Hidden connection: Impact of the gut microbiota on respiratory diseases in children (Review)

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Abstract. Respiratory tract diseases are among the most common acute infectious diseases, and their incidence is associated with geographic, age and seasonal factors. Although generally self-limiting in adults, these diseases are a leading cause of death in infants, the elderly and individuals with immune system deficiencies, and represent a major cause of mortality in Chinese children. There is a clear association between abnormalities in the gut microbiota in childhood and the development of immune and metabolic disorders later in life. Some studies have shown that the gut microbiota and its metabolites can effectively prevent and mitigate respiratory tract diseases. However, the composition of the gut microbiota in children differs from that in adults, and research on the interaction between the gut microbiota and respiratory tract diseases in children remains limited. The present review discusses the development of the gut microbiota in early life and its role in pediatric respiratory tract diseases, highlighting its influence on respiratory health and the gut-lung axis. Probiotic treatments are also discussed. While they are considered a promising approach, their widespread clinical application faces challenges with regard to safety and individual variability.

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1. Introduction

Respiratory tract diseases are a major health problem, associated with high incidence and mortality rates worldwide (1). Respiratory tract infections are caused by the invasion and reproduction of pathogenic microorganisms in the respiratory tract, and can be broadly divided into upper and lower respiratory tract infections. Upper respiratory tract infections mainly affect areas at and above the throat, and include acute and chronic rhinitis, laryngitis and pharyngitis, while lower respiratory tract infections affect areas below the throat, and include acute and chronic bronchitis and pneumonia. The World Health Organization estimates that respiratory tract diseases were the fourth leading cause of death worldwide in 2016, accounting for nearly 3 million deaths, which corresponds to ~40 deaths per 100,000 population (2).

Children are particularly vulnerable to respiratory tract diseases, with each child reported to experience up to 12 cases of respiratory tract infection per year (3). Due to their underdeveloped immune systems, children are also prone to complications from respiratory tract diseases, including bronchitis, pneumonia, sinusitis and otitis media (4). Therefore, respiratory tract infections in children pose a great threat to health. Mild cases present with local symptoms such as sneezing, nasal congestion and dry cough, while some children may also experience symptoms such as a sore throat or discomfort in the throat (5). However, severe illness can occur, particularly in infants and young children, with rapid onset, mild local symptoms and severe systemic symptoms, manifesting as irritability, high fever, anorexia and fatigue, with shock and death occurring in the most severe cases (6).

The human microbiota and its surrounding microenvironment are closely linked to metabolism and health, and dysbiosis of the microbiota is strongly associated with respiratory tract diseases. As one of the organs with the most complex microbiota, the intestines have a marked impact on human health. The gut microbiota has various effects on human physiology, which are mediated via a number of different axes, including the gut-lung (7), gut-brain (8), gut-skeletal muscle (9), gut-organ (10) and gut-cardiac axes (11). Research into the gut microbiota has explored its influence on a wide range of conditions, including cancer (12), hypertension (13), obesity (14) and respiratory diseases (15).

With the advancement of microbial research techniques, the field of human microbial ecosystems has been increasingly studied (16). Although most studies on the microbiome have focused on diseases in adults, researchers have now started to investigate the role of microbial ecosystems in pediatric respiratory diseases. Studies of adults suggest that the gut microbiota can indirectly regulate pulmonary immune function (17). The bacterial population in the gut is large and diverse compared with that in other parts of the body, making it a particularly valuable topic of research. The development of the gut microbiota begins at birth, undergoes highly dynamic changes during in the first years of life and typically stabilizes after 1-3 years (18).

In the present review, the development of the gut microbiota during early life and its roles in human health are described. In addition, the associations of the gut microbiota with pediatric respiratory tract diseases are reviewed, with a focus on syncytial viral infections, childhood asthma and cystic fibrosis. Finally, probiotic-related therapeutic approaches are discussed. The review aims to provide new insights into the relationship between gut flora and pediatric respiratory diseases.

2. Gut microbiology-related factors in infants

The innate and adaptive immune systems are known to be influenced by the composition of the gut microbiota during the first year of life (19). After birth, the immune system is not yet mature, and the first few years of life are a critical period for both microbiota establishment and maturation of the immune system (20). The microbial community participates in various processes within the body, including metabolism and regulation of the immune system, thereby playing a vital role in the overall health of infants (Fig. 1) (21).

The composition of the gut microbiota varies from birth, and differs in infants born vaginally from those born by cesarean section (22). Vaginally delivered infants are exposed to maternal vaginal and fecal microbiota, resulting in the presence of *Lactobacillus*, *Prevotella* and/or *Sneathia* in the gut microbiota (21,23). By contrast, infants delivered by cesarean section acquire microbiota from maternal skin, hospital staff or the hospital environment, including *Staphylococcus*, *Corynebacterium* and *Propionibacterium* (24,25). Infants born by cesarean section generally exhibit decreased microbial diversity compared with that of vaginally delivered infants (26). However, the gut microbiology of infants delivered by emergency cesarean section more closely resembles that of vaginal deliveries, likely due to partial exposure to the birth canal during early labor (27,28). Although the intrauterine environment was originally assumed to be sterile, the presence of a unique microbial environment has been identified in the placenta, comprising non-pathogenic commensal microbiota. This indicates that even during embryonic development, certain microorganisms may be in contact with and influence the fetus (29).

