REVIEW ARTICLE

The impact of delivery mode on neonatal microbiota development and long-term health outcomes: A literature review

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ABSTRACT

Early microbial colonization plays a foundational role in shaping the infant's immune, metabolic, and neurological development. The mode of delivery significantly influences this process. Vaginal birth enables physiological exposure to maternal microbiota, while elective cesarean section disrupts this transfer and results in delayed colonization and reduced microbial diversity. This review examines how different delivery modes affect neonatal gut microbiota composition and evaluates their long-term implications for health, with a focus on immune regulation, metabolic programming, allergic conditions, and neurodevelopmental outcomes. Relevant literature from 2010 to 2024 was reviewed using PubMed, Scopus, and Web of Science databases. Human studies comparing elective cesarean section and vaginal delivery were included if they analyzed microbiota profiles and at least one long-term clinical parameter. Out of 245 initially screened articles, 36 were selected based on methodological quality and relevance. Evidence indicates that cesarean section is associated with altered microbial succession patterns that may increase the risk of autoimmune diseases, allergies, obesity, and cognitive or behavioral disturbances. Proposed mechanisms include impaired development of regulatory T cells, reduced production of short-chain fatty acids, and dysregulated immune responses. Although a few studies suggest transient protective effects in specific clinical scenarios, these findings are inconsistent and population-dependent. Supportive interventions such as exclusive breastfeeding and microbiota-based therapies may help restore microbial balance and mitigate adverse outcomes. Future research should focus on identifying biomarkers of dysbiosis and developing personalized strategies to promote microbiota-driven health from birth.

KEY WORDS: cesarean section, intestinal microbiota, microbial transmission, immune tolerance, chronic disease

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INTRODUCTION

The human microbiota - understood as a complex ecosystem of microorganisms inhabiting body surfaces, including the gastrointestinal tract, skin, and mucous membranes - plays a fundamental role in maintaining homeostasis. It contributes to digestion, vitamin synthesis, protection against pathogens, and immune regulation. Early microbial colonization is essential for the proper maturation of the immune and metabolic systems, with long-term consequences for health throughout childhood and adulthood.

One of the key factors influencing the composition and developmental trajectory of the neonatal microbiota is the mode of delivery. Vaginal birth allows for exposure to the maternal vaginal, perineal, and anal microbiome, initiating gut colonization by symbiotic bacteria. In contrast, infants delivered by elective cesarean section do not pass through the birth canal and are instead first exposed to skin-associated flora from medical personnel and the hospital environment. This results in reduced microbial diversity and delayed microbiota maturation, which have been correlated with various adverse health outcomes and developmental alterations across multiple organ systems [1, 2].

AIM

This literature review aims to assess how the mode of delivery affects the development and composition of the neonatal gut microbiota and to identify potential long-term health consequences arising from disruptions in its colonization. The focus is placed on immune, metabolic, and neurological outcomes linked to early-life microbial patterns.

MATERIALS AND METHODS

This narrative literature review was conducted using structured searches in three major databases: PubMed, Scopus, and Web of Science. The search covered publications from 2000 to 2025 and employed standardized MeSH terms and English-language keywords, including: *cesarean section, vaginal delivery, mode of delivery, gut microbiota, infant microbiome, immune development,* and *long-term health outcomes."* Logical operators (AND, OR) were applied to refine the search strategy.

Inclusion criteria comprised original human studies (cohort, prospective, or randomized) and systematic reviews comparing elective cesarean section (ECS) - performed before the onset of labor - with physiological vaginal birth without surgical or pharmacological intervention. Eligible studies were required to assess neonatal gut microbiota composition and include at least one indicator of long-term health outcomes, such as autoimmune, allergic, metabolic, or neurodevelopmental conditions.

Exclusion criteria included:

Preterm births (<37 weeks of gestation),

Urgent or emergency cesarean sections,

Neonates with congenital anomalies or those admitted to neonatal intensive care units.

An initial pool of 245 publications was screened. After title and abstract screening, 48 articles met preliminary criteria. Full-text assessment and evaluation of methodological rigor led to the final inclusion of 36 studies in the synthesis. While this review does not follow PRISMA guidelines in full, elements of the GRADE framework were used to qualitatively rank the strength of evidence.

