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Microbiome and the Gut-Lung Axis in Emerging Viral Respiratory Infections

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ABSTRACT

The gut microbiota was once thought to be merely a component of digestion, but it is now known to have a wide range of effects, particularly on our ability to combat infections, including lung infections. The gut-lung axis, a biological dialogue in which gut microbes aid in controlling immune responses in the respiratory system, is at the centre of this discovery. In the wake of global health threats like influenza and COVID-19, this connection has become even more crucial.

Short-chain fatty acids (SCFAs), which are produced by beneficial gut microbes, aid in immune cell training, inflammation management, and the avoidance of immunological overreactions such as the hazardous cytokine storms that occur during severe viral infections. This equilibrium promotes a robust, well-balanced defence in a healthy gut. However, when the gut ecology is disrupted—by stress, antibiotics, disease, or aging—this protective link weakens.

The body may become more susceptible to severe respiratory illnesses as a result of this dysbiosis. Indeed, new research indicates that a person's gut microbial profile may affect the prognosis of viral infections.

This information is creating exciting opportunities: microbial metabolite therapies, targeted probiotics, and even faecal transplants are being researched as means of improving lung infection outcomes and boosting immunity. Doctors may soon be able to more accurately customize treatments and identify high-risk patients early with the use of gut profiling. In addition to improving digestion, knowing and taking care of our gut microbes may be essential to surviving pandemics in the future.

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Introduction

With a history that includes both historical dangers and contemporary difficulties, pulmonary viral infections have long been a major public health concern. Human history has been shaped by ancient viral infections that have caused devastating outbreaks all over the world, including influenza, measles, and the notorious smallpox. Seasonal epidemics and sporadic pandemics are caused by these viruses, which persist in circulation despite major improvements in public health and the creation of vaccines. Because influenza, in particular, can change quickly, avoiding immunity and vaccine effectiveness year after year, it continues to be a major global concern [1,2]. However, the persistence of tuberculosis and the resurgence of viruses like measles serve as a reminder that certain respiratory infections are difficult to eradicate.

Novel viral infections have emerged in recent decades, posing new risks to public health, especially in the area of pulmonary diseases. Viruses like SARS-CoV, MERS-CoV, and the most recent SARS-CoV-2 have shown how quickly pathogens can adapt, spread around the world, and cause serious respiratory illnesses. Our global health systems' vulnerabilities have been brought to light by the COVID-19 pandemic, which has also emphasized the significance of early detection, readiness, and prompt action [3,4]. In addition to posing immediate risks, these novel viruses have long-term effects on economies, societies, and health systems.

The ongoing conflict between virus adaptation and our immune system is what unites both recent and historical pulmonary viral infections. Even though vaccinations and other medical treatments have greatly decreased the prevalence of illnesses like polio and smallpox, the necessity for constant attention is highlighted by the respiratory viruses' continuous evolution. A thorough grasp of the behaviour, dynamics of transmission, and long-term impacts on public health of both established and emerging viral infections is necessary to address them. The immune system, a sophisticated network of cells, tissues, and signalling molecules, is essential to our body's defence against viral infections, particularly those that impact the respiratory system. Recent research has shown that the immune system does not function alone, despite the fact that it has historically been studied in isolation. Rather, the communities of microorganisms we host—especially those in the gut—have a significant impact on it [5].

Once thought of mainly as a digestive aid, the gut microbiota is now understood to be a potent modulator of immune responses across the body. Its interaction with the lungs, which forms what is now known as the gut-lung axis, is one of its most fascinating systemic functions. In order to affect lung immunity, microbial metabolites, immune signals, and even bacterial fragments travel from the gut through a two-way communication channel that is facilitated by this axis [6]. The gut microbiota influences how the lungs respond to viral invaders, improves mucosal defense, and controls inflammatory responses through this pathway.

Recent viral outbreaks, like COVID-19 and different influenza strains, have highlighted the stark differences in individual immune responses, making this connection urgently relevant. People with a well-balanced gut microbiome appear to recover more quickly and experience milder symptoms, according to mounting evidence [7]. Conversely, dysbiosis, or disturbances in the gut microbial ecology, can impair immune responses and result in poor viral clearance or hyperinflammation. This imbalance can be brought on by or made worse by a number of factors, including stress, the use of antibiotics, aging, and even viral infections themselves [8].

The microbiome is particularly promising because of its potential as a therapeutic target in addition to its function as an immune influencer. Enhancing host resistance and lessening the severity of respiratory infections may be achievable by restoring microbial diversity through diet, probiotics, or microbiome-based interventions. Therefore, investigating the gut-lung axis leads to new approaches to disease management and prevention in addition to expanding our knowledge of viral pathogenesis.

It is now clinically necessary to understand how microbial communities affect the progression and severity of respiratory illnesses, rather than merely being a scientific curiosity. The results of viral respiratory infections, including those brought on by new and reemerging pathogens, can differ greatly from person to person. Even in the absence of known risk factors, some patients experience mild symptoms and recover quickly, while others experience severe complications like acute respiratory distress syndrome (ARDS) or pneumonia. This variation raises the possibility of other, less evident factors at work. One such element is the stability and makeup of the gut microbiota, which has been demonstrated to affect both local immune responses in the lungs and systemic immunity. Gut microbes can influence how the body reacts to respiratory viruses by regulating inflammation, preserving the integrity of the epithelial barrier, and interacting with antiviral pathways [9]. In order to predict the severity of a disease, enhance patient outcomes, and direct individualized therapeutic approaches, it may be useful to profile and support the microbiome.

