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REVIEW

# The Role of Gut Microbiota in the Modulation of Pulmonary Immune Response to Viral Infection Through the Gut-Lung Axis

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**Abstract:** Viral respiratory infections, including influenza, respiratory syncytial virus (RSV), and SARS-CoV-2, remain major global health challenges due to their high morbidity and mortality. Emerging evidence highlights the pivotal role of the gut-lung axis in regulating pulmonary immunity. The gut microbiota communicates with the lungs via endocrine, immune, and neuroimmune pathways —particularly through metabolites such as short-chain fatty acids (SCFAs) and vagus nerve-mediated signaling—which modulate immune cells including alveolar macrophages and dendritic cells. Disruption of gut microbial balance has been linked to impaired pulmonary immune responses and increased susceptibility to infection. This review synthesizes findings from animal models and clinical studies, demonstrating that interventions such as probiotics (eg, *Lactobacillus gasseri*), prebiotics (eg, *galacto-oligosaccharides*), fecal microbiota transplantation (FMT), and Traditional Chinese Medicine (eg, *Astragalus, curcumin*) can enhance antiviral cytokine production, restore gut-lung homeostasis, and reduce lung inflammation. For example, FMT from H7N9-survivor mice improved influenza resistance in recipients, and oral probiotics reduced respiratory failure risk in COVID-19 patients. These findings suggest that gut-lung axis modulation is a promising adjunctive approach for treating viral respiratory infections. Future research should prioritize personalized microbiome-based therapies and large-scale clinical trials to validate efficacy and safety.

**Keywords:** viral respiratory infections, gut-lung axis, gut microbiota, pulmonary immunity, neuroimmune pathways

## Introduction

Pulmonary viral infections represent significant global health challenges because of their high morbidity and mortality rates.[1] These infections originate from a variety of viral families, such as Coronaviridae, which includes SARS-CoV-2, NL63, and HKU1; Paramyxoviridae, which encompasses respiratory syncytial virus (RSV) and human metapneumovirus (HMPV); Picornaviridae, represented by Rhinovirus; and Orthomyxoviridae, which contains influenza viruses.[2,3] Among these, influenza viruses and coronaviruses are the most common causes of viral pneumonia, whereas RSV, HMPV, and rhinoviruses primarily affect pediatric and elderly populations. These infections can result in severe complications, including pneumonia, acute respiratory distress syndrome (ARDS) and long-term airway remodeling. Timely administration of antiviral agents is critical to improving outcomes. Treatment strategies for severe cases are adapted to the extent of respiratory failure, and the efficacy of these drugs may be reduced by delayed administration or the development of viral resistance.

Recent research highlights the significant influence of the gut-lung axis in determining severity and outcomes of lung infections. The gut-lung axis is a sophisticated network involving endocrine, immune and nervous systems, all significantly impacted by the gut microbiota. Among the many metabolites produced by the gut microbiota, short-chain fatty acids (SCFAs) stand out as important anti-inflammatory agents. These SCFAs acting as anti-



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inflammatory agents, modulate gene expression of immune cell through epigenetic mechanisms and enhance pathogen recognition and cytokine signaling by activating G-protein-coupled receptors.[4,5] These metabolites further strengthen epithelial barriers in both the gut and lungs, enhancing mucosal defenses against infections.[6] Experimental studies using germ-free or antibiotic-treated mice have demonstrated that the depletion of gut microbiota leads to impaired antiviral immunity in the lungs, supporting the essential role of microbial communities in respiratory defense. Conversely, fecal microbiota transplantation (FMT) and SCFA supplementation have been shown to restore pulmonary immune responses, particularly by promoting the production of type I interferons (IFN-α/β) and other antiviral cytokines.[7] These effects are primarily mediated through the activation of lung-resident immune cells such as alveolar macrophages and dendritic cells, which are sensitive to gut-derived cues. Furthermore, neuroimmune interactions play a crucial role in gut-lung communication. Vagal afferent signaling has been identified as a key conduit through which intestinal stimuli modulate pulmonary immune tone. During viral infections, gut-derived neural and metabolic signals are capable of altering immune cell activation and cytokine profiles within the lung, thereby influencing the trajectory of disease progression.[8,9] Dysbiosis in the gut microbiota have been demonstrated to impair immune responses in the lungs, increasing susceptibility to viral infections.[10,11] This disruption in microbial balance can alter both innate and adaptive immune responses in lungs, increasing susceptibility to infection.

While the exact mechanisms through which the gut-lung axis influences immune responses remain a subject of ongoing research, the aim of this review is to synthesize current evidence and highlight the therapeutic benefits of its targeted manipulation in mitigating viral infections. This review will focus on the potential synergistic effects of integrating probiotics, prebiotics, and TCM to optimize the gut microbiota. We will examine how these interventions enhance the immune system by promoting beneficial microbes, increasing the production of metabolites like SCFAs, strengthening mucosal immunity, and modulating inflammatory pathways. By leveraging these approaches, our goal is to outline a more comprehensive and effective treatment model for pulmonary viral infections that is centered on regulating the gut-lung axis.

# Overview of Pulmonary Viral Infections

## Introduction of Respiratory Viruses

Respiratory viral infections lead to elevated morbidity and mortality, particularly among at-risk groups including children, the elderly, and individuals with suppressed immunity. These infections impose substantial health burdens and economic strains on individuals, families, and healthcare systems.[12] A wide range of pathogens are responsible for pulmonary viral infections, with each pathogen exhibiting distinct biological traits. Major respiratory viruses encompass influenza strains (A and B), parainfluenza strains (1–3), RSV, HMPV, rhinoviruses, adenoviruses, and human coronaviruses (HCoVs), such as SARS-CoV, MERS-CoV, and SARS-CoV-2 (Table 1).[13–27]

### Influenza Viruses

Influenza viruses, categorized under the Orthomyxoviridae family, possess segmented, negative-strand RNA genomes. These viruses are distinguished by surface glycoproteins— 18 hemagglutinin (HA) and 11 neuraminidase (NA) subtypes. HA is critical for the virus's entry into host cells, as it binds specifically to sialic acid receptors on respiratory epithelial cells, initiating infection. NA plays a pivotal role in viral propagation, assisting in the release of progeny viruses from host cells, thereby facilitating the spread of infection. Influenza viruses are particularly noted for their dynamic ability to undergo antigenic shift and drift. Antigenic shift involves the reassortment of viral genomes, particularly between different strains co-infecting a host, leading to new viral subtypes. This process can result in abrupt, significant changes in the virus's antigenic properties, potentially giving rise to pandemic strains. Antigenic drift, however, involves gradual changes through mutations in HA and NA, enabling the virus to evade pre-existing immune responses, thereby sustaining its ability to cause recurring seasonal epidemics. These mechanisms underscore the challenges in influenza vaccine formulation, necessitating annual review and adjustments to align with evolving viral strains.

**Table 1** Overview of Common Respiratory Viruses and Their Characteristics

| Virus | Category | Seasonality and Prevalence | Susceptible Populations | Pathogenic Mechanism | Immunopathogenesis | Clinical Manifestations | Negative Effects | Treatment Options | Ref |
|---|---|---|---|---|---|---|---|---|---|
| Influenza Virus (IAV) | Orthomyxoviridae | Winter, globally prevalent | Elderly, children, individuals with underlying diseases | HA and NA proteins mediate virus entry and release | Activates PRRs (eg, TLRs), triggers cytokine storm, impairs endothelial VEGF signaling Activates PRRs (eg, TLRs), triggers cytokine storm, impairs endothelial VEGF signaling | Pneumonia, cough, fever | Viral shedding, secondary bacterial infections, hospitalization | Neuraminidase inhibitors, supportive care | [13,14] |
| Coronaviruses (CoVs) | Coronaviridae | Year-round, globally prevalent | Elderly, chronic disease patients, immunocompromised | Spike protein mediates entry via ACE2 receptor | Triggers DAMP/PAMP sensing→NF-κB, JAK-STAT, TG-β pathways; cytokine storm, fibrosis Triggers DAMP/PAMP sensing→NF-κB, JAK-STAT, TG-β pathways; cytokine storm, fibrosis | Severe pneumonia, acute respiratory symptoms | Organ damage (lungs, heart), prolonged symptoms, high mortality rate | Antiviral drugs such as Remdesivir, monoclonal antibodies | [15,16] |
| Parainfluenza Virus (PIV) | Paramyxoviridae | Active in autumn and winter, primarily affects children | Toddlers, individuals with respiratory diseases | G protein mediates cell entry | Evasion of long-term immunity; seasonal outbreaks Evasion of long-term immunity; seasonal outbreaks | Mild to severe respiratory diseases | Risk of bronchiolitis, frequent reinfection | Supportive care, experimental antivirals | [17,18] |
| Respiratory Syncytial Virus (RSV) | Paramyxoviridae | High during winter and early spring, affects children and the elderly | Infants, immunocompromised elderly | G protein mediates infection | Induces Th2 inflammation, eosinophilia, Treg/effector T cell imbalance→chronic inflammation Induces Th2 inflammation, eosinophilia, Treg/effector T cell imbalance→chronic inflammation | Respiratory diseases, possible hospitalization | Risk of severe respiratory failure in infants and elderly | Monoclonal antibodies, supportive care | [19,20] |
| Human Metapneumovirus (HMPV) | Paramyxoviridae | High during winter and early spring, affects children and the elderly | Children, immunocompromised elderly | F protein mediates cell fusion and infection | Induces airway inflammation; poor long-term immunity Induces airway inflammation; poor long-term immunity | Respiratory diseases such as pneumonia, bronchitis | Recurrent infections, chronic airway disease | Supportive care | [21,22] |
| Rhinovirus (RV) | Picornaviridae | Year-round prevalence | Individuals with asthma or chronic respiratory diseases | Entry via ICAM-1 and LDLR receptors | Activates innate immunity; exacerbates airway hyperresponsiveness Activates innate immunity; exacerbates airway hyperresponsiveness | Common cold, can exacerbate asthma | Increased asthma severity, sinusitis | Symptomatic treatment, decongestants | [23–25] |
| Adenovirus (AdV) | Adenoviridae | Year-round prevalence | Children, immunocompromised individuals | Cell entry mediated by CAR receptors | Activates NF-κB and TLRs; disrupts VEGF →vascular remodeling →risk of PH Activates NF-κB and TLRs; disrupts VEGF →vascular remodeling →risk of PH | Mild to severe respiratory infections | Risk of vascular complications, including pulmonary hypertension | Supportive care, cidofovir for severe cases in immunocompromised patients | [26,27] |

## Coronaviruses (CoVs)

Coronaviruses, a subgroup within the Coronaviridae family, include notable pathogens such as SARS-CoV, MERS-CoV, and SARS-CoV-2. These positive-sense RNA viruses, which are enveloped, enter host cells through spike (S) proteins that bind to the ACE2 receptor. This binding is essential for initiating viral replication. This interaction triggers a cascade of immune responses, leading to inflammation in the lungs, which characterizes the clinical manifestations of infection. The ongoing prevalence of SARS-CoV-2, with its emergence in numerous variants, illustrates its potential shift toward becoming endemic. However, the path toward endemicity involves complex dynamics including changes in virus transmissibility, virulence, and the population's immunity.[28]

## Paramyxoviruses (Parainfluenza, RSV, HMPV)

A number of important respiratory viruses belonging to the Paramyxoviridae family significantly affect public health. These include parainfluenza viruses (PIV), RSV, and HMPV. These viruses predominantly affect children and can cause a spectrum of respiratory conditions, from mild infections to severe illnesses.