OPERATIONAL DEFINITIONS

For the purposes of this review, the following definitions of key terms have been adopted:

Vaginal birth (physiological delivery) – a spontaneous, non-instrumental birth initiated by natural uterine contractions and proceeding without surgical or pharmacological interventions (e.g., without oxytocin stimulation). This type of delivery enables the newborn to come into contact with the maternal vaginal, perineal, and anal microbiota, providing the first crucial stimulus for intestinal colonization.

Elective cesarean section (ECS) – a surgical delivery performed prior to the onset of spontaneous labor, based on predefined medical or non-medical indications. In this case, the newborn's initial microbial exposure is restricted mainly to maternal skin flora, medical personnel, and the hospital environment (including sterile surfaces and conditioned air), leading to a distinct and often delayed pattern of microbial colonization. Importantly, recent studies have shown that the length of postpartum hospital stay may further modulate this process, particularly in cesarean-born infants who experience prolonged exposure to sterile clinical settings and reduced physical contact with maternal microbiota [3, 4].

Microbiota – the entire community of microorganisms (including bacteria, archaea, fungi, and viruses) that inhabit the surfaces and internal spaces of the human body, forming a complex ecosystem closely associated with immunological, metabolic, and neurological processes. In this review, particular emphasis is placed on the gut microbiota, which during the neonatal period shapes mucosal immunity and influences the maturation of T and B lymphocytes.

EMERGING DATA: PLACENTAL AND RESPIRATORY TRACT MICROBIOTA

In recent years, the concept of the "sterile womb paradigm" has been challenged [5] detected bacterial DNA in placental tissue using 16S rRNA sequencing, suggesting the possibility of microbial "programming" in utero. However, the interpretation of these findings remains controversial due to methodological concerns - there is a risk of sample contamination, and the presence of DNA does not necessarily imply the existence of viable microorganisms [6].

Additionally, the mode of delivery also influences the composition of the respiratory and oral microbiota, which may affect infection risk and predisposition to atopic diseases in early life [2]. Cohort studies have shown that infants born via cesarean section are more frequently colonized by opportunistic bacteria in the upper respiratory tract, such as *Staphylococcus aureus* and *Klebsiella pneumoniae*, whereas beneficial strains such as *Corynebacterium* and *Dolosigranulum* are less commonly observed.

REVIEW AND DISCUSSION

NEONATAL MICROBIOTA: BIOLOGICAL FOUNDATIONS OF COLONIZATION

Colonization of the gastrointestinal tract and other body surfaces in the newborn begins immediately after birth and represents a crucial stage in the establishment of a homeostatic microbiome. During the first days of life, the microbiota undergoes dynamic shifts, with relative stabilization of its composition occurring within several months and full microbial maturity typically reached between two and three years of age. This process is shaped by numerous environmental

and perinatal factors, including exposure to maternal microorganisms, mode of delivery, feeding method, use of perinatal antibiotics, and contact with home or hospital environments [1, 2, 7].

In vaginal births, gastrointestinal colonization begins during passage through the birth canal, primarily involving maternal vaginal and intestinal microbiota. The dominant bacterial genera include:

Lactobacillus spp. – responsible for maintaining acidic pH and limiting pathogen proliferation,

Bifidobacterium spp. – producers of short-chain fatty acids (SCFAs), which strengthen the intestinal barrier and promote Treg lymphocyte development,

Bacteroides spp. – involved in modulating immune responses through interactions with TLR receptors and dendritic cells,

Prevotella spp. and non-pathogenic *Escherichia coli* strains – participating in the development of aerobic and anaerobic flora.

Additionally, skin-to-skin contact with the mother immediately after birth and breastfeeding further enhance symbiotic colonization by providing access to human milk oligosaccharides (HMOs), which selectively promote the growth of *Bifidobacterium longum* and *B. breve* [8].

In contrast, infants delivered via elective cesarean section acquire their initial microbiota primarily through contact with maternal skin, medical personnel, and the operating room environment. Their microbiota is typically dominated by:

Skin-associated bacteria: *Staphylococcus epidermidis*, *Corynebacterium spp.*, *Propionibacterium spp.*,

Environmental bacteria: *Enterobacter* spp., *Klebsiella* spp., *Clostridium difficile* – often associated with delayed gut microbiota maturation and an increased risk of opportunistic infections.