The Gut-Lung Axis: Concept and Mechanisms

The dynamic, two-way communication network between the lungs and the gut microbiota is known as the gut-lung axis. Despite their anatomical separation, these organs work together thanks to a complex interaction between immunological, metabolic, and neuroendocrine signals. This axis is based on the notion that respiratory health can be greatly impacted by changes in the gut microbiota and vice versa [10].

This cross-talk is mediated by several important pathways. Immune signalling is one of the most well-known; gut-resident microbes have the ability to alter immune cell activity and cytokine release, which in turn influences pulmonary and systemic immune responses. Additionally, the fermentation of dietary fibres produces microbial metabolites, especially short-chain fatty acids (SCFAs) like butyrate and propionate, which are essential for controlling inflammation and boosting the immune system of the lung. When dietary fibres are fermented, gut bacteria, primarily those belonging to the Firmicutes and Bacteroidetes phyla, produce important metabolites called short-chain fatty acids (SCFAs), which include acetate, propionate, and butyrate. By supplying energy to colon cells, improving mucus production, fortifying the gut barrier, and controlling local immune responses, these molecules actively promote gut health rather than merely being byproducts.

SCFAs affect distant organs like the brain and lungs after entering the bloodstream from the gut. By interacting with immune cells via receptors such as GPR41, GPR43, and GPR109, they improve antimicrobial defences, promote the development of regulatory T cells, and modulate inflammation. For example, butyrate has been demonstrated to support alveolar macrophages during respiratory infections, thereby reducing lung inflammation and enhancing the antiviral response [11].

$FoxP3^+$ regulatory T cells (Tregs), a subset of $CD4^+$ T cells that are essential for preserving immunological tolerance and avoiding excessive inflammation, are modulated in part by short-chain fatty acids (SCFAs), especially butyrate and propionate. By blocking histone deacetylases (HDACs), which modify gene expression and increase the expression of FoxP3, the master regulator of Treg development, SCFAs have a direct impact on the differentiation and function of these Tregs. By increasing the number of FoxP3 Tregs, SCFAs contribute to immune homeostasis and a decrease in inflammatory responses [12].

Controlling immune responses, avoiding autoimmunity, and reducing chronic inflammation all depend on these regulatory T cells. FoxP3 Tregs suppress overactive immune responses and limit the production of pro-inflammatory cytokines in the context of respiratory diseases, including viral infections, which can otherwise cause tissue damage and serious consequences. Therefore, one significant way that gut microbiota can affect lung immunity and the body's reaction to infection is through the promotion of Treg differentiation by SCFAs [13].

Besides affecting Tregs, SCFAs also affect the immune system as a whole by controlling the production of cytokines. SCFAs change the balance between pro-inflammatory and anti-inflammatory cytokines by interacting with immune cells like dendritic cells, macrophages, and T cells. This is important for getting rid of infections and preventing too much inflammation. For instance, butyrate lowers the levels of co-stimulatory molecules on dendritic cells, which makes it harder for them to activate T cells and encourages immune tolerance [14].

Also, SCFAs like acetate and propionate can change the levels of cytokines like IL-10 (which fights inflammation) and TNF-α (which causes inflammation). SCFAs help keep the cytokine environment just right so that the immune system doesn't get too active, like in cytokine storms, which are very bad for respiratory viral infections. Because SCFAs can change the immune system, they could be used as treatments to reduce inflammation and improve outcomes in diseases like COVID-19 and the flu [15].

Communication happens through neuronal and endocrine pathways in addition to immune and metabolic ones. The vagus nerve and

the hypothalamic-pituitary-adrenal (HPA) axis help send stress signals, hormones, and feedback from microbes between the gut and the lungs. This affects inflammation and how sensitive the lungs are to irritants.

Microbial components and metabolites can also be transported to the lungs by the systemic circulation and the mesenteric lymphatic system. They interact with immune cells after entering these pathways. This may aid in the removal of pathogens from the lungs or, in certain situations, result in detrimental inflammation. Understanding these processes enables us to comprehend how gut health can impact both your susceptibility to respiratory infections and your ability to recover from them.

Maintaining intestinal and systemic immune balance depends on the ongoing communication between the immune system and gut microbiota. Pathogen-associated molecular patterns (PAMPs) are conserved microbial molecules that are detected by pattern recognition receptors (PRRs), including Toll-like receptors (TLRs). For instance, TLR9 reacts to bacterial DNA, TLR4 detects lipopolysaccharides (LPS), and TLR2 recognizes peptidoglycans. Depending on variables like receptor location and co-receptor involvement, these receptors can either trigger defense mechanisms or encourage immune tolerance through signalling cascades [16].

