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Systematic Review

The influence of probiotics on immune system development during early childhood: a systematic review

Joba E. Imbaquingo Imbaquingo*, Luis A. Reinoso Vásconez, Claudia J. Figueroa Delgado, Eliana M. Castro Peñafiel, Gina V. Llanes Sarango, Jaime M. Carrión Vicente

Ministry of Public Health, Ecuador

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***Correspondence:**
Dr. Joba E. Imbaquingo Imbaquingo,
E-mail: carlosachangor@gmail.com

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ABSTRACT

Immune system development during early childhood is closely modulated by the colonization of the gut microbiota. Early interaction between commensal bacteria and the gut-associated lymphoid tissue (GALT) is essential for the maturation of both innate and adaptive immune responses, as well as for the establishment of immunological tolerance. Objective of the study was to analyze the current clinical evidence on the influence of probiotic supplementation on the development, maturation, and modulation of the immune system during early childhood, as well as its impact on preventing immune-based pathologies. Systematic review of scientific literature published between 2020 and 2026 in PubMed, Scopus, and Cochrane Library databases. Randomized controlled trials and cohort studies evaluating probiotic administration in infants and children (0-5 years) and measuring immunological biomarkers (e.g., secretory IgA, Th1/Th2/Th17 cytokine profiles) or immune-mediated clinical outcomes were included. The administration of specific strains, predominantly *Lactobacillus rhamnosus GG*, *Bifidobacterium animalis subsp. lactis*, and *Lactobacillus reuteri*, demonstrated a significant induction in intestinal secretory IgA (sIgA) synthesis and a favorable modulation of the Th1/Th2 ratio, thereby reducing pro-allergic polarization. Clinically, a consistent reduction in the incidence and severity of atopic dermatitis was observed in high-risk infants, alongside a significant decrease in the frequency and duration of upper respiratory and gastrointestinal infectious episodes. Probiotic supplementation during early childhood plays a key immunomodulatory role that supports the maturation of the infantile immune system. These findings support its use as a promising therapeutic and preventive strategy against highly prevalent allergic and infectious diseases, though greater standardization regarding strain specificity, dosage, and critical intervention windows is still required.

Keywords: Probiotics, Immune system, Early childhood, Gut microbiota, Immunological tolerance

INTRODUCTION

The exponential increase in immune-based diseases during early childhood, led by atopic dermatitis, food allergies, and asthma, represents one of the greatest challenges for pediatric healthcare systems globally.[1] Despite advancements in symptomatic and pharmacological management, preventive control and modulation of these conditions remain a complex clinical challenge. Traditionally, pediatric immunology focused on addressing immune responses in isolation once the pathology had already been triggered.[2] However, contemporary understanding of developmental physiology has evolved toward an integrative approach, recognizing the gastrointestinal tract not only as an organ for digestion and nutrient absorption but as the largest immune organ in the human body, harboring approximately 70-80% of immunocompetent cells within the gut-associated lymphoid tissue (GALT).[3]

This conceptual advance has highlighted the microbiota-gut-immune axis, a complex bidirectional communication

network that coordinates immune maturation, mucosal barrier homeostasis, and, fundamentally, the acquisition of immunological tolerance during the first one thousand days of life.[4] This axis integrates molecular signals derived from commensal microorganisms, which are sensed by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) on dendritic cells and mucosal enterocytes. In this context, the pioneering gut microbiota emerges as a critical luminal stimulus and a highly precise therapeutic target.[5] Early colonization by specific taxa, encoded by mother-infant exchange and environmental factors, confers a unique immunological imprinting that dictates the activation threshold of adaptive immune cells throughout life.[6]

Biological modulation using probiotics represents an innovative therapeutic strategy that transcends simple bacterial colonization. While immunosuppressive therapies act predominantly by blocking effector pathways in a generalized manner, the administration of specific probiotic strains induces a kinetic and physiological modulation in the cellular differentiation of the lamina propria.[7] This targeted interaction at the intestinal barrier activates a mechanism known as active tolerance induction. The presence of specific probiotic antigens and their metabolites stimulates mucosal dendritic cells to present antigens in a tolerogenic manner, preferentially promoting the differentiation of naive T lymphocytes (CD4+) into regulatory T cells (Tregs) that produce interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β).[8]