Studies employing 16S rRNA sequencing have demonstrated that differences in microbial composition may persist for 6-12 months or longer, particularly among formula-fed infants who are not breastfed [3]. Early colonization disturbances include reduced taxonomic diversity, delayed establishment of anaerobic communities, and decreased metabolic activity within the microbiome. Such early-life disruptions in microbial assembly are believed to influence the trajectory of immune, metabolic, and neurodevelopmental maturation [2]. For microbiota composition details, see Table 1 (Section 4.1).

LONG-TERM HEALTH CONSEQUENCES AND MICROBIOTA-DEPENDENT IMMUNOLOGICAL MECHANISMS

In the early months, something remarkable happens - the immune system learns to tell friend from foe. Gut microbes are key to this education process. In this pivotal period, mechanisms of immune response, the balance between effector and regulatory T cells, and tolerance toward environmental and dietary antigens are established. Disruptions in this process - particularly those caused by altered colonization patterns following elective cesarean delivery - may increase the risk of immunological, metabolic, and allergic diseases, even years after birth [9-11].

IMMUNOLOGICAL MECHANISMS DEPENDENT ON THE MICROBIOTA

One of the key functions of the early microbiota is to support the development of immune tolerance, defined as the immune system's ability to distinguish harmless antigens (e.g., dietary components, commensal microbiota) from threats (e.g., pathogens). A properly colonized neonatal gut provides numerous molecular signals that stimulate the maturation of dendritic cells, regulatory T cells (Treg), anti-inflammatory cytokine production, and intestinal barrier function.

Key microbiota-driven mechanisms supporting immune tolerance include:

Polysaccharide A (PSA) produced by *Bacteroides fragilis* binds to the TLR2 receptor on dendritic cells, leading to the induction of IL-10 and differentiation of naive CD4+ T cells into Tregs. These Tregs suppress the activity of Th1, Th2, and Th17 cells, thereby preventing inflammatory responses.

Butyrate, one of the main short-chain fatty acids (SCFAs), produced by *Faecalibacterium prausnitzii*, *Roseburia* spp., and *Anaerostipes* spp., enhances tight junctions between enterocytes and promotes the expression of the Foxp3 gene essential for Treg development. Butyrate also modulates the NF-κB pathway, reducing transcription of pro-inflammatory genes (e.g., IL-6, TNF-α).

Lactobacillus spp. stimulate the production of IgA in mucosal tissues and activate ILC3 cells to secrete IL-22, which supports epithelial integrity and resistance to infection.

Bifidobacterium spp. compete with pathogens for adhesion sites, produce lactic acid and acetate (lowering pH), and stimulate Paneth cells to secrete defensins - natural antimicrobial peptides.

The absence of these strains - common in infants delivered by cesarean section - results in:

↓ Treg numbers → ↑ Th17 dominance → ↑ IL-17 and IL-6 → chronic inflammation,

↓ IL-10 and TGF-β production → weakened suppressive mechanisms,

↑ exposure of enterocytes to PAMPs (e.g., LPS) → excessive activation of TLR4 → ↑ TNF-α and intestinal barrier damage [12].

Figure 1 shows the role of the microbiota in the development of immune tolerance.

Table 1. Comparison of dominant gut bacterial genera in newborns by mode of delivery

Bacterial genus	Vaginal delivery	Elective cesarean section
Bacteroides fragilis	Present, high abundance	Absent or low abundance
Bifidobacterium spp.	Present, dominant	Present, but significantly reduced
Lactobacillus spp.	Present	Rare or absent
Clostridium difficile	Rare	Present with high frequency
Staphylococcus spp.	Present in trace amounts	Dominant in the first days

Source: Adapted from [1,3,7]