Crucially, gut microbiota signals are not limited to the intestines. When immune cells-particularly dendritic cells—interact with gut microbes, they can move to lymph nodes and prime T cells, which subsequently express homing receptors that direct them to other organs, such as the lungs. It has been demonstrated that gut-derived chemicals like LPS affect lung immune cells, causing cytokine reactions like the production of IL-1β. The significance of TLR-mediated microbial sensing for preserving respiratory health has been highlighted by studies conducted in TLR-deficient mice, which have revealed decreased microbial diversity in the respiratory tract [17].

A specific class of gut microorganisms known as segmented filamentous bacteria (SFB) adheres to the intestinal lining and has a significant impact on immune development. They encourage the development of T helper 17 (Th17) cells, which generate the cytokine interleukin-17 (IL-17), which aids in pathogen defence by attracting neutrophils and encouraging the release of antimicrobial peptides. Excessive Th17 activity has been associated with autoimmune disorders, although this is advantageous in many situations. SFB colonization has been demonstrated to prevent lung infections in mice, but it can also exacerbate autoimmune lung inflammation in genetically vulnerable hosts [18].

These revelations emphasize how intricate the relationships between the immune system and microbiota are. Depending on the host's health and the makeup of the microbes, the gut microbiota can provide strong defence against infection but can also cause negative immune reactions [19].

The gut and lungs communicate through neuronal and endocrine signalling in addition to immune and metabolic pathways. Through the vagus nerve, the enteric nervous system—often referred to as the "second brain"—interacts with the central nervous system, enabling gut microbes to affect lung and brain function. Neuroactive substances like serotonin, dopamine, and gamma-aminobutyric acid (GABA) as well as some microbial metabolites have the ability to alter hormone release or activate neural pathways. These signals affect respiratory health by controlling stress responses, inflammation, and airway responsiveness. For instance, changes in gut microbiota can upset the balance of the vagus nerve, which mediates anti-inflammatory effects in the lungs. This could exacerbate respiratory infections or conditions like asthma [20].

Microbial products are transported from the gut to distant organs, such as the lungs, via the bloodstream and mesenteric lymphatic system. Small amounts of microbial metabolites, such as lipopolysaccharides and short-chain fatty acids, can safely enter the bloodstream and maintain immunological homeostasis when the gut barrier is intact. However, greater amounts of microbial components may move into the bloodstream during dysbiosis or increased gut permeability ("leaky gut"). These elements have the ability to trigger immunological reactions in distant organs like the lungs, which can affect inflammation and the vulnerability to respiratory infections. Dendritic cells in the mesenteric lymph nodes process microbial signals and aid in guiding systemic immune responses, making them crucial filters and communication centres [21].

Gut Microbiota's Role in Host Immunity

The development and regulation of the host's immune system are significantly influenced by the gut microbiota, a dynamic and highly diverse ecosystem of microorganisms that live in the gastrointestinal tract. These microbes actively contribute to the development of both innate and adaptive immunity, impacting immune-cell function and signaling pathways throughout the body, going far beyond simply assisting with digestion (Figure 1).

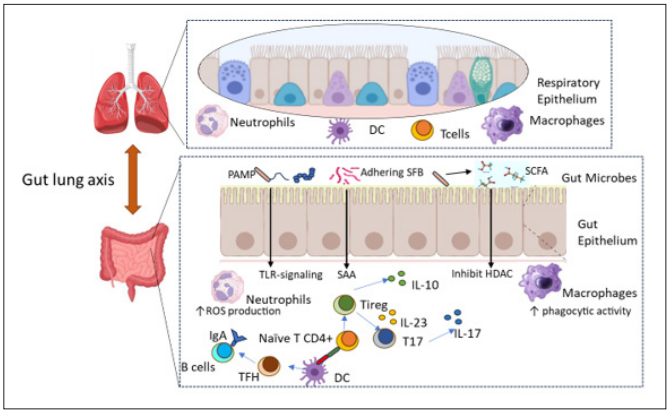


Figure 1: The gut-lung axis: The image illustrates the gut-lung axis, a bidirectional crosstalk between the gut and respiratory systems via microbial and immune pathways. Commensal microbiota activate macrophages, enhance ROS in neutrophils, and stimulate DCs and naïve T cells, promoting differentiation into Th1, Th2, Th17, and Tregs that release anti-inflammatory cytokines. SCFAs, PAMPs, TLRs, and HDAC inhibition modulate immunity, while SFB-induced SAA boosts anti-inflammatory responses. Tfh cells aid B cell activation and IgA secretion, supporting viral clearance through phagocytosis and ROS.

Shaping of Innate and Adaptive Immunity

The cross-talk between gut microbiota and the host immune system begins early in life and continues throughout. Commensal microbes help "educate" the immune system, particularly by promoting maturation of gut-associated lymphoid tissue (GALT). They contribute to the formation of physical and immunological barriers and support development of immune tolerance. Innate immunity benefits from microbial exposure by enhancing the

pattern-recognition capabilities of cells such as dendritic cells and macrophages, which rely on microbial-derived signals to distinguish harmful pathogens from harmless antigens.

Meanwhile, adaptive immunity is guided by microbial interactions that influence the balance and function of T and B lymphocytes. Certain bacterial strains drive immunoglobulin A (IgA) production—bolstering mucosal immunity—while others influence T-cell differentiation, critical for maintaining homeostasis and responding appropriately to infections [22,23].

