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# Role of the Airway Microbiome in Respiratory Infections and Asthma in Children

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The respiratory tract can be colonized with bacterial, fungal, and viral microorganisms, and the whole of the microbiota, their genes, and the surrounding environment is collectively termed the microbiome. Increasing evidence indicates that the respiratory microbiome has an important role in respiratory health and disease and is both impacted by and potentially contributes to the severity of symptomatic respiratory viral infections and asthma in children. A deeper understanding of the complex interactions between bacteria, viruses, and the host will provide further comprehension into the drivers and mechanisms of respiratory health and disease and will impart opportunities for clinical therapies.

**Keywords:** respiratory infections, asthma, microbiome, microbiota, respiratory syncytial virus, rhinovirus

## Introduction

The human microbiome refers to the 10–100 trillion symbiotic microbial cells, the genes harbored within these microorganisms, and the surrounding environmental conditions within the host.[1–3] Recent research has revealed that the human respiratory tract is composed of complex microbial communities that are diverse, heterogeneous, and dynamic in nature.[4–6] Modern molecular techniques have even shown that the lung, long thought to be sterile, is colonized by a myriad of microorganisms. Indeed, the entire respiratory tract from the lung to the nasopharyngeal and nasal cavities is colonized with bacterial, fungal, and viral microorganisms.[7–10] The totality of these microbes and their interactions with each other and the environment make up the respiratory microbiome. Importantly, there is increasing evidence that respiratory microbiota play a critical role in health and disease, particularly in children.[11–14]

Although our understanding of the complex interactions between the microorganisms, host cells, and host immune system are still in their infancy, recent studies are beginning to provide insight into how these factors control respiratory development, homeostasis, and disease. As we continue to understand the role and underlying mechanisms of the microbiome in respiratory disease, we may be able to exploit it as a biomarker of disease risk or treatment effectiveness. Furthermore, controlling and altering the microbiome may provide an opportunity for therapeutic interventions to reduce the severity of respiratory infections, prevent the development of wheezing and asthma, reduce asthma exacerbations, and improve vaccine efficacy. In this review, we discuss the factors surrounding the development of the pediatric respiratory tract microbiota, factors that influence the composition of the microbiota, and our current knowledge on how these factors contribute to the severity of viral infections and respiratory disease. Although fungal and viral colonization of the respiratory tract can occur, studies of the role of the mycobiome and commensal virome in pediatric respiratory health and disease are limited, and consequently in this review we will focus on the bacterial element of the microbiome.[8–10]

### *Development of the pediatric respiratory tract microbiota*

The pediatric respiratory tract microbiome is extremely heterogeneous and dynamic.[5,14] At birth, the respiratory tract is exposed to and quickly colonized by microbial organisms. During the first months of life, the respiratory microbiome composition is in flux and is affected by numerous entities, including feeding, environmental exposures, season, use of antibiotics, and infections.[14–16] Microbial colonization of the upper respiratory tract has been shown to

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occur within 24 h after birth and is initially characterized by a dominance of *Streptococcus viridans* and *Gemella* spp., bacteria, which are commonly found in other areas of the body.[14,17] However, during the first week of life, the respiratory tract begins to develop a niche-specific community pattern, where *Staphylococcus aureus* and *Corynebacterium* replace the originally colonizing bacteria and become the dominant microorganisms.[17] The most dramatic changes in the respiratory microbiome occur during the first 2 months.[14,17] For the next 6 months, the respiratory microbiome continues to mature, the relative abundance of *S. aureus* declines, and an increase in *Moraxella, Streptococcus, Haemophilus, Dolosigranulum, Alloiococcus,* and *Prevotella* has been observed.[12–14,17]

Limited evidence suggests that the mode of delivery may be the first major influence on the composition of the respiratory microbiome.[14,18–20] In 1 study, infants born by Caesarian section showed a delay in overall development of respiratory microbiome profiles as compared with those born vaginally.[21] However, by 6 months of age, there were no significant differences between the 2 groups.[21] Specifically, a reduction in colonization of health-associated bacteria, *Corynebacterium* and *Dolosigranulum,* was found during the first few weeks of life.[21] However, the sample size in this study was relatively small ($n = 102$ children with $n = 761$ samples), and the authors even suggested that the differences were subtle but significant.[21] Yet, mode of delivery has been found to impact other microbiome niches such as the gut and skin, and, thus, it is reasonable that it could impact the respiratory tract as well.[15,22–24] Further studies on the role of mode of child delivery on the respiratory microbiome are needed to expand our understanding of this relationship.

