Long-Term Respiratory Consequences of Early-Life Respiratory Viral Infections: A Pragmatic Approach to Fundamental Questions

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Learning objectives:

1. To describe the evidence for causal associations between early-life respiratory infections and later respiratory morbidity, including asthma.

2. To explain the conceptual difference in establishing causal evidence versus a pragmatic approach to the long-term effects of infant respiratory viral infection on subsequent childhood wheeze and asthma.

3. To discuss remaining gaps in our knowledge of the relationship between early-life respiratory viral illnesses and later asthma development.

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Early-life viral infection can have profound effects on the developing lung and immune systems, both important in asthma development. For decades, research has aimed to establish whether there is a causal link between these viral infections as an exposure and asthma later in childhood. Establishing causality will remain important, but new insights regarding early-life viral infection as an exposure, the recognition of asthma as a heterogeneous outcome, and the shared genetic susceptibility to both suggest a refocus from answering the theoretical question of causality toward additional pragmatic approaches focusing on improving patient outcomes across the spectrum of respiratory disease. This *Clinical Commentary* reviews the evidence on the consequences of early-life viral infection and aims to look beyond the question of causality, suggesting a research agenda specifically aimed at what matters for human development, and for the quality of life of current and future patients with wheezing disorders. **(J Allergy Clin Immunol Pract 2022;10:664-70)**

Key words: *Respiratory infection; Respiratory syncytial virus; Human rhinovirus; Asthma; Pragmatic approach*

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INTRODUCTION

The first years of human life are marked by peak incidence rates of respiratory infections,[1] while encompassing a crucial phase in lung

Abbreviations used
HRV- human rhinovirus
RSV- respiratory syncytial virus

and immune system development. Respiratory syncytial virus (RSV) and human rhinovirus (HRV) are the most common etiologies of acute respiratory infection in infants and preschool children.[2] Simultaneously, the majority of postnatal alveolarization and establishment of microbiomes in the airways and the gut occur during these years. For decades, scientists have analyzed whether interplay between respiratory infections and pulmonary development is essential to the development of the most prominent pulmonary disease phenotypes in childhood and adolescence: wheezing and asthma. Fundamental questions are "do respiratory infections in infancy and early childhood cause asthma?" and "could we prevent asthma by preventing early-life respiratory infections?"

Although answers to these questions are irrefutably important—and not only to purist scientists—are these the questions that also matter most to our patients? This *Clinical Commentary* aimed to review the evidence and the theoretical question of causality and put it into context for what matters for human development and the quality of life of current and future patients with wheezing disorders. This pragmatic approach focuses on to what extent the relation between respiratory infections and chronic respiratory morbidity is important for the goals of direct improvement of patient outcomes and possible long-term protection that might be afforded by preventive health interventions, including vaccines. For example, the question of "could we prevent asthma by preventing early-life respiratory infections?" may be rephrased as "do we have candidate interventions that modify early-life respiratory infections that are likely to have longer term significant benefit on later respiratory morbidity?" To complete the pragmatic approach, we highlight research gaps and opportunities particularly relevant to help achieve patient-oriented and population health goals.

PART 1. AIRWAY AND IMMUNE ALTERATIONS BY EARLY-LIFE RESPIRATORY VIRAL INFECTIONS

Structural lung damage

Early-life viral respiratory infection is universal and can result in clinical features ranging from asymptomatic episodes to severe pneumonia or bronchiolitis, involving sloughing of epithelial cells, heavy mucus secretion, airway obstruction, atelectasis, and air trapping.[2] RSV in particular disrupts distal airway epithelium, resulting in occupied bronchiolar lumen.[3] Resulting symptoms are generally self-limiting, but accumulated evidence indicates the possibility of long-term pulmonary dysfunction dependent on viral etiology and initial disease severity,[4] resulting in an obstructive or "small airway" disease.[5] Animal studies have demonstrated that a respiratory viral infection can lead to sustained histologic changes, mucous cell metaplasia, and airway hyperreactivity,[6-9] but it is unclear whether similar persisting histological sequelae are present in humans, and whether lower respiratory symptoms with viral illness are necessary, or infection alone is sufficient.

