitations remain, including substantial heterogeneity in strains, dosage, initiation thresholds, and duration of treatment; insufficient statistical power due to low baseline NEC incidence and restricted external validity between large negative single-strain RCTs and small positive or mechanistic trials. Future research should focus on standardized, adequately powered, head-to-head randomized controlled trials of specific strains in extremely preterm and very low birth weight populations.

2.1.2 Feeding Intolerance (FI)

A 2022 double-blind, placebo-controlled randomized clinical trial by Sowden *et al*. [2] found that combined use of *Lactobacillus acidophilus* and *Bifidobacterium* significantly reduced the incidence of FI. The probiotic group also achieved full enteral feeding sooner and regained birth weight earlier than the placebo group [7]. In studies conducted by Indrio and colleagues [8,9] in Italy, preterm infants with mean gestational ages of approximately 30 weeks and 34 weeks. Supplementation at 10^8 CFU/day for one month effectively reduced FI occurrence and shortened the time to full enteral nutrition. A meta-analysis of nine studies involving 1244 preterm infants with FI concluded that probiotics promote early growth and reduce FI incidence, although it did not identify preferred specific strains [58]. Similarly, a recent systematic review and meta-analysis in extremely preterm infants reported a non-significant but consistent trend toward improved feeding tolerance with probiotic supplementation, reflected by shorter time to full enteral feeding and reduced reliance on parenteral nutrition [59].

2.1.3 Antibiotic-Associated Diarrhea (AAD)

Neonates have a relatively weak immune barrier, making them prone to infections. Common neonatal infections include pneumonia, necrotizing enterocolitis, and sepsis. Antibiotics are often used to treat these conditions. However, prolonged antibiotic use can significantly disrupt the composition and function of the gut microbiota, and this antibiotic-associated dysbiosis may persist even after therapy concludes [60]. Probiotics may prevent AAD through multiple mechanisms, including modulating intestinal microbiota, increasing short-chain fatty acid production, regulating bile acid metabolism, and enhancing gut barrier function and immune responses [61].

Between 2008 and 2011, Wu *et al*. [10] administered *Lactobacillus bifidus* triplex tablets to neonates with purulent meningitis during antibiotic treatment, and the study demonstrated a significant reduction in the incidence of AAD and a delay in its onset. In 2013, Liu *et al*. [11] reported that children on long-term antibiotic therapy who received *Bacillus subtilis* bifidus granules had a significantly lower incidence of AAD (2%) compared to the control group (36%). Collectively, these studies indicate that probiotic intervention can delay or even prevent the occurrence of AAD. Several studies further suggest that probiotics can aid in the treatment of neonatal AAD. They can alleviate symptom severity (e.g., diarrhea, abdominal pain) and shorten the duration of AAD. A randomized controlled trial in 2021 confirmed that *Clostridium butyricum* and *Bifidobacterium* infantis live powder can alleviate clinical symptoms of antibiotic-associated diarrhea, such as abdominal pain and diarrhea [12]. Feng Aimin and others investigated the therapeutic effects of a bivalent probiotic (*Clostridium butyricum* and *Bifidobacterium infantis*) versus *Saccharomyces boulardii* for AAD. The bivalent probiotic showed superior outcomes regarding time to diarrhea cessation, hospitalization duration, and the overall therapeutic efficacy [13]. This conclusion is corroborated by the findings of a clinical study carried out by Du and Wang in 2020 [14]. The superior efficacy of the bivalent preparation may be attributable to its combination of multiple bacterial strains, which more closely mimics the normal proportion of intestinal flora in the human body.

A 2017 multi-center randomized controlled trial in China showed that administration of *Saccharomyces boulardii* alongside antibiotics significantly reduced the incidence of diarrhea in children receiving one or more antibiotics for ≥5 days, with a reduction of over 60%. Moreover, within 14 days after antibiotic cessation, the intervention group's risk of diarrhea remained more than 80% lower than that of the control group [15]. In 2024, a prospective study by Zhang *et al*. [16] in China found that both *Saccharomyces boulardii* and *Bifidobacterium* effec-

tively improved intestinal health and prevented AAD in infants and young children, with no significant difference between them. The study also found no significant difference in fecal coccobacilli counts at 14 and 21 days after *Bifidobacterium* administration, suggesting maximal microbiota modulation was achieved by day 14, with prolonged supplementation offering no additional benefit. A 2019 systematic review by Guo *et al*. [62], covering children aged 3 days to 18 years, indicated that *Lacticaseibacillus rhamnosus* and *Saccharomyces boulardii* were the most promising probiotics for AAD prevention, with daily doses $>5 \times 10^9$ CFU showing superior efficacy. Notably, these studies included children across a broad age range (3 days to 18 years) and were not tailored specifically to neonates. Nonetheless, they offer valuable insights for strain selection, dosage, and intervention duration in neonatal AAD. In contrast, an RCT by Lukasik *et al*. [17] involving children aged 3 months to 18 years found that *Bifidobacterium* and *Lactobacillus acidophilus* decreased the risk of diarrhea during and up to 7 days after antibiotic therapy, but did not specifically reduce the risk of AAD, highlighting how variations in the definition of AAD can influence clinical trial outcomes and their interpretation.

