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GUT MICROBIOTA PATTERNS IN PEDIATRIC RESPIRATORY INFECTIONS: A SYSTEMATIC REVIEW OF MICROBIAL SIGNATURES

PADRÕES DA MICROBIOTA INTESTINAL NAS INFECÇÕES RESPIRATÓRIAS PEDIÁTRICAS: UMA REVISÃO SISTEMÁTICA DOS PERFIS MICROBIANOS

PATRONES DE LA MICROBIOTA INTESTINAL EN LAS INFECCIONES RESPIRATORIAS PEDIÁTRICAS: UNA REVISIÓN SISTEMÁTICA DE LOS PERFILES MICROBIANOS

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ABSTRACT

Early-life gut microbiota plays a crucial role in immune maturation and has been increasingly associated with host responses to infectious diseases. Emerging evidence highlights the gut–lung axis as an important component of pediatric respiratory health, yet child-focused syntheses remain limited. This systematic review with qualitative analysis summarizes recent original studies evaluating gut microbiota profiles in children with acute respiratory infections, providing a child-specific perspective distinct from reviews that combine age groups or focus on single pathogens. PubMed and the Virtual Health Library were systematically searched and the data were extracted using a structured matrix to identify patterns in microbial composition and methodological strengths and gaps. Twelve studies (2019–2025) including participants aged 0–18 years with conditions such as COVID-19, respiratory syncytial virus infection, bronchiolitis, and recurrent respiratory tract infections met predefined inclusion criteria. Across studies, children with respiratory infections consistently exhibited gut dysbiosis, characterized by depletion of beneficial taxa and enrichment of pro-inflammatory genera. While methodological differences, including study design, sampling timing, and handling of confounders, limited direct quantitative comparisons, patterns of microbial alterations were identifiable. Overall, this review highlights a consistent association between gut microbiota alterations and pediatric respiratory infections, supporting the relevance of the gut–lung axis in early life. Nevertheless, methodological heterogeneity prevents inference about cause-and-effect relationships, highlighting the need for well-designed longitudinal and interventional studies to better understand the directionality of these associations.

KEYWORDS: *Gut-lung axis. Respiratory infections. Pediatric microbiome. Systematic review.*

RESUMO

A microbiota intestinal nos primeiros anos de vida desempenha papel fundamental na maturação do sistema imunológico e tem sido associada às respostas do hospedeiro às doenças infecciosas.

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Evidências emergentes destacam o eixo intestino-pulmão como componente importante da saúde respiratória pediátrica, embora sínteses específicas da população infantil ainda sejam limitadas. Esta revisão sistemática com análise qualitativa sintetiza estudos originais sobre os perfis da microbiota intestinal em crianças com infecções respiratórias agudas, oferecendo uma perspectiva específica dessa população. Foram realizadas buscas sistemáticas nas bases PubMed e Biblioteca Virtual em Saúde. Os dados foram extraídos por meio de uma matriz estruturada para identificar padrões de composição microbiana, pontos fortes e lacunas metodológicas. Doze estudos publicados entre 2019 e 2025, envolvendo participantes de 0 a 18 anos com COVID-19, infecção pelo vírus sincicial respiratório, bronquiolite e infecções recorrentes do trato respiratório, atenderam aos critérios de inclusão predefinidos. Os estudos demonstraram disbiose intestinal consistente, caracterizada pela redução de táxons benéficos e pelo enriquecimento de gêneros associados à inflamação. Diferenças metodológicas, incluindo delineamento dos estudos, momento da coleta das amostras e controle de fatores de confusão, limitaram as comparações quantitativas diretas, embora tenham sido identificados padrões de alterações microbianas. A revisão evidencia uma associação consistente entre alterações da microbiota intestinal e infecções respiratórias pediátricas, reforçando a relevância do eixo intestino-pulmão nos primeiros anos de vida. Entretanto, a heterogeneidade metodológica impede estabelecer relações de causa e efeito, destacando a necessidade de estudos longitudinais e de intervenção bem delineados para esclarecer a direção dessas associações.

PALAVRAS-CHAVE: Eixo intestino-pulmão. Infecções respiratórias. Microbioma pediátrico. Revisão sistemática.

RESUMEN

La microbiota intestinal durante los primeros años de vida desempeña un papel fundamental en la maduración del sistema inmunitario y se ha asociado con las respuestas del huésped ante enfermedades infecciosas. La evidencia emergente destaca el eje intestino-pulmón como componente importante de la salud respiratoria pediátrica, aunque las síntesis específicas en niños siguen siendo limitadas. Esta revisión sistemática con análisis cualitativo sintetiza estudios originales sobre los perfiles de la microbiota intestinal en niños con infecciones respiratorias agudas. Se realizaron búsquedas en PubMed y la Biblioteca Virtual en Salud. Los datos se extrajeron mediante una matriz estructurada para identificar patrones microbianos y lagunas metodológicas. Doce estudios publicados entre 2019 y 2025, con participantes de 0 a 18 años con COVID-19, infección por el virus respiratorio sincitial, bronquiolitis e infecciones respiratorias recurrentes, cumplieron los criterios de inclusión. Los estudios evidenciaron disbiosis intestinal, caracterizada por la reducción de taxones beneficiosos y el enriquecimiento de géneros asociados con la inflamación. Las diferencias metodológicas, incluidos los diseños de estudio, el momento de la recolección de muestras y el control de factores de confusión, limitaron las comparaciones cuantitativas, aunque se identificaron patrones de alteración microbiana. La revisión muestra una asociación consistente entre las alteraciones de la microbiota intestinal y las infecciones respiratorias pediátricas, lo que refuerza la relevancia del eje intestino-pulmón en los primeros años de vida. Sin embargo, la heterogeneidad metodológica impide establecer causalidad y destaca la necesidad de estudios longitudinales y de intervención bien diseñados para esclarecer la dirección de estas asociaciones.

PALABRAS CLAVE*: Eje intestino-pulmón. Infecciones respiratorias. Microbioma pediátrico. Revisión sistemática.*

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1. INTRODUCTION

In early childhood, the gut microbiota plays a central role in endocrine, metabolic, and immune maturation. During this critical developmental window, host–microbe interactions can have lasting immunological effects, and disruptions have been associated with increased susceptibility to childhood diseases [1-2].

Despite their anatomical distinctness, the gut and lungs maintain functional communication. Alterations in the gut microbiota have been associated with changes in respiratory immunity and pulmonary homeostasis, forming the gut–lung axis [3]. The microbiota is thought to modulate respiratory function primarily through two proposed mechanisms: microbial metabolites may reach the lungs and modulate immune responses, and immune cells or mediators originating in the gut may migrate to the respiratory tract and contribute to inflammation [4]. Increasing evidence links the composition and function of the microbiome to pulmonary disorders, including chronic obstructive pulmonary disease, asthma, and acute lower respiratory infections [5].

Given the increasing recognition of the gut–lung axis and its potential relevance for pediatric respiratory health, there is a growing need to consolidate current knowledge on how early-life gut microbiota composition influences potential vulnerability to respiratory infections. Although recent reviews have examined interactions between the intestinal microbiota and respiratory diseases, most have emphasized mechanistic pathways, chronic respiratory disorders, or broad discussions that combine findings from mixed age groups [6]. Other syntheses have focused predominantly on specific viral pathogens, such as influenza, respiratory syncytial virus, or SARS-CoV-2 [7], or have explored immune and metabolic implications without providing detailed analyses of primary pediatric evidence [8].

To address gaps in the pediatric literature, the present systematic review with qualitative analysis synthesizes recent original studies investigating fecal microbiota profiles in the context of acute respiratory infections. This review identifies microbial patterns and evaluates methodological strengths and limitations in recent pediatric studies of acute respiratory infections.

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2. METHODOLOGY

2.1. Research Strategy

This systematic review with qualitative analysis was developed following predefined methodological steps, including the formulation of the research question, selection of databases, definition of descriptors, and establishment of inclusion and exclusion criteria [9].