Airway epithelial reprogramming

Early-life viral respiratory infection can severely affect the human airway epithelium,[10] because the virus uses airway epithelial cells for replication. Programmed cell death through apoptosis or necroptosis is used to remove virally infected cells, limiting viral spread.[11] Recent evidence indicates that especially necroptosis in the context of RSV (and its murine equivalent) may negatively impact immunopathology and contribute to development of wheezing disease: inhibition of the necroptosis protected against experimental asthma in a preclinical mouse model.[12] The same researchers found that specifically RSV bronchiolitis is characterized by necroptosis-associated alarmin release. Both RSV and HRV, using the CX3CR1 and cadherin-related family member 3 receptors, respectively, bind to the epithelium and can disturb its function in ways associated with enhanced asthma disease and type 2 immune response.[13] Together, these findings suggest that interfering with this airway epithelial cell targeting and necroptosis may lead to preventive strategies for asthma.[11] However, given the marked differences in epithelial infectivity and injury between RSV and HRV,[14] such strategies will likely be pathogen-specific.

Altered immune system development

In respiratory viral infection, the same airway epithelium initiates the antiviral immune response and recruitment of effector cells after recognition via Toll-like receptors. Aside from the short-term inflammatory process that can lead to acute respiratory symptoms, there is evidence for delayed damage as a result of immune system activation. RSV infection is associated with a skew of the immune system toward the type 2 phenotype and IL-17A production, mechanisms associated with (allergic) asthma.[15-20] Once type 2 cells are recruited, a positive feedback loop with release of IL-4, IL-13, chemoattraction of eosinophils, hyperresponsiveness, and mucus production results in exacerbated immune-inflammatory responses.[21] Type 2 cells express IL-10, which is critical in regulating the immune response, and is associated with postbronchiolitis wheeze.[15] However, genetic host variability appears important, because heterozygotism for certain IL-10 polymorphisms associated with genetic interactions may protect against severe RSV bronchiolitis.[15,22,23] Although much less is known about potential immune alterations by other respiratory viruses, HRV infection appears to share RSV's tendency to skew toward a type 2 immune response, albeit primarily via IL-33 production.[16]

Development of the early-life microbiome

Intertwined with the immune system and essential to postnatal development of the respiratory tract are dynamics in the composition of its microbial residents. Early-life viral infections can lead to structural alterations in that composition, some of which are associated with wheezing later in life.

The relationships between the upper airway microbiome and RSV infection are likely to be bidirectional. A prospective longitudinal study demonstrated that upper airway microbiome patterns differ between infants who do and do not develop RSV infections, and these differences are detectable before, during, and after infection.[24] Thus, specific microbiome patterns may actually predispose to RSV infection.

Several studies have identified nasal microbiome alterations in the setting of RSV infections specific to the viral etiology, with differences noted between infections with RSV and HRV.[25] The severity of acute RSV infection is associated with specific microbiome patterns, with RSV hospitalization being positively associated with Haemophilus *influenzae* and Streptococcus-dominated microbiomes and negatively associated with

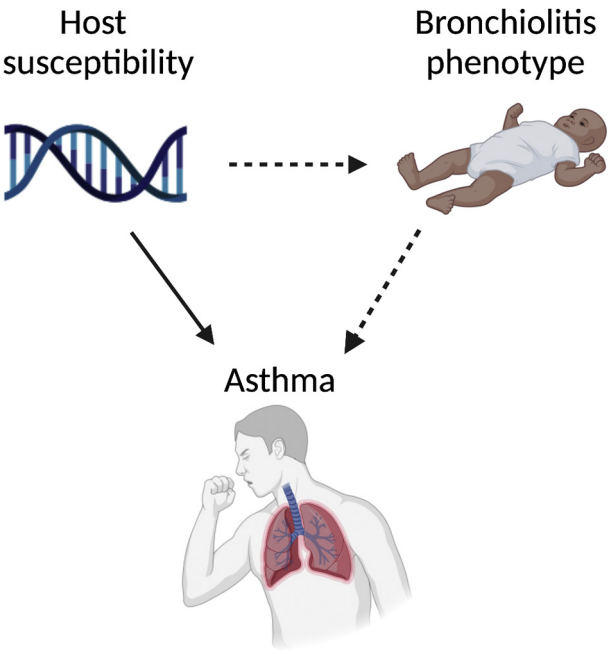

FIGURE 1. A classic approach in evaluating the association between early-life respiratory infection and asthma phenotypes: establishing causality. Dashed arrows depict hypothesized causality. Created with BioRender.com.