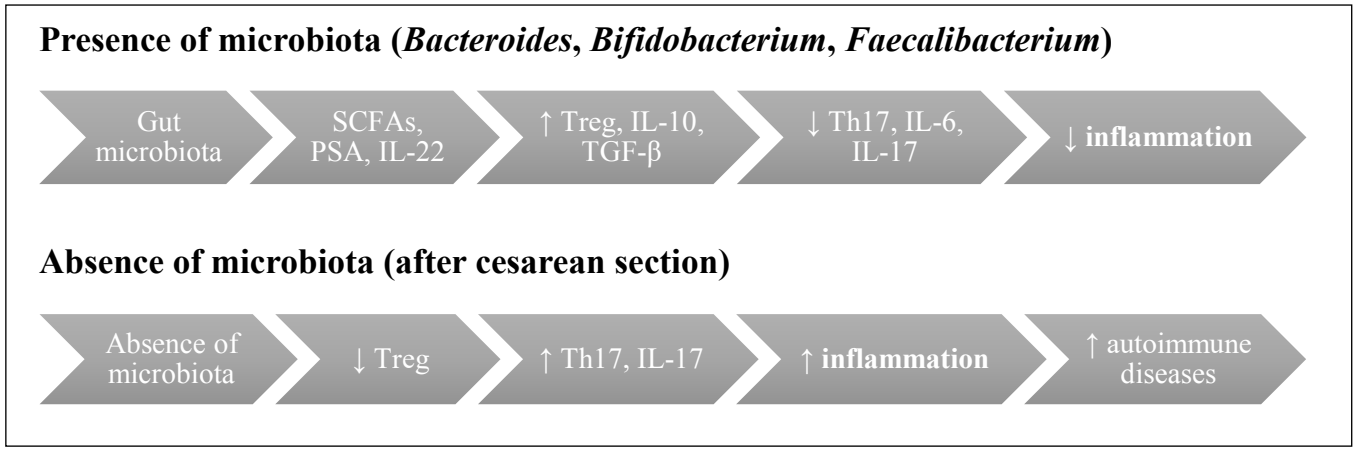

Fig. 1. The role of the microbiota in the development of immune tolerance
Source: Author's compilation based on: [9-13].

ALLERGIC AND ATOPIC DISEASES

Population studies have demonstrated that children born via cesarean section are at a higher risk of developing atopic conditions such as bronchial asthma, atopic dermatitis (AD), and food allergies. A meta-analysis by Rutayisire [14] estimated that this risk increases by 30% to 50% compared to vaginally delivered children.

A key role is played by the deficiency of *Bifidobacterium infantis* and *Bacteroides* spp., resulting in Th2-dominant responses - overproduction of IL-4, IL-5, and IL-13, along with elevated serum IgE levels. Dysbiosis also impairs SCFA production and impairs gut barrier function, facilitating allergen translocation and initiation of inflammatory responses [11].

METABOLIC DISEASES

Data from the CHILD Cohort Study (2024) [15] indicated that children delivered via cesarean section exhibited higher BMI as early as age five. This correlated with an increased abundance of fermentative *Firmicutes* bacteria and reduced numbers of *Bacteroidetes*, leading to more efficient energy extraction from food and increased fat storage - the so-called "obesogenic microbiome."

Furthermore, reduced SCFA production weakens activation of GPR41/43 receptors in adipose tissue and the intestines, affecting glucose metabolism, appetite regulation, and low-grade inflammation. These disturbances may predispose individuals to childhood obesity, insulin resistance, and type 2 diabetes [16].

AUTOIMMUNE AND INFLAMMATORY BOWEL DISEASES

Disruptions in early microbial colonization may initiate processes leading to autoimmune and inflammatory disorders. Children born by cesarean section have limited exposure to *Bacteroides fragilis* and *Faecalibacterium prausnitzii* - bacteria crucial for Treg induction and the IL-10/TGF-β cytokine balance.

Lack of these microbial signals may contribute to:

Type 1 diabetes – due to Th1-skewed responses and destruction of pancreatic β-cells,

Inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis) – *via* compromised gut barrier, LPS translocation, and NF-κB activation,

Other autoimmune disorders (e.g., celiac disease, psoriasis) – where microbiota influence antigen presentation and activation of CD8+ effector T cells [10].