The earliest microbiota colonizing the infant gut are aerobic or parthenogenetic anaerobic bacteria, such as Enterobacteriaceae, *Enterococcus* and *Staphylococcus*. As anerobic bacteria increase and oxygen is consumed, the first strict anaerobes begin to proliferate, including *Bifidobacterium*, *Clostridium* and *Lactobacillus*. Among these, *Bifidobacterium* is one of the most predominant bacterial genera in the gut microbiota of human infants (30). In addition, preterm infants born at less than 37 weeks' gestation typically exhibit a reduced gut microbial diversity and lower levels of *Bifidobacterium* and *Lactobacillus acidophilus* (*L. acidophilus*) (31). Their gut microbiota may be altered due to factors such as exposure to medication or artificial feeding (32). Preterm infants also exhibit delayed gut colonization by commensal anerobic microorganisms, such as *Bifidobacterium* or *Lactobacillus*, and significantly elevated fecal levels of pathogenic microorganisms, including Enterobacteriaceae and *Enterococcus* (33,34).

Research has consistently demonstrated that breastfeeding provides a wide range of health benefits for infants (35). Breast milk contains various bioactive components essential for infant growth and development, including immunomodulatory factors, growth hormones, antimicrobials and prebiotics (36). It has been hypothesized that the inability of human milk oligosaccharides, which are abundant in breast milk, to be digested by infants plays a crucial role in shaping of the infant gut microbiota and protecting against infection (37,38).

Breast milk has its own microbiota, containing $1x10^2$-$1x10^4$ viable bacteria/ml. Dominant genera include *Staphylococcus*, *Streptococcus*, *Lactobacillus* and *Bifidobacterium*, which promotes the formation of the intestinal microbiota in the infant (39). In addition to promoting colonization of the intestinal tract, breast milk is rich in immunoglobulins, such as immunoglobulins A, G and M, and maternal immune cells, both of which play important roles in infant immune defense and health (37,38).

The gut microbiota of formula-fed infants consists primarily of parthenogenetic anaerobes, such as *Lactobacillus* and *Clostridium*. Differences between the microbial communities of breastfed and formula-fed infants have been associated with long-term health outcomes, including an increased risk of developing allergic disease in formula-fed infants, whereas breastfeeding is protective (40). To address this, prebiotics such as short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides are often added to formula milk. They selectively promote the growth of *Bifidobacterium* and reduce the abundance of *Enterococcus* and *Escherichia coli*, thereby improving the composition of the gut microbiota (41). Although current infant formulas are unable to fully replicate the beneficial effects of breast milk on the gut microbiota, advances in prebiotic formulations have been shown to have a positive effect on infants (such as establish the gut microbiota and promote the colonization of bifidobacteria) (42).

Antibiotic treatment and malnutrition are two major factors that affect the gut microbiota, leading to gut dysbiosis (43). Disturbances during early life can impair the composition, maturation and function of the gut microbiota, leading to adverse health consequences later in life. While antibiotics are commonly used to treat bacterial infections, they destroy commensal bacteria in addition to harmful bacteria, thereby triggering intestinal dysbiosis (44). Early use of antibiotics has been shown to reduce the number of bifidobacteria in the neonatal gut, and broad-spectrum antibiotics can significantly alter the composition and structure of the gut microbiota, reducing its diversity by >25% (45,46). In addition, maternal antibiotic use during pregnancy and