In summary, substantial evidence confirms the efficacy of probiotics in both preventing and treating AAD. *Saccharomyces boulardii* and *Lacticaseibacillus rhamnosus* have the strongest evidence base, while *Clostridium butyricum* and *Bifidobacterium longum* may also provide benefits in children. Early administration of probiotics alongside antibiotics is recommended to minimize disruption of the gut microbiota and mucosal barrier. However, the optimal duration of probiotic therapy requires further clinical investigation.

2.1.4 Mechanism

A substantial body of randomised controlled trials shows that probiotics help prevent disease and serve as adjuncts to therapy across diverse gastrointestinal conditions. Recent experimental and translational work has clarified the biological underpinnings of these effects, pointing to mechanisms that span the intestinal barrier, immune modulation, and metabolic support.

Probiotics reshape the gut microbiota by encouraging the colonisation and expansion of beneficial taxa such as *Bifidobacterium* and *Lactobacillus*, while curbing the overgrowth of potential pathogens to preserve microbial homeostasis. A healthier community structure limits pathogen adhesion and translocation, thereby reducing the likelihood of intestinal barrier injury. In addition to these microbiota-mediated actions, certain strains directly upregulate tight junction proteins in intestinal epithelial cells—including occludin, claudin, and ZO-1. By reinforcing intercellular integrity, probiotics help normalise mucosal permeability and support the recovery of barrier function [63,64].

Probiotics shape host immunity by remodelling the microbial community and by directly engaging receptors on epithelial and immune cells, including TLR2, TLR4, and TLR9. Through these interactions they tune key signalling pathways—most notably NF-κB and MAPK. A substantial body of evidence shows that probiotics downregulate pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and upregulate anti-inflammatory mediators (IL-10, TGF-β), thereby tempering excessive inflammation and sustaining immune homeostasis [65]. These effects are clinically relevant: they limit intestinal mucosal injury, foster immune tolerance, and improve feeding tolerance.

Probiotic-derived short-chain fatty acids—acetate, propionate, and butyrate—serve as the main fuel for colonocytes. Beyond energising the epithelium, SCFAs stimulate epithelial proliferation and repair, trigger mucus secretion from goblet cells, bolster antimicrobial peptide production, and preserve an acidic luminal milieu that suppresses pathogenic growth [66]. Collectively, this metabolic support is pivotal during intestinal inflammation and tissue repair, accelerating the recovery of mucosal structure and function.

Probiotics operate along intersecting pathways: they fortify the intestinal epithelial barrier; directly calibrate signalling to dampen inflammation; and harness microbial metabolites to optimise the intestinal milieu and drive epithelial repair. Taken together, these actions offer a strong biological rationale for the clinical benefits reported in NEC, FI, and AAD.

2.2 Infectious Diseases

Neonatal sepsis is a common infectious disease and a leading cause of neonatal mortality. A prospective study by Madan *et al*. [67] (United States) showed that preterm infants experienced a decline in gut microbiota diversity preceding the development of late-onset sepsis (LOS), which persisted until sepsis onset. This suggests a role for the gut microbiota in the pathogenesis of LOS. However, evidence supporting probiotic use for the prevention or treatment of neonatal sepsis remains limited.

A prospective, double-blind randomized controlled trial conducted by Serce Pehlevan *et al*. [18] in Turkey (2020) found that administration of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* to very low birth weight infants (gestational age $\leq$32 weeks, birth weight $\leq$1500 g) did not significantly reduce LOS incidence compared to controls. Similarly, a 2021 retrospective study by Granger *et al*. [19] (UK) showed no overall benefit, and in extremely preterm infants ($<$28 weeks), the intervention group even had a higher incidence of LOS than the control group (30.2% vs 22.4%, p = 0.04). Retrospective studies by Sharpe *et al*. [20] (Australia, 2018) and Alshaikh *et al*. [68] (Canada, 2025) also reported negative results. Meta-analyses by Deshmukh and Patole [69] (2021), Li *et al*. [70] (China, 2021), and Thomas *et al*. [71] (2023) further con-

firmed the weak evidence supporting probiotics for reducing LOS incidence.