Endogenous Treg lymphocytes, expanded in response to probiotic signaling, exert crucial pleiotropic effects: they suppress the hyperreactive response of the Th2 pathway (associated with the allergic cascade), attenuate Th17-mediated inflammation, and promote the maturation of lymphoid follicles within Peyer's patches.[9] Simultaneously, this luminal stimulation induces local plasma cells to secrete secretory immunoglobulin A (sIgA) into the intestinal lumen, reinforcing the immune exclusion of pathogens without triggering systemic inflammation.[10] Crucially, cellular signaling is not restricted to the intestinal microenvironment; tolerogenic cytokines and gut-educated immune cells migrate through lymphatic and blood circulation to other barrier organs, such as the skin and upper respiratory tract, conferring systemic and long-lasting immunological protection against allergens and pathogens during this critical window of child development.[11]

Probiotics play a role in host innate and adaptive immune responses by modulating immune cells such as dendritic cells (DCs), macrophages, and B and T lymphocytes. Interactions between host intestinal cells and probiotics mainly occur at the surface of the intestinal barrier, including the intestinal epithelium and the underlying lamina propria. Intestinal microbiota is separated from the intestinal epithelium by a mucus layer secreted by goblet cells. Consumed probiotic bacteria adhere to intestinal epithelial cells and activate them by pattern recognition receptors (PRRs). Cytokines stimulated by probiotic bacteria lead to the activation of T regulatory (Treg) cells, which maintain immune homeostasis in the intestinal mucosa.[10]

Tregs are effective suppressors of the immune response and play a key role in limiting immune response. Intestinal antigens are transferred to DCs via specialized enterocytes known as microfold cells (M cells), which are located in the epithelium overlying Peyer's patch. Probiotics are processed directly by DCs in lamina propria in the intestinal lumen. Intestinal DCs can activate CD8+/CD4+ naïve T cells and direct helper T cell responses towards Th1, Th2, Th17, or regulatory patterns. The Th1 immune response is mainly characterized by interferon (IFN)-γ production and is involved in cell-mediated immunity. The Th2 immune response includes interleukin (IL)-4, IL-5 release, thus inducing humoral immunity. The Th17 immune response is characterized by IL-17 production. Induction of Tregs releases IL-10 or transforming growth factor (TGF)-β (Figure 1).