Influence on Alveolar Macrophage Activation

The systemic effects of the gut microbiota are not confined to the gastrointestinal tract. Microbial metabolites such as short-chain fatty acids (SCFAs)—especially butyrate and acetate—enter the bloodstream and modulate immune responses in distal organs. One example is their influence on alveolar macrophages in the lungs: these first-line defenders exhibit enhanced phagocytic activity and anti-inflammatory cytokine production when conditioned by microbial metabolites. This gut-lung axis helps explain how gut dysbiosis can predispose individuals to respiratory infections and inflammation [24].

Influence on Neutrophil Function

Neutrophils, essential for rapid immune responses, are also shaped by gut microbial cues. Microbiota-derived signals regulate neutrophil development in the bone marrow and enhance their migration and reactive oxygen-species production in peripheral tissues. In germ-free or antibiotic-treated mice, neutrophil responses are blunted, underscoring the microbiota's critical role in maintaining their functional competence [25].

Influence on T-Cell Polarization (Th1, Th2, Th17, Treg)

Modulating T-cell polarization is a particularly complex part of the microbiota–immune interaction. Depending on the context and microbial makeup, gut microbes assist in guiding naïve CD4 T cells into different effector or regulatory subsets. Segmented filamentous bacteria and other pro-inflammatory commensals frequently trigger Th1 and Th17 responses, which are crucial for defense against intracellular pathogens and fungi. Microbial absence or changed microbial patterns can affect Th2 responses, which are generally associated with allergic reactions and helminth defense. Clostridium clusters IV and XIVa, as well as SCFA signaling through G-protein-coupled receptors like GPR43, greatly increase T-regulatory (Treg) cells, which are crucial for immune tolerance [26]. Immune homeostasis depends on the delicate balance between these T-cell subsets; disruption of this balance, frequently brought on by gut dysbiosis, can lead to autoimmunity or chronic inflammation.

Production of Anti-Inflammatory and Pro-Resolving Mediators

Gut microbes generate pro-resolving and anti-inflammatory mediators. Histone deacetylase activity is influenced by SCFAs such as propionate and butyrate, which upregulate anti-inflammatory genes. Microbial molecules have the ability to increase the cytokines transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), which reduce inflammation and restore tissue balance. Additionally, they support lipid mediators that actively promote inflammation resolution, such as protectins and resolvins [27].

Recent advances reveal multiple mechanisms through which gut microbes interact with the immune system. Microbial components—TLR and NLR ligands—and metabolites such as SCFAs and aryl-hydrocarbon-receptor ligands exert significant immunomodulatory effects. These signals influence local gut epithelial cells and immune populations and circulate systemically to affect distal organs [22].

In Peyer's patches, specialized T cells (FoxP3$^+$ Tregs and T-follicular-helper/ex-Th17 cells) support B-cell maturation and secretory IgA (sIgA) production, maintaining microbial balance [28]. Early-life colonization by segmented filamentous bacteria (SFB) primes immunity: SFB promote Th17 differentiation via the ILC3/IL-22/SAA1/2 axis, leading to IL-17A release for mucosal defense [29]. Innate lymphoid cells type 3 (ILC3s) add IL-22 to control microbes and fortify the barrier; loss of MHC II on ILC3s unleashes CD4$^+$ T-cell responses against commensals [30]. Early microbial exposure also limits pro-inflammatory invariant natural-killer-T (iNKT)-cell expansion through microbially derived sphingolipids [31].

Colonization with Bacteroides fragilis further balances Th1/Th2 responses via its polysaccharide A (PSA). Captured by dendritic cells in a TLR2-dependent manner and alongside TGF-β, PSA drives inducible Tregs that produce IL-10 to sustain tolerance; a shift toward IL-23, however, tips the scale to Th17 expansion and inflammation [32].

Dysbiosis and Pulmonary Infection Susceptibility

Disruptions to the body's microbial balance—referred to as dysbiosis—can significantly increase the risk of disease or worsen existing conditions. This occurs when beneficial microbes are depleted, allowing opportunistic pathogens, or pathobionts, to overgrow. The imbalance reduces microbial diversity and weakens protective functions, enabling potentially harmful organisms to flourish. While not a disease itself, dysbiosis contributes to various inflammatory and infectious conditions across different organ systems (Table 1).

Table 1: Role of the Gut Microbiome in Viral Respiratory Infections: Alterations, Mechanisms, Impact on Immunity and Key Findings

Viral Infection	Gut Microbiome Alterations	Mechanisms Involved	Impact on Host Immunity	Key Findings
Influenza A Virus (IAV)	Decreased diversity; depletion of Lactobacillus, Bifidobacterium	SCFA modulation of IFN signaling; gut-lung axis crosstalk	Reduced CD8$^+$ T cell responses; heightened inflammation	Antibiotic-induced dysbiosis worsens IAV severity (Ichinohe et al., 2011)
SARS-CoV-2 (COVID-19)	Enrichment of Coprobacillus, Clostridium ramosum; loss of F. prausnitzii	Barrier dysfunction; systemic inflammation; cytokine storm	Impaired antiviral response; elevated IL-6 and TNF-α	Gut dysbiosis correlates with COVID-19 severity (Zuo et al., 2020)