Types 1–3 of PIV are particularly linked to croup in children, characterized by a distinctive barking cough and difficulty breathing. These viruses can also lead to more severe respiratory conditions like pneumonia and bronchiolitis, primarily during the winter months when viral transmission peaks.

RSV utilizes a protein that plays a key role in its attachment to and fusion with the host cell membrane.[29] This virus is notorious for causing severe respiratory symptoms, including wheezing and difficulty breathing, and is known for its recurrent infections due to the inadequate development of long-lasting immunity.[30,31] This lack of durable immunity is partly due to the virus's ability to escape immune detection and antigenic variability.

HMPV primarily targets children and the elderly but also poses a significant risk to immunocompromised adults. It infects host cells via the fusion (F) protein, initiating respiratory ailments that range from mild cold-like symptoms to more serious conditions.

## Rhinovirus (RV)

Rhinoviruses, members of the Enterovirus genus within the Picornaviridae family, are the most common causative agents of the common cold. These non-enveloped, positive-sense single-stranded RNA viruses comprise over 160 serotypes, classified into three species: RV-A, RV-B, and RV-C.[32]

RVs primarily infect the epithelial cells of the upper respiratory tract, particularly the nasal mucosa. Viral entry is mediated through interactions with specific host receptors—most notably intercellular adhesion molecule-1 (ICAM-1) for major-group RVs—triggering a localized inflammatory response.[33] This leads to typical cold symptoms such as rhinorrhea, nasal congestion, sore throat, and cough. Although these symptoms are generally mild and self-limiting in healthy individuals, the clinical significance of RVs lies in their capacity to exacerbate chronic respiratory conditions.

Rhinovirus is a leading cause of acute exacerbations in asthma and chronic obstructive pulmonary disease (COPD), where it induces heightened airway inflammation, mucus hypersecretion, and impaired epithelial integrity.[34] Notably, RV-C has been associated with more severe respiratory symptoms and poorer outcomes, particularly in children. Moreover, RV is not limited to upper respiratory infections—it can also infect the lower respiratory tract, causing bronchiolitis and pneumonia in high-risk populations, including infants, older adults, and immunocompromised individuals. These findings underscore the broad clinical impact of RVs on respiratory health.

## Adenovirus (AdV)

Adenoviruses, comprising a group of non-enveloped, double-stranded DNA viruses, are capable of infecting both the upper and lower respiratory tracts. These viruses are known for their robustness, lacking an envelope, which allows them to resist degradation in the external environment and contributes to their transmission efficiency. Clinically, adenovirus infections can manifest a spectrum of symptoms ranging from mild cold-like symptoms to severe conditions. This variability in symptom severity can often be attributed to both viral factors, such as the specific adenovirus serotype involved, and host factors, including age, immune status, and pre-existing respiratory conditions. Adenoviruses are also notable for their ability to persist in the host. This persistence can take the form of latent infections where the virus remains dormant within the host cells for extended periods, potentially reactivating under conditions of immune

suppression. The mechanisms behind this persistence include evasion of host immune surveillance, possibly through the modulation of antigen presentation and induction of immune tolerance. These features contribute to the risk of recurrent infections, particularly in immunocompromised individuals or those with chronic respiratory conditions.

Coinfections involving respiratory viruses such as Influenza A Virus (IAV), SARS-CoV-2, RSV, RV, HMPV, PIV, Human Bocavirus (HBoV), and AdV are of significant clinical concern. These coinfections are not uncommon and can lead to more severe clinical outcomes compared to infections involving a single virus. The interactions between different respiratory pathogens can exacerbate the severity of respiratory symptoms, increase viral load, and prolong illness duration, complicating the diagnosis and management of respiratory diseases. Epidemiological studies have demonstrated that such coinfections, particularly during peak respiratory virus seasons, significantly impact patient outcomes.

## Impact of Respiratory Viral Infections

Respiratory viral infections can cause a variety of symptoms, ranging from mild upper respiratory issues like cough, fever, and sore throat, to more serious conditions such as viral pneumonia, which has the potential to develop into ARDS[35,36] (Figure 1). ARDS is marked by widespread inflammation in the lungs, hypoxemia, and disrupted gas exchange, often resulting from viral infection that damages alveolar epithelial cells and causes endothelial dysfunction. While respiratory viruses are often associated with acute illness, recent research indicates that these viruses can also remain in both the upper and lower respiratory tracts of asymptomatic children, integrating into the normal microbiome. Molecular analysis of nasopharyngeal samples from these individuals has detected human rhinovirus (hRV), adenovirus, RSV, PIVs, HMPV, and seasonal human coronaviruses. These findings suggest that viral colonization in the respiratory tract can take place without resulting in apparent symptoms.[37,38]

Influenza viruses, including IAV and IBV, are major contributors to these outcomes. Although they typically cause mild to moderate symptoms such as fever and sore throat, they can also lead to viral pneumonia, especially in high-risk groups. IAV and IBV trigger an immediate innate immune response, with viral components recognized by pattern recognition receptors (PRRs), including TLRs on alveolar epithelial cells. IAV infection initiates immune activation through a cascade of signaling pathways. Endothelial cell damage, resulting in increased vascular permeability and edema, is partly mediated by the downregulation of protective factors such as vascular endothelial growth factor (VEGF),

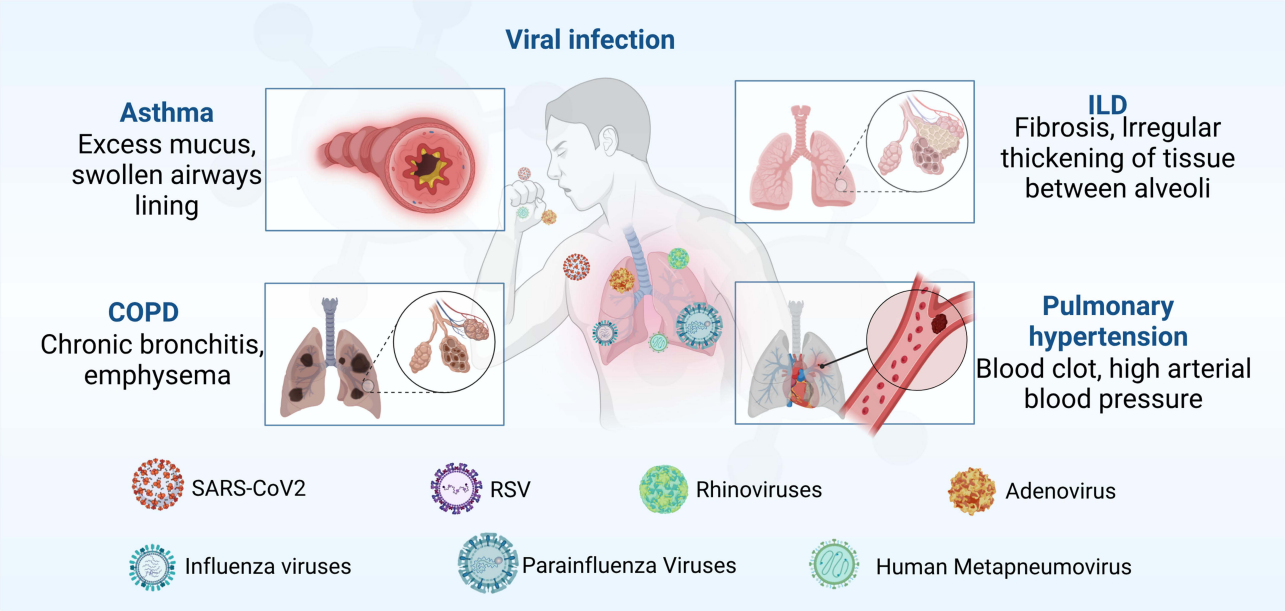


**Figure 1** Viral infections exacerbate respiratory diseases. In asthma, viral infections result in increased mucus production and swelling of airway linings. In Chronic Obstructive Pulmonary Disease (COPD), these infections intensify chronic bronchitis and accelerate emphysema progression. Additionally, in pulmonary fibrosis, viral infections contribute to irregular thickening of tissue between alveoli. Activation of inflammatory pathways such as NF-κB and Toll-like receptors (TLRs) by these infections further exacerbates pulmonary hypertension through inflammation and vascular remodeling.


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impairing normal endothelial function and exacerbating lung injury. IAV can lead to primary viral pneumonia, which may rapidly progress to respiratory failure and death. Histopathologically, IAV-induced lung damage shares similarities with other forms of ARDS, including alveolar epithelial cell apoptosis, loss of alveolar barrier function, and severe hypoxemia. This endothelial dysfunction, compounded by a pro-inflammatory immune response, worsens lung injury and fluid accumulation, further impairing oxygen exchange. Targeting both the viral infection and the host immune response is essential for improving patient outcomes in severe IAV infections and ARDS.[39]

Likewise, SARS-CoV-2, the causative agent of COVID-19, has had a profound global health impact since 2019. In severe cases, the infection leads to extensive lung inflammation, fibrosis, and long-term respiratory impairment. A hallmark of severe COVID-19 is the cytokine storm—an exaggerated immune response triggered by viral binding of the spike protein to ACE2 receptors. This interaction initiates the release of damage-associated and pathogen-associated molecular patterns (DAMPs and PAMPs), which activate pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). This cascade stimulates multiple pro-inflammatory pathways, including the NF-κB and JAK-STAT pathways, resulting in the release of cytokines such as IL-1β, IL-6, and TNF-α. These mediators recruit neutrophils, macrophages, and lymphocytes, amplifying lung inflammation. The TGF-β pathway is particularly implicated in promoting pulmonary fibrosis. Dysregulation of these signaling networks contributes to acute respiratory distress syndrome (ARDS) and long-term complications such as impaired oxygenation and post-acute sequelae ("long COVID").