However, a retrospective study conducted in New Zealand found that *Bifidobacterium bifidum* and *Lactobacillus rhamnosus* reduced the prevalence of LOS in preterm infants with a gestational age of less than 32 weeks [21]. A randomized, double-blind, placebo-controlled clinical trial of 4556 neonates found that a 7-day synbiotic intervention with Lactobacillus plantarum (10^9 CFU) and oligofructose reduced sepsis incidence and all-cause mortality [22]. Dermyshi *et al.*'s meta-analysis [72] of 30 RCTs and 14 observational studies showed probiotics lowered LOS incidence in very low birth weight infants (1000–1500 g), but not in extremely low birth weight infants ($<$1000 g). RCTs by Güney-Varal *et al.* [23] in Turkey also demonstrated benefits of *Lactobacillus* and *Bifidobacterium* strains in preterm infants $\leq$32 weeks gestation.

Overall, the evidence supporting probiotics for preventing neonatal LOS remains weak and requires confirmation by additional clinical trials. In terms of probiotic and feeding interactions, a 2017 meta-analysis concluded that the beneficial effect of probiotics on lowering LOS incidence is only confirmed in exclusively breastfed preterm infants [73]. This finding is consistent with the conclusions of a study by Li *et al.* (2021) [70]. Additionally, a systematic review has shown that exclusive breastfeeding itself does not reduce LOS incidence [74], suggesting that probiotic supplementation in exclusively breastfed neonates may help lower the incidence of LOS. Furthermore, a 2023 meta-analysis indicated that the combination of single probiotic strains with lactoferrin represents the most effective intervention for reducing LOS, while multi-strain probiotics demonstrated moderate efficacy against LOS [57]. A limitation of this analysis, however, is that it did not specify which strain combinations were particularly optimal.

2.3 Neonatal Hyperbilirubinemia

Neonates are susceptible to elevated bilirubin levels due to factors such as the short lifespan of erythrocytes, immature hepatic function, and enhanced enterohepatic circulation, which can lead to neonatal hyperbilirubinemia. Untreated significant hyperbilirubinemia can affect the development of the central nervous system, potentially causing permanent sequelae. Currently, the most commonly used effective and safe clinical intervention is phototherapy. It enables the photoisomerization of unconjugated bilirubin to form water-soluble lumirubin, which is excreted directly through bile and urine without hepatic processing. However, phototherapy may cause adverse reactions such as fever, rash, and diarrhea, potentially linked to increased intestinal peristalsis and microbiota disruption.

Zhang *et al.* [75] reported that phototherapy altered the intestinal microbiota, with significant decreases in *Alistipes putredinis* and unclassified *Cellvibrio*, and notable increases in *Clostridium bolteae*, *Enterobacter cloacae*, and *Enterococcus faecium*. Yuan *et al.* [24] evaluated the use of *Lactobacillus rhamnosus* in full-term infants with hyperbilirubinemia receiving phototherapy. They found that microbiota changes after phototherapy were more pronounced in controls than in the probiotic group, suggesting that *L. rhamnosus* may mitigate microbiota disruption, promote faster recovery of depleted intestinal flora, and reduce diarrhea frequency in jaundiced neonates.

Beyond modulating phototherapy-induced intestinal dysbiosis and mitigating its adverse effects, numerous clinical studies have confirmed that probiotics exert adjunctive function in the treatment of neonatal hyperbilirubinemia. Specifically, they can significantly reduce serum bilirubin levels in full-term neonates and late preterm infants, shorten the duration of jaundice, and thereby improve prognosis. Fan *et al.* [76] proposed mechanisms, including regulation of the intestinal microbiota, reduction of β-glucuronidase (β-GD) activity, inhibited bilirubin enterohepatic circulation, protected hepatic function to enhance bilirubin conjugation, and stimulated intestinal peristalsis and bilirubin excretion. Current evidence indicates that effective probiotic strains include *Bifidobacterium* [25], *Bacillus subtilis* [77], *Clostridium butyricum* [78], *Saccharomyces boulardii* [26,27], and *Bacillus licheniformis* [28], among others.

International studies include Mutlu *et al.* [29], who found that intervention with *Lactobacillus rhamnosus* in healthy neonates resulted in significantly lower serum bilirubin levels and bilirubin rebound 36 hours post-phototherapy compared to controls. This finding indicates that early probiotic intervention can reduce bilirubin levels, decrease the incidence of neonatal hyperbilirubinemia, and delay the onset of the condition. In Iran, Eghbalian *et al.* [30] showed that a probiotic complex shortened phototherapy duration and hospital stay for full-term hyperbilirubinemic infants. Nasief *et al.* [27] and Demirel *et al.* [31] have confirmed that Saccharomyces boulardii helps in the adjuvant treatment of hyperbilirubinemia in preterm infants. Clinical studies on *Bifidobacterium animalis* have also verified its efficacy as an adjuvant treatment for neonatal hyperbilirubinemia [25].