LONG-TERM HEALTH CONSEQUENCES OF MICROBIOTA DISTURBANCES DEPENDENT ON MODE OF DELIVERY

The influence of gut microbiota on host health extends far beyond the digestive system, playing a key

role in the development of the immune, metabolic, and nervous systems, as well as in the regulation of inflammatory responses and the functioning of the body's protective barriers. The first months of life are particularly critical, as this is the period during which the intestinal colonization profile is established. Disruptions in this process - typical for infants born via elective cesarean section - can initiate a cascade of abnormal microbial and immunological signals, resulting in lasting phenotypic changes and an increased risk of many chronic diseases.

AUTOIMMUNE DISEASES

Disrupted immune education resulting from neonatal dysbiosis can lead to the loss of tolerance to self-antigens and, consequently, to the development of autoimmune diseases.

Type 1 Diabetes – In genetically predisposed children (HLA-DQ2/DQ8), the absence of *Bifidobacterium longum* and *Bacteroides fragilis* correlates with reduced induction of Treg lymphocytes and excessive activation of the Th1 response. Reduced production of PSA and SCFAs limits the secretion of IL-10 and TGF-β, facilitating the destruction of pancreatic β cells by cytotoxic CD8+ lymphocytes.

Crohn's Disease and Ulcerative Colitis (IBD) – A decrease in the presence of *Faecalibacterium prausnitzii*, a key butyrate producer, leads to increased intestinal epithelial permeability, LPS translocation, and NF-κB activation. The outcome is chronic inflammation, monocyte recruitment, and Th17 response induction.

Multiple Sclerosis (MS) – Meta-analyses have shown that alterations in the microbiota (reduced *Akkermansia muciniphila*, *Prevotella*, and increased *Methanobrevibacter*) occur already in the prodromal phase of MS. Dysbiosis affects microglial cells and the blood–brain barrier through SCFA and IL-6 signaling [17].

Celiac Disease – An increased number of *Escherichia coli* and decreased *Bifidobacterium breve* promote pro-inflammatory presentation of gluten peptides. IL-15 and IFN-γ support the activation of cytotoxic CD8+ lymphocytes and enterocyte apoptosis.

ALLERGIC AND ATOPIC DISEASES

Neonatal microbiota shapes the immune response profile, influencing the Th1/Th2 balance and the activation of mucosal tolerance mechanisms. Dysbiosis may predispose to atopic phenotypes.

Bronchial Asthma – Reduced abundance of *Bacteroides* and *Bifidobacterium* in C-section infants increases Th2 pathway activation, resulting in overproduction of IL-4, IL-5, IL-13, and elevated serum IgE. Diminished stimulation of TLR2/TLR4 further limits Treg activation.

Atopic Dermatitis (AD) – Reduced presence of *Lactobacillus rhamnosus* and *Bifidobacterium longum* weakens the skin barrier and lowers IL-10 and SCFA production, promoting colonization by *Staphylococcus aureus* and allergen penetration.

Food Allergies – The absence of colonization by bacteria that stimulate oral tolerance results in limited TGF-β and IL-10 production and a dominance of IgE-dependent mechanisms [11].

METABOLIC DISEASES

Gut microbiota plays a crucial role in regulating lipid and carbohydrate metabolism as well as hormonal signaling within the gut-brain axis. Alterations in early microbial composition following cesarean section have been linked to disturbances in metabolic programming and energy balance.

Childhood Obesity – An altered *Firmicutes/Bacteroidetes* ratio in C-section infants is associated with enhanced polysaccharide fermentation, excess acetate, and activation of GPR41/43 receptors. This promotes lipogenesis, increased energy harvest from the diet, and accelerated weight gain [15].

Type 2 Diabetes and Insulin Resistance – Bacterial LPS activates TLR4 on adipose tissue macrophages and pancreatic β cells. The resulting pro-inflammatory cytokines (IL-1β, TNF-α) impair insulin signaling and contribute to glucotoxicity.

Metabolic Syndrome – Reduced production of short-chain fatty acids (SCFAs), particularly butyrate and acetate, weakens GLP-1 and PYY signaling, leading to hyperphagia, insulin resistance, and low-grade chronic inflammation [18, 19].