Although the gastrointestinal microbiome incurs obvious changes influenced by our diet, the mechanisms whereby alterations in the respiratory microbiome might occur from diet are more obscure; nonetheless, evidence suggests that infant feeding may also impact the respiratory microbiome.[18,25] In 1 study, breastfed children have shown increased *Dolosigranulum* and *Corynebacterium* in their nasopharyngeal microbiome and decreased abundance of *Staphylococcus*, *Prevotella,* and *Veillonella* as compared with formula-fed infants at 6 weeks of age.[16] As with the mode of delivery studies, at 6 months of age, there was no difference in the nasopharyngeal microbiome of breastfed and formula-fed children, suggesting that differences may be short-lived.[16] More research is needed to determine the duration and effects of the changes caused by diet on the developing airway microbiome.

There are numerous other exposures and variables that might induce perturbations of the airway microbiome. Seasonal differences in pediatric respiratory microbiome communities have been noted, with distinct profiles that occur in fall/winter as compared with spring months.[13,26] Although it is unclear what causes these seasonal differences, the authors controlled for respiratory viral infection and speculated that the differences may be due to temperature, humidity, and/or allergen exposures.[11] Other influences on the respiratory microbiome include antibiotic use, however, whether or not antibiotics have a negative or long-term impact is unclear and further clarification is required.[13,27,28] The possibility of other influences exists, which will also require additional studies.

### *Implications of viral infection on the respiratory bacterial microbiota in children*

When considering the airway microbiome, it is impossible to exclude the impact of respiratory infections, especially viral infections, on the composition of the bacteria present. All children are exposed to and become infected with a myriad of respiratory pathogens during their first years of life, and a complex relationship between microbial communities of commensal and potentially pathogenic bacteria and respiratory viruses exists.[29–31] However, it is difficult to delineate if respiratory bacterial composition creates an environment that is more suitable for viral infection and thus increases the susceptibility to, duration of, or severity of an acute respiratory viral infection, or, if, conversely, viral infections lead to changes in microbial composition that subsequently cause an increase in pathogenic bacterial and/or fungal infections. Indeed, there is evidence that both situations may occur.[13,29,32–35] Studies suggest that a microbiome composed of a specific type of bacteria, often referred to as opportunistic or potentially pathogenic bacteria, may lead to increased susceptibility to and severity of respiratory viral infections.[13,29,35] Alternatively, other studies have found that respiratory viral infections are associated with and can lead to changes in the microbiome communities that may persist and predispose for additional infections and long-term airway diseases, such as asthma and wheezing.[32–34] Most studies that have investigated respiratory viral infections and the microbiome have focused on 2 of the most important pediatric pathogens: respiratory syncytial virus (RSV) and human rhinovirus (RV).[13,29,32–34]