In addition to their direct acute effects, respiratory viruses like influenza and rhinovirus significantly exacerbate chronic conditions including asthma and COPD. These viruses can disrupt airway clearance mechanisms, increase airway hyperresponsiveness, and intensify inflammatory cascades, making patients more susceptible to exacerbations. Influenza, in particular, is a major contributor to acute exacerbations of COPD, ranking as the second most frequently identified virus (22.5%) in such instances.[40] Significantly, RSV infection induces airway hyperresponsiveness, which is a characteristic feature of both asthma and COPD exacerbations. This response is partly due to the secretion of T-helper 2 (Th2) cytokines. These cytokines drive eosinophilic inflammation and stimulate excessive mucus secretion. Through their regulation of local immune responses, they are essential in the process of airway remodeling and the advancement of COPD.[41,42]

Rhinoviruses are known to trigger severe asthma attacks due to their ability to induce airway inflammation and hyperresponsiveness. Additionally, RSV can cause bronchiolitis, pneumonia, and long-term complications like airway remodeling and chronic hyperreactivity.[43–45] Additionally, RSV infection has been found to alter the balance between regulatory T cells (Tregs) and effector T cells in the lungs, thereby decreasing immune tolerance and fostering a persistent pro-inflammatory environment even after the infection subsides. This ongoing inflammation heightens the vulnerability to subsequent viral infections, which can aggravate existing respiratory conditions. Moreover, RSV infection also has been shown to disrupt the balance T cells in the lungs, reducing immune tolerance and promoting a pro-inflammatory state that can persist long after the infection has resolved. This chronic inflammation can lead to increased susceptibility to future viral infections, further exacerbating respiratory conditions.

Adenoviruses, another significant respiratory pathogen, activate signaling pathways like NF-κB and TLRs, leading to inflammation and vascular remodeling. This process plays a role in the onset of pulmonary hypertension (PH), as adenoviral infections interfere with VEGF signaling pathways, which aggravates pulmonary vascular remodeling and exacerbates the severity of PH.[46] Additionally, adenoviral infection has a profound impact on vascular remodeling in the lungs. Adenoviruses can disrupt the signaling of VEGF, which plays a key role in maintaining normal endothelial cell function and promoting vascular integrity. Disruption of VEGF signaling results in pulmonary vascular remodeling, characterized by thickening of the vascular walls and increased vascular permeability, which can lead to the development of PH. The combination of chronic inflammation and pulmonary vascular changes increases the burden on the right side of the heart, contributing to the development of cor pulmonale in severe cases of adenoviral infection.

Viral infections significantly increase the risk of secondary bacterial infections, particularly in the context of influenza.[47] Viral-induced disruption of lung epithelial integrity weakens natural barriers and promotes bacterial colonization, often leading to secondary pneumonia. Historical data from the 1918 influenza pandemic indicate that over 95% of fatalities were due to bacterial co-infections, highlighting their clinical impact. Secondary bacterial infections, especially with pathogens like Streptococcus pneumoniae, worsen disease outcomes by exacerbating lung

injury and increasing the risk of acute respiratory distress syndrome (ARDS).[48] For example, studies have shown that influenza patients who develop bacterial pneumonia have higher rates of hospitalization and mortality. In a multicenter study, 23% of influenza patients developed secondary pneumonia, compared to 44% in non-influenza viral infections—accompanied by longer hospital stays and more frequent ICU admissions. Mechanistically, co-infection enhances bacterial adhesion. IAV infection induces surface expression of glycoprotein 96 (GP96) on epithelial cells, which facilitates *S. pneumoniae* binding via integrin αV.[49] Similarly, RSV promotes pneumococcal attachment through interactions between its G glycoprotein and bacterial penicillin-binding protein 1a.[50] These interactions increase the severity of infection and complicate clinical management.

## Pulmonary Defense Virus Barriers

The pulmonary immune system employs a sophisticated multi-layered defense mechanism designed to protect against respiratory pathogens while ensuring the lungs' vital functions are maintained.

### Epithelial Barrier

The respiratory epithelial barrier comprises tightly interconnected cells that provide critical physical defense against pathogens while enabling mucociliary clearance. This system involves mucus secretion to trap inhaled particulates and microbes, coordinated ciliary propulsion to expel debris toward the oropharynx,[51] and molecular-level pathogen neutralization through antimicrobial peptides (AMPs) such as defensins, lysozyme, and lactoferrin.[52]

Defensins, for example, disrupt microbial membranes by inserting into bacterial cell membranes and forming pores, which compromise cellular integrity and lead to pathogen death.[53] Lactoferrin, an iron-binding glycoprotein, inhibits pathogen growth by sequestering free iron, a nutrient essential for many bacteria and viruses. In addition, lactoferrin has significant antiviral properties, especially against enveloped viruses such as RSV and influenza, by binding to viral particles and preventing them from attaching to host cell receptors.[54] Similarly, lysozyme primarily degrades peptidoglycan in bacterial walls, while its antiviral effects are mediated through immunomodulation, enhancing innate immune activation and leukocyte recruitment in upper airway mucosa.[55]

During viral respiratory infections, pathogen progression from the upper to lower respiratory tract leads to alveolar epithelial cell (AEC) invasion, where viral replication predominates. AECs critically orchestrate innate immunity by releasing mediators such as, a cytokine essential for activating and recruiting myeloid phagocytes (eg, alveolar macrophages, dendritic cells) to clear pathogens.[56] While GM-CSF production in AECs is classically triggered by bacterial pathogens via Toll-like receptor (TLR) signaling (eg, TLR4/MyD88 axis), emerging evidence highlights its role in viral infections through distinct TLR pathways (eg, TLR3/TRIF).[57] This dual mechanism underscores AECs as pivotal regulators of both antibacterial and antiviral defenses.[58]

### Microbiome Barrier

The pulmonary microbiome is essential in defending against respiratory viral infections through three synergistic mechanisms: strengthening the epithelial barrier, modulating immune responses, and competing with pathogens for resources.[59] While the lung microbiome exhibits lower diversity compared to the gut microbiome, it typically contains bacteria from several phyla, including *Bacteroides, Firmicutes*, and *Proteobacteria*, as well as additional microbial groups such as *Actinobacteria* and *Fusobacteria*. These microbial communities contribute to lung health via various mechanisms, including the generation of bioactive molecules and immune-modulating substances.[60]

Some species, including *Bacteroides thetaiotaomicron*, generate SCFAs support the integrity of the epithelial barrier by enhancing the expression of tight junction proteins such as occludin and claudin, which are essential for blocking pathogen infiltration.[60] Additionally, some microbes residing in the lungs produce antimicrobial compounds, including bacteriocins and antiviral peptides. These compounds directly inhibit viral replication and bacterial growth.[61] For instance, *Lactobacillus* and *Bifidobacterium* strains exhibit antiviral effects against respiratory viruses, including influenza and RSV.[62] However, the specific antiviral mechanisms of Bifidobacterium breve against influenza are still under investigation, emphasizing the need for further research to fully understand its potential. Microbial-derived surfactin analogs can inhibit influenza hemagglutinin-mediated membrane fusion, while lantibiotics like nisin Z block viral RNA

polymerase activity.[63,64] One of the key defense strategies employed by the lung microbiome is competitive exclusion, whereby resident microbes outcompete pathogens for nutrients and space, thus limiting pathogen colonization.[65]

The structure of the lung microbiome is influenced by several environmental factors, genetic predispositions, and host health.[66] Disruptions to this microbiome, such as those caused by antibiotic use, pollution exposure, or respiratory infections, can lead to dysbiosis, impairing immune defenses and increasing susceptibility to viral infections.

## Immune Barrier

The pulmonary immune system employs a highly coordinated defense strategy against respiratory pathogens, integrating both innate and adaptive immune mechanisms.[67] This system functions to detect, neutralize, and eliminate invading pathogens, ensuring both immediate protection and long-term immunity.

### Innate Immune Mechanisms

Alveolar macrophages, situated in the alveoli, form the first line of defense. These cells are critical for identifying and clearing airborne pathogens by engaging in processes such as phagocytosis, presenting antigens to T cells, and secreting pro-inflammatory cytokines, including TNF-α and IL-1β.[68,69] These cytokines play a pivotal role in regulating inflammation and attracting other immune cells, including neutrophils and DCs.

DCs play an essential role in linking the innate and adaptive immune systems. They engulf pathogens, process the antigens, and migrate to lymph nodes, where they initiate T cell-dependent immune responses. There are different subtypes of DCs, such as myeloid DCs and plasmacytoid DCs, each with distinct functions. Plasmacytoid DCs are particularly important for producing type I interferons, which are critical for early defense against viral infections, including influenza and RSV. IFN-α/β play a critical role in establishing an viral resistance state in both infected and surrounding cells, thereby limiting viral replication.[70] These interferons activate various antiviral responses, including the induction of antiviral enzymes such as MX1 and the enhancement of cytotoxic activity of NK cells and cytotoxic T lymphocytes (CTLs), which are essential for eliminating virus-infected cells.[71] In contrast, myeloid DCs are primarily involved in antigen presentation to naive T cells and in promoting the differentiation of T helper (Th) cells into specific subsets (eg, Th1, Th2, Th17), which fine-tune the immune response based on the pathogen type and the surrounding inflammatory signals.

Neutrophils and natural killer (NK) cells are essential in the early phases of infection. Neutrophils are typically among the first immune cells to reach infection sites, particularly during bacterial pneumonia. They perform phagocytosis and unleash neutrophil extracellular traps to capture pathogens. NK cells play a key role in combating viral infections by identifying and eliminating virus-infected cells that have reduced the expression of MHC class I molecules, a strategy commonly used by viruses to evade the immune system. Stimulated by cytokines such as IL-12 and IL-18, NK cells enhance their cytotoxic activity, contributing to the elimination of infected cells. In the lungs, NK cells serve as an early defense against both viral infections and bacterial pneumonia, directly killing infected cells and interacting with macrophages and DCs to modulate inflammation and promote T cell activation.