Human Rhinovirus (HRV)	Reduced SCFA-producing bacteria; microbial immaturity	SCFA-driven regulation of immune tolerance	Increased wheezing and asthma risk post-HRV	SCFA levels predict HRV severity in children (Roslund et al., 2020)
Parainfluenza Virus (PIV)	Understudied; likely decrease in beneficial anaerobes	TLR and IL-1 signaling; gut-epithelial immune modulation	Impaired mucosal defense, especially in children	Animal models suggest microbiome supports viral clearance (Garcia et al.,2020)
Enteroviruses (e.g., EV-D68)	Gut virome-microbiome imbalance; increased Enterobacteriaceae	Microbial regulation of intestinal immune cells; IFN responses	Enhanced neuroinvasion potential and respiratory exacerbation	Dysbiosis may promote systemic dissemination of enteroviruses (Rasquinha et al., 2022)
Adenovirus	Possible barrier dysfunction and gut inflammation	TLR signaling, IL-6 mediated immune activation	Systemic inflammation, GI symptoms during infection	Gut alterations may amplify adenoviral pathogenesis (Wasimuddin, 2019)

Several factors can induce dysbiosis, including antibiotic overuse, which indiscriminately eliminates commensal bacteria; poor dietary habits, particularly diets low in fiber and high in fat or sugar; chronic infections; and aging, which naturally alters the gut microbiome's composition and resilience over time [33]. Each of these factors disturbs microbial ecology, compromising immune function and disrupting homeostasis.

The impact of dysbiosis extends far beyond the gut. A major consequence is weakened mucosal immunity, especially in the lungs. Disruption of the gut microbiota can impair the gut–lung axis—a bidirectional communication network between these two organs. When this axis is compromised, the lungs become more susceptible to colonization by respiratory pathogens that would typically be kept in check by a well-regulated immune system [34]. Additionally, microbial translocation—the leakage of bacteria or their products across the intestinal barrier into the bloodstream—can lead to systemic inflammation, which exacerbates tissue damage and weakens host defenses, increasing vulnerability to pulmonary infections [35].

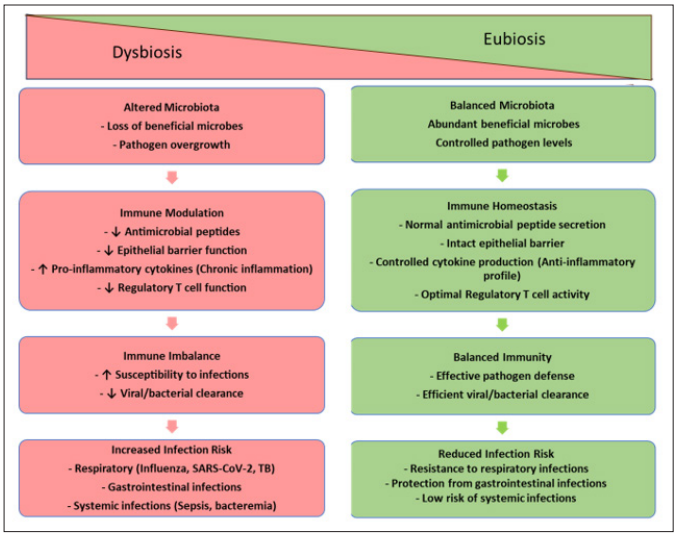
With the advancement of metaomics technologies such as 16S rRNA sequencing and shotgun metagenomics, scientists now have a deeper understanding of the microbiome's structure across different ages, sexes, diets, and geographic locations [36-38]. These tools have defined both the composition of a healthy microbiome and the ways in which it becomes disrupted in disease states [39,40].

It's interesting to note that metagenomic analyses have revealed complex microbial communities in previously believed sterile regions, like the lungs [41]. Traditional culture-based techniques have confirmed these results, confirming the validity of sequencing-based insights [41]. The significance of microbial communities in respiratory health has been further highlighted since 2010 when research revealed that people with respiratory conditions like cystic fibrosis, asthma, and chronic obstructive pulmonary disease (COPD) have unique lung microbiota profiles [42,44].

Furthermore, it has been shown that the gut-lung axis is a crucial pathway that affects pulmonary immunity [45,46]. The focus of this review is on respiratory infectious diseases, which include both acute and chronic conditions brought on by airborne pathogens. It investigates how commensal bacteria offer defense against these infections, especially in experimental models of dysbiosis. The significance of the gut-lung axis in coordinating immune responses during respiratory challenges is highlighted by these studies.

According to one theoretical framework, environmental stressors such as infections, allergens, dietary modifications, and genetic predispositions can encourage dysbiosis, which results in a decrease in microbial diversity and a disturbance of the immune system in the lungs or gut. In such contexts, pathobionts may dominate while beneficial microbes decline, impairing leukocyte activation and trafficking, and contributing to lung injury. Restoring microbial balance using probiotic interventions may help re-establish homeostasis by modulating immune responses and promoting the production of anti-inflammatory mediators such as short-chain fatty acids and cytokines at both local (lung) and systemic (gut) levels [45]. This intricate interplay represents the essence of the gut–lung axis, illustrating how distant mucosal sites communicate and co-regulate immune defense (Table 2).