Notably, longitudinal studies confirm that cesarean-delivered infants exhibit delayed SCFA maturation and distinct microbial succession patterns throughout the first year of life, suggesting a mechanistic link between early dysbiosis and later metabolic alterations [1].

NEUROLOGICAL AND PSYCHIATRIC DISORDERS

The gut-brain axis represents a bidirectional neuroimmune communication pathway through which the intestinal microbiota influences neurogenesis, neurotransmitter homeostasis, and the development of social and emotional behaviors [20,21]. Experimental and clinical studies increasingly support the hypothesis that early-life dysbiosis, particularly after cesarean delivery, can disrupt neural signaling and alter stress response systems, predisposing to neurodevelopmental and behavioral disorders [21].

Autism Spectrum Disorder (ASD) – Deficiencies in bacteria responsible for producing γ-aminobutyric acid (GABA), such as *Lactobacillus reuteri*, and for regulating serotonin synthesis via tryptophan metabolism (*Bifidobacterium* spp.), together with elevated concentrations of propionic acid produced by *Clostridium* spp., may impair CNS maturation and synaptic plasticity [21,22].

Attention Deficit Hyperactivity Disorder (ADHD) – The microbiota modulates dopamine and norepinephrine availability in the prefrontal cortex and nucleus accumbens, thereby influencing impulsivity and attention. Dysbiosis is associated with synaptic instability and reduced neuroplasticity.

Depression and Anxiety Disorders – An overrepresentation of proinflammatory bacteria such as *Desulfovibrio* and *Enterobacteriaceae* correlates with elevated IL-6 and TNF-α levels and decreased BDNF concentration, which limits hippocampal neurogenesis and resilience to stress [20].

OTHER CONDITIONS

Irritable Bowel Syndrome (IBS) – Dysbiosis with a dominance of *Proteobacteria* and reduced *Lactobacillus* results in loosened tight junctions, increased intestinal permeability, and mast cell activation, which are responsible for abdominal pain and visceral hypersensitivity.

Skin Diseases (Acne, Psoriasis) – Microbiota disturbances modulate the skin cytokine profile (IL-17, IL-23), affecting keratinocyte proliferation and angiogenesis.

Increased Susceptibility to Infections – A deficiency in bacteria that stimulate IgA secretion (e.g., *Bifidobacterium breve*) and IL-22 impairs mucosal defense in the respiratory and gastrointestinal tracts, increasing susceptibility to viral and bacterial infections.

CRITICAL CONSIDERATIONS ON THE LITERATURE BASE

Despite a growing body of literature linking mode of delivery to microbiota development and long-term health, many existing studies are subject to significant methodological limitations. Observational and cohort designs often preclude causal inference and may be affected by uncontrolled confounding factors such as perinatal antibiotic use, environmental exposures, breastfeeding practices, or socioeconomic status. Additionally, regional variations in microbiota composition and differing definitions of dysbiosis complicate the generalizability of findings across populations. Future research should strive for standardized microbiota profiling methods, longitudinal follow-up, and more rigorous control of potential confounders.

POTENTIAL BENEFICIAL ASPECTS OF COLONIZATION FOLLOWING ELECTIVE CESAREAN SECTION

While the majority of literature emphasizes the adverse effects of altered gut colonization in infants born via elective cesarean section, some studies report potential short-term or context-specific protective phenomena. These observations remain preliminary, often population-dependent, and require further confirmation through large-scale prospective studies.

POTENTIAL PROTECTION AGAINST SELECTED INFECTIONS

The microbiota of cesarean-born neonates is frequently enriched with aerobic skin- and environment-associated bacteria, including *Staphylococcus epidermidis*, *Corynebacterium spp.*, and *Micrococcus spp.* These organisms are capable of producing antimicrobial compounds - such as lysozyme, hydrogen peroxide, and bacteriocins - which may transiently inhibit the growth of Gram-negative pathogens like *Klebsiella pneumoniae* and *Enterobacter spp.* [22]. Although such effects are limited in scope and do not constitute a functionally mature microbiota, they may provide early, nonspecific microbial defense under certain conditions.

Additionally, some data suggest reduced colonization by enteropathogens such as *Campylobacter jejuni* and *Salmonella* spp. in cesarean-born infants, which could be beneficial in regions with limited sanitation and high rates of gastrointestinal infections [23].