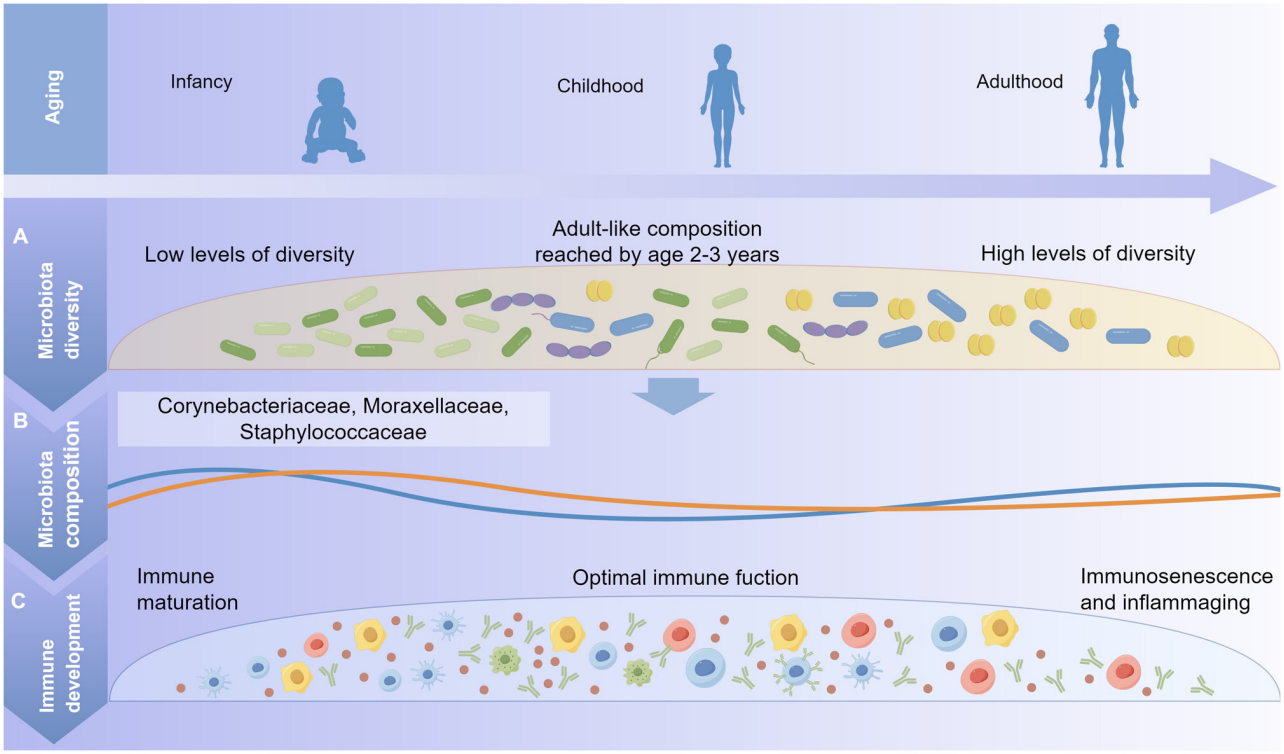

Figure 1. Gut microbiota in infants. (A) Microbiota diversity is initially low in infancy but gradually increases, reaching an adult-like composition by 2-3 years of age, although the overall diversity remains lower than that observed in adults. (B) In healthy infants, the nasopharyngeal microbiome is characterized by a high abundance of Corynebacteriaceae, Moraxellaceae and Staphylococcaceae during the first few months of life. (C) The microbial community plays a crucial role in infant health by supporting metabolic processes and modulating the immune system.

breastfeeding has been linked with neonatal microflora dysbiosis (47,48). Antibiotics reduce the diversity of the breast milk microbiota, thereby decreasing the abundance of *Bifidobacterium* in the neonatal gut (49). Malnourished children also exhibit disturbed intestinal flora, characterized by a significant reduction in *Bifidobacterium* and an altered ratio of aerobic to anaerobic bacteria in fecal samples, resembling immature intestinal flora (50). Malnutrition may also promote inflammation, impair nutrient absorption and exacerbate gut microflora dysbiosis (51,52). Some of the factors influencing the gut microbiota in early life are summarized in Table I (23,53-58).

3. Pediatric respiratory diseases and gut microbiota

The close relationship between the gut and lungs can be partly attributed to their shared embryonic origin and the fact that both are exposed to the external environment via the oral cavity and pharynx, which share physiological and structural features (59,60). Although the mechanisms underlying the gut-lung axis are not fully understood, the gut microbiota and its metabolites play an important role in host defense. Metabolites produced by the commensal gut microbiota activate and regulate certain cellular responses required to maintain inflammatory tone, thereby promoting microbiota-host homeostasis (61). The anaerobic fermentation of dietary fiber by the gut microbiota produces short-chain fatty acids with immunomodulatory functions, including the inhibition of immune cell chemotaxis and adhesion, induction of anti-inflammatory cytokine expression, and stimulation of apoptosis in immune cells (62). These fatty acid metabolites also increase the number and function of T regulatory (Treg), T helper (Th) 1 and Th17 effector cells through the inhibition of histone deacetylases, thereby reducing excessive inflammation and immune responses in respiratory tract diseases (63).

There are significant differences in the overall gut microbiome composition between patients with chronic obstructive pulmonary disease (COPD) and healthy individuals (64). The fecal microbiome of patients with COPD shows increased abundances of *Streptococcus, Rothia*, *Romboutsia, Streptococcus* spp., and *Escherichia*, with *Streptococcus* considered to be a key factor differentiating samples from patients with COPD from those from healthy individuals (65). The gut microbiota is particularly relevant to respiratory health. For example, exposure to gut commensal bacteria immediately after birth has been shown to promote the migration of group 3 innate lymphoid cells into the lungs of neonatal mice to help defend against pneumonia, whereas the same treatment in adult mice has limited effects on pneumonia susceptibility (66). Another study in mice demonstrated that colonization with gut microbes during the neonatal period reduces the likelihood of allergic asthma by preventing ovalbumin-induced aggregation of invariant natural killer T cells to the lungs and by reducing hypermethylation of the CC motif chemokine ligand 16 gene (67).

The administration of microbial metabolites, microbial components or probiotics to mice improves their immune response and survival when exposed to lung pathogens, with detectable changes in the microbiota of the gut and lungs (68). A study by Luoto *et al* (69) found that prebiotic treatment

Table I. Effects of different factors on the intestinal microbiota in early life.

First author, year	Factors	Gut microbiota influence	(Refs.)
Dominguez-Bello *et al*, 2010	Vaginal delivery	*Lactobacillus*↑, *Prevotella*↑, *Sneathia*↑	(23)
Moles *et al*, 2013	Preterm delivery	*Enterococcus*↑, *Staphylococcus*↑, Bacilli↑, Proteobacteria↑, *Bifidobacterium*↓, *Lactobacillus*↓	(53)
Dominguez-Bello *et al*, 2010	Cesarean section	*Staphylococcus*↑, *Corynebacterium*↑, *Propionibacterium*↑, *Lactobacillus*↓, *Bifidobacterium*↓, *Bacteroides*↓	(23)
Fernández *et al*, 2013	Breastfeeding	*Staphylococcus*↑, *Streptococcus*↑, lactic acid bacteria↑, *Bifidobacterium*↑	(54)
Mountzouris *et al*, 2002	Formula-feeding	*Bacteroides*↑, *Clostridium*↑, parthenogenetic anaerobes↑	(55)
Barrett *et al*, 2013	Antibiotics treatment	*Bifidobacterium*↓, *Bacteroides*↓	(56)
Fouhy *et al*, 2012	Antibiotics treatment	*Bifidobacterium*↓, Proteobacteria↑, Actinobacteria↓, *Lactobacillus*↓	(57)
Fallani *et al*, 2010	Geographical location	Northern Europe: *Bifidobacterium*↑, *Clostridium*↑, *Atopobium*↑; Southern Europe: Eubacteria↑, *Lactobacillus*↑, *Bacteroides*↑	(58)