### Adaptive Immune Mechanisms

T cells, including both CD4+ and CD8+ subtypes, are pivotal in the antiviral immune response.[72,73] CD4+ T cells enhance the bactericidal activity of macrophages and activate other immune cells, playing a crucial role in orchestrating the overall immune response.[74] Th1 cells specifically enhance classical macrophage activation by releasing IFN-γ, which triggers the destruction of intracellular pathogens and stimulates the production of inflammatory cytokines, including TNF-α and IL-1β. This pathway is essential for clearing viral infections, such as influenza and RSV, where controlling intracellular viral replication is paramount. Conversely, Th2 cells drive alternative macrophage activation and are involved in promoting eosinophilic inflammation, IgE production, and mucus secretion, as seen in allergic diseases like asthma. Th2-mediated inflammation is also implicated in viral asthma exacerbations, where viral infections, such as RSV or influenza, worsen asthma symptoms by intensifying airway inflammation and mucus hypersecretion.

CD8+ cytotoxic T lymphocytes (CTLs) are central to the immune response against virus-infected cells. They identify viral peptides displayed on MHC class I molecules and, upon interaction, secrete perforin and granzymes. This process

triggers apoptosis in infected cells, effectively inhibiting viral replication. This cytotoxic activity is critical for the clearance of acute viral infections in the lung, including influenza. However, in chronic infections, such as those seen in patients with persistent respiratory conditions (eg, RSV in COPD patients), T cell exhaustion may occur. This phenomenon, induced by continuous antigen exposure, leads to a decline in CD8+ CTL function, with reduced cytotoxicity and impaired cytokine production. This dysregulation contributes to prolonged infection and chronic inflammation within the lungs (Zhao et al, 2020).

Furthermore, memory T cells formed during the first infection offer prolonged immunity, allowing the immune system to respond more quickly and effectively when encountering the same pathogen again. This memory response significantly reduces the severity and duration of re-infections.[75–77] Resident memory T cells (TRM) are particularly important in providing immediate protection against reinfection in the lungs. Unlike circulating memory T cells, TRM cells do not need to migrate back from secondary lymphoid organs to respond to a pathogen. Upon re-exposure, memory CD4+ T cells help activate macrophages and coordinate T cell responses, while memory CD8+ T cells directly recognize and eliminate virus-infected cells through cytotoxic mechanisms, including the release of perforin and granzymes. This rapid reactivation of memory T cells is vital in preventing secondary infections and facilitating faster viral clearance.

B cells contribute significantly to the immune response by producing antibodies that neutralize viruses and facilitate their removal through opsonization, thereby enhancing phagocytosis. Memory B cells are essential for long-term immunity by producing high-affinity antibodies upon subsequent exposure to the same pathogen.[78] These antibodies are crucial for neutralizing viruses and preventing reinfection. Upon reinfection, memory B cells swiftly differentiate into plasma cells, which secrete substantial quantities of antibodies, offering rapid protection, typically within hours to days after re-exposure. The processes of affinity maturation and class switching that take place during the initial immune response further refine the specificity and potency of the antibodies produced by memory B cells. In lungs, local plasma cells are capable of quickly producing IgA antibodies, offering protection at the mucosal surfaces before a broader systemic immune response is activated.

Together, these immune components—macrophages, T cells, NK cells, memory B cells and immune effector molecules—form a multi-layered defense against respiratory pathogens, ensuring both immediate and long-lasting immunity.

## Current Treatment Strategies and Limitations

Current antiviral therapies, such as neuraminidase inhibitors like oseltamivir and zanamivir, target key steps in the viral replication cycle. These medications inhibit the neuraminidase enzyme, which plays a crucial role in releasing new virions from infected cells.[79,80] By blocking the virus's ability to spread to adjacent cells, neuraminidase inhibitors help to lessen both the intensity and length of the infection, especially when administered early in the course of the disease. However, the effectiveness of these treatments may vary depending on several factors, including the timing of treatment, the specific virus strain, and the immune status of the patient. Early intervention is crucial to optimize therapeutic outcomes, as delayed treatment may result in reduced effectiveness and more severe disease progression.[81]

In addition to neuraminidase inhibitors, research is exploring alternative antiviral strategies aimed at targeting different stages of the viral replication cycle. A promising avenue of research is the use of interferons, particularly IFN-α/β, which are essential for initiating an antiviral state in infected cells.[82] These interferons inhibit viral replication, enhance the cytotoxic activity of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), and activate immune responses that help control viral infections. While interferons hold promise for modulating the immune response, their clinical use remains complex due to the need for optimal dosing and timing to balance efficacy with potential adverse effects.[83]

Furthermore, the global health challenge posed by recent respiratory virus pandemics spurred research into repurposing existing medications. One drug that gained significant public attention was ivermectin, an anti-parasitic agent. Despite some early preclinical studies suggesting potential antiviral activity, numerous large-scale, randomized clinical trials were conducted to evaluate its efficacy.[84] Major health organizations, including the World Health Organization (WHO) and the National Institutes of Health (NIH), have concluded from this extensive evidence that ivermectin

provides no clinical benefit in treating respiratory viral infections like COVID-19 and do not recommend its use for this purpose.[85]

Vaccination is a cornerstone in controlling respiratory viral infections. Several vaccine platforms have been created, such as whole-virus, split-virion, subunit, live attenuated, and virosome-based vaccines. These vaccines are designed to stimulate robust immune responses and have demonstrated efficacy in preventing diseases such as influenza.[86] Additionally, newer technologies, such as self-amplifying RNA (saRNA) vaccines, offer promising alternatives. These vaccines work by boosting in vivo antigen generation, resulting in a stronger immune response. This characteristic is especially beneficial for fighting pathogens that undergo rapid mutation, such as influenza. Preclinical studies have demonstrated that saRNA influenza vaccine candidates can produce potent, cross-reactive immune responses against pandemic and seasonal influenza strains, such as A(H5N1) and A(H1N1).[87]

For patients with severe respiratory failure, treatment strategies are tailored to the degree of hypoxia and respiratory compromise. High-flow oxygen is administered to patients with early hypoxia, while non-invasive ventilation is often used in cases of moderate ARDS to avoid the risks associated with intubation. In more severe cases of respiratory failure, mechanical ventilation may be necessary, accompanied by lung-protective strategies such as using low tidal volumes to minimize ventilator-induced lung injury and carefully managing fluids to reduce the risk of pulmonary edema.[88]

Despite recent advancements in treatment and prevention, respiratory viruses continue to employ sophisticated immune evasion strategies to escape detection and destruction by the host's immune system.[89,90] For example, viruses such as influenza and RSV can inhibit key interferon (IFN) signaling pathways, thereby impairing the host's ability to mount a robust antiviral response. In addition to suppressing IFN signaling, these viruses can also disrupt the functionality of DCs, which play a critical role in initiating adaptive immune responses.[83] Chronic exposure to viral antigens can lead to the upregulation of immune checkpoint molecules, such as PD-1, on T cells, which impairs their function and diminishes their ability to clear the infection. This exhaustion is marked by a decline in T cell activity, leaving the host more vulnerable to secondary infections and prolonged inflammation. Furthermore, the high mutation rates of many respiratory viruses contribute to antigenic variation, allowing the virus to evade immune recognition.[91] This variability significantly reduces the effectiveness of both innate and adaptive immune responses, making it challenging for the host to eliminate the infection. In cases of chronic viral infections, the immune system may undergo a phenomenon known as immune exhaustion.

Given these immune evasion mechanisms, it is essential to develop integrated treatment strategies that not only target the acute phase of infection but also address the long-term consequences of viral persistence and immune dysregulation. Addressing these challenges is critical for improving patient outcomes and reducing the public health burden of chronic respiratory viral infections.

## Gut-Lung Axis Crosstalk

The gut-lung axis acts as crucial links between the gastrointestinal and respiratory systems, significantly contributing to pulmonary health through various direct and indirect pathways. Factors like diet, stress, and the use of broad-spectrum antibiotics can influence the diversity and structure of the gut microbiota. This imbalance has been linked to the onset of respiratory illness. For instance, changes in the gut microbiota can influence immune responses in the lungs, thereby affecting the progression and outcomes of respiratory illnesses.[59] Understanding how these changes in the gut microbiota contribute to lung immune responses will require an interdisciplinary approach, integrating knowledge from immunology, microbiology, neurology, and endocrinology. These insights are crucial for unraveling the intricate mechanisms that govern gut-lung interactions and their implications for respiratory health.[92,93]

### Changes in Intestinal Microflora After Respiratory Virus Infection

Respiratory viral infections are increasingly recognized as significant modifiers of gut metabolic and microbial ecosystems, revealing intricate bidirectional connections between the lung and intestine. Recent studies indicate that respiratory viral infections can significantly disrupt the gut microbiota, impacting both gastrointestinal health and systemic immunity.[94]

Viral infections of the respiratory tract, such as those caused by IAV, RSV, and coronaviruses, are often associated with gastrointestinal symptoms, including abdominal discomfort, nausea, vomiting, and diarrhea. Animal studies, particularly in mice infected with IAV, have demonstrated intestinal injury characterized by reduced colon length, loss of the small intestine's mucosal layer, and mild diarrhea. Alongside these structural changes, an upregulation of inflammatory cytokines and interferon-stimulated gene expression has been observed, highlighting a shared inflammatory axis between the gut and the lungs.