Some studies challenge the use of probiotics in neonatal hyperbilirubinemia. Santosa *et al.* [32] in Japan, using *Bifidobacterium animalis* to intervene in healthy term neonates, found that probiotics showed no significant effect in reducing bilirubin levels during the first five days of life. A randomized controlled trial by Serce *et al.* [33] concluded that *Saccharomyces boulardii* had no marked impact on the clinical course of neonatal hyperbilirubinemia. Furthermore, after pooling nine randomized controlled trials, Deshmukh *et al.* [79] found only limited, low-quality evidence supporting probiotics for shortening phototherapy duration in jaundiced neonates, thus not recommending their routine use of probiotics for preventing or treating neonatal jaundice.

Regarding probiotic selection, no adequate controlled studies have confirmed that multi-strain formulations are more effective than single strains. Conversely, when comparing *Saccharomyces boulardii* and *Lactobacillus casei* in treating neonatal pathologic jaundice, Sun *et al*. [34] found that both strains, when combined with phototherapy, significantly improved treatment efficacy for neonatal pathologic jaundice, with no significant difference in efficacy between the two strains.

Research on probiotic-aided therapy for neonatal hyperbilirubinemia is predominantly from Asian countries, whereas research on this topic in European nations remains relatively limited. This disparity may relate to the lack of internationally unified diagnostic criteria for neonatal hyperbilirubinemia, which could influence the reported incidence rates of this condition across different countries. Additionally, subjects in previous studies have exclusively included late preterm infants and term infants with a gestational age of $\geq$34 weeks, leaving a notable gap in clinical research data for preterm infants at $<$34 weeks' gestation.

Mechanism

In neonatal hyperbilirubinaemia, emerging work shows a layered mode of action: beyond reshaping the gut environment, probiotics tune metabolic and signalling checkpoints that, in turn, influence bilirubin production, conversion, and clearance. These convergent effects help explain their growing therapeutic promise.

In early neonatal life the gut microbiota is immature: aerobes predominate, while obligate anaerobes such as *Bifidobacterium* and *Lactobacillus* are relatively scarce [80]. This imbalance drives the accumulation of harmful metabolites, facilitating both the production and uptake of bilirubin. Probiotic supplementation accelerates the colonisation and expansion of beneficial taxa and curbs the growth of potential pathogens (e.g., Enterobacteriaceae and Enterococcus), thereby restoring microbial homeostasis. As the community adopts a healthier profile, bilirubin output falls and the intestinal environment stabilises—setting the stage for the spontaneous clearance of jaundice.

Probiotics also blunt the enterohepatic circulation. In the neonatal gut, β-glucuronidase hydrolyses conjugated bilirubin to its unconjugated form, which is readily reabsorbed and sustains hyperbilirubinaemia [81]. By producing acid, probiotics lower the luminal pH, suppressing enzyme-producing bacteria and directly diminishing enzymatic activity; the result is less hydrolysis of conjugated bilirubin. An acidified intestinal milieu further promotes anaerobe growth, yielding a more stable ecosystem that disfavors bilirubin reabsorption.

Probiotics also meaningfully influence gut motility. By generating SCFAs, they trigger contractions of the intestinal smooth muscle, sharpen gastrointestinal peristalsis, and ease the excretion of bilirubin with the faeces [82]. As the lumen becomes more acidic and its osmotic pressure rises, water secretion increases and stools are diluted, which further hastens transit. Evidence from several studies indicates that multi-strain formulations containing *Bifidobacterium* and *Lactobacillus* acidophilus act synergistically to boost motility and support bilirubin metabolism, resulting in a marked reduction in the duration of jaundice.

Overall, probiotics operate along a continuum: they restore microbial balance, suppress β-glucuronidase activity, interrupt the enterohepatic recycling of bilirubin, and enhance motility and elimination—shifting the system from "less production" to "less reabsorption" to "more excretion". This coherent biological orchestration positions probiotics as a valuable adjunct to phototherapy in neonatal jaundice and offers a credible, evidence-informed pathway for non-pharmacological intervention.

2.4 Respiratory System

Recent mechanistic research has expanded to identify the gut-lung axis, with several studies confirming beneficial effects of probiotics on respiratory diseases.

2.4.1 Ventilator-Associated Pneumonia (VAP)

VAP is defined as infectious inflammation of the lung parenchyma occurring $\geq$48 hours after the initiation and up to 48 hours after discontinuation of mechanical ventilation. In recent years, advances in perinatal medicine have led to the survival of increasingly premature infants, increased mechanical ventilation use, and a rising VAP incidence. Once VAP occurs in infants, treatment becomes more challenging, hospital stay is prolonged, and in severe cases it can be life-threatening.

Only a limited number of studies have reported the use of probiotics in VAP. In the neonatal intensive care unit (NICU) population, a randomized controlled trial enrolling full-term infants (gestational age 37–42 weeks) requiring invasive mechanical ventilation showed that daily supplementation with a probiotic preparation containing 2 $\times$ 10^9 CFU of Bifidobacterium animalis subsp. lactis BB-12 was associated with a significantly lower incidence of VAP, as well as shorter duration of mechanical ventilation and NICU stay. It has been proposed that probiotics may reduce the risk of respiratory pathogen colonization and pulmonary infection by enhancing mucosal barrier function, inhibiting pathogen adhesion and translocation, and modulating innate and adaptive immune responses [35].