The search was conducted in PubMed and the Virtual Health Library (VHL) using controlled vocabulary (MeSH and DeCS) combined with free-text terms related to pediatric populations, gut microbiota, and respiratory or infectious diseases. The complete search strategies and exact Boolean combinations used for each database are detailed in Supplementary Table S1.

Searches were conducted without restrictions on study design and included articles published in English, Portuguese, or Spanish up to September 2025. Three authors independently conducted the search and initial screening. Discrepancies were resolved by consensus [10]. The review followed PRISMA 2020 guidelines where applicable.

2.2. Study Selection

The initial search retrieved 1,303 records from PubMed (n = 732) and the Virtual Health Library (VHL) (n = 571). After removing 435 duplicate records, 868 records remained for screening. Titles and abstracts were screened according to the predefined inclusion and exclusion criteria, resulting in the exclusion of 794. The remaining 74 articles were assessed in the subsequent selection phase, in which 62 reviews, meta-analyses, and editorials were excluded. Ultimately, 12 original studies were included in the review. The study selection process is summarized in Figure 1.

2.3. Data Extraction and Qualitative Analysis

Data were extracted into a structured knowledge matrix using Microsoft Excel 2019. Extracted variables included study population and age range, study design, sample size, timing of stool sampling, microbiota profiling method, main outcomes, and consideration of confounders. Tables 1 and 2 summarize these characteristics, methodologies, and main findings.

Given the substantial methodological heterogeneity of included studies, including study design, sampling timing, microbiome techniques, and handling of confounders, no quantitative synthesis was performed. Instead, a qualitative approach was applied to identify key microbial patterns and contextualize methodological features.

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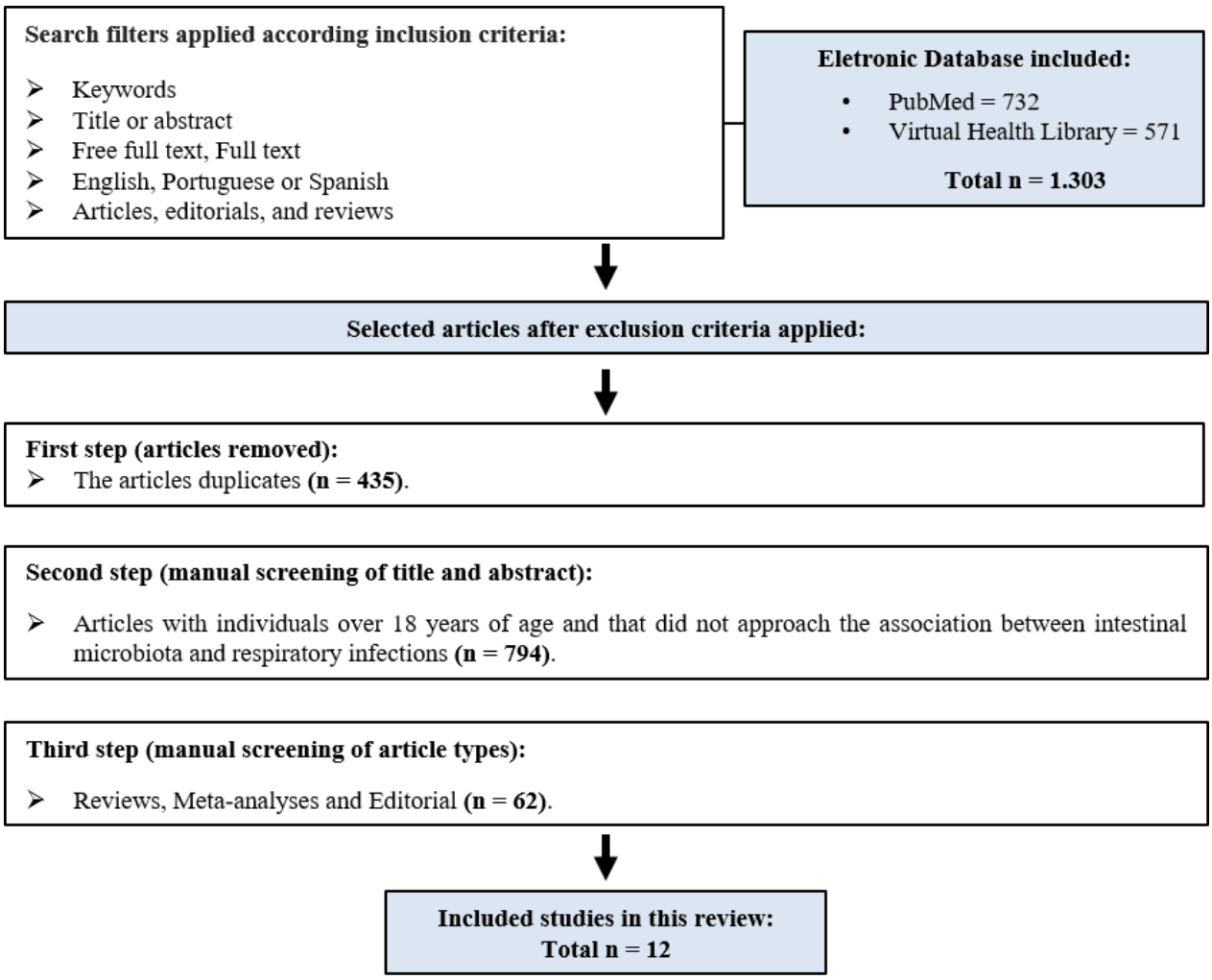
Figure 1. Flow diagram illustrating all stages of the study selection process



Source: Authors.

2.4. Methodological Quality Assessment

The methodological quality of included studies was independently assessed by three reviewers using Joanna Briggs Institute (JBI) critical appraisal checklists for cohort and cross-sectional studies [11]. Each item was classified as yes (Y), no (N), unclear (U), or not applicable (NA). The assessment informed the narrative synthesis, highlighting methodological strengths and limitations. Detailed results are presented in Supplementary Tables S2 and S3.

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3. RESULTS AND DISCUSSION

3.1. Results

3.1.1. Characteristics of Included Studies

A total of 12 studies were included in this review and considered for data extraction. The characteristics of the selected studies are summarized in Table 1. The included studies investigated the relationship between gut microbiota composition and respiratory infections in children, predominantly infants and young children, encompassing COVID-19 (n = 6), general respiratory tract infections (RTIs; n = 4), bronchiolitis (n = 1), and respiratory syncytial virus (RSV) infection (n = 1).

Table 1. Characteristics of the included studies investigating the relationship between gut microbiota and respiratory infections in children

Authors (Year)	Title	Country / Setting	Study Design	Population (age)	Microbiota Assessment Method
Li *et al.* 2019 [16]	Intestinal microbiota dysbiosis in children with recurrent respiratory tract infections	The Affiliated Hospital of the Medical College Qingdao University, China	Analytical cross-sectional study	A total of 26 (4 months to 6 years) children with recurrent respiratory tract infection (RRTIs) and 23 (4 months to 12 years) healthy volunteers.	Microbial DNA was extracted from fecal samples using the OMEGAsoil DNA Kit according to manufacturer's protocols. The V3–V4 region of the bacterial 16S ribosomal RNA gene was amplified by PCR. The PCR products were quantified using the QuantiFluor™-ST Blue Fluorescence Quantitative System (Promega) and the initial quantitative results from electrophoresis.
Harding *et al.* 2020 [15]	Altered gut microbiota in infants is associated with respiratory syncytial virus disease severity	Bonheur Children's Hospital and Outpatient Clinic, United States of America	Analytical cross-sectional study	A total of 58 (35.8 – 37.4 weeks) infants hospitalized with respiratory syncytial virus (RSV) and 37 (38.9 weeks) healthy controls.	Fecal DNA was extracted (QIAamp PowerFecal Kit), and the V4 region of the 16S rRNA gene was sequenced using Illumina MiSeq. Resulting sequencing data was analyzed using Qiime 2 pipeline with a 99% OTU identification by GreenGenes database.