Table 2: Differences Between Eubiosis and Dysbiosis of the Gut Microbiome in Viral Respiratory Infections



Clinical Evidence Linking Gut Microbiome to Pulmonary Infections

Influenza

Influenza virus infections primarily cause respiratory illness but can also lead to gastrointestinal complications, highlighting the virus's systemic impact [47]. Animal model studies demonstrate that severe influenza A virus (IAV) strains, such as H1N1 and H5N1, can significantly disrupt gut microbiota composition and increase susceptibility to secondary enteric infections [48].

This influenza-induced dysbiosis is thought to influence the host immune environment by promoting gut inflammation and weakening intestinal barrier function [49, 50].

Recent research shows that IAV infection reduces the production of short-chain fatty acids (SCFAs)—key microbial metabolites that maintain gut barrier integrity and regulate immune responses [48]. Reduced SCFA levels, especially acetate, correlate with increased vulnerability to bacterial lung infections like Streptococcus pneumoniae [51]. SCFAs also enhance host defense by stimulating antimicrobial peptide production, which helps control pathogenic bacterial overgrowth in the gut [52].

Evidence from both human and animal studies suggests that influenza impairs gut immune cell populations, including intraepithelial lymphocytes (IELs) in the small intestine, thereby weakening gut immunity [47]. Such immune dysregulation can permit microbial components like lipopolysaccharides (LPS) to translocate into the bloodstream, triggering systemic inflammation that worsens lung injury and viral replication [53]. For instance, H9N2 avian influenza virus infection disrupts gut microbial balance, induces pro-inflammatory cytokine release, increases harmful bacteria such as Escherichia coli, and decreases beneficial genera like Lactobacillus [54, 55].

SARS-CoV-2

SARS-CoV-2, the virus causing COVID-19, interacts significantly with the gut microbiota. It enters cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, highly expressed not only in lungs but also along the gastrointestinal tract [56]. The co-expression of ACE2 and the protease TMPRSS2 in the small intestine facilitates gastrointestinal infection by SARS-CoV-2 [57, 58].

Upon infection, viral RNA is detected by innate immune sensors such as TLR7/8 and RIG-I, triggering an antiviral response characterized by type I and III interferons, chemokines, and pro-inflammatory cytokines [59]. While essential for viral control, excessive immune activation can cause cytokine storms in severe COVID-19, contributing to acute respiratory distress syndrome (ARDS) [60].

Emerging evidence implicates gut dysbiosis in COVID-19 severity [61,62]. SARS-CoV-2 infection associates with reductions in beneficial gut microbes like Faecalibacterium prausnitzii and Bifidobacterium, especially in the large intestine [62]. This microbial imbalance disrupts immune regulation, heightens pro-inflammatory responses, and exacerbates tissue damage [63]. Animal studies using transgenic mice expressing human ACE2 confirm that SARS-CoV-2 alters gut microbiota composition dose-dependently after intranasal inoculation [64].

Infectious viral particles have been detected in rectal mucosa, suggesting the gastrointestinal tract serves as a secondary replication site for SARS-CoV-2 [65, 66]. These findings underscore the importance of further research on the gut–lung axis in COVID-19 to understand disease progression and long-term consequences such as long COVID.

Rhinovirus

Rhinoviruses are the leading cause of the common cold, yet their impact extends beyond mild upper respiratory tract infections, particularly in vulnerable individuals such as children with asthma or adults with chronic lung conditions. Recent research emphasizes the role of the gut microbiome in modulating immune responses to respiratory infections like rhinovirus through the gut–lung axis—a bidirectional pathway that connects the gastrointestinal and respiratory systems via immune and microbial metabolites. A balanced gut microbiota enhances mucosal immunity, reduces airway inflammation, and promotes the production of regulatory cytokines and short-chain fatty acids (SCFAs), which contribute to antiviral defense [67,68]. These systems have been demonstrated to be compromised by dysbiosis, or microbial imbalance, which raises the risk and intensity of rhinovirus infections [69,70]. Furthermore, rhinovirus outcomes can be influenced by the nasopharyngeal microbiome; specific bacterial profiles have been linked to increased inflammation or longer illness duration [71,72]. Research suggests that probiotic and prebiotic treatments could help regulate these immune responses mediated by the microbiota, providing promising supplemental strategies to avoid or lessen respiratory viral infections [73–76]. Maintaining microbial homeostasis may be crucial for efficient immune responses to rhinovirus and other respiratory viruses as our knowledge of the microbiome's systemic effects expands.

Adenoviruses

In the context of host–microbiome interactions, adenoviruses—which can cause a wide range of illnesses from mild respiratory infections to gastroenteritis and conjunctivitis—are being studied more and more. Adenoviral infections usually resolve on their own, but in children and immunocompromised people, they can worsen. Recent research has demonstrated how the gut microbiota affects the pathogenesis of adenoviruses, highlighting the gut-lung axis's immune-regulatory function. Changes in the composition of gut microbes, especially an overabundance of opportunistic pathogens and a loss of beneficial commensals, can weaken mucosal immunity, increase susceptibility to viruses, and prolong illness [77,78]. For instance, research has demonstrated that adenovirus infection may cause microbial dysbiosis, which is linked to inflammation and weakened gut barrier integrity. This condition is typified by a decrease in Bacteroides and an increase in bacteria such as Neisseria [79,80].