Clinical studies on probiotics for VAP prevention remain limited in number, with those focusing on neonatal VAP being exceedingly scarce. Notably, an international RCT involving children under 12 years of age demonstrated that prophylactic administration of probiotics (*Lactobacillus* and *Bifidobacterium* at 3 $\times$ 10^9 CFU/day, administered for 7 days or until discharge) reduced the incidence of VAP in Pediatric Intensive Care Unit (PICU) patients [36]. This finding provides valuable reference for future neonatal VAP

trials, and it awaits further studies to confirm effectiveness and clarify mechanisms.

2.4.2 Respiratory Tract Infection

A randomized, double-blind, placebo-controlled trial in Finland (2000–2003) gave full-term newborns a 6-month intervention with multi-strain probiotics including *Lacticaseibacillus rhamnosus* GG and LC705, *Bifidobacterium lactis* Bb99, and *Propionibacterium freudenreichii* subsp. *shermanii* JS. During the intervention period, no adverse reactions were observed in the trial group, and the probiotic group had a lower frequency of respiratory infections [37]. A prospective clinical study in Ukraine in 2011 used Escherichia coli Nissle 1917 to supplement late preterm infants. The study found that within 28 days after birth, the proportion of acute respiratory infections (ARI) in the trial group was significantly lower than in the control group (10.0% vs 43.7%, $p = 0.008$) [38]. A multi-center RCT in France found that *Lactobacillus fermentum* had a similar effect [39]. However, an RCT in Japan using *Lactobacillus fermentum* for late preterm infants (gestational age <37 weeks) yielded negative results [40].

2.4.3 Bronchopulmonary Dysplasia

BPD, a common complication in preterm infants, remains incompletely understood in its pathogenesis. Traditionally, BPD has been associated with factors such as immature lung development, hyperoxic exposure, and inflammatory responses. Recent studies, however, emphasize a close association with intestinal microbiota via the gut-lung axis. Intestinal dysbiosis may promote BPD progression, suggesting that probiotics could potentially prevent or treat BPD through this axis [83].

A retrospective clinical study in China in 2021 found that *Clostridium butyricum* helped reduce the risk of BPD in extremely preterm infants (gestational age ≤ 32 weeks) [41]. A clinical randomized controlled trial by Li *et al*. [42] in 2024 also reached similar conclusions: *Clostridium butyricum* helped reduce the incidence of BPD in extremely preterm infants, and also shortened the oxygen administration time and hospital stay of infants.

Evidence for the use of probiotics in respiratory diseases remains limited, and the optimal timing, dosage, and duration of intervention are not well defined. Studies on VAP, ARI, and BPD are generally small-scale and heterogeneous, making it difficult to draw firm conclusions. Notably, some reports have suggested that administration of bifidobacteria within 24 hours of initiating mechanical ventilation, continued for approximately one week, may reduce both respiratory and gastrointestinal bacterial colonization in ventilated infants [43,44]. However, this observation is based on a small number of studies and requires confirmation through well-designed, adequately powered randomized controlled trials. At present, the optimal timing for probiotic intervention in respiratory disease is currently uncertain, and further methodologically robust clinical research is needed to establish evidence-based recommendations.

2.5 Allergic Reaction Disease

Allergies occur when the immune system overreacts to environmental or food antigens, manifesting as inflammatory symptoms such as eczema, rhinitis, vomiting, and diarrhea. In infancy and early childhood, the primary allergic disorders include eczema, erythema, and cow's milk protein allergy.

2.5.1 Eczema

As eczema peaks in infancy and early childhood rather than the neonatal period, research on probiotics for preventing and treating neonatal eczema is scarce. However, given that probiotics can exert positive effects during infancy and adolescence, early probiotic intervention in the neonatal period may reduce the subsequent development and progression of allergic diseases in infants and children.

Sun *et al*.'s 2021 meta-analysis [84] demonstrated that combinations of *Lactobacillus* and *Bifidobacterium* strains significantly reduced eczema incidence in children under three years of age. Notably, probiotic administration initiated early during pregnancy exhibited greater efficacy.

A 2025 RCT by Puisto *et al*. [45] reported similar findings: perinatal maternal probiotic intervention with *Lactobacillus rhamnosus*, *Lactobacillus paracasei*, and *Bifidobacterium bifidum* reduced the risk of atopic eczema in infants within the first 2 years of life. Notably, this protective effect appeared independent of gut microbiota modulation, as no statistically significant differences in gut microbial composition were detected between the groups. Additionally, a meta-analysis demonstrated that *Lactobacillus rhamnosus* effectively reduced eczema incidence. In the included studies, the timing of interventions ranged from 2–4 weeks prior to delivery to 6 months–2 years postpartum. The analysis revealed that this benefit was most pronounced during follow-up periods of up to 2 years and 6–7 years. By contrast, no statistically significant reduction in the incidence of atopic eczema was observed at 4–5 years or 10–11 years of follow-up [85].