Staphylococcus aureus abundance.[26] Viral clearance has been demonstrated to be delayed in the setting of a *Haemophilus*-dominated nasopharyngeal microbiota,[27] whereas viral susceptibility and inflammation can be increased by its presence.[28] Notably, HRV infections do not appear to have the same *H influenzae*—associated pattern as RSV infections, suggesting that either the airway microbial patterns that increase susceptibility to establishing infection, or the airway microbial patterns resulting from infection differ between the 2 viruses.[25,29]

In addition to the interactions of RSV infection and the upper airway microbiome during acute bronchiolitis, the relationship between microbiome structure and subsequent respiratory outcomes, such as recurrent wheezing and asthma, draws interest. Infants with microbiomes dominated by *Streptococcus pneumoniae or Moraxella catharralis* are at increased risk of subsequent asthma at age 5 years,[30] whereas nasopharyngeal presence of *Lactobacillus* is associated with a protective effect on wheezing by age 2 years.[31] Early-life antibiotic use is associated with risk of asthma even after adjusting for genetic and environmental factors in a discordant twin study, suggesting antibiotic stewardship as a potential prevention strategy.[32]

Airway and immune alterations—Do they lead to chronic disease?

There is now a wide body of data proving that early-life respiratory infection—in particular by RSV—can induce structural changes that last beyond initial infection, and several of these have a demonstrable or pathogenetic plausible link with subsequent wheezing or asthma. *However, we need to know whether the changes lead to chronic, persisting disease, and whether we can intervene and improve clinical outcomes.* For clinicians, implications of the findings are currently limited beyond proof-of-concept; it is unclear what changes translate well to the human model, and there are no known interventions to mitigate structural changes toward beneficial outcomes. Human clinical studies of infants are challenging in identifying structural changes as a pure consequence of viral infection. Still, with recent developments in immunomodulation and probiotic therapeutic concepts, unraveling the complex host-virus interactions and related structural changes remains certainly worthwhile, as new target points for clinical prevention may arise in addition to vaccination.

PART 2. ASTHMA AS A POTENTIAL CONSEQUENCE OF RESPIRATORY INFECTIONS

The potential for early respiratory infection to lead to developmental alterations of the airway epithelium and immune system raises the question of whether these alterations can accumulate, are durable, and lead to chronic disease. The hypothesis that a respiratory infection early in life can contribute to the development of asthma later in life is the most prominent example of this, and originates from the association between bronchiolitis and subsequent wheezing disease.[33,34] However, both bronchiolitis and asthma are highly heterogeneous syndromes and multifactorial diseases rather than circumscript entities with distinct pathophysiology and etiology.[35,36] A potential causal role of early-life respiratory infection in asthma development is thus limited by measurement of both the exposure and the outcome, but—unlike for instance genetic factors—there is the potential for intervention, such as prevention, delay, or immunization. This is an important driver of attempts to unravel the distinction between the hypothesis and the main alternative explanation of the correlation between early-life viral disease and later asthma: a prior genetic susceptibility for both (Figure 1).

Asthma as a heterogeneous syndrome

"Phenotypes" of asthma, groups of patients with shared clinical characteristics, have been recognized since Rackemann's observation that some patients developed asthma in childhood in association with allergic sensitization, whereas others developed asthma later in life and had lesser sensitization despite relatively low lung function.[37] Later studies found that patients lacking airway eosinophils had less airway remodeling yet lower forced expiratory volume and significant symptomology despite aggressive corticosteroid treatment,[38] highlighting the variation in response to this standard treatment approach.[39] Phenotypes of wheezing and allergic sensitization are also found in early life.[40] This recognition of asthma heterogeneity fueled attempts to describe pathobiologically distinct "endotypes" of asthma for the purpose of personalized, more effective treatment.[41] Currently, there are 2 predominant endotypes that are considered in clinical practice. The first is defined by upregulation of type-2 immune pathways (ie, IL-4, IL-5, and IL-13 gene sets) and is termed T2-"high" asthma.[42,43] These patients are more allergic, have more airway and systemic eosinophils and greater bronchial hyperreactivity,[44,45] but also tend to respond well to initiation of inhaled corticosteroids.[44] The other endotype is T2-"low" asthma, a less distinct entity defined loosely as asthma in the absence of prominent T2-pathway signatures.