Shao et al. [3], in their 2020 cohort study involving over 100 neonates from eastern China, reported C. difficile colonization in 72% of infants delivered by cesarean section - significantly higher than the 41% observed in vaginally born peers. This was particularly evident among formula-fed infants who did not attend daycare. While this finding may appear concerning, it likely reflects delayed microbial succession rather than true pathogenic colonization.

HYPOTHETICAL REDUCTION IN IMMUNE HYPERACTIVATION

In rare clinical scenarios, such as prematurity or congenital immunodeficiency, the delayed colonization associated with cesarean birth has been speculated to offer protection by limiting early immune overstimulation. Reduced exposure to microbial ligands may attenuate neonatal Th1/Th17 activation and decrease proinflammatory cytokine responses. Some studies report lower TLR4 and TLR9 expression levels in cesarean-born infants, which could reduce PAMP-induced inflammation

[19,24]. These hypotheses remain largely unconfirmed and warrant further mechanistic exploration.

INCONCLUSIVE ASSOCIATIONS WITH CELIAC DISEASE RISK

A cohort study by Sevelsted et al. [25] indicated a lower incidence of celiac disease among cesarean-born children carrying HLA-DQ2/8 alleles. The authors proposed that reduced colonization by *Bacteroides* spp. and lower early LPS exposure might modulate TLR4 activity, reducing autoimmune activation [10]. However, other studies have found contrary trends - linking cesarean birth to a higher risk of celiac disease - likely due to dysbiosis and impaired tolerance development [10,25]. Current evidence remains contradictory and insufficient to draw firm conclusions. More longitudinal studies are needed before we can confirm whether these trends are biologically meaningful or simply statistical noise.

CRITICAL PERSPECTIVE AND LIMITATIONS

Despite the above observations, most findings originate from observational studies with limited sample sizes, population heterogeneity, and incomplete control of confounding variables such as antibiotic use, breastfeeding, or hospital length of stay. Moreover, several seemingly beneficial effects — such as reduced pathogen carriage or dampened inflammation — may in fact reflect microbiota immaturity rather than a physiologically adaptive state.

It is therefore crucial to interpret these findings within context. The current evidence for protective aspects of cesarean-associated colonization is limited in duration, highly variable across populations, and does not offset the well-documented immunological, metabolic, and neurodevelopmental risks associated with disrupted early-life microbial exposure due to bypassing the birth canal. These interpretations align with the *hygiene hypothesis*, which proposes that reduced early microbial contact contributes to the rising prevalence of allergic and immune-mediated diseases in modern societies [13].

FACTORS MODIFYING MICROBIOTA COLONIZATION

Although this review focuses on the influence of the mode of delivery on microbiota development, it is essential to acknowledge factors that may modify the trajectory of microbial colonization in newborns - either by supporting or disrupting this process. Particularly significant are breastfeeding, antibiotic therapy, environmental exposure, and interpersonal contact during the first weeks of life.

BREASTFEEDING

One of the most well-documented factors that can compensate for microbiota colonization disturbances in infants born via cesarean section is breastfeeding. Human milk contains over 200 types of human milk oligosaccharides (HMOs), which are indigestible by the infant but selectively stimulate the growth of symbiotic strains of the genus *Bifidobacterium* - especially *B. longum* subsp. *infantis*.

Research by Bogaert et al. (2023) [8] demonstrated that cesarean-delivered newborns who were exclusively breastfed regained a microbiota composition similar to that of vaginally delivered infants within the first 6 weeks of life. Furthermore, HMOs promote the production of short-chain fatty acids (SCFAs), support the maturation of the intestinal barrier, and inhibit the growth of pathogenic bacteria.

ANTIBIOTIC THERAPY

Perinatal antibiotic use - both in mothers during the peripartum period and in newborns - significantly impacts microbiota composition, particularly by reducing anaerobic bacteria. In combination with cesarean delivery, this often leads to persistent dysbiosis lasting several months. Even a single prophylactic dose of antibiotics can inhibit colonization by *Bacteroides* and *Bifidobacterium* species.