In one of the most influential respiratory microbiome and infection studies, researchers from Australia found that colonization with *Streptococcus*, *Moraxella,* and *Haemophilus* were associated with acute respiratory infections (ARI) and increased risk of progression to lower respiratory tract infection.[13] In this study, *Haemophilus* was most commonly associated with ARI and was rarely seen in healthy infants <12 months of age, and a combination of RSV and *Moraxella* was associated with an increased risk of fever and more severe clinical symptoms.[13] A high abundance of *Corynebacterium, Staphylococcus*, and *Alloiococcus* was uncommon during ARI, and odds ratio analysis showed that the presence of these bacteria was actually protective against ARI.[13] Recently, Teo et al. have expounded upon the original studies to show that the nasopharyngeal microbiome of children who wheeze changes to a small range of pathogenic bacteria (*Moraxella*, *Streptococcus*, and *Haemophilus*) before detection of any viral pathogens or even symptoms.[36] The combination of allergic sensitization and colonization with *Moraxella*, *Streptococccus*, and *Haemophilus* was also associated with persistent wheeze in school-age children.[36] Other studies of RSV infection and respiratory microbiome have found similar patterns of bacterial communities during ARI.[32] In 1 study, infants with an acute RSV infection had a higher relative abundance of *Streptococcus*, *Moraxella*, and *Haemophilus* in their nasopharyngeal microbiome as compared with healthy infants.[32] However, in a separate study, RSV infection was only noted to be associated with a high abundance of *Streptococcus*, and in contrast, a low abundance of *Moraxella* and *Haemophilus* was reported.[30] In a study of

1,005 infants under the age of 1 by Hasegawa et al., 4 major nasopharyngeal microbiota profiles associated with severity of bronchiolitis were identified.[37] Three of the 4 profiles were dominated by *Haemophilis, Moraxella, or Streptococcus*, whereas the fourth profile had the highest bacterial richness and alpha diversity index.[37] In another study, investigating the functional interactions of viral infections and microbial communities found that distinct bacterially derived metabolic pathways were only seen in RSV infection in combination with *Streptococcus* and *Moraxella* and not *Haemophilus*, suggesting that only these viral–bacterial combinations might contribute to pathogenicity.[38] Other studies have shown that upper respiratory tract colonization with *Streptococcus, Haemophilus,* and/or *Staphylococcus* during RSV infection increases the risk of hospitalization independent of age.[29–31]

In addition to RSV, there have been multiple studies that have investigated RV infections and the respiratory microbiome. In a prospective longitudinal cohort study of the first year of life, RV was associated with higher bacterial density and lower alpha diversity, and these changes occurred only during symptomatic RV infections.[33] Similar to the aforementioned Australia and RSV studies, the authors found that in symptomatic RV infections, there was a higher abundance of *Moraxella* and lower abundance of *Staphylococcus*.[33] Importantly in this study, specific microbiome composition was not a risk factor for RV infections or associated with severity of infection, but changes seen during RV infection persisted for up to 3 weeks after infection, suggesting that it was the influence of the virus on the microbiome and not vice versa.[33] In a separate longitudinal cohort study, symptomatic RV infection was also found to be associated with a higher abundance of *Moraxella*, but asymptomatic RV infection was associated with increased abundance of *Dolosigranulum* and *Corynebacterium*.[34] In functional experiments, findings suggested that RSV and RV utilize different metabolic pathways, and in contrast to RSV infection described earlier, distinct bacterially derived metabolic pathways were only seen when RV and *Haemophilus* were together, suggesting that the combination of this virus and bacteria, but not other combinations might lead to increased pathogenicity.[38]

Differential findings in these studies may be due to geographical or population differences, yearly or seasonal variation in strains of RV, and/or laboratory and bioinformatic discrepancies. Nonetheless, despite the variability in the RSV and RV studies, the majority of analyses consistently find a positive association between *Streptococcus, Moraxella,* and *Haemophilus*, and ARI and a negative or protective association with *Corynebacterium* and *Staphylococcus.* Importantly, less is known about other common pediatric respiratory viruses, human metapneumovirus, the parainfluenza viruses, the adenoviruses, and the influenza viruses, and their association with the respiratory microbiome. Additional research is needed to elucidate the relationships between these viruses and the respiratory microbiome to determine if there is a similar association with distinct microbiome communities and infections with these pathogens.