Asthma heterogeneity is further complicated by unique developmental differences among age groups. School-age children with asthma tend to have more episodic disease triggered by viral or allergen exposures, with asymptomatic periods between

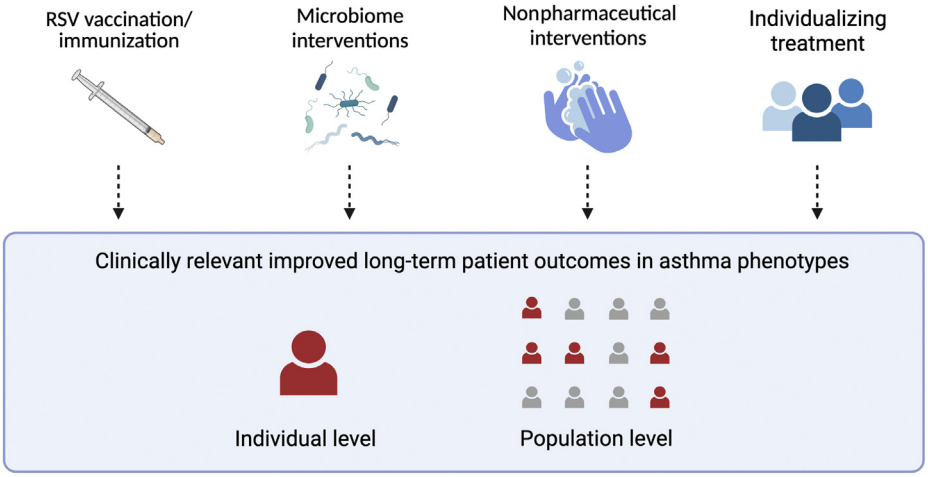

FIGURE 2. A pragmatic approach toward evaluating the association between early-life respiratory infection and asthma phenotypes: directly targeting improved patient outcomes using interventions. Dashed arrows depict hypothesized causality. Created with BioRender.com.

these episodes.[46] Most school-age children with asthma (>80%) also have aeroallergen sensitization,[47-50] similar to the T2-"high" endotype described in adults,[51] but significant airway obstruction is relatively uncommon despite symptoms.[50,52-54]

Preschool children differ markedly from school-age children. Nearly 50% of these experience at least 1 wheezing episode before age 6 years,[55] yet there is significant variability in wheezing pathobiology[56-59] and the severity, frequency, and persistence of wheezing in later childhood.[60-67] Furthermore, only one-quarter of infant and preschool children with wheezing have aeroallergen sensitization, and timing and pattern of sensitization may be more important than sensitization alone.[40,68-70]

Studies have shown that nearly 50% of preschool children with recurrent wheezing have bacterial infection of the lower airways[68,71] independent of viral infection.[72] A recent unsupervised cluster analysis of preschool children with recurrent wheezing undergoing bronchoalveolar lavage identified 4 clusters of children distinguished by atopy and lower respiratory infection profiles; the atopic cluster was dominated by Moraxella, whereas the nonatopic cluster was dominated by *Haemophilus*, *S aureus*, and *Streptococcus*.[73] More studies are needed to unravel the interplay of early-life respiratory infections and to identify resultant endotypes, as well as corresponding clinically useful phenotypes for the purpose of individualized pharmacotherapy and wheeze and asthma prevention in children.

What evidence is currently available for a causal relationship between early-life respiratory infections and development of asthma phenotypes later in life? A recent systematic review and meta-analysis assessed the strength of evidence from observational studies for a causal effect of RSV lower respiratory tract infections and subsequent wheezing illness.[74] Among 35 exposure studies, those controlling for genetic influences yielded smaller effect estimates, indicative of (partial) genetic susceptibility rather than a fully causal relationship. The additional meta-analysis of 8 RSV immunoprophylaxis studies did not provide compelling evidence for a causal relationship either, potentially due to limited power.[74-76] Beyond RSV, HRV-associated wheeze is strongly associated with subsequent wheezing and later asthma in birth cohort studies.[77] However, allergic sensitization appears to be required, and may in turn increase susceptibility to HRV-associated wheeze; this points toward shared heredity for HRV-associated wheeze and allergic sensitization.[78,79]

The accumulated evidence does not prove, but also does not rule out, a causal contribution of viral respiratory infections to asthma disease: other respiratory viruses, cumulative effect of early-life respiratory viruses, and gene-virus interactions are understudied, and the extension of immunoprophylaxis randomized controlled trials is unlikely to provide additional insights due to insufficient power.[76] Finally, studies to date have focused on severe clinical phenotypes of respiratory infection rather than on infection itself. The clinical spectrum of respiratory viral illness is wide, and the assumption that the phenotype of (severe) bronchiolitis is the exposure that matters may not be true.[80] Severe RSV or HRV are not exposures per se, but imprecise clinical phenotypes of infection, and their association with asthma may be confounded by shared heredity to both diseases.[77,80] Immunoprophylaxis and even vaccination mitigate, but do not prevent, infection; thus, trials evaluating these agents cannot fully answer the question of causality. The perfect alternative—randomized studies of infection versus noninfection—cannot be considered because of obvious ethical concerns.