Pathogenesis of respiratory viral infections frequently triggers robust IFN-α/β production in pulmonary tissues. For instance, IFN-α/β has been shown to regulate dendritic cells (DCs) and macrophages, promoting anti-inflammatory cytokine production such as IL-10 while suppressing pro-inflammatory pathways like Th17 responses.[95] These cytokines exert direct antiviral effects by activating the JAK-STAT signaling cascade, which promotes the transcription of interferon-stimulated genes (ISGs) encoding viral restriction factors like MX1 and IFITM3.[96,97] Emerging evidence suggests IFN-α/β may also indirectly modulate gut microbiota composition through systemic immune crosstalk. However, sustained or excessive IFN signaling has been linked to dysbiosis, which is marked by a reduction in protective, often strictly anaerobic, microbes like the butyrate-producer Faecalibacterium prausnitzii, and an overgrowth of opportunistic pathogens, including Escherichia coli and Klebsiella pneumoniae.[98]

Recent research has shown that COVID-19 can induce notable changes in the gut microbiota, including a decrease in beneficial, anti-inflammatory bacteria and a simultaneous increase in opportunistic pathogens. For instance, the populations of opportunistic pathogens like *Escherichia coli, Klebsiella pneumoniae, Salmonella enterica, Enterococcus faecium*, and *Staphylococcus auricularis* have been frequently observed to proliferate. In contrast, beneficial commensal bacteria, which are typically anaerobic and known for their anti-inflammatory properties by producing short-SCFAs, experience significant depletion. This includes key species like *Faecalibacterium prausnitzii* and *Bacteroides vulgatus*.[99]

Certain pathogenic strains, including *Coprobacillus, Clostridium ramosum*, and *Clostridium hathewayi*, have been associated with increased inflammatory responses in individuals with COVID-19. However, the precise mechanisms underlying their link to the severity of the disease are not yet completely understood.[100] Infections have also demonstrated profound alterations in gut microbiota composition. Next-generation sequencing of fecal samples from H7N9-infected individuals has revealed enrichment of opportunistic pathogens such as *Enterococcus faecium* and *Clostridium sp. 7 2 43FAA*, with a concurrent reduction in beneficial, anaerobic, butyrate-producing microbes like *Roseburia inulinivorans*.[101,102] RSV has been associated with changes in bacterial families, including a reduction in the generally beneficial, anaerobic Muribaculaceae family and an increase in the genus *Alistipes*, whose role is context-dependent as some species are beneficial while others can be opportunistic.[103]

These infections can substantially alter the gut metabolome, with notable shifts in lipid metabolism and the production of SCFAs. For instance, fecal metabolomic analyses following RSV infection have documented increased levels of sphingolipids, polyunsaturated fatty acids, or valerate, an SCFA, suggesting that viral infections may influence energy balance and inflammation-related metabolic pathways.[104]

## Mechnism in Intestinal Microflora After Respiratory Virus Infection

### Immune Modulation

The microbiome is crucial for maintaining immune homeostasis through its interaction with immune cells like macrophages and dendritic cells (Figure 2). This interaction helps maintain a balanced immune response, preventing both an inadequate response that could allow viral growth and an overly strong response that may lead to inflammatory tissue damage.[105] The gut-lung axis involves intricate immune interactions mediated by mucosal immune tissues, particularly gut-associated lymphoid tissue (GALT) and bronchus-associated lymphoid tissue (BALT). GALT plays a central part in modulating immune responses to the gut microbiota, while BALT primarily coordinates the immune defense against respiratory pathogens. Together, they establish a systemic network where gut-derived signals influence lung immunity and vice versa.

Evidence supports the existence of a common mucosal response, in which immune signals from the gut microbiota and its metabolites influence immune function at distant mucosal sites, including the lungs. The gut microbiota activates lung-resident cells, such as alveolar macrophages and dendritic cells,[106] which subsequently enhance type I interferon

production. Furthermore, immune cells stimulated in the mesenteric lymph nodes can enter the systemic circulation via the thoracic duct, the body's largest lymphatic vessel.[107] Guided by chemotactic signals, these cells migrate to the lungs and contribute to immune surveillance and response at sites of infection or inflammation. These primed cells can migrate to the lungs via the bloodstream or lymphatic system, modulating local immune responses upon arrival. Chemokine receptors, including CCR6 and CXCR3, play essential roles in directing this migration, guiding immune cells to the lungs in response to specific inflammatory signals. Chemokines such as CXCL8 (IL-8), CCL2, and CXCL10 are critical for orchestrating immune cell migration to the lungs during infections.[108] CXCL8, a potent neutrophil chemoattractant, initiates a rapid immune response by recruiting neutrophils to infection sites, where they phagocytose pathogens and release pro-inflammatory cytokines. CCL2 primarily recruits monocytes, which differentiate into macrophages within lung tissue. GALT-associated macrophages often exhibit an anti-inflammatory phenotype that helps regulate immune responses locally. These macrophages can either migrate to the lungs or exert remote effects by modulating pulmonary immune activity, ensuring that respiratory function is preserved while controlling inflammation. These macrophages perform dual roles: clearing pathogens through phagocytosis and modulating the inflammatory environment to promote tissue repair. CXCL10, a key chemokine in T cell migration, directs activated T cells—such as memory and effector T cells—to the lungs. This is especially important during viral infections, including influenza and RSV, as these T cells contribute to the clearance of infected cells and enhance immune memory.

T cell trafficking from secondary lymphoid organs, including the GALT, plays an integral role in the lungs' adaptive immune responses, aiding in immune tolerance and preventing excessive inflammation. Regulatory T cells (Tregs), generated in the GALT, are crucial for controlling immune system activation. Immune cells are directed toward the lungs by chemokine receptors such as CCR6 and CXCR3, ensuring a well-organized response to inflammatory cues. Dendritic cells capture antigens from the gut lumen and migrate to mesenteric lymph nodes, where they initiate T cell activation. These activated T cells subsequently differentiate into various subsets, including Th1, Th17, and Tregs. Gut dysbiosis, which disrupts the equilibrium between Th1 and Th2 cells, can worsen lung damage during respiratory infections.[109] Th17 cells, essential for mucosal immunity, migrate to the lungs where they help maintain mucosal integrity and activate inflammatory responses vital for defense against pathogens. This immune response leads to an influx of neutrophils and T lymphocytes into the intestines, forming lymphoid aggregates that contribute immune cells capable of infiltrating other organs, including the lungs.

### Microbial Signals Influence

In the gut, immune cells interact with the microbiota, becoming activated by microbial signals and metabolites derived from gut microbiota (as discussed in the Metabolic Influence section)[110,111] (Figure 2). These microbial signals are essential for regulating immune responses and maintaining homeostasis.

Microorganisms, particularly those within the gut, provide a constant source of MAMPs and PAMPs. These molecular signals are recognized by PRRs on host cells. Key PRRs include TLRs and nucleotide-binding oligomerization domain (NOD)-like receptors, which detect specific microbial components.[112] For instance, TLR4 interacts with lipopolysaccharides (LPS) derived from Gram-negative bacteria, while TLR2 detects peptidoglycans present in Gram-positive bacteria and some fungi. The activation of PRRs results in the production of pro-inflammatory cytokines. This receptor activation initiates signaling pathways, primarily through the MyD88 pathway, which culminates in the activation of key transcription factors, including NF-κB and MAPKs.

Gut commensal bacteria is critical for priming baseline interferon (IFN) signaling through tonic TLR stimulation, thereby establishing a bidirectional regulatory loop between the gut and lungs.[96] Notably, in the absence of a healthy microbiota—as observed in antibiotic-treated (ABX) mice—responses to type I and II interferons are dysfunctional, resulting in reduced viral control. These findings underscore the microbiota's role in setting the activation threshold of the innate immune system, a prerequisite for effective antiviral immunity.[113] Moreover, certain bacterial species, including Segmented Filamentous Bacteria (SFB), have been identified as key factors in immune regulation. Research, such as that conducted by Ngo et al, shows that the colonization of SFB in the gut leads to the reprogramming of alveolar macrophages (AMs).[114] This reprogramming enhances AM proliferation, complement production, and phagocytic activity, thereby providing improved protection against various respiratory viruses.[114]

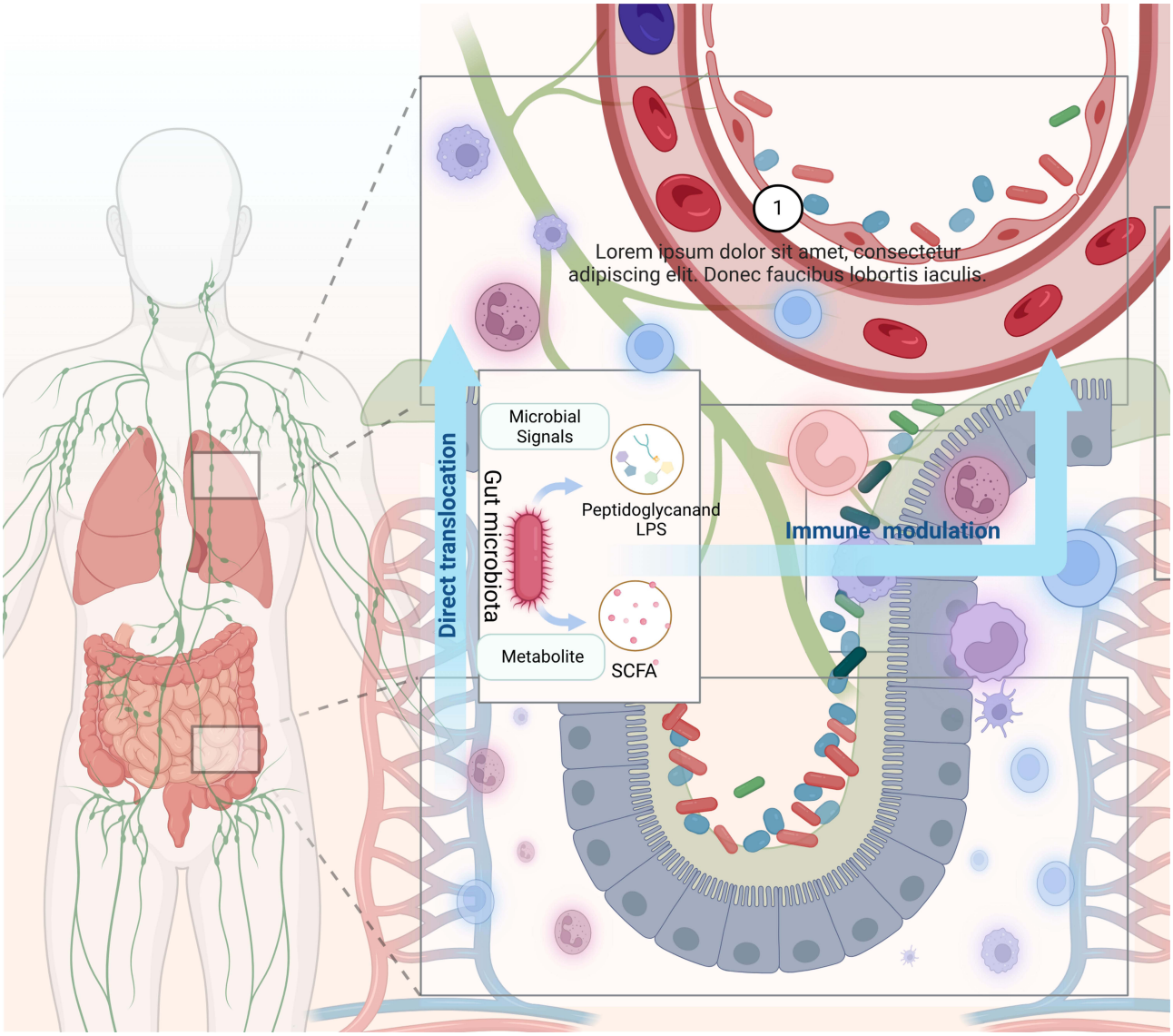


**Figure 2** Pathways of Gut-Lung Axis Communication. Through direct translocation, gut bacteria can migrate to the lungs, directly altering the pulmonary environment. The pathway involves modulation of immune response, influenced by presence of gut microbiota or its metabolic byproducts, impacting overall respiratory health.