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Reyman *et al.* 2021 [13]	Microbial community networks across body sites are associated with susceptibility to respiratory infections in infants	Netherlands	Longitudinal cohort study	112 healthy infants born at term (≥37 weeks gestational age). Infants were divided into three groups based on the distribution of the number of respiratory tract infections (RTIs) they experienced over the first year of life (0–2 RTIs, 3–4 RTIs, 5–7 RTIs).	DNA extraction and library preparation of the bacterial 16S rRNA gene V4 region was performed. All pools were sequenced on the Illumina MiSeq platform. Of the 1,250 available samples obtained from the three niches at 1 week, 2, 4, and 6 months of life of 112 healthy infants, 1,248 samples fulfilled our quality threshold (433 faecal samples, 430 nasopharyngeal samples, and 385 saliva samples).
Xu *et al.* 2021 [14]	Progressive deterioration of the upper respiratory tract and the gut microbiomes in children during the early infection stages of COVID-19	Shanghai Public Health Clinical Center, Children's Hospital of Fudan University, China	Longitudinal cohort study	Nine COVID-19 children aged between 7 and 139 months were enrolled, together with 14 age-matched healthy control children	A total of 103 samples, including 31 nasal swabs, 28 throat swabs, and 44 feces, were collected from these patients. Twenty-five samples from 14 age-matched healthy children were used as controls. All samples were subjected to high-throughput sequencing of the V4-region of bacterial 16S-rRNA gene to characterize the microbiota.
Moroishi *et al.* 2022 [18]	The relationship between the gut microbiome and the risk of respiratory infections among newborns	United States of America	Longitudinal cohort study	The analysis included 465 infants with 16S data and 185 infants with metagenomics data. Infant stool samples were collected at a regularly scheduled ~6-week postpartum follow-up appointments. Caregivers were interviewed by telephone when infants were approximately 4, 8, and 12 months old. During each interview, caregivers reported whether the child had experienced upper or lower respiratory tract infections, acute respiratory symptoms, or	The study measured the fecal microbiome of infant stool as a measure of the infant gut microbiome. A Zymo DNA extraction kit (Zymo Research) was used for DNA extraction from thawed samples. The V4-V5 hypervariable region of the bacterial 16S rRNA gene was sequenced using Illumina MiSeq. A subset of stool samples was also sequenced with NGS and shotgun metagenomics sequencing.

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				diarrhea since the previous contact.	
Romani *et al.* 2022 [22]	The Relationship Between Pediatric Gut Microbiota and SARS-CoV-2 Infection	Bambino Gesù Children's Hospital, Italy	Longitudinal cohort study	68 COVID-19 patients (median age of 6.5 years), 16 Non–COVID-19 patients (median age of 4.4 years), 4 affected by multisystem inflammatory syndrome (median age was 11.7 years), and 95 healthy (controls age-matched with patients).	16S rRNA targeted metagenomics was performed on stool samples; sequencing with Illumina MiSeq; data analyzed using QIIME2.
Gutiérrez-Díaz *et al.* 2023 [12]	Microbial and immune faecal determinants in infants hospitalized with COVID-19 reflect bifidobacterial dysbiosis and immature intestinal immunity	Hospital Universitario Central de Asturias, Complejo Hospitalario Universitario de Santiago de Compostela, Hospital Universitario y Politécnico La Fe, Hospital Universitario Infantil Niño Jesús, Hospital Universitario Virgen del Rocío and Hospital Regional Universitario de Málaga, Spain	Analytical cross-sectional study	A total of 20 newborns were included, 11 patients with COVID-19, and 9 healthy controls. While patients in the newborns' group had an average age of 1.9 ± 0.6 months, the average age of controls was 1.7 ± 0.8 months. On the other hand, the toddlers' group was composed of 8 patients with COVID-19 and 9 healthy controls. The median age of patients in this group was 17 ± 7.7 months and 11 ± 4.8 months for controls.	Stool collection within first 12h after hospital admission. DNA extraction; 16S rDNA and ITS sequencing.

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Marzano *et al.* 2023 [20]	The metaproteome of the gut microbiota in pediatric patients affected by COVID-19	Bambino Gesù Children's Hospital, Italy	Analytical cross-sectional study	21 patients with COVID-19, ranging in age from 1 to 16 years (mean of 10 years ± 5) and 21 healthy subjects (CTRLs) of the same age-range (min 1 − max 16 years, mean of 10 years ± 4).	Pediatric COVID-19 patients and age-/sex-matched healthy controls provided stool samples. Bacterial proteins were extracted and analyzed via nanoLC-ESI-MS/MS. Taxonomic and functional profiling was performed using MetaLab-MAG.
Wang *et al.* 2023 [21]	Altered gut microbiota composition in children and their caregivers infected with the SARS-CoV-2 Omicron variant	Shanghai Children's Hospital and Renji Hospital, School of Medicine, Shanghai Jiao Tong University, China	Analytical cross-sectional study	The median age of the 59 pediatric COVID-19 patients was 4.8 years and the median of 52 healthy children was 5 years.	Gut microbiota composition was analyzed using 16S rRNA gene sequencing of stool samples. DNA was extracted, PCR-amplified, and sequenced on an Illumina MiSeq platform.
Cabrera-Rubio *et al.* 2024 [17]	Gut and respiratory tract microbiota in children younger than 12 months hospitalized for bronchiolitis compared with healthy children: can we predict the severity and medium-term respiratory outcome?	Severo Ochoa University Hospital and La Paz University Hospital, Spain	Longitudinal cohort study	96 infants (57 hospitalized for bronchiolitis and 39 controls). Infants younger than 1 year (3.8 ± 3.0 months) admitted for bronchiolitis and healthy infants younger than 1 year (6.1 ± 3.5 months).	Gut (feces) and respiratory (nasopharyngeal aspirate) microbial profiles were analyzed by 16S rRNA amplicon sequencing. Microbial profiles were determined by the V3–V4 variable region of the 16S rRNA gene sequencing, following PE250 Illumina strategy sequencing protocols. From the 96 infants included in the study, 187 available samples were included in the analysis (94 fecal samples and 93 respiratory samples).
Piazzesi *et al.* 2024 [23]	The pediatric gut bacteriome and virome in response to SARS-CoV-2 infection.	Bambino Gesù Children's Hospital, Italy	Analytical cross-sectional study	22 patients with COVID-19 and 22 healthy controls. Pre-teen (7-12 years) Teenagers (13-18 years).	DNA was extracted from stool samples. Shotgun metagenomic sequencing libraries were prepared with Illumina's Tagmentation Protocol.