2.5.2 Cow's Milk Protein Allergy (CMPA)

CMPA is the most prevalent food allergy in neonates, characteristically manifesting with clinical features such as cutaneous eczema, respiratory symptoms, and gastrointestinal disturbances. However, due to the immature immune response and other unique physiological characteristics of neonates, the clinical manifestations of CMPA often lack specificity, frequently leading to misdiagnosis as conditions like neonatal necrotizing enterocolitis, sepsis, among others [86]. While strict avoidance of milk proteins constitutes the cornerstone of therapy, emerging evidence supports adjuvant use of probiotics to alleviate allergy-related symptoms.

Luo and Zhang's study [46] showed that compared with the control group, after three months of continuous oral administration of probiotics (*Bifidobacterium lactis* BB12 + *Lacticaseibacillus rhamnosus* GG) in children with CMPA, significant statistical differences were observed in clinical symptoms such as vomiting, diarrhea, and food refusal, as well as in weight-for-age scores. However, no significant differences were noted during the first 1–2 months of intervention. These results indicate that probiotics should be administered for at least three months to significantly improve infant gastrointestinal function, thereby promoting nutritional metabolism and supporting weight gain in infants. Nocerino *et al.* [47] from Italy reported that the time to achieve immune tolerance was shortened in CMPA infants fed hydrolyzed formula supplemented with *Lactobacillus rhamnosus*. In addition, a six-month intervention with *Bifidobacterium* TMC3115 reduced allergic symptoms in CMPA infants, which is associated with an increased probiotic and decreased pathogenic bacteria proportion in the gut.

2.5.3 Mechanism

Probiotics recalibrate immune polarity by restoring the balance between Th1 and Th2 activity. Under allergic conditions, immunity is typically skewed towards a Th2 profile, with elevated IL-4, IL-5, and IL-13 driving IgE production and mast-cell degranulation. By shaping dendritic-cell differentiation and antigen presentation, probiotics enhance Th1-type signalling—most notably IFN-γ—which reins in the exaggerated Th2 response and re-establishes immune homeostasis [87,88]. This fine-tuned redirection of the response is a central way in which probiotics mitigate allergic disease.

Probiotics engage the host immunoregulatory network, driving the differentiation and expansion of regulatory T cells (Treg) [89]. By releasing IL-10 and TGF-β, Treg dampen effector T-cell activity and quell inflammation, creating an immunosuppressive microenvironment. Evidence indicates that targeted strains—most notably *Lactobacillus rhamnosus* GG and *Bifidobacterium longum*—can raise peripheral Treg frequencies and boost their regulatory capacity, thereby softening antigen-provoked responses in allergic individuals [90].

Through complementary mechanisms, probiotics foster immune tolerance. They lower IgE concentrations, weakening immune complex–mediated allergic reactions; simultaneously they restrain overactivation of mast cells and basophils, curbing histamine release and easing symptoms at their origin [3]. Probiotic derivatives also signal via intestinal epithelial receptors to reinforce barrier function and limit antigen translocation, helping the immune system to recognise that harmless exposures need not be treated as threats.

Probiotics do more than quell inflammation: they retune the immune network's "tone", guiding an overresponsive system back into balance—from restoring homeostasis to fostering tolerance. This measured, long-lasting modulation gives probiotics a distinctive biological appeal in the prevention and treatment of allergic disease.

3. Probiotic and Micronutrient Status

Although probiotics may influence human micronutrient status, research specifically targeting neonates remains scarce. Accordingly, this discussion focuses primarily on pediatric populations, while incorporating evidence from adult cohorts and non-clinical studies to inform potential applications in children and, and by extension neonates.

Micronutrient deficiencies pose a significant global health challenge, especially for children vulnerable due to rapid growth, unbalanced diets, and their high burden of infectious diseases. In addition to aiding food digestion and absorption, probiotic bacteria can synthesize various water-soluble vitamins, such as folate, riboflavin, vitamin B12, thiamine, and pyridoxine, and enhance the absorption of minerals like calcium, iron, and zinc. Compared to fortification using synthetically produced nutrients, modulation of host nutrient status through vitamin-producing and absorption-promoting probiotics is more physiologically aligned with natural metabolic pathways, potentially minimizing adverse effects.