with a mixture of galacto-oligosaccharides and polydextrose, or probiotic supplementation with *Lactobacillus rhamnosus* GG (LGG), reduced the incidence of upper respiratory tract infections in preterm neonates. Similarly, Maldonado *et al* (70) observed a reduced incidence of respiratory and gastrointestinal infections in neonates following the administration of *Lactobacillus fermentum* and galacto-oligosaccharides. In addition, a meta-analysis of 23 trials and 6,269 children performed by Wang *et al* (71) demonstrated that probiotic supplementation reduced the incidence of upper respiratory tract infections, with the evidence rated as moderate quality.

Gastrointestinal symptoms such as loss of appetite, nausea and vomiting occur in 20-60% of patients with coronavirus disease 19 (COVID-19). These symptoms may appear earlier than respiratory symptoms exhibit an association with severe disease progression (72). Differences in the composition of the gut microbiota between individuals infected with COVID-19 and controls have been detected, with reductions of *Faecalibacterium prausnitzii* and *Bifidobacterium bifidum (B. bifidum)* populations in COVID-19-infected patients, which are inversely correlated with disease severity (73,74).

The remainder of this section examines the relationship between the gut microbiota and respiratory tract diseases, focusing on respiratory syncytial virus (RSV) infections, childhood asthma and cystic fibrosis.

RSV infection. RSV belongs to the genus *Orthopneumovirus* in the family *Pneumoviridae*, and is a single-stranded, negative-stranded RNA respiratory virus containing an envelope (75). Humans are the only natural host of RSV, which is mainly transmitted by droplets and contact, is highly contagious and has a high risk of severe disease (76). First-time RSV infections in infants and young children can lead to severe, sometimes fatal, bronchiolitis. The high infectivity of RSV can lead to frequent reinfections in children, even multiple infections within the same season (77). RSV infections may adversely affect lung development, increasing susceptibility to wheezing and asthma following infection. Current treatment is supportive, as no safe and effective specific antiviral therapy currently exists. RSV is a leading cause of severe acute lower respiratory tract infections in infants and children, and the most common cause of viral lower respiratory tract infections in children <5 years old. It is a global public health concern due to being highly contagious with the potential to cause localized outbreaks or epidemics (78). Globally, pneumonia occurs in ~11.7% of children with RSV (79), and ~61% of pediatric cases require hospitalization (80). Infants and young children <2 years of age account for more than half of all RSV infections, resulting in 160,000-200,000 child deaths annually, making RSV the second leading cause of infant mortality after newborn conditions (81).

Harding *et al* (82) collected fecal samples from 95 RSV-positive infants within 72 h of admittance to hospital to investigate their gut microbiota. The authors found a significant increase in the abundance of Clostridia, Odoribacteraceae, Lactobacillaceae and Actinobacteria in samples from RSV-positive infants. Jang *et al* (83) studied the association between fecal microbiome profiles and bronchiolitis in hospitalized infants with bronchiolitis, 65% of whom had RSV infection. The findings of the study suggested that the gut microbiota of RSV-infected infants may impact host immune responses. In addition, the diversity of the gut microbiota in RSV-positive infants was observed to be associated with disease severity. Retrospective studies have found that breastfed infants experience less severe RSV infection, shorter hospital stays and a reduced need for oxygen therapy than formula-fed infants (84,85). The mode of delivery has also been shown to impact RSV infection outcomes in infants. A cohort study of all children born in Denmark between 1997-2003 found that caesarean section increased the risk of hospitalization and severe RSV disease in the first two years of life (86). These findings highlight how feeding and birthing practices have a direct impact on infant gut microbiota, and

suggest a correlation of RSV infection severity with the composition of the infant gut microbiome.

Early in life, RSV infection can bias immune responses toward Th2 or Th17 pathways. This is due to the presence of thymic stromal lymphopoietin released by airway epithelial cells, which activates the Th2 response via $CD4^+$ T cells and type 2 innate lymphocytes (87). Another study found that the RSV infection of dendritic cells alters histone methylation in the promoter region of pro-inflammatory cytokines, thereby reducing innate Th1-associated inflammatory responses and shifting immunity towards Th2 inflammation (88). Both clinical and animal studies indicate that this RSV-induced immune profile persists even after recovery from infection (89,90). Notably, the gut microbiota can suppress inflammation and modulate the immune response. A systematic review of the literature suggests that the gut microbiome of RSV-infected individuals differs from that of healthy controls (91), a finding supported by a study of animals (92). Furthermore, a summary review reports that the administration of bacterial lysates designed to act on the gut microbiota modulates immunity and reduces the frequency and severity of respiratory infections in children (93).