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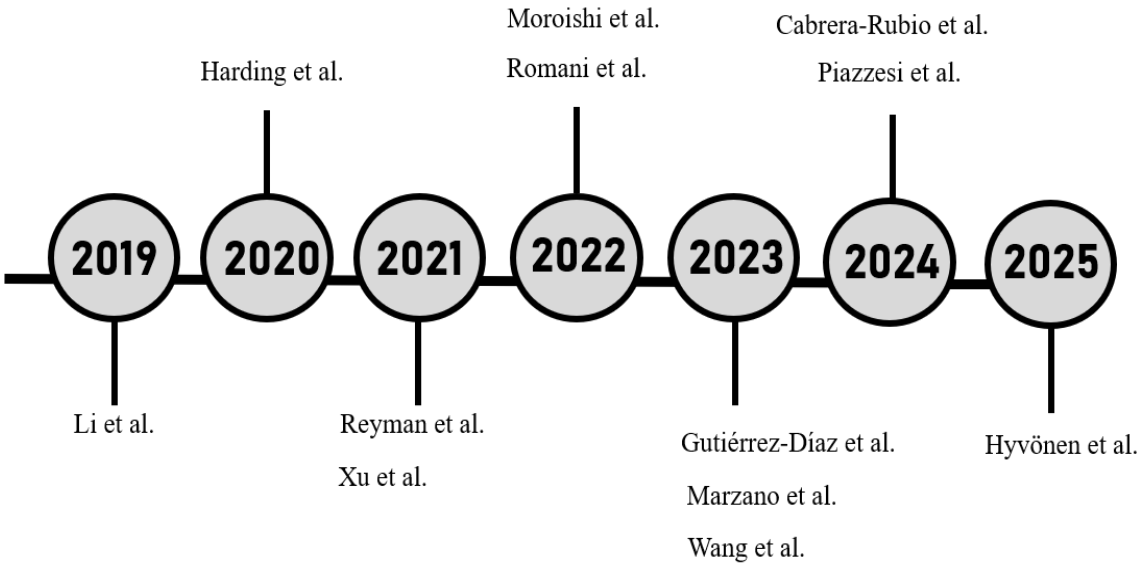
Hyvönen *et al.* 2025 [19]	The association of maternal and infant early gut microbiota with respiratory infections in infants	Helsinki region, Finland	Longitudinal cohort study	178 infants who developed a respiratory tract infection (RTI) episode within the first 6 months of life and had an available fecal sample at weeks 3 and 6 as well as 143 infants without such infections serving as controls.	Fecal DNA extraction and preparation of the samples for V3-V4 16S ribosomal ribonucleic acid (rRNA) gene amplicon sequencing.

Source: Authors.

Studies were mainly conducted in China and Italy, with remaining studies distributed across other regions. Although no publication year restrictions were applied, only studies published from 2019 onward met the inclusion criteria (Figure 2).

Figure 2. Timeline showing the publication years of the 12 studies included in this review



Source: Authors.

3.1.2. Study Populations, Designs, and Methodological Approaches

Most studies focused on infants under 12 months, with fewer including older children or adolescents. Several studies investigated young children up to 5 years, while others included children up to 12 years. Only a few studies assessed adolescents up to 18 years.

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Study designs included cross-sectional [12,15,16,20,21,23] and cohort studies [13,14,17-19,22]. Microbiota profiling was primarily performed using 16S rRNA gene sequencing, which enabled taxonomic characterization at the genus and phylum levels. A subset of studies employed shotgun metagenomics or metaproteomics, allowing functional assessment of microbial metabolism, virulence, and stress response pathways.

Many highlighted small sample sizes, which reduced statistical power and limited subgroup analyses. The observational designs, often cross-sectional or cohort-based, were frequently cited as barriers to establishing causal relationships between gut microbiota composition and respiratory infections. Observational designs and single time-point sampling were common, which, along with incomplete control of confounders such as antibiotic exposure, feeding practices, delivery mode, gestational age, and environmental factors, hindered causal inference and cross-study comparability. Some studies also relied on clinical records or caregiver-reported symptoms to define respiratory infections, had short follow-up periods, and were conducted in restricted geographic or clinical settings.

Methodological quality was assessed using Joanna Briggs Institute checklists for cohort and cross-sectional studies (Supplementary Tables S2 and S3). Overall, studies demonstrated moderate to high quality: cohort studies generally reported well-defined exposures and outcomes, though follow-up completeness was often unclear; cross-sectional studies adequately described populations and exposures, but confounding factors were inconsistently addressed. Across all studies, substantial methodological heterogeneity was evident. Supplementary Table S4 summarizes key methodological differences among included studies, including study design, timing of stool sampling relative to infection onset, and management of antibiotic exposure, which may influence gut microbiota composition and limit cross-study comparability.

3.1.3. Main Findings from the Included Studies

The articles included in this review cover a broad spectrum of pediatric respiratory conditions. Together, these studies describe associations between gut microbiota composition and pediatric respiratory outcomes. The following subsections summarize the key microbiota alterations reported across these conditions. A detailed synthesis of these findings is presented in Table 2.

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Table 2. Main findings of the included studies on gut microbiota alterations associated with respiratory infections in children

Authors (Year)	Title	Microbial species identified	Impact on Gut Microbiota	Association with Respiratory Infections
Li *et al.* 2019 [16]	Intestinal microbiota dysbiosis in children with recurrent respiratory tract infections.	The bacterial microbiota analysis showed that the *Firmicutes* were the most predominant phylum, contributing 56.7% and 54.57% of the microbiota in healthy volunteers and recurrent respiratory tract infections (RRTI) patients, respectively. The second most dominant phyla in healthy volunteers and RRTI patients was the *Bacteroidetes*. However, there was a clear decrease in both the *Verrucomicrobia* and *Tenericutes* phyla in the RRTI patients compared to the control group. Otherwise, there was a moderate decrease in the *Firmicutes* and *Actinobacteria* phyla in the RRTI group. Of the remaining taxa, two phyla, including the *Bacteroidetes* and the *Proteobacteria*, were more enriched in RRTI patients. It is worth noting that *Enterococcus* was overrepresented in the RRTI group relative to the controls. Conversely, the abundance of *Eubacterium* was significantly decreased in the RRTI group.	Disease (RRTI) may be the most important factor contributing to changes in the gut bacterial structure. In other words, the development of RRTI may contribute to the microbiota imbalance. The gut microbiome of RRTI patients had a reduced species richness, as well as a significant shift in the overall microbial diversity.	RRTI was strongly linked to gut dysbiosis, characterized by reduced diversity, loss of beneficial taxa, and overgrowth of opportunistic bacteria.
Harding *et al.* 2020 [15]	Altered gut microbiota in infants is associated with respiratory syncytial virus disease severity	At the genus level, we observed S24_7, *Odoribacter*, and *Oribacterium* being associated with severe respiratory syncytial virus (RSV) and *Clostridiales* and *Coriobacteriaceae* being associated with moderate disease. S24_7 is increased in severe patients compared to control patients while *Moraxellaceae* is decreased. At the genus level, S24_7 is again increased in severe patients compared to control patients while *Tissierella soehngenia* is decreased.	RSV infection was associated with significant alterations in gut microbiota composition. Biomarker analysis confirmed a unique microbial signature associated with severe RSV, suggesting a dysbiotic pattern linked to disease severity.	Specific microbial shifts were associated with RSV severity, with distinct taxa predicting more severe clinical presentations.