Moreover, they stimulate DCs and T cells, bridging innate and adaptive immunity. The resulting immune response not only addresses the immediate microbial threat but also shapes the long-term adaptive immune landscape, demonstrating the interconnected nature of gut microbiota, pattern recognition, and systemic immune regulation. Recent investigations have shown a critical role of the microbiome in inflammasome activation, an essential immune defense pathway. These signals stimulate robust caspase-1–dependent production of IL-1β and IL-18, which enhance dendritic cell (DC) migration from the lungs to lymph nodes.[115] This migration primes T cells, strengthening the adaptive immune response.

### Influence of Gut Microbiota-Derived Metabolite

Metabolites produced by the gut microbiota are crucial in modulating immune responses across various organs, including the lungs (Figure 2). Among the most significant metabolites are SCFAs—specifically butyrate, propionate, and acetate—which are produced by gut bacteria through the fermentation of dietary fibers. The absorption of SCFAs occurs via solute transporters such as MCT1 (SLC16A1) and SMCT1 (SLC5A8), as well as through passive diffusion. Once inside cells, SCFAs can serve as substrates for various metabolic processes or activate G-protein-coupled receptors (GPCRs), such as

GPR41 (FFAR3), GPR43 (FFAR2), and GPR109A (HCAR2). These receptors mediate intracellular signaling pathways that influence inflammatory and metabolic responses, shaping immune reactivity.[116,117]

Interestingly, the accumulation of SCFAs within the lung mucosa after systemic circulation is limited.[118] However, gut-derived SCFAs primarily exert their effects by influencing peripheral immune cells, which subsequently migrate to the lungs. Once within the lung microenvironment, these SCFA-primed immune cells help balance inflammation. Among SCFAs, butyrate emerges as a particularly vital metabolite in regulating immune responses.[5] Recent studies have demonstrated that butyrate exerts protective and anti-inflammatory effects in various lung diseases—including asthma, idiopathic pulmonary fibrosis (IPF), ARDS, and allergic airway inflammation—through mechanisms such as HDAC inhibition, epigenetic regulation, and activation of FFAR2/FFAR3 receptors.[118] SCFAs, especially butyrate, have been found to promote the function of regulatory T cells (Tregs) by inducing epigenetic changes, including the inhibition of histone deacetylases.[5] Tregs are crucial for preventing excessive immune activation, particularly during respiratory infections. Beyond Tregs, SCFAs also influence other immune pathways, including the Th17 and Th1/Th2 balance, which are essential for mounting appropriate immune responses to infections and preventing autoimmune dysregulation.[119] In addition to promoting T cells differentiation, dietary fiber-derived SCFAs facilitate rapid and sustained effector T cell responses. For instance, elevated serum acetate levels following bacterial infections have been shown to rapidly recall memory CD8+ T cells, shifting their metabolism toward glycolysis and enabling a quicker response to infection. In contrast, naive T cells rely primarily on oxidative phosphorylation for energy production.[120] When activated, metabolic and functional changes in CD8+ T cells are, in part, driven by SCFAs, which interact with the FFAR3 receptor to mediate these adaptations.[121] Additionally, SCFAs affect the activity of monocytes and macrophages through the FFAR3 receptor. This interaction triggers the release of Ly6c− monocytes from the bone marrow, which then differentiate into alternatively activated macrophages (AAMs) when they infiltrate the lungs.[122] AAMs play a crucial role in managing the accumulation of cytotoxic neutrophils in the airways, thereby reducing tissue damage. Notably, the increase in Ly6c− patrolling monocytes does not result in a decrease in the Ly6c+ inflammatory monocyte subset, ensuring the preservation of vital antiviral responses. Furthermore, SCFAs promote the synthesis of antimicrobial peptides (AMPs), such as defensins and cathelicidins, which directly combat pathogens. For instance, Lactobacillus species, which produce SCFAs, enhance AMP production in epithelial cells, bolstering the body's direct defenses against pathogens like influenza and RSV.[123]

In addition to SCFAs, bile acids produced by gut bacteria—particularly deoxycholic acid (DCA) and other secondary bile acids—play a significant role in lung immunity. Gut bacteria such as *Clostridium scindens* and *Clostridium sordellii* convert primary bile acids into secondary bile acids, which then circulate systemically. These bile acids interact with receptors including TGR5 and FXR, which are expressed on immune cells within the lungs.[107] TGR5 influences immune cell migration and reduces inflammation, while FXR modulates innate and adaptive immune responses.[124] Activation of TGR5 has been shown to enhance antiviral.[125] Together, these bile acid-receptor interactions shape the lung's immune landscape and contribute to a more controlled and effective response to viral pathogens.

In addition, GLP-1 receptor agonists, which are mainly prescribed for the treatment of type 2 diabetes and obesity, have been studied for their possible impact on lung health, particularly in the context of viral infections. Research indicates that GLP-1 receptors are present in various lung cells, such as alveolar epithelial cells and immune cells, suggesting that GLP-1 receptor agonists could influence pulmonary function. Some studies have reported that these agonists can influence immune responses, potentially decreasing inflammation and boosting antiviral defenses. For instance, treatment with GLP-1 receptor agonists in RSV-infected mice led to decreased numbers of certain immune cells and reduced inflammation.[126] However, additional studies are required to elucidate the precise role of GLP-1 receptor agonists in viral lung infections and their therapeutic potential in this context.

### Gut Microbiota Translocation

The epithelial barrier of the gut plays a crucial role in preventing the movement of microbial components into the bloodstream. Impairment of the gut-lung barrier, commonly seen in conditions such as sepsis, critical illness, or chronic inflammation, facilitates the movement of microbial components—such as bacteria or bacterial fragments—from the gut to distant organs, including the lungs.[127] Respiratory viral infections further compromise gut integrity by increasing

intestinal permeability, a phenomenon known as "leaky gut" which permits bacteria and toxins normally confined to the gut to enter the bloodstream. Once in the respiratory tract, these pathogens may colonize lung tissue, exacerbate ongoing viral infections, and overwhelm the pulmonary immune system. This disruption of immune homeostasis between the gut and lungs heightens susceptibility to respiratory diseases and intensifies infection severity.[128]

Bacteria originating from the gut are commonly found in the lung microbiome, a finding observed in both experimental murine sepsis models and humans diagnosed with ARDS. In these murine models of sepsis, the lung microbiota was mainly composed of viable gut-derived bacteria. Ecological analysis showed that the primary source of bacteria in the lungs was the lower gastrointestinal tract, rather than the upper respiratory tract.[129] This suggests a significant gut-lung axis in the pathogenesis of pulmonary conditions such as ARDS and sepsis.

## Therapeutic Strategies in Pulmonary Viral Defense via Gut-Lung Axis

Therapeutic strategies aimed at enhancing pulmonary viral defense through modulation of the gut-lung axis have garnered great attention in recent years (Table 2).[88,130–134] Amid growing evidence of bidirectional interactions between the gut microbiome and lung health, treatment strategies targeting this axis have emerged as promising interventions. These strategies encompass fecal microbiota transplantation (FMT), the use of probiotics, dietary changes, and TCM. Each of these strategies seeks to restore or modulate the gut microbiome in order to improve lung function, enhance immune responses, and potentially reduce the severity of pulmonary diseases.

### FMT

FMT has emerged as a promising therapeutic approach for leveraging the gut-lung axis to enhance immune defenses against respiratory viral infections.[7] By transferring a healthy and diverse gut microbiome from a donor to a recipient, FMT aims to restore microbial balance in the gut, which in turn influences systemic immune responses and lung immunity.

In one study, fecal transfers from mice that survived influenza H7N9 infection conferred protection to recipient mice challenged with the influenza A virus, suggesting that specific gut microbiota compositions can enhance resistance to respiratory infections.[135] For example, changes in gut-derived metabolites such as short-chain fatty acids (SCFAs) may modulate lung inflammation and immune responses, contributing to improved lung health. However, the exact biological mechanisms linking gut microbiota restoration to lung immune modulation require further investigation.

Recent clinical studies have explored the impact of FMT on patients with chronic respiratory conditions, including those susceptible to viral infections like influenza and COVID-19. These investigations have reported promising outcomes, such as reduced frequency and severity of viral exacerbations, decreased hospitalization rates, and improved overall quality of life.[136,137] However, it is important to note that these studies often involve small sample sizes and have limitations, such as short-term follow-up periods. Therefore, more robust, placebo-controlled trials with larger and more diverse populations are necessary to verify the efficacy and safety of FMT in treating respiratory diseases. Longitudinal studies are particularly needed to assess the sustainability of FMT's effects on both gut health and lung immunity over time.

### Probiotics

Probiotics consist of live microorganisms that offer health benefits to the host when consumed in adequate amounts. Extensive research has been conducted on their positive effects on the gastrointestinal system and their role in modulating immune responses. Notably, genera like *Lactobacillus, Bifidobacterium*, and *Streptococcus* have demonstrated significant health benefits. These probiotics can modulate immune function by influencing the activity of dendritic cells and macrophages, which are essential for antigen presentation and T-cell activation.[138] Furthermore, certain bacterial species in the gut are capable of promoting the production of antiviral compounds such as interferons, which are vital for controlling viral replication.[138] For example, Lactobacillus species can influence cytokine production and modify immune responses, thereby enhancing the ability to combat respiratory infections such as influenza. RSV, and SARS-CoV-2.[139] For example, administering heat-killed Lactobacillus gasseri TMC0356 increased mRNA expression of IL-12, IL-15, and IL-21 in Peyer's patches, reduced viral titers in the lungs, and improved clinical symptoms in mice.[140]