Childhood asthma. The prevalence of asthma in children aged 5-14 years is ~10%, making it the most common chronic disease worldwide. Validated tools or methods to confirm the diagnosis of asthma in children <5 years of age are lacking, despite asthma-like symptoms appearing before the age of 2 years in some cases (94,95). Asthma is a complex disease characterized by clinical symptoms such as wheezing, cough, chest tightness and dyspnoea, along with bronchial obstruction, hyper-responsiveness to triggers such as infections, allergies, pollution, climate or physical activity, and airway inflammation. Symptoms vary with age, exposure to triggers or treatment (96). Asthma can also be classified into subtypes, with the most common childhood form being allergy-related and mediated by Th2 cells (97). Th2 cell-mediated asthma is characterized by airway eosinophilic inflammation, activated by innate epithelial mediators, including IL-25 and IL-33, and thymic stromal lymphopoietin. These mediators are secreted by airway epithelial cells in response to allergens, smoke, pollutants, microbes and other irritants. Genetic and epigenetic factors have been shown to influence the development of asthma (98).

The gut microbiota has been demonstrated to play a role in childhood asthma. In a cohort study, children born to mothers with asthma had immature gut microbiota at 1 year of age, which was associated with an increased risk of developing asthma by age 5 years, whereas this association was not observed in children without maternal asthma (99). The study observed that the abundance of *Veillonella* in the intestines of children born to asthmatic mothers at 1 year was positively associated with asthma at 5 years, while the abundance of *Enterococcus faecalis* (*E. faecalis*), *Bifidobacterium*, *Roseburia*, *Alistipes*, *Dialister*, Lachnospiraceae *incertae sedis* and *Ruminococcus* was negatively associated. Another study found that newborns with a higher abundance of *E. faecalis*, *Bifidobacterium*, *Lactobacillus* and *Akkermansia* in the gut microbiota had a lower 4-year risk of developing asthma (100). Factors such as mode of delivery, feeding practices and antibiotic use have been shown to influence the gut microbiota in infants, and these same factors are epidemiologically associated with the development of asthma in children. It has been suggested that the adverse effects of antibiotic use on childhood asthma may be mediated by interference with the gut microbiota in infancy, for example, by altering the relative abundance of various microbes in the gut microbiota and inducing dysbiosis (101). A study on breastfeeding and childhood asthma confirmed that part of the protective effect of breast milk on childhood asthma is mediated by the composition of the early gut microbiota (102). In addition, a higher abundance of beneficial bacteria, such as *Bifidobacterium longum* (*B. longum*), in the gut microbiota early in life has been associated with a reduced risk of asthma (103). A recent population-based and prospective cohort study conducted in British Columbia, Canada further suggested that the judicious use of antibiotics in infancy and early childhood may protect the gut microbiota and help to reduce the incidence of asthma in children (104). Collectively, these findings support a link between childhood asthma and the gut microbiota.

Studies have shown that the neonatal microbiota in children with allergic diseases, such as allergic asthma, is associated with increased Th2 and decreased Treg cell numbers (105). In addition, the colon, skin and lungs of germ-free mice have been found to exhibit increased Th2 and reduced Treg cell numbers, which can be altered by exposure to commensal microbes early in life (106). Furthermore, an increased abundance of commensal bacteria, including *Lactobacillus*, *Clostridium*, *Lactobacillus* and *Veillonella*, is associated with improved Treg cell function and may provide protection against diseases such as childhood asthma (107).

Cystic fibrosis. Cystic fibrosis is an autosomal recessive disorder affecting mucus- and sweat-producing cells that affects multiple organs, primarily the lungs and digestive system. It leads to impaired mucus clearance and bacterial infections of the airways (108). This disease is predominantly prevalent in Caucasian populations, with estimated prevalence rates of 1/3,000 in Europe and 1/6,000 worldwide (109). Cystic fibrosis lung disease is characterized by thickened airway secretions, bacterial infection and inflammation, which progressively cause airway destruction, leading to bronchiectasis and ultimately respiratory failure (110). This condition is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which leads to the defective function or absence of CFTR protein, affects the cells that produce mucus and sweat, causing the mucus to thicken and block the airways in the lungs. This protein is a chloride channel in the epithelial cell membrane that also regulates the activity of sodium channels (111).

It is now widely accepted that the relationship between the microbiota and cystic fibrosis is bidirectional. CFTR dysfunction leads to aberrant colonization of the gut and respiratory microbiota, which in turn alters the intestinal and airway microenvironment (112). A study showed that cystic fibrosis-induced changes in the lungmicrobiota cause changes in the gut microbiota (113). Patients with cystic fibrosis have been found to exhibit reduced abundances of Ruminococcaceae, *Bifidobacterium*, *Bacteroides* and *Roseburia* in the gut, which are normally considered to be

healthy commensal gut microbiota (114-116), and are associated with anti-inflammatory activity, fermentation, and immune regulation *in vivo* (117,118). Unlike the gut microbiota of healthy children, an increased abundance of *Enterococcus*, *Enterobacter* and *Escherichia* has been observed in the intestines of patients with cystic fibrosis, however, there is no evidence indicating that this variation is definitively associated with pathogenicity (119-121). The functional characteristics of the gut microbiota in pediatric patients with cystic fibrosis differ significantly from those without cystic fibrosis (122). Manor *et al* (123) found that the gut micribiota of pediatric patients with cystic fibrosis have an increased propensity to metabolize short-chain fatty acids, nutrients and antioxidants, with enriched short-chain fatty acid metabolic pathways and reduced fatty acid biosynthetic pathways, microbiota dysbiosis and functional imbalance are highly evident, with functional disparities linked to malabsorption and inflammation. In addition, another study showed that, despite severe dysbiosis, the gut microbiota in patients with cystic fibrosis retains the ability to produce short-chain fatty acids by the fermentation of starch (124).