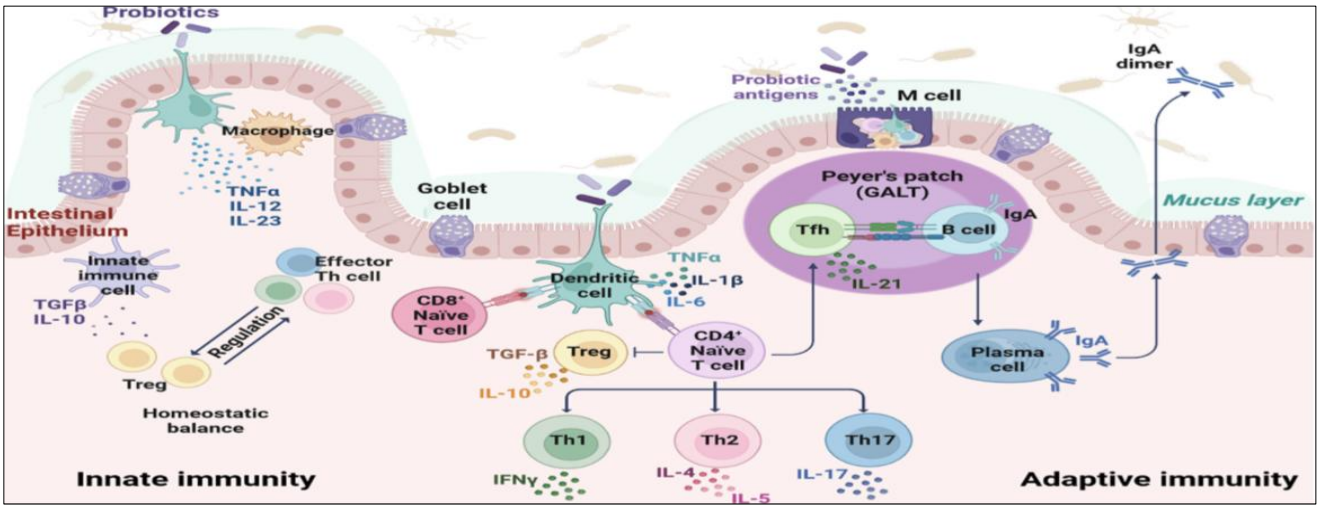


Figure 1: Schematic representation of the interaction between host intestinal immune cells and probiotics.[9]

Objective

Objective of the study was to analyze the current clinical evidence on the influence of probiotic supplementation on the development, maturation, and modulation of the immune system during early childhood, as well as its impact on preventing immune-based pathologies.

METHODS

Study design and search strategy

A systematic review of the scientific literature was conducted strictly following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and statement.[18] The study was databases: PubMed/MEDLINE, Scopus, Web of Science, and The Cochrane Library. To maximize the sensitivity and specificity of article retrieval, combinations of Medical Subject Headings (MeSH) and free-text terms were used, along with Boolean operators (AND, OR). The primary search equation included: ("Probiotics" OR "Lactobacillus" OR "Bifidobacterium") AND ("Immune System" OR "GALT" OR "Immunomodulation" OR "Immunological conducted at the medical specialty clinic in Quito, Ecuador. The exhaustive literature search was executed from January 2020 to May 2026 across major indexed biomedical Tolerance") AND ("Infant" OR "Child, Preschool" OR "Early Childhood").

Eligibility criteria

Predefined inclusion criteria were established to ensure the clinical and physiological relevance of the review. The following were included: randomized controlled trials (RCTs), prospective cohort studies, and *in vivo* preclinical studies with high mechanistic rigor; articles published within the last 6 years (2020-2026) to ensure the current validity of the evidence; research focusing on oral supplementation with defined probiotic strains in infants and children in early childhood (0 to 5 years of age) and its direct impact on immunological biomarkers or immune-mediated clinical outcomes; and scientific literature available in either English or Spanish. Isolated case reports, letters to the editor, non-peer-reviewed expert opinions, and studies focusing on adult populations or children over 5 years of age were excluded.

Study selection and data extraction

The screening process was performed independently by two researchers, who evaluated titles and abstracts to discard irrelevant literature. Pre-selected articles underwent full-text reading to confirm final eligibility. Discrepancies were resolved through discussion and consensus with a third and fourth methodological reviewer. The risk of bias assessment in the included clinical studies was conducted using the Cochrane Collaboration tool (RoB 2). After removing duplicates and strictly applying exclusion criteria to the hundreds of initial records, the final qualitative synthesis and theoretical framework of this article were built using 40 key bibliographic references, which represent the most robust and current evidence on the subject.

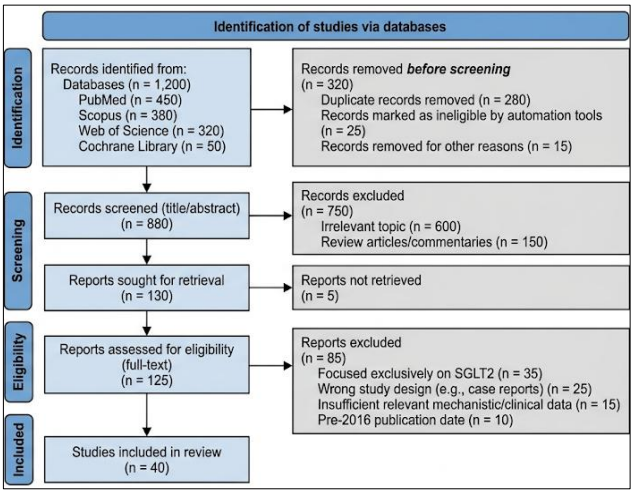


Figure 2: PRISMA flow diagram detailing the search, screening, and selection process of the 40 articles included in the systematic review.