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Reyman *et al.* 2021 [13]	Microbial community networks across body sites are associated with susceptibility to respiratory infections in infants	The phylum Firmicutes was predominant among fecal samples. A total of 595 bacterial Operational Taxonomical Unit (OTUs) were identified, with a gradual increase of *Bifidobacterium* during the first six months of life. The hub species unique to the 0–2 respiratory tract infections (RTI) networks included previously reported respiratory health-associated OTUs such as *Neisseria lactamica*, *Dolosigranulum pigrum* and *Corynebacterium* OTUs. Also, OTUs associated with the production of butyrates, such as *Ruminococcus bromii*, *Megasphaera*, and *Anaerostipes*, were found to be hub species in the 0–2 RTI networks. Alternatively, hub species in the 5–7 RTI networks included OTUs previously associated with poorer respiratory health, such as the proteobacterial OTUs *Haemophilus*, *Haemophilus haemolyticus*, and *Neisseria*, and the anaerobic *Lachnospiraceae*. Additionally, *Actinobaculum schaalii* is often associated with (invasive) infections, the proinflammatory *Ruminococcus gnavus* and the faecal pH increasing *Peptostreptococcaceae* were hub species for the networks of infants who experienced 5–7 RTIs.	The study showed that infants with different frequencies of RTIs had distinct gut microbial network structures. In children with 0–2 RTIs, the gut networks were enriched with beneficial butyrate-producing species along with health-associated taxa such as *Dolosigranulum pigrum* and *Corynebacterium*. In contrast, infants who experienced 5–7 RTIs exhibited gut networks dominated by potentially pathogenic or inflammatory species.	The composition of gut microbial hub species was strongly associated with RTI frequency. Beneficial butyrate-producing and health-associated species predominated in children with fewer RTIs (0–2), suggesting a protective gut microbial profile. Conversely, infants with recurrent RTIs (5–7 episodes) showed enrichment of taxa linked to respiratory pathogens, inflammation, and infection susceptibility.
Xu *et al.* 2021 [14]	Progressive deterioration of the upper respiratory tract and the gut microbiomes in children during the early infection stages of COVID-19	In the gut microbiota of children with COVID-19, three main community types were identified, designated as COVID-GUT I, II, and III. COVID-GUT I resembled a healthy microbiota and included genera such as *Prevotella*, *Porphyromonas*, *Finegoldia*, and *Anaerococcus*. COVID-GUT II showed moderate dysbiosis and was characterized mainly by *Bacteroides* and *Pseudomonas*, along with other opportunistic bacteria. COVID-GUT III represented severe dysbiosis with low diversity and was dominated by	Marked gut dysbiosis characterized by reduced commensal diversity, and increased abundance of opportunistic genera (e.g., *Pseudomonas*, *Herbaspirillum*, *Burkholderia*). Progressive dysbiosis identified across gut community types (GUT I–III).	COVID-19 infection was associated with disrupted respiratory microbiota, reduced richness, dominance of *Proteobacteria*, and expansion of opportunistic pathogens (e.g., *Pseudomonas*). Gut and respiratory dysbiosis appeared linked, suggesting a gut–lung axis alteration during respiratory infection.

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		Bacteroides and *Parasutterella*, a genus associated with intestinal inflammation. This cluster also included pathogenic and environmental bacteria such as *Pseudomonas veronii*, *Streptococcus mitis*, *Herbaspirillum*, *Burkholderia*, and *Comamonadaceae_U*. Overall, the gut microbiota of COVID-19 children showed a reduction in commensal bacteria and an increase in opportunistic pathogenic and environmental bacteria, suggesting a progressive dysbiosis during and after infection.		
Moroishi *et al.* 2022 [18]	The relationship between the gut microbiome and the risk of respiratory infections among newborns	The five most common genera in our 16S data were *Escherichia/Shigella*, *Bacteroides*, *Bifidobacterium*, *Klebsiella*, and *Enterococcus*. The five most common species in our metagenomics data were *Bifidobacterium longum*, unclassified *Escherichia* species, *Escherichia coli*, *Bifidobacterium breve*, and *Gemella haemolysans*. *Veillonella* unclassified was positively associated with having an additional respiratory infection or symptom of respiratory infection in the first year of life. In examining specific outcomes, we found that diarrhea was positively associated with the relative abundance of *Streptococcus peroris* and negatively associated with the relative abundance of *Streptococcus salivarius*. Stratified by delivery mode, we found that having an additional respiratory infection or symptom of respiratory infection was positively associated with *Haemophilus influenzae* among cesarean-delivered infants. *Veillonella parvula* and *Corynebacterium pseudodiphtheriticum* were positively associated, while *Clostridium butyricum* and	Higher alpha diversity in stool samples was associated with a greater number of respiratory infections and symptoms during the first year of life. Specific taxa, including *Veillonella* spp., *Corynebacterium pseudodiphtheriticum*, and *Haemophilus influenzae* were linked to microbial patterns suggestive of gut dysbiosis associated with later respiratory outcomes. Conversely, beneficial or potentially protective taxa (*Clostridium butyricum*, *Coprobacillus* spp.) were less abundant in infants experiencing more respiratory infections.	Higher gut microbial diversity was paradoxically associated with a greater number of infections and symptoms. The abundance of *Veillonella* spp. and *Corynebacterium pseudodiphtheriticum* were positively associated with upper respiratory infections, while *Haemophilus influenzae* was linked to additional respiratory symptoms in cesarean-delivered infants. In contrast, higher levels of *Clostridium butyricum* and unclassified *Coprobacillus* were associated with a reduced risk of URTIs, suggesting potential protective roles.

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		Coprobacillus unclassified were negatively associated, with a risk of an additional upper RTI among infants delivered by cesarean section.		
Romani *et al.* 2022 [22]	The Relationship Between Pediatric Gut Microbiota and SARS-CoV-2 Infection	In children with COVID-19, the gut microbiota showed a significant reduction in *Bifidobacterium*, *Blautia*, *Collinsella*, *Eggerthella*, *Coprococcus*, *Ruminococcus*, and *Akkermansia* compared with healthy controls. Conversely, there was an increased abundance of *Faecalibacterium*, *Fusobacterium*, *Neisseria*, and members of *Bacteroidetes*. At the family level, COVID-19 patients presented higher levels of *Veillonellaceae*, *Neisseriaceae*, *Bacteroidaceae*, and *Fusobacteriaceae*, while *Bifidobacteriaceae*, *Coriobacteriaceae*, *Clostridiaceae*, *Peptostreptococcaceae*, and *Verrucomicrobiaceae* were significantly reduced. At the phylum level, COVID-19 children exhibited increased *Fusobacteria* and *Bacteroidetes*, with a decrease in *Actinobacteria* and *Verrucomicrobia*.	SARS-CoV-2 infection was associated with a significant reduction in gut microbial diversity (α-diversity), depletion of beneficial taxa (*Bifidobacterium*, *Akkermansia,* *Ruminococcus*), and enrichment of pro-inflammatory or opportunistic taxa (*Fusobacterium*, *Neisseria*). These shifts indicate gut dysbiosis in pediatric patients with COVID-19.	The authors suggest that, although SARS-CoV-2 induces gut dysbiosis, the pediatric gut microbiota may exert anti-inflammatory effects that help modulate disease severity, potentially contributing to the milder clinical course observed in children with COVID-19. The findings highlight a possible protective role of the gut microbiota in the respiratory response to SARS-CoV-2, supporting the concept of the gut–lung axis in pediatric infection.
Gutiérrez-Díaz *et al.* 2023 [12]	Microbial and immune faecal determinants in infants hospitalized with COVID-19 reflect bifidobacterial dysbiosis and immature intestinal immunity	Analysis of faecal microbial 16S sequences showed that *Actinobacteria* abundance was lower in COVID-19 patients in both age groups (newborns and toddlers) as compared with controls. In the newborns group, we observed that the most abundant families were represented by *Bifidobacteriaceae* and *Enterobacteriaceae*. Sequences belonging to the family *Bifidobacteriaceae* were more abundant in faecal samples from the control group compared with samples from patients with COVID-19. On the other hand, the relative abundance of *Enterobacteriaceae* family was higher in patients with COVID-19 than in controls. In the	Marked change with respect to control healthy infants in both groups (newborns and toddlers) that mainly consisted in a reduction in the percentage of sequences belonging to the *Actinobacteria* phylum and *Bifidobacteriaceae* family. A higher diversity of bifidobacteria, in terms of number of different species, was observed in patients with COVID-19 as compared with controls. Relative abundance and number of species of	The faecal microbiota alterations observed in infants with COVID-19 suggest a disturbance in the gut–immune axis that may contribute to poorer respiratory outcomes. The depletion of *Bifidobacterium*, particularly *Bifidobacterium breve*, is clinically relevant because this genus plays key roles in early immune maturation, antiviral defense, and regulation of systemic inflammation. Conversely, the increase