There is a well-established link between severe acute respiratory virus infection and the development or exacerbation of asthma later in life, particularly with regard to RSV and RV infections.[39–42] Children who suffer a severe RSV infection requiring hospitalization are significantly more likely to develop asthma.[39,40] In addition, between 60% and 80% of children with asthma exacerbations seen in the emergency department will have a concomitant RV infection.[41,42] A growing body of evidence indicates that the respiratory microbiome is an important contributor to this relationship as well. Reported in 2007, data obtained from cultured aspirates from the hypopharyngeal region of 321 neonates in the Copenhagen Prospective Studies on Asthma in Childhood cohort, a prospective birth cohort study, revealed that colonization with *Streptococcus, Moraxella,* and/or *Haemophilus* at 4 weeks of age was a significant risk factor for incidence of asthma at age 3.[11] Similarly, a separate study analyzing nasopharyngeal samples from 234 children during their first year of life reported early asymptomatic colonization with *Streptococcus*, which occurred in 14% of children, was a strong asthma predictor at age 5.[13] Another study using anterior nasal swabs to investigate the role of the microbiome in the development of rhinitis and rhinitis with wheeze ($n = 122$) found lower total bacterial diversity and lower abundance of *Corynebacterium* and *Staphylococcus* in these children.[12]

These microbiome characteristics may not be unique to children. Studies by Hilty et al., analyzing nasal, oropharynx, and left upper lobe samples revealed *Haemophilus* species was more often present in the upper and lower airways of adults with asthma or chronic obstructive pulmonary disease, as well as asthmatic children.[4] A recent study using nasal swabs also found that healthy controls, subjects with nonexacerbated asthma, and subjects with exacerbated asthma had distinct microbiome compositions.[43] Furthermore, there was a trend toward lower bacterial diversity in asthmatics and more so in asthmatics suffering exacerbations.[43] Other studies have focused on the role of the microbiome alone or in combination with a viral infection on asthma exacerbations. Multiple studies examining nasal samples and secretions have reported that RV-induced asthma exacerbations are associated with the presence of abundant levels of *Streptococcus* and *Moraxella*.[34,44]

Although all children are exposed to and infected with RSV and RV in the first few years of life, only a subset develops severe disease and require clinical management, including intubation, mechanical ventilation, or the use of oxygen. Furthermore, although severe viral infections early in life are highly correlated with development of asthma and wheezing, again only a subset of children with severe viral infections go on to develop asthma. Interestingly, the microbial profiles seen during acute RSV and RV infections are similar to those that are reported in children with an increased risk of childhood asthma and during asthma exacerbations.[13,32,34] Consequently, it is convenient to speculate that the differential outcomes in children may be partially explained by either the microbial communities present during acute infection or persistent alterations in the respiratory microbiome caused by the viral infections. More research is needed to fully establish the mechanisms of this relationship. In particular, more longitudinal and case-control studies are needed that examine the microbiome in healthy children and in children with an ARI that do not require medical interventions.

Taken together, recent studies have revealed that the respiratory microbiome is clearly heterogeneous, dynamic, and an important aspect of respiratory health and disease.

Early evidence suggests that in healthy children the respiratory microbiome is more likely to be dominantly colonized by *Corynebacterium, Staphylococcus, Dolosigranulum,* and/or *Alloiococcus*; conversely, a respiratory microbiome that is dominated by *Streptococcus*, *Moraxella,* or *Haemophilus* is more likely to be associated with ARI, wheezing, and development and exacerbations of asthma. However, additional studies are needed to confirm these findings, clarify discrepancies, explain outliers, and reveal the mechanisms behind these relationships. Nonetheless, it is likely that in addition to other factors, including genetics and environmental exposures, the microbiome does contribute both in a protective and negative manner to the severity of ARI and asthma. A deeper understanding of these complex bacterial, viral, and host interactions will undoubtedly provide further insight into the drivers and mechanisms of respiratory health and disease, and will provide opportunities for intervention. In the near future, the respiratory microbiome will be an important source to inform clinical management strategies. For example, future clinical tests to evaluate respiratory health and disease in children should assess the microbiome and use the information to help evaluate disease risk. Development of new therapies should also take into account the potential impact on the respiratory microbiome, and additional research is needed to assess the efficacy of respiratory microbiome modulation as a possible therapeutic intervention.

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## Authors' Contributions

All the authors listed have made substantial, direct, and intellectual contributions to the work and approved it for publication.

## Author Disclosure Statement

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