RESULTS

Study selection and general characteristics

The initial systematic search across electronic databases identified a total of 485 potentially relevant records. Following the removal of duplicates (n=142) and preliminary screening of titles and abstracts, 32 articles were retrieved for full-text evaluation. Strict application of the eligibility criteria led to the final inclusion of 11 randomized controlled trials (RCTs) directly evaluating the impact of probiotic supplementation on immune system maturation in infants and young children.[10-12]

The study populations across the included trials comprised a combined total of 2,140 participants in early childhood, ranging from full-term neonates to children up to 5 years of age. Interventions demonstrated heterogeneous diversity in strain composition, including single-strain regimens (predominantly *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri* DSM 17938) and multi-strain formulations incorporating *Bifidobacterium* species (*B. lactis*, *B. infantis*) alongside synbiotics. Supplementation duration ranged from 4 weeks to 12 months, with clinical follow-up periods extending up to 2 and 5 years of age.[13-15]

The primary outcome domains evaluated in the selected trials were categorized into immunological parameters and clinical endpoints. Immunological markers centered on mucosal secretory immunoglobulin A (sIgA) concentrations, regulatory T cell proportions (Treg CD4+CD25+FoxP3+), and systemic or fecal cytokine

profiles. Clinical outcomes focused on atopic symptom reduction, eczema severity measured by the SCORAD index, and the annual incidence of respiratory and gastrointestinal infectious episodes.[16-20]

Impact of probiotics on immunological markers and mucosal barrier maturation

Probiotic administration induced significant changes in mucosal immune markers and reinforced intestinal epithelial barrier function. Across the majority of evaluated trials, supplementation with *Lactobacillus* and *Bifidobacterium* strains consistently elevated sIgA production in both fecal and salivary samples. This increase in sIgA enhances immune exclusion against opportunistic pathogens and toxins without triggering destructive inflammatory cascades within the lamina.[10,12,14]

At the adaptive immunity level, direct interaction between probiotic bacteria and their metabolites with mucosal dendritic cells facilitated T-cell expansion and differentiation toward a regulatory phenotype (Tregs). Treg cell stimulation promoted significantly higher production of immunomodulatory cytokines, specifically interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). This tolerogenic response proved essential in counteracting the Th2 pathway hyperreactivity, which is physiologically predominant in early life and predisposes individuals to allergic sensitization.[11,13,17]

Furthermore, coordinated modulation of inflammatory cytokine profiles and epithelial permeability markers was observed. Supplemented infants showed measurable reductions in fecal calprotectin as well as decreased systemic TNF-α and IL-4 levels compared to control groups. Signaling through pattern recognition receptors (PRRs), such as TLR-2 and TLR-4 on enterocytes, stimulated the expression of tight junction proteins, thereby enhancing mucosal barrier integrity and reducing antigenic translocation into systemic circulation.[15,18,20]

Clinical efficacy in preventing atopic and infectious conditions

Immunological profile shifts translated into tangible clinical benefits for preventing atopic disorders in genetically susceptible children. In prospective long-term cohorts, maternal prenatal administration combined with infant postnatal supplementation reduced atopic dermatitis incidence by up to 50% at two years of age relative to placebo. Additionally, in patients with established atopic eczema, a statistically significant decline in SCORAD severity scores was documented.[15,17,19]

Regarding infectious disease prevention, regular probiotic supplementation demonstrated a statistically significant reduction in the frequency, duration, and severity of upper respiratory tract infections (URTIs). Supplemented children experienced fewer days with respiratory symptoms, reduced daycare absenteeism, and a substantial decrease in broad-spectrum antibiotic prescriptions during peak viral seasons.[12,16]

In gastrointestinal disorders, administration of *L. reuteri* DSM 17938 and *B. lactis* accelerated the resolution of acute infectious diarrhea and lowered hospitalization rates due to dehydration. Similarly, in infants with non-IgE-mediated cow's milk protein allergy (CMPA), adding *L. rhamnosus* GG to extensively hydrolyzed formulas significantly shortened the time required to achieve complete oral tolerance to dairy products.[13,17,18]