**Table 2** Research on Gut-Lung Axis-Based Approaches for Treating Viral Pulmonary Infections

| Method | Research Subjects | Intervention | Treatment Duration | Results | Ref |
|---|---|---|---|---|---|
| Probiotics | Patients with COVID-19 | *B. longum*, *L. bulgaricus*, *S. thermophilus* | 3 doses daily for up to 7 days | symptom remission↑, risk of respiratory failure↓, ICU transfer rates↓, mortality rates↓ | [88] |
| | Infant C57BL/6 mice and 7-week-old female BALB/c mice with Influenza virus H1N1 strain PR8 | $1 \times 10^8$ CFU viable or 200 μg heat-killed *L. rhamnosus GG* | Intranasal administration 8 days | survival rate↑, lung inflammation↓ | [130] |
| Dietary | Patients with Influenza virus strains: A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (B) | Beta-glucan, Galacto-oligosaccharides | 14 weeks of enteral feeding, 4 weeks of follow-up | fecal *bifidobacteria* counts↑, antibody titers↑ | [131] |
| | BALB/c mice with Trivalent Influenza Vaccine (TIV) | oligosaccharides (2′-FL), short-chain galacto-oligosaccharides, long-chain fructo-oligosaccharides | Oral supplementation for up to 84 days | TIV-specific antibodie↑, immune responsess↑ | [132] |
| FMT | C57BL/6 Mice (Wild-type and Tlr7−/−) with Influenza virus (FM1 strain) | fecal from untreated group and a mix of *B. longum, L. bulgaricus, S. thermophilus* | Oral administration for up to 32days | restored intestinal flora, pulmonary inflammation↓, TLR7 signaling pathway↑ | [133] |
| | Male BALB/c mice Influenza A virus (H1N1, A/FM/1/47 strain) | fecal from donor mice treated with houttuynia cordata polysaccharides | Oral gavage during the first 4 days | gut microbiota diversity↑, fecal acetate levels↑, pulmonary inflammation↓ | [134] |

Notably, peptides derived from Lactobacillus and Paenibacillus species have shown potential to bind to the ACE2 receptor, which may block the binding of SARS-CoV-2 to host cells, providing a novel avenue for therapeutic intervention in viral infections.[141] The probiotic effects of *Bifidobacterium* and *Streptococcus* species, while also significant, are often complementary to those of *Lactobacillus*. *Bifidobacterium* species are particularly involved in maintaining gut barrier integrity and modulating inflammation, while *Streptococcus* species, particularly *Streptococcus thermophilus*, are known for their role in promoting digestive health and may have specific applications in oral health.[142] Among Lactobacillus strains, *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* are among the most extensively studied for their immunomodulatory and respiratory protective effects. *L. rhamnosus* enhances innate and adaptive immunity by activating TLRs, MAPK, and NF-κB signaling pathways, upregulating IFN-γ, IL-10, and IL-12, and boosting the function of helper T cells and NK cells.[143] In respiratory infections, nasal or oral administration of *L. rhamnosus* CRL1505 has been shown to increase resistance to RSV and *Streptococcus pneumoniae*, reduce lung inflammation, and lower eosinophil recruitment. *L. acidophilus*, on the other hand, modulates systemic and mucosal immunity by increasing IgA, IgG, and IgM levels, while reducing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-5.[144] These genera work together within the gut microbiome to balance microbial populations and regulate host immune responses, ultimately supporting overall health and potentially reducing the risk of infections.

Recent clinical studies have investigated the potential benefits of probiotics in managing Viral respiratory Infections, yielding promising yet preliminary results. In one study involving 70 COVID-19 patients, those receiving oral probiotics, including strains such as Streptococcus thermophilus DSM 32345, Lactobacillus acidophilus DSM 32241, and Lactobacillus brevis DSM 27961, exhibited an 8-fold reduction in the risk of developing respiratory failure compared to those receiving standard treatment alone.[145] In a separate trial with 58 hospitalized COVID-19 patients, those receiving a probiotic regimen containing Bifidobacterium, Lactobacillus, and Streptococcus exhibited improved metabolic profiles, including increased serum levels of arginine, asparagine, and lactate. These changes could support better energy metabolism, potentially reducing the risk of chronic fatigue, which is a common post-viral symptom.[146] For clinical application, the dosage of probiotics is crucial. Commonly used dosages in recent literature typically range from approximately $2 \times 10^9$ CFU/day to $1 \times 10^{10}$ CFU/day, depending on the specific strain and clinical objectives. For instance, *Lactobacillus rhamnosus GG* is commonly administered at a dose of approximately $1 \times 10^9$ CFU/day, which has demonstrated efficacy in reducing respiratory and gastrointestinal infections in clinical studies.[147] In a clinical trial involving respiratory viral infections, a commercially available probiotic formula containing strains such as *Streptococcus thermophilus* DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, and *Lactobacillus brevis* DSM 27961 (*Sivomixx*®) was administered at a total daily dose of approximately $2.4 \times 10^{12}$ CFU, divided equally into three doses.[148] Similarly, Lactobacillus rhamnosus CRL1505 demonstrated beneficial effects on respiratory health at a dosage of approximately $1 \times 10^8$ CFU/day.[149] These findings indicate that a daily probiotic dosage between $2 \times 10^9$ to $1 \times 10^{10}$ CFU is commonly effective and safe for promoting respiratory and immune health.

While these findings are encouraging, it's important to note that the studies often involved small sample sizes and had limitations such as short-term follow-up periods. Therefore, more robust, placebo-controlled trials with larger and more diverse populations are necessary to verify the efficacy and safety of probiotics in managing respiratory viral infections.

## Prebiotics and Dietary Modification

Recent studies emphasize the critical impact of dietary interventions on the gut-lung axis and their role in strengthening immune defenses against respiratory viral infections. Specifically, supplementation with SCFAs and the consumption of high-fiber diets have been shown to alter the composition of the gut microbiota. This change subsequently boosts immune functions in both the intestines and lungs, helping to correct gut dysbiosis and decrease inflammation. By promoting a more balanced immune response, these dietary strategies may reduce the severity of complications from respiratory infections such as influenza. The fermentation of dietary fiber by gut bacteria results in the production of SCFAs like butyrate, which possess anti-inflammatory effects. Despite concerns that this process could suppress immune

protection, research has demonstrated that fermentable fiber can significantly improve survival outcomes in mice infected with influenza.[118]

Moreover, the benefits of dietary fiber extend beyond SCFAs. Prebiotics like β-glucans (BGS) and galacto-oligosaccharides (GOS) are increasingly recognized for their role in promoting gut health. BGS, derived from sources like yeast, fungi, and oats, has demonstrated immune-enhancing properties, while GOS, sourced from lactose, is known to stimulate the growth and activity of beneficial gut bacteria, especially bifidobacteria and lactobacilli. In addition to GOS and BGS, fructooligosaccharides (FOS) and inulin are two other well-characterized prebiotics that support gut and immune health by selectively promoting the growth of beneficial microbes. FOS are short-chain fructose-based fibers found in onions, garlic, and asparagus, which stimulate the proliferation of *Bifidobacterium* and *Lactobacillus*, while inhibiting pathogens such as *Clostridium* and *E. coli*. Their fermentation produces SCFAs, enhances mineral absorption, relieves constipation, and supports glycemic control.[150,151] Inulin, a longer-chain fructan present in chicory root, bananas, and leeks, also enriches bifidobacteria and reduces pro-inflammatory bacteria such as *Desulfovibrio*.[152] Inulin has been shown to upregulate tight junction proteins (eg, occludin, claudin-1), increase secretory IgA and mucin secretion, and stimulate the production of antimicrobial peptides from Paneth cells—thereby strengthening intestinal barrier integrity and modulating immune responses. Both FOS and inulin contribute to increased SCFA production (acetate, propionate, and butyrate), helping to reinforce the gut-lung axis through anti-inflammatory and immunoregulatory mechanisms.

To facilitate practical dietary application, several recommended food sources and their daily intake levels are provided based on existing literature. FOS-rich foods include onions (0.4–2.8 g/100 g), garlic (0.5–2 g/100 g), asparagus (2–3 g/100 g), and chicory root (35–47 g/100 g), with beneficial effects commonly reported at intakes of approximately 3–10 grams per day.[153,154] Inulin is highly abundant in chicory root (35–48 g/100 g), Jerusalem artichokes (16–20 g/100 g), garlic (9–16 g/100 g), onions (1–8 g/100 g), and bananas (0.3–0.7 g/100 g), typically exerting beneficial effects at doses ranging from 5 to 15 grams per day, depending on individual tolerance.[155,156] GOS are naturally found in fermented dairy products (such as yogurt and kefir) and commercial supplements, with daily intake recommendations typically between 2 to 7 grams for noticeable health improvements.[157,158] β-glucans are notably present in oats (2–7% by weight), barley (3–11%), mushrooms, and baker's yeast, with immunomodulatory effects generally achieved with a daily consumption of 3 grams or more.[159,160] Incorporating these foods into regular meals—such as consuming oatmeal or barley cereals, adding garlic and onions to vegetable dishes, and including bananas or chicory-based products—can support beneficial gut microbiota changes and enhance respiratory immune defenses via the gut-lung axis Together, these prebiotics help maintain a healthy gut microbiota, support digestive function, and bolster overall health, indirectly contributing to a more resilient immune system.[131]

These dietary interventions provide a promising avenue for improving immune resilience and reducing the impact of respiratory viral infections by targeting the interconnected gut-lung axis.

## Traditional Chinese Medicine

Emerging evidence suggests that compounds derived from Traditional Chinese Medicine (TCM) play significant roles in modulating the gut-lung axis, potentially enhancing immune defenses against respiratory viral infections. TCM offers a range of natural compounds, including Astragalus (Huang Qi) and curcumin, which are increasingly recognized for their potential to influence both gut and lung health.

Astragalus, a key herb in TCM, is known for its ability to strengthen gut barrier function and modulate gut microbiota.[161] The polysaccharides and saponins present in Astragalus promote both innate and adaptive immune responses. These compounds are particularly effective in enhancing mucosal immunity by boosting the production of secretory IgA in the gut, which plays a crucial role in protecting the mucosal surfaces from pathogens.[162]

Curcumin is widely recognized for its strong anti-inflammatory and antioxidant effects. In the context of respiratory viral infections, it aids in modulating immune responses by decreasing the levels of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, while simultaneously boosting the production of anti-inflammatory mediators like IL-10. These actions contribute to alleviating excessive inflammation in the lungs, thereby lowering the likelihood of complications, including viral pneumonia.[163] Beyond its immunomodulatory effects, curcumin positively influences gut microbiota composition, promoting the growth of beneficial species like Lactobacillus and Bifidobacterium. These microbiota

changes further support immune homeostasis in both the gut and lungs. Animal studies have shown that curcumin supplementation can decrease lung inflammation and viral load, suggesting potential therapeutic benefits in viral respiratory infections.