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		toddlers' group, a significant reduction in the proportions of sequences belonging to *Bifidobacteriaceae* family was observed in patients compared to controls. Relative abundance of *Enterococcaceae* family sequences was significantly higher in controls compared with patients.	bifidobacteria were different, with more presence of sequences assigned to *Bifidobacterium breve* in healthy control infants.	in *Enterobacteriaceae*, a family often associated with dysbiosis and heightened inflammatory responses, may exacerbate systemic immune imbalance, potentially worsening respiratory susceptibility or severity.
Marzano *et al.* 2023 [20]	The metaproteome of the gut microbiota in pediatric patients affected by COVID-19	Considering the total number of bacterial protein groups (PGs) and their expression level, the most significant variations in the number of over- and underexpressed PGs were identified in the *Bacillota phylum* (391 overexpressed PGs vs. 155 under-expressed in COVID-19s), with special reference to the *Oscillospiraceae* family (280 over- vs. 42 underexpressed), and to the *Faecalibacterium* (48 over- vs. 10 underexpressed) and *Ruminococcus* (213 over- vs. 6 under-expressed) genera. Also, the *Clostridiaceae* family (9 vs. 3 PGs) and the *Clostridium* genus (8 vs. 3 PGs) showed a different regulation. Regarding the *Actinomycetota* phylum, the most important differences were observed for the *Bifidobacteriaceae* family (5 vs. 11 PGs) and for the *Bifidobacterium* genus (5 vs. 10 PGs). Lastly, *Bacteroidota* phylum showed remarkable difference for the *Bacteroidaceae* family and the *Bacteroides* genus (7 vs. 3 PGs).	COVID-19 in pediatric patients was associated with differential expression of gut microbial protein groups, reflecting functional shifts rather than direct taxonomic changes. The majority of altered proteins were related to metabolic processes (e.g., tryptophan, butanoate, fatty acid, and bile acid metabolism), antibiotic resistance, virulence, and DNA repair and recombination pathways. These changes suggest that the gut microbiota of children with COVID-19 exhibits altered metabolic activity and stress responses, potentially contributing to the milder clinical manifestations observed in this population.	Functional alterations in the gut microbiota suggest potential systemic effects relevant to respiratory immunity. Enhanced expression of proteins related to tryptophan and butyrate pathways, both crucial for anti-inflammatory and antiviral defense, may contribute to the generally milder respiratory clinical course observed in children with COVID-19. The modulation of microbial metabolism, virulence, and stress-response mechanisms may influence immune responses beyond the gut, including pulmonary inflammation and viral control. These shifts may represent microbiota-derived compensatory mechanisms that modulate respiratory disease severity.
Wang *et al.* 2023 [21]	Altered gut microbiota composition in children and their caregivers infected with the SARS-CoV	In contrast with the healthy children, the abundances of the dominant bacterial phyla *Actinobacteria* and *Firmicutes* were significantly decreased, whereas the abundances of the phyla *Bacteroidetes*, *Proteobacteria*, and *Verrucomicrobiota* were increased in COVID-19 children. The dominant	COVID-19 children showed significant alterations in gut microbiota composition compared to healthy children. Decreased abundances of dominant phyla *Actinobacteria* and *Firmicutes*; increased	The microbial profile of COVID-19 children reveals depletion of beneficial genera (e.g., *Bifidobacterium*, *Blautia*) and enrichment of taxa previously linked to inflammation (e.g., *Escherichia-Shigella*,

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	-2 Omicron variant	genera were *Bacteroides*, *Bifidobacterium*, *Blautia*, and *Faecalibacterium* in both healthy children and COVID-19 children. To compare the taxonomic profiles between COVID-19 and healthy children, genera with a relative abundance larger than 0.01% in each sample were selected. The data showed that fecal samples from COVID-19 children exhibited higher relative abundances of *Fusobacterium*, *Akkermansia*, *Sutterella*, *Veillonella*, *Lachnospira*, *Parasutterella*, *Prevotella*, *Parabacteroides*, *Lachnoclostridium*, *Escherichia-Shigella*, and *Bacteroides* and lower relative abundances of *Collinsella*, *Eubacterium hallii* group, *Dorea*, *Fusicatenibacter*, *Romboutsia*, *Streptococcus*, *Blautia*, and *Bifidobacterium* than those of healthy children.	*Bacteroidetes*, *Proteobacteria*, and *Verrucomicrobiota*. Reduced beneficial genera and increased potentially pathogenic or dysbiosis-associated genera.	*Fusobacterium*, *Veillonella*). *Veillonella*, in particular, has been associated with respiratory tract infections and increased airway inflammation. Such dysbiosis may enhance systemic inflammatory signaling and contribute to altered immune responses to SARS-CoV-2, affecting respiratory outcomes.
Cabrera-Rubio *et al.* 2024 [17]	Gut and respiratory tract microbiota in children younger than 12 months hospitalized for bronchiolitis compared with healthy children: can we predict the severity and medium-term respiratory outcome?	In the gut, the distinct genera between the cases and the control group were *Escherichia/Shigella* (21.8% vs 18.8%; P = 0.33), *Bacteroides* (17.2% vs 14.2%; P = 0.31), *Clostridium* (10.4% vs 7.4%; P = 0.34), *Enterobacter* (4.2% vs 2.6%; P = 0.12), *Klebsiella* (3.7% vs 3.1%; P = 0.03), and *Streptococcus* (4% vs 2%; P = 0.92). In contrast, the least representative genera in cases compared to controls were *Bifidobacterium* (21.1% vs 20.3%; P = 0.35), *Faecalibacterium* (3.3% vs 0.3%; P < 0.0001), *Veillonella* (4.9% vs 4.8%; P ≤ 0.00102), and *Akkermansia* (5.7% vs 3.7%; P = 0.03). When performing gut analysis, *Clostridium*, *Veillonella*, *Enterococcus*, *Escherichia/Shigella*, *Bifidobacterium*, *Klebsiella*, *Streptococcus*, *Clostridium* sensu stricto, *Bacteroides*, *Enterobacter*, and *Collinsella* genera were more predictively relevant in infants with bronchiolitis than in the controls, as	The study demonstrates that infants with bronchiolitis exhibit reduced gut microbial richness, suggesting that decreased gut biodiversity may predispose young children to more severe respiratory infections. The gut microbiota profile appeared closely associated with disease severity and viral etiology. Genera such as *Bifidobacterium*, *Faecalibacterium*, *Akkermansia*, *Veillonella*, and *Escherichia/Shigella* were linked to specific viral pathogens and to the likelihood of recurrent wheezing. Additionally, enrichment of *Klebsiella* and *Streptococcus* was strongly associated with severe bronchiolitis and	Alterations in the gut microbiota were strongly associated with both the severity of bronchiolitis and subsequent respiratory outcomes. Infants with lower intestinal microbial richness were more likely to present severe respiratory symptoms, viral coinfections, and increased respiratory microbiota diversity. Specific gut microbial patterns, including higher levels of *Streptococcus*, *Klebsiella*, and *Clostridium* were predictive of severe bronchiolitis, recurrent wheezing, and future respiratory admissions.