The dynamic relationship between the gut microbiota and respiratory tract diseases in children is increasingly being recognized. Further in-depth research is required to provide researchers and clinicians with a more comprehensive and innovative perspective on the management of childhood respiratory diseases.

4. Probiotic treatment

Currently, traditional treatments for respiratory diseases rely heavily on antibiotics and antiviral drugs, which must be used with caution in infants and young children to avoid short- or long-term adverse effects. Widespread use of antibiotics can lead to serious issues, such as drug resistance, reduced therapeutic efficacy and a substantial societal burden (125). Probiotics have emerged as effective agents for the regulation of intestinal microecology and have gained attention in clinical studies for the prevention and treatment of respiratory diseases in children. Probiotics are generally defined as live microorganisms that can positively influence host health (126). They have been widely used as medicines, food additives or nutritional supplements for the prevention and treatment of pediatric diseases due to their recognized beneficial effects (127). Evidence-based medical findings have shown that oral probiotics are effective in preventing respiratory diseases and reducing recurrence rates in healthy children without any adverse side effects (128). Probiotic intake can promote a healthy upper respiratory microbiota and enhance resistance to viral invasion (129,130). The gut microbiota influences immune responses in multiple mucosal systems, playing a crucial role in the maintenance of physiological homeostasis and human health, while dysbiosis of the gut microbiota increases susceptibility to respiratory diseases (131). Although the etiology of respiratory diseases is multifaceted, the ability of probiotics to modulate microecological balance and immune responses has attracted considerable attention in treatment strategies for respiratory diseases (Fig. 2) (132).

Lactobacillus and *Bifidobacterium* are widely used probiotics that secrete a variety of beneficial compounds, including vitamins, short-chain fatty acids, bacteriocins and exopolysaccharides (133,134). Most children are susceptible to respiratory illnesses because their immature immune systema are not yet strong enough to combat the invasion of various pathogens. Probiotics play a crucial role in the prevention and treatment of respiratory diseases by inhibiting pathogens, enhancing host defenses such as the epithelial barrier, and modulating both innate and adaptive immunity (135).

Probiotics protect the integrity of the epithelial barrier by activating pattern recognition receptors on epithelial cells through microbe-associated molecular patterns that regulate tight and adhesion junctions (136). They also disrupt the microenvironments of pathogens through competition for epithelial cell adhesion sites, nutrient depletion and the secretions of antimicrobial compounds (137). In addition, probiotic metabolites play an important role in respiratory diseases by modulating the differentiation of immune cells and controlling the immune response via G protein-coupled receptors and histone deacetylases (138).

Gut-associated lymphoid tissue is an important component of the peripheral immune system, and probiotics have been shown to enhance systemic immunity and indirectly strengthen respiratory defense by the modulation of this tissue (139). They also mediate innate immune responses through pattern recognition receptors, particularly toll-like receptors (TLRs), which recognize and bind to pathogen-associated molecular patterns on the surface of pathogenic microorganisms and activate signaling pathways, such as the nuclear factor-κB and mitogen-activated protein kinase pathways, to regulate the secretion of pro-inflammatory cytokines (140). For example, *Lactococcus lactis* (*L. lactis*) enhances Th1 cell differentiation and upregulates the expression of cytokines IL-12, IFN-γ and TNF-α via TLR2, TLR3 and TLR9 pathways (141).

LGG is currently one of the most widely used probiotics due to its tolerance of stomach acid and bile. Studies have shown that LGG can regulate the balance of microbiota in the gut, reducing harmful bacteria such as *Bacteroides* and *Proteus*, and increasing beneficial bacteria such as *Lactobacillus*, *Bifidobacterium* and butyric acid-producing bacteria (142,143). In addition, LGG modulates the host immune system, helping to prevent and treat infections by triggering an inflammatory response and activating macrophages, which protect intestinal epithelial cells (144). Several studies have demonstrated that LGG has favorable preventive, therapeutic and curative effects on respiratory diseases in children. In a randomized trial involving 281 children, LGG significantly reduced the risk of upper respiratory tract infections and shortened the duration of respiratory symptoms (145), while a meta-analysis of four randomized controlled trials with 1,805 participants showed that LGG reduces the incidence of acute otitis media while also reducing antibiotic use (146). Other studies have demonstrated that LGG significantly reduces the overall risk of respiratory infection and shortens the duration of respiratory symptoms in children (147). However, although LGG significantly improves respiratory symptoms, it does not appear to inhibit viral activity in respiratory tract infections in children (148). Interestingly, in another randomized study involving 619 participants aged 2-6 years, LGG effectively relieved symptoms of upper respiratory tract infection, but was not effective in reducing the incidence of these infections (149).