Furthermore, it has been shown that microbial metabolites, like short-chain fatty acids (SCFAs), have important immunomodulatory effects that affect both systemic and local immune responses. Interestingly, SCFAs may control latent adenovirus reactivation in lymphoid tissues such as the tonsils, indicating that metabolic cues derived from the gut may influence viral persistence and recurrence [81,82]. These relationships show a complicated feedback loop in which adenoviruses alter the microbiota, which in turn influences immune responses and viral replication. Probiotics and dietary changes that promote a balanced microbiome may improve host defences, lower systemic inflammation, and lessen the severity of adenoviral disease [83-86]. Novel microbiome-based therapeutic approaches against adenoviral and other viral infections may be possible with further investigation into this interaction.

Human metapneumovirus

Human metapneumovirus (hMPV) is a significant respiratory pathogen, particularly affecting infants, the elderly, and immunocompromised individuals. While its primary impact is on the respiratory tract—causing symptoms such as bronchiolitis and pneumonia—emerging research suggests that hMPV may also interact with the gut microbiome through the gut–lung axis [87,88]. This axis enables bidirectional communication between

the respiratory and gastrointestinal systems, mediated by immune signalling, microbial metabolites, and neuroendocrine pathways. Though hMPV does not typically cause direct gastrointestinal infection, it can influence gut immunity by altering systemic cytokine profiles, mucosal signalling, and immune cell recruitment [89,90]. Interestingly, studies in murine models have shown that respiratory hMPV infection can affect gut-associated lymphoid tissues, resulting in changes in secretory IgA levels and antimicrobial peptide expression, even in the absence of detectable viral RNA in the intestines [91,92].

Moreover, respiratory viral infections often lead to changes in diet, fever, and antibiotic use, all of which can further disturb the gut microbial balance [93]. Infections such as hMPV can contribute to gut dysbiosis—an imbalance in microbial populations characterized by decreased beneficial commensals like Bifidobacteria and Lactobacillus, and an overgrowth of pro-inflammatory species [94,95]. These changes may result in less butyrate and other short-chain fatty acids (SCFAs), which are essential for immune response regulation and epithelial integrity [96]. The host's capacity to reduce inflammation and manage secondary infections may be jeopardized by this imbalance. Furthermore, by affecting the growth and function of T cells and dendritic cells, which are essential for antiviral defines, changed microbiota may modify the immune response to hMPV [97,98]. The use of probiotics, prebiotics, and postbiotics to improve mucosal immunity and restore microbial balance during respiratory viral infections, including those brought on by hMPV, is becoming more and more popular [99-101]. While more clinical research is needed, these findings suggest that targeting the gut microbiota may offer a novel supportive strategy to mitigate the severity and duration of hMPV-related illness [102,103].

Human Parainfluenza Viruses

Human parainfluenza viruses (HPIVs) are important causes of respiratory infections, especially in young children, older adults, and those with weakened immune systems. Although these viruses primarily infect the respiratory tract, recent studies suggest that HPIV infections also influence the gut microbiome through the gut–lung axis, a complex communication network linking the respiratory and gastrointestinal systems via immune signalling, microbial metabolites, and neural pathways [104]. Respiratory viral infections such as those caused by HPIV can disrupt this axis, leading to imbalances in gut microbial communities. This disruption results from systemic inflammation, changes in feeding behaviour during illness, and inflammatory cytokine release, which together can impair gut barrier function and alter microbial diversity [105,106]. Such gut dysbiosis may contribute to increased inflammation, worsening disease outcomes, and heightened risk of secondary infections.

Additionally, the gut microbiota plays a crucial role in regulating immune responses during respiratory infections. Beneficial gut bacteria produce short-chain fatty acids (SCFAs) like butyrate and acetate, which exert anti-inflammatory effects and support the integrity of the gut lining [107,108]. During HPIV infections, reductions in SCFA-producing bacteria have been observed, potentially weakening host defences and prolonging illness [109]. Probiotic treatments have demonstrated potential in restoring gut microbial balance and enhancing antiviral immunity by stimulating the production of type I interferons and other immune mediators [110,111]. This interplay highlights the therapeutic promise of microbiota-targeted approaches to reduce the severity and duration of HPIV infections. Understanding this gut–lung crosstalk is vital for developing comprehensive strategies to manage respiratory viral diseases and improve patient outcomes [112-114].

Enteroviruses

Enteroviruses are a diverse group of RNA viruses known primarily for causing diseases ranging from mild respiratory illnesses to severe systemic infections. Although their impact on the respiratory tract is well-recognized, recent evidence highlights the important role of the gut microbiome in shaping the immune response to enteroviral infections [114]. Enteroviruses often enter the host via the oral-fecal route, establishing infection initially in the gastrointestinal tract, where they interact closely with the resident gut microbiota. This interaction can influence viral replication and pathogenesis, as commensal microbes either enhance or inhibit viral infectivity through modulation of immune responses and production of metabolites [115,116]. Disruption of gut microbial communities—either by viral infection or antibiotic use—can weaken mucosal immunity and increase susceptibility to enterovirus-associated respiratory diseases.