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		well as in infants with severe bronchiolitis, positive viral detection, viral coinfection, recurrent wheezing, ≥3 wheezing episodes, respiratory admissions, and prescription for chronic asthma treatment. In the gut microbiota, the genera *Bifidobacterium*, *Faecalibacterium*, *Escherichia/Shigella*, *Veillonella*, and *Akkermansia* tended to be associated with the type of virus and recurrent wheezing. While *Streptococcus* and *Klebsiella* were associated with severe bronchiolitis, viral coinfection, and recurrent wheezing. Moreover, respiratory admissions during follow-up were related to *Clostridium* species.	viral coinfections, highlighting potential microbial signatures that may influence immune responses and respiratory outcomes in early life.	
Piazzesi *et al.* 2024 [23]	The pediatric gut bacteriome and virome in response to SARS-CoV-2 infection	SARS-CoV-2 infected patients had significantly reduced proportions of *Actinobacteriota* and increased the proportions of *Bacteroidia* compared to healthy age-matched controls. Significant decrease in *Bifidobacterium* and an over-abundance of *Parabacteroides*, *Odoribacter* and *Ruminococcus gnavus*, as well as an enrichment of the *Faecalibacterium genus* and several *Faecalibacterium prausnitzii* subspecies in COVID-19 patients cohort. Furthermore, abundance of *Eubacterium* genus and *Alistipes* genus was also found in the pediatric patients compared with control patients.	The findings indicate that SARS-CoV-2 infection substantially reshapes the pediatric gut microbiota, leading to a distinct microbial signature characterized by the simultaneous enrichment of pro-inflammatory taxa (e.g., *Parabacteroides*, *Ruminococcus gnavus*, *Alistipes*) and anti-inflammatory or immunomodulatory bacteria such as *Faecalibacterium prausnitzii*. The depletion of *Bifidobacterium*, a key early-life commensal associated with immune maturation, highlights a potential disruption of normal gut homeostasis.	Although the study focused on gut microbial changes, the authors suggest that this unique microbial pattern, combining inflammatory and protective taxa, may help explain the generally mild clinical course of COVID-19 in children. The presence of immunomodulatory bacteria, such as *Faecalibacterium prausnitzii*, has been linked to reduced viral infectivity and more controlled inflammatory responses, which could limit respiratory severity. Conversely, the expansion of pro-inflammatory gut bacteria may contribute to immune activation pathways associated with respiratory symptoms.
Hyvönen *et al.*	The association	The two most predominant bacteria of the microbiota at family level were	The study indicates that specific early-life microbial	Early deviations in gut microbiota composition

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2025 [19]	of maternal and infant early gut microbiota with respiratory infections in infants	*Bifidobacteriaceae* and *Enterobacteriaceae* at the age of 3 and 6 weeks in all infant groups. The most significant difference in the microbiota composition at family level in the fecal samples at 3 weeks of age was that infants who developed a respiratory tract infection (RTI) within the first 3 months of life had a higher abundance of *Rikenellaceae* and *Verrucomicrobiaceae*, followed by increased *Prevotellaceae*, *Actinomycetaceae*, *Coriobacteriaceae* and *Micrococcaceae* compared to that in control group. The higher abundance of *Prevotellaceae* was also seen in infants developing RTI within the first six months of life. Only this higher abundance of *Prevotellaceae* persisted in the samples taken at 6 weeks of age but only in infants developing an RTI within the first 3 months of life. The higher relative abundance of *Faecalibacterium*, a major butyrate producer, and *Peptoniphilus* was also observed in infants developing RTIs within the first 6 months of life, while *Anaerostipes* was less abundant. The relative abundance analysis from the samples taken at 6 weeks of age revealed a concomitant strong decrease of *Anaerostipes* in infants developing an RTI within the first three and 6 months of life. We also found a higher abundance of six genera (*Prevotella*, *Macellibacteroides*, *Catenibacterium*, *Subdoligranulum*, *Faecalibacterium*, and *Atopobium*) in infants developing infection within the first 3 months of life.	shifts, rather than overall diversity changes, are associated with increased susceptibility to respiratory infections. Infants who developed RTIs displayed a distinct gut microbial signature characterized by increases in *Prevotellaceae*, inflammation-linked taxa, and butyrate-producing genera such as *Faecalibacterium*, alongside a consistent reduction in *Anaerostipes*. These compositional deviations suggest that gut ecological imbalance during the first weeks of life may influence immune development, thereby increasing vulnerability to RTIs.	were associated with a greater risk of developing RTIs during infancy. Infants with increased abundances of *Prevotella*, *Faecalibacterium*, *Peptoniphilus*, and several inflammation-associated families during the first 3–6 weeks of life were more likely to experience RTIs within the first 3 or 6 months. The persistent reduction in *Anaerostipes*, coupled with enrichment of taxa linked to mucosal inflammation, suggests that early gut dysbiosis may modulate immune responses in a way that predisposes infants to respiratory infections. The findings highlight the gut microbiota as a potential early-life marker for respiratory disease susceptibility.

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3.1.4. Gut Microbiota in Children with Respiratory Infections

3.1.4.1. COVID-19

Children infected with SARS-CoV-2 exhibited marked alterations in gut microbiota composition. In the study by Xu *et al.* (2021) [14], the COVID-19 children presented a marked reduction in core commensal bacteria and an increased abundance of opportunistic and environmental taxa, most notably *Pseudomonas*, *Herbaspirillum*, *Burkholderia*, and *Parasutterella*, the latter being associated with intestinal inflammation.

In agreement, Romani *et al.* (2022) [22] also reported significant microbiota alterations compared with healthy controls. Infected children showed a significant reduction in beneficial genera such as *Bifidobacterium*, *Blautia*, *Collinsella*, *Eggerthella*, *Coprococcus*, *Ruminococcus*, and *Akkermansia*, alongside an increased abundance of *Faecalibacterium*, *Fusobacterium*, *Neisseria*, and several *Bacteroidetes* members.

Analysis of faecal samples revealed that infants hospitalized with COVID-19 showed a marked dysbiosis characterized primarily by reduced levels of *Actinobacteria* and, in particular, *Bifidobacteriaceae*, across both age groups (newborns and toddlers). In newborns, *Bifidobacteriaceae* and *Enterobacteriaceae* were the dominant families; however, *Bifidobacteriaceae* were significantly less abundant in COVID-19 patients than in healthy controls, while *Enterobacteriaceae* were proportionally higher among infected infants. Toddlers with COVID-19 exhibited reduced relative abundance of *Bifidobacteriaceae* compared with controls [12].

Functional metaproteomic analysis revealed major shifts in microbial metabolism rather than drastic taxonomic changes. Marzano *et al.* (2023) [20] observed that differential expression of microbial protein groups occurred within the *Bacillota* (formerly *Firmicutes*) phylum, especially in *Oscillospiraceae*, *Faecalibacterium*, and *Ruminococcus*, which exhibited many more over-expressed than under-expressed proteins. Functional changes were also detected in *Clostridiaceae*, *Bifidobacteriaceae*, *Bifidobacterium*, and *Bacteroidaceae*. These proteins were primarily linked to key metabolic pathways, including tryptophan, butyrate, fatty acid, and bile acid metabolism, as well as antibiotic resistance and virulence responses.

Additional evidence from Wang *et al.* (2023) [21] shows depletion of beneficial genera (e.g., *Bifidobacterium*, *Blautia*) and enrichment of taxa previously linked to inflammation (e.g., *Escherichia-Shigella*, *Fusobacterium*, *Veillonella*). *Veillonella*, in particular, has been associated with respiratory tract infections and increased airway inflammation. Such dysbiosis may contribute to altered immune responses to SARS-CoV-2.

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Finally, Piazzesi *et al.* (2024) [23] reported that pediatric patients infected with SARS-CoV-2 exhibited marked alterations in gut microbiota composition compared to age-matched healthy controls. COVID-19 children showed significantly reduced proportions of *Actinobacteriota*, along with an increased relative abundance of *Bacteroidia*. At the genus level, SARS-CoV-2 infection was associated with a notable depletion of *Bifidobacterium* and an overabundance of *Parabacteroides*, *Odoribacter*, and *Ruminococcus gnavus*. Additionally, the COVID-19 cohort displayed an enrichment of the *Faecalibacterium genus*, including several *Faecalibacterium prausnitzii* subspecies, as well as higher levels of *Eubacterium* and *Alistipes* compared with healthy children.

3.1.4.2. Respiratory Tract Infections (RTIs) and Recurrent Respiratory Tract Infections (RRTIs)

Children with RRTIs present reduced microbial diversity and an increased abundance of *Enterococcus*, alongside decreased levels of *Eubacterium, Faecalibacterium* and *Bifidobacterium* in the RRTI group compared to those in the normal control group, indicating an association between gut microbiota composition and infection recurrence [16].