Although these findings are promising, many TCM-based therapies lack robust validation through large-scale, randomized controlled trials. Additional studies are necessary to elucidate the mechanisms by which TCM compounds and dietary strategies influence the gut-lung axis, as well as to assess their clinical efficacy, safety, and potential integration into conventional treatment protocols.[164]

# Challenges and Prospect

## Challenges

The gut-lung axis is gradually recognized as a critical pathway in shaping immune responses and mitigating the severity of pulmonary viral infections. This interconnected system provides a promising frontier for developing new therapeutic strategies. By addressing these hurdles, the field can move closer to optimizing therapies that harness the gut-lung axis for bolstering pulmonary viral defense.

### The Double-Edged Sword of Antibiotics

Antibiotic use during respiratory viral infections can have complex effects on the immune system, particularly by disrupting the gut microbiota and altering immune responses.[114,165] For example, antibiotics such as oral neomycin have been shown to diminish pulmonary antiviral immunity by selectively depleting gut-resident Gram-positive bacteria (eg, the *Clostridiales* family), even while leaving nasal microbiota intact. This gut dysbiosis can impair systemic and pulmonary immune defenses against pathogens like influenza, underscoring the weight of the gut-lung axis in sustaining respiratory health.[114]

Interestingly, despite these negative effects, antibiotics can also have unexpected benefits in certain contexts. For example, intranasal administration of neomycin has been shown to enhance immune responses against respiratory viruses by inducing interferon-stimulated genes (ISGs) in the nasal mucosa, independent of the commensal microbiota.[166] Neomycin treatment, for instance, has been shown to mitigate the transmission of SARS-CoV-2 in hamsters, reduce upper respiratory infections, and improve outcomes in mouse models infected with highly virulent influenza A virus strains. In human studies, intranasal neomycin-containing ointments have demonstrated tolerability and the ability to induce ISG expression in a subset of participants.[167] These findings highlight the complex, dual role of antibiotics: they can either hinder antiviral immunity by disrupting the gut microbiota or bolster certain immune responses under specific conditions.

Additionally, certain immune-mediated consequences of viral infections may be attenuated by antibiotic-induced shifts in the gut microbiota. For instance, post-influenza increases in Th17 cells have been linked to intestinal injury, and neutralizing IL-17A can reduce this damage. Interestingly, antibiotic depletion of gut bacteria diminishes IL-17A production, thereby attenuating influenza-associated intestinal injury. These results indicate a complex interaction between antibiotic use, the composition of the gut microbiota, and immune function in the context of respiratory viral infections.[166]

When utilizing the gut-lung axis for antiviral therapy targeting respiratory infections, it is essential to account for the multifaceted effects of antibiotic use. Antibiotics are essential for protecting against bacterial co-infections; however, they can also disrupt the gut microbiota, a crucial component in regulating immune responses and defending the respiratory system. Balancing these dual impacts requires careful consideration and informed decision-making to devise the most effective treatment strategy. When utilizing the gut-lung axis for antiviral therapy targeting respiratory infections, it is essential to account for the multifaceted effects of antibiotic use. Antibiotics can provide critical protection against bacterial co-infections, yet they also have the potential to disrupt the gut microbiota could regulate immune and respiratory defense. Balancing these dual impacts requires careful consideration and informed decision-making to devise the most effective treatment strategy.

### Potential Infectious Risks

Probiotics have shown promise as a therapeutic intervention for pulmonary viral infections by enhancing mucosal immunity and mitigating pulmonary inflammation. The application of probiotics in immunocompromised individuals and other high-risk groups requires thorough evaluation due to safety concerns. These populations include recipients of HSCT, neutropenic patients with an absolute neutrophil count less than 500/mm³, and preterm neonates with a gestational age under 32 weeks. Lactobacillus rhamnosus GG (LGG), a commonly used probiotic strain, has been associated with cases of bacteremia in immunocompromised patients. For example, a case study documented LGG bacteremia in an adult with severe active ulcerative colitis undergoing corticosteroid treatment. Genotypic analysis confirmed that the bloodstream isolate was identical to the ingested probiotic strain.[168] These cases suggest that LGG can translocate from the gut to the bloodstream, particularly when the intestinal barrier is compromised or immune defenses are weakened. Similarly, the probiotic yeast Saccharomyces boulardii has been associated with fungemia in susceptible individuals.[135] A man in his 70s was hospitalized in the intensive care unit with severe COVID-19 and received treatment with dexamethasone and tocilizumab. Following his recovery from the virus, he developed Clostridium butyricum bacteraemia and non-occlusive mesenteric ischaemia, which ultimately resulted in his death. For a month, he had been taking C. butyricum MIYAIRI 588 fine granules as a probiotic supplement. Analysis of single nucleotide polymorphisms (SNPs) showed that the genome of the C. butyricum strain from his blood culture matched that of the C. butyricum MIYAIRI 588 fine granules.[169]

Given these risks, it is imperative for clinicians to assess individual patient factors—such as immune status, underlying health conditions, and the integrity of the gastrointestinal tract.[135]

## Prospect

### Integration with Precision Medicine

Personalized medicine, which tailors interventions based on an individual's genomic, microbiomic, and immunological profiles, holds significant promise for optimizing respiratory health. For instance, genetic variations in certain populations may make supplementing specific probiotics more challenging, requiring a targeted selection of strains or prebiotics that align with those genetic differences. Additionally, differences in gut and lung microbiota profiles among individuals mean that generalized probiotic supplementation may fail to produce the desired outcomes. Instead, interventions should focus on addressing the specific points of dysbiosis within the individual's microbial ecosystem.

By tailoring treatment strategies to a person's unique microbial composition, immune status, and genetic predispositions, personalized medicine offers the potential for more precise and effective therapies, ultimately improving patient outcomes in respiratory care. Realizing this potential involves integrating data from genomics, microbiomics, and immunology using advanced computational tools and sophisticated data analysis techniques. Current bioinformatics approaches, particularly machine learning algorithms, are instrumental in identifying patterns within these datasets. Such tools enable predictions about how an individual's biological profile may influence their response to various treatments.

Clinical implementation of personalized medicine targeting the gut-lung axis requires a multi-omics integration strategy. This may include metagenomic sequencing of enteric bacteriophages, metabolomic profiling of microbial-derived aryl hydrocarbon receptor (AhR) ligands, and single-cell immunotranscriptomics of pulmonary CD103+ DCs. Emerging pharmacomicrobiomics approaches, such as metatranscriptomic profiling of host-probiotic interactions (eg, TLR2/4 activation thresholds) and machine learning-based risk prediction models (eg, AUC 0.89 for bacteremia), enable clinicians to develop personalized treatment protocols. By analyzing an individual's immune status — including cytokine profiles, immune cell populations, and genetic factors influencing immune responses — clinicians can devise targeted strategies to precisely modulate immune functions and improve respiratory health outcomes.[170]

### Integration with Traditional Therapies

The gut microbiota influences not only the body's reaction to natural infections but also contributes to the effectiveness of vaccines. Researches have shown that the microbiome can influence immune responses to vaccines, including influenza vaccines, by modulating innate and adaptive immunity.[171] As such, understanding the gut-lung-microbiota interplay may open avenues to optimize vaccine performance.

Furthermore, various TCM treatments impact the composition and function of the gut microbiota, thereby mediating their therapeutic effects. For instance, individuals experiencing gut dysbiosis might benefit from TCM compounds such as Astragalus and curcumin, both of which could reduce inflammation and enhance immunity. Although these results are encouraging, further large-scale clinical trials are necessary to confirm the safety, effectiveness, and microbiota-specific outcomes of TCM interventions. Moreover, individualized approaches, including precise dosing and personalized treatment strategies, must be tested to maximize their therapeutic potential.

Those findings highlight the significance of considering microbiome health in conjunction with both TCM interventions and traditional vaccination strategies to enhance overall respiratory health.

### Nanomedicine Integration

A promising area of future research lies in nanotechnology, which could be used to deliver probiotics, prebiotics, or immune-modulating compounds directly to the gut or lungs. Researchers can engineer nanoparticles to target specific microbial populations in the gut or deliver signals that activate immune cells, thereby enhancing immune responses and improving antiviral immunity. Although this approach is still in its early stages, advancements in nanomedicine could offer a dual strategy for enhancing both microbial balance and immune responses, potentially improving therapeutic outcomes in respiratory infections.[172] For instance, polymeric nanoparticles have been utilized to transport and deliver probiotics effectively, protecting them from harsh gastrointestinal conditions and ensuring their release in the colon.[173,174] While these applications are still in early stages, advancements in nanotechnology could provide a dual approach to enhancing both microbial balance and immune responses in the fight against respiratory viruses.[175]

The concept of enhancing lung immunity through probiotics has led to innovative therapeutic strategies, notably the integration of engineered bacteria and nanocarrier technologies. Engineered probiotics are being developed to produce specific antiviral compounds within the gut. These compounds can be taken up into the bloodstream and exert effects on distant tissues, including the lungs. For instance, synthetic biology techniques have been employed to design probiotics capable of generating bioactive peptides with antiviral properties.[176] These advancements in engineered probiotics and nanocarrier technologies offer exciting avenues for optimizing the gut-lung axis and bolstering body's defense mechanisms against respiratory infections.

## Conclusion

The gut-lung axis is a critical bidirectional communication network through which the gut microbiota actively regulates pulmonary immunity. This modulation is driven by specific mechanisms, including the systemic influence of microbial metabolites like SCFAs, which are produced via the fermentation of dietary fiber. SCFAs influence immune cell function through epigenetic modifications and G-protein-coupled receptors. Furthermore, the microbiota is crucial for priming immune cells within GALT, which can subsequently migrate to the lungs to coordinate an effective immune response. Disruption of this homeostasis, known as dysbiosis, significantly impairs these protective functions. Viral respiratory infections are a common cause of such imbalances, leading to compromised epithelial barrier integrity and weakened antiviral responses, such as diminished interferon signaling. This impairment increases host susceptibility not only to the primary viral pathogen but also to severe secondary bacterial pneumonia.

Consequently, therapeutically targeting the gut-lung axis has emerged as a promising strategy to enhance respiratory health and mitigate viral infections. Interventions are designed to restore microbial equilibrium and bolster host defenses. These include the administration of probiotics, which introduce beneficial microbes that can modulate the activity of dendritic cells and macrophages, and FMT, which re-establishes a diverse and healthy microbial community. Dietary modifications using high-fiber prebiotics are also effective, as they provide the necessary substrates to fuel the production of beneficial SCFAs. Additionally, compounds from TCM offer a multifaceted approach by interacting with microbial communities to modulate key immune pathways, including cytokine production and immune cell activation. Collectively, these strategies work to fortify mucosal defenses, enhance systemic immune function, and attenuate the excessive inflammation that characterizes severe viral disease.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests for this work.

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