3.1 Mineral Status

3.1.1 Iron

The relationship between probiotics and mineral status is complex. The systematic review by Apte *et al.* [91] analyzed the differences in the effects of probiotics on iron absorption between women and children. Through nalyzing 29 studies (14 in women of reproductive age, 15 in children), results for iron absorption were more favorable in women. Meta-analysis of six studies demonstrated a mean increase in serum ferritin of 2.45 ng/mL ($p = 0.009$) with moderate-quality evidence. More importantly, pooled data from eight studies on fractional iron absorption indicated a mean increase of 0.74% ($p = 0.02$), with particularly pronounced effects for galacto-oligosaccharides (GOS) and *Lactiplantibacillus plantarum* 299v. In contrast, the results for children were less encouraging. Meta-analysis of eight studies showed no significant change in hemoglobin, and four studies reported no improvement in serum ferritin.

3.1.2 Calcium and Zinc

The effects of probiotics on calcium and zinc nutrition also vary across populations. A randomized controlled trial by Agustina *et al.* [48] demonstrated that supplementation with *Lactobacillus reuteri* or *L. casei* failed to significantly improve serum calcium and zinc levels among children aged 1–6 years. However, positive results were observed in elderly [92] and postmenopausal women [93]. With regard to zinc, probiotics and zinc appear to exert a synergistic effect. In a randomized, double-blind, placebo-

controlled trial involving Indonesian children aged 12–24 months, four groups received either placebo, *Lactobacillus plantarum* IS-10506 (10^{10} CFU/day), zinc (8 mg/day), or the probiotic-zinc combination for 90 days. Neither probiotic nor zinc alone significantly improved serum zinc versus baseline, whereas combined supplementation significantly increased serum zinc levels [49].

3.2 Vitamin

3.2.1 Fat-Soluble Vitamins A and D

In clinical studies, randomized double-blind trials and open-label trials in children have shown that probiotic or combined prebiotic-probiotic interventions do not produce a marked improvement in vitamin A status. However, for vitamin D, an upward trend in serum levels was observed when multi-strain formulations containing *Lactobacillus plantarum*, *L. acidophilus*, *Bifidobacterium infantis*, and *B. lactis* were used [50], although statistical significance was not always clearly reported and results varied across populations. Studies in both pregnant women and children suggest that the effects depend on strain type (e.g., *L. reuteri*, *B. animalis*), dosage, and duration of intervention, and the findings remain inconsistent. Therefore, current evidence is insufficient to establish a consistent beneficial effect of probiotics on vitamin A or D status.

3.2.2 Water-Soluble Vitamins B

Evidence supporting the role of probiotics in enhancing the production of water-soluble B vitamins is relatively strong; however, this effect appears to be highly strain-specific rather than rather than a general property of a genus. Lactic acid bacteria and bifidobacteria are recognized as key contributors to B-vitamin production in the human gut, yet their synthetic capacity, the spectrum of vitamins produced, and the bioavailability of these compounds vary substantially among different strains. An animal study has shown that *Bifidobacterium adolescentis* can produce vitamin B9 (folate) [94]. A human study has also confirmed that *Bifidobacterium adolescentis* DSM 18350, *B. adolescentis* DSM 18352, and *B. pseudocatenulatum* DSM 18353 are capable of synthesizing and secreting folate in the human intestinal environment, thereby providing a constant additional source of endogenous folate within the gut lumen [95]. However, the number of high-quality randomized controlled trials is small, and direct evidence in pediatric populations, particularly in neonates, remains scarce.

Animals, plants, and fungi are incapable of vitamin B12 (cobalamin) production and it is exclusively synthesized by microorganisms. *Lactobacillus reuteri* CRL1098 was shown to be the first lactic acid bacteria strain able to produce a cobalamin-like compound [96]. *In vitro* studies have demonstrated that Lactobacillus plantarum is also capable of producing vitamin B12 [97]. In addition to direct synthesis, probiotics may improve vitamin B12 status by modulating gut microbiota composition, potentially reducing the abundance of bacterial species that degrade this vitamin [98].

Collectively, these findings indicate that while probiotics contribute significantly to B-vitamin availability, their effects are not uniform across vitamins and species. This highlights the need for precise, strain-level selection and validation in probiotic applications, particularly when targeting specific vitamins or addressing the needs of vulnerable populations such as children.

4. Safety of Probiotic Applications

In clinical practice, most patients tolerate probiotics without adverse effects, with only a small minority reporting gastrointestinal issues. While the majority of current clinical trials and practical applications have not associated probiotic use with significant adverse events, some studies highlight a potential risk of probiotic-associated sepsis, particularly in preterm infants.

Kulkarni *et al.*'s systematic review [99] included 16 reports involving 32 newborns with probiotic sepsis (blood/cerebrospinal fluid cultures positive for the administered probiotic strains, accompanied by clinical manifestations of infection). Two of these newborns died (one death was unrelated to probiotic supplementation), and the rest were successfully treated with antibiotic and antifungal therapy. The probiotics involved included *Bifidobacterium longum*, *Bifidobacterium breve*, *Lactobacillus rhamnosus*, *Lactobacillus reuteri*. Most cases were preterm infants with a gestational age of less than 32 weeks. A 2025 meta-analysis by Feldman *et al.* [100], incorporating 63 studies with over 20,000 participants, evaluated the risk-benefit ratio of probiotics in preterm infants and found the overall incidence of probiotic sepsis to be less than 0.04%, supporting a favorable benefit-risk profile.