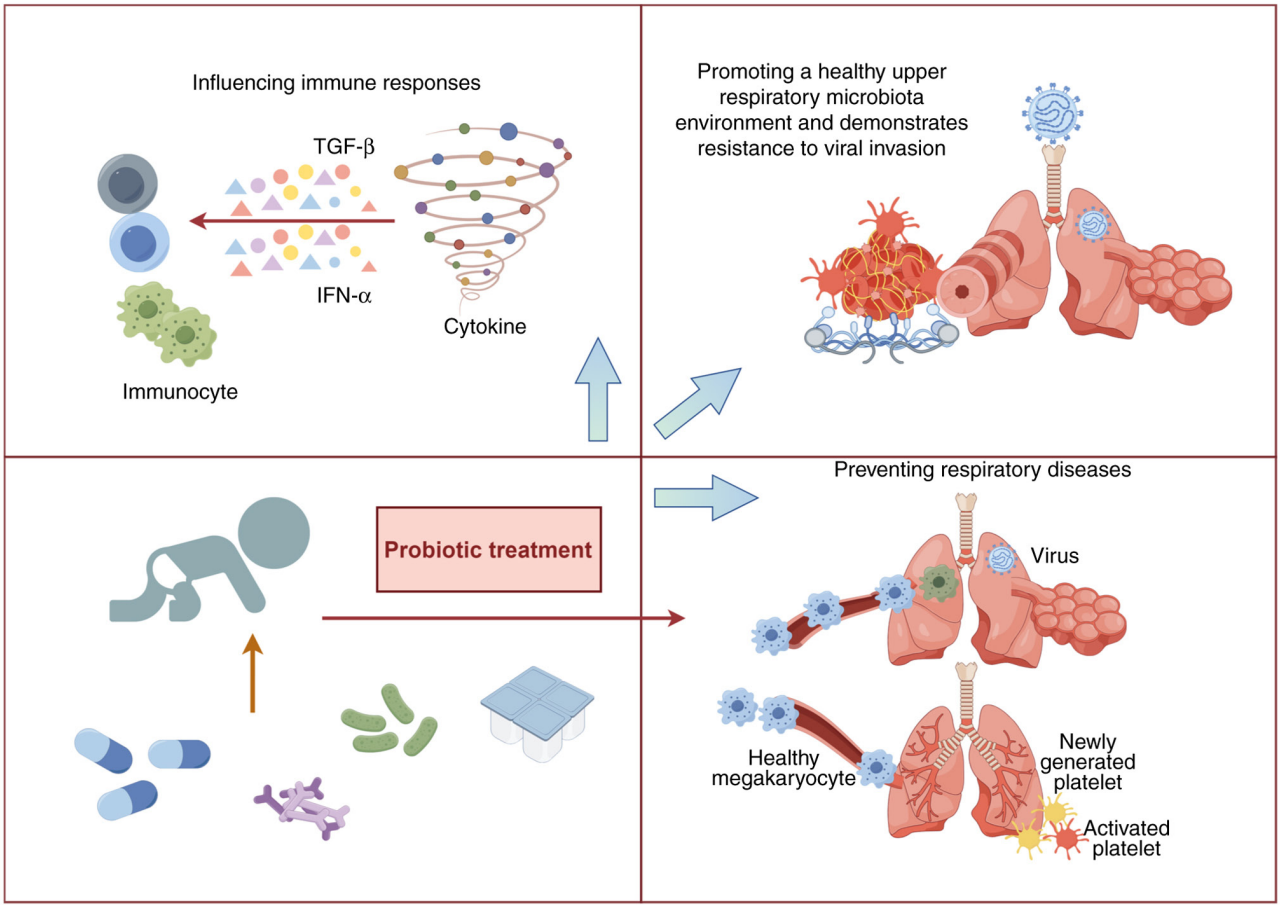

Figure 2. Benefits of probiotic treatment.

Despite the multifaceted health benefits of LGG, the results of the studies show some inconsistency, suggesting that the efficacy of probiotics may differ among individuals.

Bifidobacteria are a group of probiotics commonly found in the human gut, particularly in infants. Their numbers and species diversity tend to decline with age (150). Studies have shown that bifidobacteria play an important preventive role in the maintenance of a healthy gut microbiota by regulating gut microbial metabolism, promoting intestinal motility, adhering to and degrading harmful substances, and enhancing host immune function (151). *B. longum* has been shown to regulate the Th1/Th2 immune system balance. In a study in Malaysian preschool children, *B. longum* BB536 significantly increased the abundance of anti-inflammatory and immunomodulatory bacteria in the feces, thereby preventing upper respiratory tract diseases via modulation of the gut microbiota (152). Another study showed that the early administration of *Bifidobacterium animalis* subspecies *Lactobacillus bifidus* BB-12 to infants reduced the risk of early infections and respiratory tract infections (153).

Probiotic complexes are preparations containing multiple probiotic strains that regulate the composition and diversity of the intestinal flora, protect intestinal barrier function, and reduce inflammation and intestinal damage. Probiotic complexes have demonstrated superior efficacy than single strains in maintaining gut health, modulating immune function and single strain resistance issues (154). Probiotic complexes have shown the potential to play a positive role in the prevention and treatment of recurrent respiratory infections. For example, oral quadruple probiotic tablets containing *B. bifidum*, *L. acidophilus*, *E. faecalis* and *Bacillus cereus* not only increased the abundance of the beneficial gut bacteria *B. bifidum* and *L. lactis*, but also significantly reduced the mean annual frequency of acute respiratory infections and antibiotic use (155). Also, another probiotic preparation containing *Bifidobacterium animalis* subspecies *Lactobacillus bifidus* BB-12 and *E. faecalis* L3 significantly increased salivary immunoglobulin levels and reduced the risk of upper respiratory tract infections in healthy children (156). In addition, a nasal spray comprising *Streptococcus salivarius* 24SMB and *Streptococcus oralis* 89a was found to be effective in relieving the symptoms of recurrent respiratory infections in children (157). Another clinical study also supports the benefits of probiotic complexes, with a marked reduction in the incidence of respiratory infections in children treated with oral probiotics compared with placebo-treated controls, in addition to a lack of adverse effects (158).