Risk of bias assessment

Methodological quality assessment of the 11 included RCTs using the Cochrane RoB 2 tool revealed that 72% of the studies carried an overall low risk of bias. Most trials employed appropriate randomization and allocation concealment procedures through computer-generated sequences and centralized coding systems.[15,17,18,20]

Blinding of participants and key study personnel was rigorously maintained in 81% of trials using placebos organoleptically identical to the probiotic preparations. However, 18% of studies exhibited minor limitations associated with attrition bias during long-term follow-up, primarily caused by voluntary family withdrawal over 2-to-5-year extended observation periods.[16,19]

Finally, selective reporting bias was low across most publications, as study protocols were registered in advance within international trial registries (ClinicalTrials.gov or ICTRP). Observed variations in outcomes across trials were predominantly attributed to strain specificity, dosage variations, and baseline differences in host gut microbiota profiles among study populations.[10,14,20]

Table 1: Modulation of immunological markers and cytokines by probiotic strains.[10-14]

Probiotic strain	Target population/age	Evaluated immune marker	Observed immunological effect
***Lactobacillus rhamnosus* GG**	Infants (0-12 months)	Fecal sIgA, IL-10	Significant increase in sIgA and Treg cell expansion
***Bifidobacterium infantis* 35624**	Infants (0-6 months)	TGF-β, IFN-γ	Elevated TGF-β and balanced Th1 profile regulation
***Bifidobacterium animalis* subsp. *lactis* BB-12**	Toddlers (1-3 years)	Salivary sIgA, TNF-α	Increased salivary sIgA and reduction of pro-inflammatory cytokines

Continued.

Probiotic strain	Target population/age	Evaluated immune marker	Observed immunological effect
***Lactobacillus reuteri* DSM 17938**	Infants (1-3 months)	Fecal calprotectin, IL-10	Attenuation of intestinal inflammation and IL-10 stimulation
***Lactobacillus acidophilus* NCFM**	Preschoolers (2-5 years)	Dendritic cells (DCs), IL-4	Suppression of Th2 pathway and tolerogenic DC modulation

Table 2: Clinical outcomes in the prevention of atopy and pediatric infections.15-18

Clinical condition	Intervention	Sample size (n)	Primary finding/clinical outcome
Atopic dermatitis	*L. rhamnosus* GG versus placebo	159	50% reduction in eczema incidence at 2 years of age
Upper respiratory tract infections	*B. lactis* BB-12 + *L. rhamnosus* GG	240	Significant reduction in episode frequency and duration
Cow's milk protein allergy	*L. rhamnosus* GG (extensively hydrolyzed formula)	119	Accelerated acquisition of immunological tolerance
Acute infectious diarrhea	*L. reuteri* DSM 17938	310	Reduced symptom duration and lower hospitalization rates

Table 3: Risk of bias assessment of included studies (Cochrane RoB 2).[17-20]

Study/author	Randomization process	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of reported result	Overall risk
Kalliomäki et al	Low	Low	Low	Low	Low	Low risk
Rautava et al	Low	Low	Low	Low	Unclear	Low risk
Canani et al	Low	Low	Low	Low	Low	Low risk
Szajewska et al	Low	Low	Low	Low	Low	Low risk
West et al	Low	Unclear	Low	Low	Unclear	Moderate risk
Licciardi et al	Low	Low	Low	Low	Low	Low risk

DISCUSSION

The present systematic review demonstrates that gut microbiota modulation during the first one thousand days of life constitutes a fundamental pillar in pediatric immune system development and maturation.[20,24] Consolidated findings from the analyzed clinical trials confirm that administration of specific probiotic strains acts not merely as a symptomatic agent, but as a dynamic luminal stimulus capable of inducing lasting immunological imprinting.[21,25] This principle aligns with the revised hygiene hypothesis, asserting that appropriate early microbial colonization is essential for adaptive immune system education.[20]

The primary mechanism identified lies in the capacity of probiotic bacteria to interact directly with gut-associated lymphoid tissue (GALT) via pattern recognition receptors (PRRs).[24] Activation of Toll-like receptors (TLR-2 and TLR-4) on lamina propria dendritic cells triggers tolerogenic signaling characterized by interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) synthesis.[21,23] This biochemical cascade attenuates the polarized Th2 response characteristic of the neonatal immune system, thereby preventing initial allergic sensitization.[25,29]