Asthma as a potential consequence—Is there a clinically relevant causal effect?

All other things being equal, can delaying or preventing infection during infancy significantly decrease the burden of asthma? The answers may differ between the individual level and the population level. A causal role of early-life viral respiratory infection in asthma development is not excluded, but currently not proven by a significant body of clinical literature. Furthermore, the contribution of environment to asthma development is likely multifactorial (with numerous factors contributing additive or multiplicative) as for many chronic diseases, and therefore large effect sizes of a single causal contribution are unlikely, or limited to small subgroups. Consequently, this limits the potential for interventions aiming to prevent infection at the individual level. Still, analogous to targeting second-hand smoke exposure or cholesterol levels in preventing cardiovascular

disease, targeting viral respiratory infections for preventing asthma may still have a significant impact at the population level. Given the limited understanding of asthma development and lack of alternative target points that allow for intervention, further research using carefully designed studies is essential.[80,81] Pragmatically however, the clinical aim of any current prevention of early-life viral respiratory infection, including prophylaxis and vaccination, need to primarily focus on prevention of short-term burden of severe disease until it is established that there is an impact on long-term respiratory outcomes.

A PRAGMATIC RESEARCH AGENDA

Untangling complex interactions between host, environment, and viral infections in the development of wheezing phenotypes, including establishing causality, will remain prominent and important challenges for years to come. Understanding RSV and HRV,[30,82] subsequent recurrent wheeze,[83] and asthma phenotypes and endotypes[84–86] will continue to be important, because imprecision in both the exposures and outcomes of interest pose significant problems in estimating effects. Further understanding of endotypes will provide additional insights into upstream events and mechanisms of disease development. For clinicians, as both the impact of early-life respiratory viral infections and asthma continue to increase globally, clinical research may pragmatically focus on producing and evaluating candidate intervention strategies that can help prevent the burden of these phenotypes while understanding the mechanisms through which early-life viral infections impact future respiratory health, work that may guide identification of risk groups for targeted intervention (Figure 2). Currently, clinical care will need to continue to focus on optimal treatment of childhood wheezing disorders until there are proven preventive interventions.[87,88] For the future, we identify the following gaps to be addressed:

- Identifying endotypes of RSV and HRV infection that contribute to chronic respiratory morbidity, and endotypes of asthma that may result from early-life infection.
- Advancing individualized treatment including identification of infants at increased risk of the long-term effects of early-life viral infections; evidence shows potential for endotype/phenotype-based treatment approaches,[87,89] and asthma-risk indexes may be particularly helpful to identify target populations at early age.[90]
- Identifying critical windows of early-life susceptibility during which prevention or delay of infection may have the greatest impact; animal models suggest that delaying infection can reduce later morbidity.[17]
- Determining potential for airway and gut microbiome interventions to decrease the burden of early-life respiratory infection and subsequent respiratory morbidity, such as antibiotic stewardship initiatives or probiotic supplementation; *Lactobacillus* studies constitute a promising example.[31,91]
- Determining whether a differential role of respiratory viral subtypes in acute and chronic disease development exists, especially because viral subtype may relate to the effectiveness of protective interventions.[92]
- Estimating individual versus cumulative impact of respiratory viruses on chronic respiratory outcomes; some studies suggest the number rather than the viral etiology of infections is what matters.[93]
- Determining the impact of both nonpharmaceutical and pharmaceutical interventions on respiratory virus prevention, reduction of wheezing illness, and chronic respiratory morbidity,[94,95] in particular capitalizing on the unique natural experiment of the severe acute respiratory syndrome pandemic given its profound impact on other circulating respiratory viral infections.[96]

CONCLUSIONS

The burden of early-life respiratory viral disease is significant, as is childhood asthma. Both are singularly important focuses of disease prevention, but whether early-life infection contributes to chronic wheeze and asthma development, and whether risk of these outcomes might be modified by prevention or delay of early-life respiratory infection, is yet to be realized. New insights regarding early-life viral infection and not just bronchiolitis as an exposure, the recognition of asthma as a heterogeneous outcome, and the shared genetic susceptibility to both suggest a refocus from answering the theoretical question of causality toward a pragmatic approach focusing on improving patient outcomes across the spectrum of childhood wheeze and asthma. To increase the chance of development of clinically relevant applications, this approach should consider the relevance and impact of interventions not only at the individual level but also at the population level.

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