Reyman et al. (2021) [13] reported distinct gut microbial network hubs according to the frequency of respiratory tract infections. Infants with 0-2 RTIs exhibited hubs dominated by taxa such as Neisseria lactamica, Dolosigranulum pigrum, and *Corynebacterium,* as well as several butyrate-producing genera. In contrast, infants with 5-7 RTIs showed network hubs enriched in taxa including *Haemophilus* spp., *Ruminococcus gnavus,* and other bacterial groups, alongside cariogenic species such as *Bifidobacterium dentium* and *Parascardovia denticolens.*

Moroishi *et al.* (2022) [18] reported that the early infant gut microbiome was dominated by the genera *Escherichia/Shigella*, *Bacteroides*, *Bifidobacterium*, *Klebsiella*, and *Enterococcus*. At the species level, the most abundant taxa included *Bifidobacterium longum*, unclassified *Escherichia*, *Escherichia coli*, *Bifidobacterium breve*, and *Gemella haemolysans*. A higher relative abundance of unclassified *Veillonella* was positively associated with the occurrence of additional respiratory infection episodes reported during the first year of life. Delivery mode modified several associations: among cesarean-delivered infants, increased *Veillonella parvula* and *Corynebacterium pseudodiphtheriticum* were linked to a greater risk of upper respiratory infections (URTIs), while *Clostridium butyricum* and unclassified *Coprobacillus* were associated with reduced risk. Additionally, *Haemophilus influenzae* abundance was associated with an increased likelihood of extra respiratory infections among cesarean-born infants. Gastrointestinal

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symptoms also showed associations: diarrhea correlated positively with *Streptococcus peroris* and negatively with *Streptococcus salivarius*.

Hyvönen *et al.* (2025) [19] found that, at both 3 and 6 weeks of age, the infant gut microbiota was dominated by the families *Bifidobacteriaceae* and *Enterobacteriaceae*. However, infants presenting RTIs during follow-up showed distinct gut microbiota compositions already at 3 weeks of age. These infants showed higher abundances of *Rikenellaceae* and *Verrucomicrobiaceae*, followed by increased levels of *Prevotellaceae*, *Actinomycetaceae*, *Coriobacteriaceae*, and *Micrococcaceae*, compared with healthy controls. *Prevotellaceae* remained elevated at 6 weeks of age in infants who developed RTIs within the first 3 months of life. At 6 weeks, these infants also showed a higher relative abundance of *Faecalibacterium*, a major butyrate-producing genus, and *Peptoniphilus*, whereas *Anaerostipes* was consistently reduced. The relative abundance of *Anaerostipes* showed a strong decrease in infants who developed RTIs within both the first 3 months and the first 6 months of life.

3.1.4.3. Respiratory Syncytial Virus (RSV) and Bronchiolitis

Studies investigating respiratory syncytial virus (RSV) and bronchiolitis reveal consistent alterations in the gut microbiota of affected infants. Harding *et al.* (2020) [15] reported a significant enrichment in *S24_7*, *Clostridiales*, *Odoribacteraceae*, *Lactobacillaceae*, and *Actinomyces* in RSV (moderate and severe) when compared with controls. At the genus level, S24_7 is increased in severe patients compared to control patients while *Tissierella soehngenia* is decreased.

Similar patterns were observed in infants hospitalized with bronchiolitis, who displayed distinct microbial signatures compared with healthy infants. The most abundant genera in bronchiolitis cases were *Escherichia/Shigella*, *Bacteroides*, *Clostridium*, *Enterobacter*, *Klebsiella*, and *Streptococcus*. In contrast, cases had lower relative abundance of *Bifidobacterium*, *Faecalibacterium*, *Veillonella*, and *Akkermansia*. Predictive analysis identified several genera, including *Clostridium*, *Veillonella*, *Enterococcus*, *Escherichia/Shigella*, *Bifidobacterium*, *Klebsiella*, *Streptococcus*, *Bacteroides*, and *Enterobacter*, as highly relevant for distinguishing infants with bronchiolitis from controls and for characterizing severe disease and viral coinfection [17].

3.2. Discussion

This review reinforces the growing evidence that early-life gut microbiota composition is closely associated with immune maturation and susceptibility to pediatric respiratory infections

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[7]. Across the twelve included studies, a consistent pattern emerged in which children with respiratory infections exhibited depletion of key commensal and immunomodulatory taxa, particularly Bifidobacterium, members of Actinobacteria, and several butyrate-producing genera.

Supporting this pattern, Gutiérrez-Díaz *et al.* (2023) [12] reported greater abundance and species richness of *Bifidobacterium*, especially *B. breve*, in healthy infants, while Piazzesi *et al.* (2024) [23] suggested that its depletion may reflect disruption of normal immune-related microbial maturation. Moroishi *et al.* (2022) [18] further demonstrated that lower levels of protective taxa, such as *Clostridium butyricum*, were associated with increased frequency of respiratory events.

Conversely, multiple studies described enrichment of opportunistic and inflammation-associated taxa, particularly within *Proteobacteria*, in children with respiratory infections. More severe or recurrent disease was often associated with microbial profiles enriched in these taxa [15], whereas children with fewer infections exhibited microbiota structures dominated by beneficial hub species [13].

Importantly, these findings do not support a simple linear relationship between “beneficial” taxa and respiratory health. Hyvönen *et al.* (2025) [19] showed that higher early abundance of typically beneficial adult-associated butyrate producers, such as *Faecalibacterium*, predicted subsequent respiratory infections. This suggests that premature or dysregulated microbial maturation, rather than the presence of specific taxa alone, may influence disease susceptibility. These findings highlight the importance of ecological context and developmental timing in interpreting microbiota–health relationships during early life.

Longitudinal observations in several studies indicate that microbiota alterations may precede or accompany the onset of respiratory infections. However, due to the predominantly observational nature of the evidence, these temporal associations cannot establish causality. In addition to compositional changes, functional dysbiosis has also been reported. Marzano *et al.* (2023) [20] demonstrated alterations in microbial metabolic pathways and stress-response proteins, suggesting that functional shifts in the microbiome may play a relevant role in host–pathogen interactions.

Substantial heterogeneity across studies further complicates interpretation. Variations in diet, breastfeeding practices, antibiotic exposure, environmental factors, and clinical interventions all influence gut microbiota composition [24–26]. Methodological differences, including study design, sample size, microbiota profiling techniques, sampling timing, and control of confounding factors, limit comparability and generalizability. Antibiotic exposure, in particular, was consistently

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identified as a major confounder. Moreover, many studies assessed microbiota during or after acute illness, making it difficult to disentangle cause and consequence.

Taken together, the current body of evidence supports an associative, rather than causal, relationship between gut microbiota alterations and pediatric respiratory infections. The observed bidirectional interactions between the gut and lungs further reinforce the complexity of this relationship. Future research should prioritize well-designed, multi-center longitudinal studies with standardized methodologies and integrated functional analyses. Such approaches will be essential to clarify causal pathways and to support the development of microbiota-targeted strategies for the prevention and management of respiratory infections in children.

4. CONCLUSION

This review highlights consistent associations between early-life gut microbiota composition and pediatric respiratory infections, including COVID-19, RSV, bronchiolitis, and recurrent RTIs. Across studies, affected children commonly exhibited reduced microbial diversity, depletion of key commensal and immunomodulatory taxa, particularly *Bifidobacterium*, and enrichment of opportunistic or inflammation-associated microorganisms.

Importantly, the findings also suggest that microbiota–health relationships in early life are not strictly linear, as alterations in microbial maturation timing and ecological balance may influence susceptibility to respiratory infections. Evidence supporting microbiota alterations preceding infection onset was limited to a small number of studies, while most investigations assessed microbiota during or after acute illness, restricting the ability to determine temporal relationships.

Overall, these results reinforce the relevance of the gut–lung axis in early immune development while underscoring the complexity and bidirectionality of this relationship. Future research should prioritize well-designed, multi-center longitudinal and interventional studies with standardized methodologies and integrated functional analyses. Such approaches will be essential to clarify causal pathways and to support the development of microbiota-targeted strategies for the prevention and management of pediatric respiratory infections.

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