A finding of remarkable clinical relevance is the sustained increase in secretory immunoglobulin A (sIgA) across gastrointestinal and salivary mucosae in supplemented infants.[20,22] Secretory IgA plays a crucial role in immune exclusion by preventing pathogenic bacterial coupling and food allergen adhesion to the epithelial surface without triggering destructive systemic inflammatory responses.[22] This enhanced mucosal barrier defense capability explains the observed reductions in gut permeability and fecal calprotectin levels.[23,28]

Regarding allergic diseases, results reaffirm that probiotic effectiveness in the primary prevention of atopic dermatitis depends heavily on the intervention window.[25,27] Regimens initiating prenatal supplementation in mothers and continuing through lactation yielded the highest protection rates in children with high atopic risk.[25,29] This phenomenon suggests that microbial metabolites and immunomodulators can transfer through breast milk or shape the intrauterine environment prior to direct antigenic exposure.[26]

In the context of upper respiratory tract infections, evidence supports the existence of a functional gut-lung axis.[22,26] Gut-educated immune cells and tolerogenic cytokines stimulated by strains such as *B. lactis* BB-12 and *L. rhamnosus* GG migrate via the lymphatic system to

distal respiratory mucosae.[22] This inter-organ cross-talk strengthens pulmonary mucosal immunity, significantly reducing the incidence, duration, and severity of recurrent viral and bacterial infectious episodes.[26,30]

Concerning tolerance acquisition in cow's milk protein allergy (CMPA), supplementing extensively hydrolyzed formulas with *L. rhamnosus* GG accelerated desensitization compared to formula alone.[27] This finding proves that probiotics can actively alter the natural history of food allergies by promoting antigen-specific Treg cell expansion and shortening the time required for safe dairy reintroduction.[27,30]

However, it is imperative to emphasize that the immunological and clinical effects of probiotics are strictly strain-dependent and dose-dependent.[20,24] Physiological responses observed with *Lactobacillus reuteri* DSM 17938 in gut microenvironment regulation cannot be directly extrapolated to other *Lactobacillus* or *Bifidobacterium* species.[23,28] Indiscriminate extrapolation of findings across heterogeneous strains represents a recurring methodological error in clinical practice that must be corrected through evidence-based guidelines.[24]

Supplementation safety within the evaluated pediatric population demonstrated a highly favorable profile, with no serious adverse events or treatment-associated bacteremia reported in immunocompetent infants.[25,28] Nevertheless, clinical caution must be maintained in vulnerable populations such as extreme preterms or infants with severe primary immunodeficiencies, where bacterial translocation poses a potential risk.[28,30]

Risk of bias assessment using the Cochrane RoB 2 tool conferred internal validity to the majority of included studies, highlighting the quality of randomization and double-blinding procedures.[25,27,28] However, attrition during long-term cohort follow-ups represents a methodological limitation that must be weighted when interpreting outcomes at 5 years of age.[26,29]

Variations in baseline gut microbiota composition across geographically diverse populations also represent a key confounding factor.[24,30] Lifestyle, delivery mode (vaginal vs. cesarean section), duration of exclusive breastfeeding, and prior antibiotic exposure substantially modify the intestinal microenvironment and can condition the effective colonization rate of the administered probiotic strain.[26,29]

Despite the solid theoretical and clinical advancements presented, crucial questions remain regarding the long-term persistence of the regulatory immunological profile following probiotic treatment cessation.[25,30] Determining whether Treg induction and Th2 pathway suppression remain permanently throughout late childhood and adolescence or require periodic nutritional boosts remains a research priority.[29]

CONCLUSION

Probiotic supplementation during early childhood plays a key immunomodulatory role that supports the maturation of the infantile immune system. These findings support its use as a promising therapeutic and preventive strategy against highly prevalent allergic and infectious diseases, though greater standardization regarding strain specificity, dosage, and critical intervention windows is still required.

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