SOCIAL AND ENVIRONMENTAL CONTACT

Exposure to microorganisms through contact with siblings, caregivers, domestic animals, as well as through environmental hygiene and place of residence, also plays an important role in shaping microbiota development. Children raised in rural settings or exposed to soil and animal microbiota more frequently exhibit greater microbial diversity and a lower risk of atopic diseases (a phenomenon known as the "old friends hypothesis" or the expanded hygiene hypothesis).

POTENTIAL THERAPEUTIC INTERVENTIONS

In light of the risk of disrupted microbiota colonization in newborns, increasing interest is being directed toward microbiota-targeted interventions aimed at restoring a healthy microbial profile in cesarean-born infants. Pilot studies on vaginal microbiota transplantation (vaginal seeding) suggest that transferring the

maternal microbiome to the newborn immediately after birth may partially recreate the physiological colonization pattern. Additionally, third-generation probiotic formulations - containing specific strains of *Bifidobacterium* and *Faecalibacterium* - are being developed, with demonstrated potential to modulate immune responses and promote SCFA production. However, further research is required to assess the safety and efficacy of these interventions in diverse population groups.

LIMITATIONS OF THE REVIEW

This review has several limitations that should be acknowledged. First, although a systematic search strategy was employed, the review may be subject to selection bias, as only English-language publications and human studies were included. Second, heterogeneity in study design, microbiota assessment methods (e.g., 16S rRNA vs. metagenomics), and outcome definitions limits direct comparability and meta-analysis. Third, the long-term outcomes reported in the literature are often based on self-reported or registry-based data, which may not fully capture subtle neurodevelopmental or immunological phenotypes. Lastly, potential publication bias may lead to an overrepresentation of studies reporting significant associations. These limitations - including potential publication bias - should be considered when interpreting the findings of this review.

CONCLUSIONS

The evidence gathered in this review demonstrates that the mode of delivery exerts a profound influence on the early development of the neonatal microbiota, which in turn shapes the maturation of immune, metabolic, neurological, and barrier functions. Vaginal delivery provides the newborn with physiological exposure to maternal vaginal, perineal, and fecal microbiota, thereby ensuring balanced colonization and supporting the proper development of biological systems. In contrast, elective cesarean section consistently leads to delayed microbial succession, reduced taxonomic diversity, and altered colonization patterns, which have been linked to an increased risk of allergic, autoimmune, metabolic, and neuroinflammatory conditions. These associations are underpinned by well-documented mechanisms, including impaired differentiation of regulatory T cells, reduced signaling mediated by short-chain fatty acids, enhanced activation of TLR4 receptors, and the maintenance of low-grade inflammation. Although a small number of studies report potential protective effects of alternative colonization trajectories, such as reduced carriage of selected pathogens, these findings appear transient, context-dependent, and of limited clinical relevance.

From a clinical perspective, the implications of these findings highlight the importance of promoting delivery modes and neonatal practices that favor healthy microbiota development. Whenever medically feasible, vaginal birth should be supported as the optimal route of delivery. In addition, early initiation and continuation of breastfeeding play a crucial compensatory role, while the avoidance of unnecessary perinatal antibiotic exposure remains essential. New approaches, such as microbiota-targeted therapies and vaginal seeding, are emerging as potentially valuable interventions, but their safety and efficacy must be rigorously confirmed before widespread adoption. At the population level, educational initiatives aimed at prospective parents and the integration of microbiota health into public health frameworks may further contribute to reducing long-term disease risks associated with disrupted neonatal colonization.

Future research should focus on identifying reliable biomarkers of neonatal dysbiosis, as these could allow early recognition and intervention. In parallel, there is a pressing need for the development of restorative strategies, including advanced probiotic formulations and personalized therapeutic approaches tailored to individual microbiota profiles. Moreover, the design of large-scale, longitudinal cohort studies integrating microbiological, immunological, and clinical outcomes will be essential to clarify causal relationships and strengthen the evidence base. Only through such efforts will it be possible to transform current knowledge into effective, individualized strategies that protect and promote microbiota-driven health from the very beginning of life.

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DATA AVAILABILITY

Data supporting the findings are available from the corresponding author upon request

CONFLICT OF INTEREST
The Authors declare no conflict of interest

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