Moreover, the gut microbiome exerts systemic effects through the production of bioactive molecules such as short-chain fatty acids (SCFAs) that regulate inflammation and antiviral defense mechanisms [117]. For instance, SCFAs have been shown to strengthen epithelial barrier functions and enhance the activity of immune cells critical for controlling viral infections in the lungs [118]. Probiotic interventions targeting the gut microbiota have demonstrated promising results in reducing enterovirus load and alleviating respiratory symptoms, suggesting a novel therapeutic avenue [119,120]. Understanding the complex crosstalk between enteroviruses, the gut microbiota, and the host immune system offers exciting potential to develop microbiome-based strategies that improve outcomes in respiratory infections caused by enteroviruses.

Potential Interventions

By improving the gut microbiome and its systemic effects, probiotics, prebiotics, and synbiotics present promising, non-invasive ways to boost immunity and lessen the burden of viral respiratory infections. By increasing secretory IgA, encouraging regulatory T cells, and reducing pro-inflammatory cytokines, probiotics like Lactobacillus and Bifidobacterium species help restore microbial diversity, fortify the gut barrier, and fine-tune immune responses [121,122]. By specifically feeding beneficial gut microbes, prebiotics such as inulin and fructooligosaccharides (FOS) produce short-chain fatty acids (SCFAs) like butyrate, which support gut integrity and regulate systemic and local immunity [123]. Through the gut-lung axis, a channel of communication between the respiratory and gastrointestinal systems, these modifications may indirectly promote lung health [124]. By enhancing microbial survival and activity in the gut, synbiotics—which combine probiotics and prebiotics—further amplify these benefits and fortify the body's antiviral defenses [125]. When combined, these treatments may be useful adjuncts in lowering the incidence and severity of viral respiratory infections in addition to promoting the maintenance of a healthy gut ecology (Figure 2).

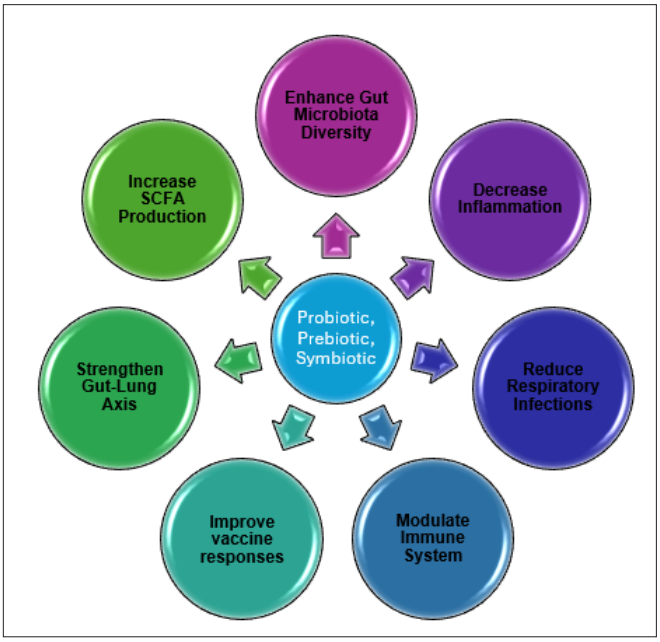


Figure 2: Benefits of Probiotics, Prebiotics and Symbiotics in Viral Respiratory Infection Immunity

Current Gaps and Future Directions

Despite increasing recognition of the gut–lung axis in respiratory health, several critical gaps remain. Firstly, there is a pressing need for large-scale, longitudinal human studies to elucidate how gut microbiota dynamics influence the onset, progression, and resolution of pulmonary infections over time. Most existing evidence derives from cross-sectional or animal studies, limiting direct clinical translation [121].

Secondly, mechanistic insights into the roles of specific microbial taxa and their metabolites—such as short-chain fatty acids (SCFAs), bile acids, and microbial peptides—are still insufficient. Clarifying these pathways is vital to move beyond correlative associations and establish causal links [122].

Thirdly, comprehensive integration of multi-omics data—including metagenomics, metabolomics, transcriptomics, and proteomics—is necessary to achieve a systems-level understanding of host–microbe interactions. However, methodological and computational challenges continue to impede such integrative analyses [123].

Finally, clinical application of microbiome-targeted therapies remains limited by the absence of standardized protocols for interventions like probiotics, prebiotics, dietary modifications, and fecal microbiota transplantation. Well-designed clinical trials and consensus guidelines are essential to ensure reproducibility and effective implementation in respiratory care settings [124].

Conclusion

The gut microbiome is a central regulator of pulmonary immune responses and significantly influences the clinical trajectory of respiratory infections. Alterations in gut microbial communities can modulate systemic inflammation, immune cell function, and susceptibility to chronic and infectious lung diseases such as COPD, asthma, and viral pneumonias.

Leveraging the gut–lung axis holds great promise for developing innovative strategies in disease prevention, prognosis, and treatment. Realizing this potential will require collaborative, interdisciplinary research bridging microbiology, immunology, clinical medicine, and computational biology. As technological advances continue and personalized medicine gains traction, microbiome-targeted interventions are poised to become integral components in the management of respiratory diseases [125-130].

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