However, potential under-detection due to diagnostic limitations worth consideration. In the studies included by Feldman *et al.* [100], only two large observational studies involving 562 infants captured all 8 probiotic sepsis events, both of which emphasized unique detection methods. One study used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry for improved strain identification, while the other extended blood culture time to 7 days (noting that the growth period of *Bacillus brevis* under aerobic conditions is 133 hours), thus capturing relevant probiotic bacteremia cases. Similarly, Abda *et al.* [101] identified probiotic bacteremia cases through aerobic blood culture for 10–21 days, far exceeding the current clinical standard of 5 days for blood culture.

A 2025 clinical study by Athalye-Jape *et al.* [51] found no statistically significant differences in gut microbial changes or clinical outcomes between groups receiving heat-inactivated and live *Bifidobacterium*, suggesting that heat-inactivated probiotics may offer benefits while circumventing the risk of probiotic sepsis.

In conclusion, current attitudes toward probiotic safety are generally positive, with an extremely low incidence of probiotic sepsis and effective antibiotic intervention. However, the possibility of missed diagnoses due to monitoring limitations cannot be overlooked. Recent research suggests that using heat-inactivated probiotics may circumvent the risks associated with live probiotics.

5. Future Perspectives

Natural probiotics help sustain gut homeostasis and support host health, yet real-world effectiveness is constrained by strain specificity, inter-individual variability, and the host microenvironment. Typically sourced from fermented foods or commensal flora, most strains colonise only transiently, narrowing the window for interaction with resident microbes. Because their activity hinges on native gene-expression programmes and lacks tunable control, strains differ widely in metabolite output, immune modulation, and barrier support. This variability underlies the lack of consensus on which strains to use, at what dose, and for how long, and it limits both comparability and reproducibility across studies. While several trials report benefits, results often vary by population and disease model—and sometimes point in opposite directions. Survival and adhesion are frequently poor in the complex gut milieu, yielding short-lived colonisation and waning therapeutic effect. Although generally safe, live preparations can rarely cause bacteraemia, catheter contamination, or horizontal transfer of resistance genes; caution is therefore warranted in preterm infants and in immunocompromised individuals [102].

Rapid progress in synthetic biology has catalysed the rise of genetically modified probiotics (GMPs), providing ways to surmount the functional variability of natural strains. By combining targeted gene editing, pathway re-engineering, and tunable regulatory circuits, investigators can programme probiotic chassis with bespoke therapeutic functions—sensing pathological cues, producing anti-inflammatory peptides, or detoxifying harmful metabolites [103]. Notably, engineered *Escherichia coli* Nissle 1917 strains can detect oxidative stress within the gut and release anti-inflammatory effectors, while embedded biosensors finely control therapeutic-protein expression. Together, these capabilities show promise for gastrointestinal disorders and metabolic dysregulation [104,105], marking a shift from passive micro-ecological modulation to genuinely programmable living medicines.

The rollout of GMPs is still limited by safety and regulatory hurdles. Exogenous gene insertion can compromise genomic stability and enable the horizontal transfer of antimicrobial-resistance genes, creating risks of environmental spread [104]. Accordingly, engineered strains must maintain reliable function and incorporate rigorous biocontainment to prevent escape or onward transmission. Within current frameworks, genetically modified probiotics are regulated as live biotherapeutic products (LBPs) and are required to meet pharmaceutical-grade expectations for genetic stability, traceability, and manufacturing consistency. These higher safeguards elevate safety but inevitably slow the pace of clinical translation.

On balance, natural probiotics benefit from a favourable safety profile and an extensive record of use, yet functional uncertainty and poor colonisation limit their application and impede the standardisation of efficacy. In contrast, genetically modified probiotics offer compelling scope for precise control and targeted therapy, with the potential to deliver directed immune modulation, metabolic correction, and both prevention and treatment of disease. Looking ahead, progress hinges on striking the right balance between safety, functional stability, and ecological containment. The end-point is a shift from empirical formulations to rationally designed, bioengineered—and ultimately programmable—therapeutic platforms.

Availability of Data and Materials

The clinical study used and analyzed during the current study are available from PubMed and CNKI on reasonable request.

Author Contributions

ZS: designed the research study, performed the research, writing original draft, writing-review and editing. YY: designed the research study, performed the research, writing-review and editing. JC: designed the research study, performed the research, writing-review and editing. FZ: designed the research study, performed the research, writing-review and editing. JZ: Conceptualization, Funding acquisition, Investigation, Resources, Software, Visualization, Writing-review & editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGpt-4.0 to check spell and grammar. After using this

tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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