Although numerous probiotic products have been shown to be safe, their use can also cause adverse reactions (159). Probiotics have been reported to cause gastrointestinal side effects, including diarrhea and bloating (160). In addition, probiotics may facilitate the lateral transfer of antibiotic resistance genes to other microorganisms (161,162). There have been some reports that probiotics can act as opportunistic

Table II. Functions of probiotic therapy.

First author/s, year	Probiotic	Function	(Refs.)
Gentle and Lal, 2020	*Lactobacillus* combination	Reduces neutrophil inflammation and improves lung function	(168)
Carvalho *et al*, 2020	*Lactobacillus rhamnosus*	Significantly reduces levels of pro-inflammatory cytokines, thereby reducing peribronchial inflammation, alveolar hyperplasia, collagen deposition and elastin fiber destruction	(169)
Fangous *et al*, 2019	*Lactobacillus fermentum*, *Lactobacillus paraesei* and *Lactobacillus zeae*	Inhibits virulence factors, reduces inflammatory cytokines and increases cell viability	(170)
Zelaya *et al*, 2014	*Lactobacillus rhamnosus*	Regulates immune response, increases TNF-α and IFN-γ production, reduces tissue damage caused by pneumococcal infection, and increases IL-10 levels in the lungs and blood	(171)
Fangous *et al*, 2021	*Lactobacillus* combination	Reduces intestinal inflammation and prevents deterioration of lung function	(172)

pathogens in immunocompromised individuals, potentially leading to life-threatening diseases such as pneumonia, endocarditis and sepsis (163-165). Therefore, further research is necessary to evaluate probiotic therapies for respiratory diseases, particularly regarding individual differences and safety issues.

Certain probiotics have demonstrated beneficial effects. For example, a combination of *Lactobacillus* and *B. bifidum* has exhibited an association with reduced inflammation, and may have the ability to ameliorate inflammatory conditions (166). In addition, *Lactobaccillus plantarum* has been shown to regulate oxidative stress, inflammation and gut microbiota dysbiosis *in vivo*, while promoting intestinal motility and mucin production (167). Some of the key effects and underlying mechanisms of probiotic therapy are summarized in Table II (168-172). However, the mechanisms by which different probiotics exert their effects on the human body remain unclear, highlighting the need for further comprehensive research.

When considering any treatment, safety is a priority for pediatric populations. The comprehensive reporting of all adverse events, particularly long-term safety outcomes, is critical to meaningfully advance the evidence base in this area (173). A meta-analysis of COPD performed by Su *et al* (174) suggested that probiotics can improve lung function and structure, and reduce inflammation. However, the experimental results were suggested to have some limitations, particularly regarding the efficacy and safety of long-term probiotic use. Li *et al* (175) conducted a 12-week randomized controlled trial, which demonstrated that *Bifidobacterium infantis* YLGB-1496 exhibited excellent safety and tolerability in infants and effectively alleviated the gastrointestinal discomfort associated with respiratory diseases.

Further research is necessary to validate the long-term efficacy and safety of probiotics, even though a number of studies have indicated that probiotic therapy is safe (176-178).

5. Discussion and conclusions

The present review first described the development of gut microbiota in the early stages of life and their critical role in human health. It then introduced the gut-lung axis as an important bidirectional communication system, reviewed the relationship between the gut microbiota and three pediatric respiratory tract diseases, and concluded with a summary of probiotic therapies.

The concept of the gut-lung axis is crucial for understanding respiratory disease. The gut microbiota and human health interact with each other, but the underlying mechanisms remain unclear and require further study. The development of a healthy gut microbiota is strongly associated with respiratory health and the development of the immune system in children. Therefore, in-depth investigation of the gut microbiota composition and function during early childhood may help to predict future health, prevent diseases and clarify the underlying mechanisms.

Probiotic therapy offers a novel approach for the prevention and treatment of respiratory diseases. Increasing evidence suggests that probiotics can be used to relieve symptoms, reduce disease recurrence and reduce the use of antibiotics. Reducing antibiotic exposure is important in children, as antibiotics can lead to dysbiosis of the gut microbiota, leading to lower host resistance and contributing to the global issue of antibiotic resistance.

However, the limitations of probiotic treatments must be acknowledged. Their exact mechanisms remain unclear, and therapeutic effects may vary. In addition, the roles of probiotic preparations in the microenvironments of different diseases require further investigation. The development of more effective composite probiotic preparations appears to be a promising area of research. Although studies have shown that probiotic therapy is generally safe, with no serious side effects or adverse symptoms reported, safety assessments of probiotic treatments remain limited to certain populations;

therefore, more research on safety is necessary. Finally, the lack of unified industry or clinical guidelines for probiotic use remains a barrier. The standardization of usage methods in daily life and clinical practice will be essential to expand the prospects for probiotic treatments in pediatric respiratory care.

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MZ and YH reviewed the literature and wrote the manuscript. YJ and LC conceived and designed the study. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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