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Impact of Viral Lower Respiratory Tract Infection (LRTI) in Early Childhood (0–2 Years) on Lung Growth and Development and Lifelong Trajectories of Pulmonary Health: A National Institutes of Health (NIH) Workshop Summary

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ABSTRACT

Viral lower respiratory tract infections (LRTI) are ubiquitous in early life. They are disproportionately severe in infants and toddlers (0–2 years), leading to more than 100,000 hospitalizations in the United States per year. The recent relative resilience to severe Coronavirus disease (COVID-19) observed in young children is surprising. These observations, taken together, underscore current knowledge gaps in the pathogenesis of viral lower respiratory tract diseases in young children and respiratory developmental immunology. Further, early-life respiratory viral infections could have a lasting impact on lung development with potential life-long pulmonary sequelae. Modern molecular methods, including high-resolution spatial and single-cell technologies, in concert with longitudinal observational studies beginning in the prenatal period and continuing into early childhood, promise to elucidate

For a complete list of the NIH Workshop Participants of the 'Viral Lower Respiratory Tract Infections in Infancy and Early Childhood-Immunological and Developmental Aspects', see the Acknowledgments section.

developmental pulmonary and immunophenotypes following early-life viral infections and their impact on trajectories of future respiratory health. In November 2019, under the auspices of a multi-disciplinary Workshop convened by the National Heart Lung Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, experts came together to highlight the challenges of respiratory viral infections, particularly in early childhood, and emphasize the knowledge gaps in immune, virological, developmental, and clinical factors that contribute to disease severity and long-term pulmonary morbidity from viral LRTI in children. We hope that the scientific community will view these challenges in clinical care on pulmonary health trajectories and disease burden not as a window of susceptibility but as a window of opportunity.

1 | Introduction

Despite the remarkable and speedy progress in understanding COVID-19 infection, which has led to the rapid development and deployment of effective vaccines, the pandemic highlights the urgency to advance knowledge regarding the ramifications of viral LRTI throughout its lifespan. COVID-19, like respiratory illnesses caused by the influenza virus and respiratory syncytial virus (RSV), reveals knowledge gaps in the prevention and treatment of acute respiratory viral infections and mitigation of pulmonary sequelae in children. The ubiquitous nature of respiratory viruses, lifetime repeated exposures, and the robustness of host immunological, pathological, and regenerative responses set the lifelong trajectory of pulmonary health, beginning in fetal life. The viral pandemic that has affected all aspects of global society emphasizes a need to understand the pleiotropic elements of scientific and societal responses to LRTI.

2 | Epidemiology and Impact of Viral LRTI, Global, and National Perspective

The social and economic impact of respiratory viral infections is substantial [1], with more than 500,000 hospitalizations for LRTI in children under 18 years of age, most commonly from RSV and influenza infections [2–7]. RSV is the leading cause of LRTI (including bronchiolitis and pneumonia) in young children worldwide and the second leading cause of infant mortality in resource-limited countries [8, 9]. In addition, influenza viruses cause significant morbidity and mortality in children across all age groups [10–12]. Recent surges in pediatric hospitalizations for viral respiratory illnesses are of urgent concern.

Although severe influenza typically impacts adults with preexisting conditions, children with and without risk factors have been hospitalized with severe influenza [13]. Despite the high morbidity and mortality associated with COVID-19 in adults, most pediatric patients have been spared from severe disease [14]. These findings may change as the virus mutates [15]. These differences highlight the impact of developmental age and the causative pathogen. Other respiratory viruses, such as parainfluenza viruses, human metapneumovirus, and endemic coronaviruses, are associated with many hospitalizations in children. Rhinoviruses that were previously viewed as a cause of upper respiratory infections are now commonly identified in children hospitalized with LRTI, wheezing episodes, and asthma exacerbations [16–19], providing compelling evidence that they induce disease in the lower respiratory tract. Herein, we emphasize three key areas of inquiry regarding the pathogenesis of respiratory viral infections, particularly in early childhood: immunology and the host response, respiratory viruses in the young, and translational and clinical aspects. We highlight the knowledge gaps to improve understanding of immune, virological, developmental, and clinical factors contributing to disease severity and long-term pulmonary morbidity from viral LRTI in children and potential directions for future research (Table 1).

3 | How Does the Host Response to Pneumonia in Children Differ From Adults?

The first cells encountered by a microbe in the lung are epithelial cells, macrophages, and dendritic cells; thus, their responses are critical in rapidly amplifying and modulating effective immune resistance [20–22] (Figure 1). Lymphocytes in the newborn lung, including $CD4^+$ T cells, $CD8^+$ T cells, B cells, innate lymphoid cells, mucosal-associated invariant T cells, and others, direct and modulate pulmonary defenses [23, 24]. These cells and pathways are influenced by a strong type 2 T helper cell (Th2) bias, which further directs the defense activities of the newborn lung in response to infection in ways distinct from the immune response in adults. Tissue resilience and the resolution of pulmonary inflammation in the newborn lungs involve cytoprotective pathways [23] and autocrine and paracrine signaling mediated by pro-resolving Th2 cytokines [20, 25]. The inflection point between positive feedback loops amplifying inflammation and the subsequent resolution stages of infection is yet to be defined. Factors determining fully or partially effective resolution or persistent harmful effects must be elucidated.

Respiratory infections are ubiquitous, and the pulmonary defenses of all but the very youngest of children are influenced by their respiratory infection history. The newborn infant's immune system is already partially programmed *in utero* by the infections and immune responses that have occurred in their mother [26]. Although lung defenses change dramatically after the resolution of prior infections [27–29], the mechanisms protecting more experienced lungs as children age are poorly understood. While the lower rate of pneumonia in young, healthy adults likely results from naturally acquired heterotypic immune memory [28] and trained innate immunity [30] generated by prior infections, the mechanisms underlying this alveolar resilience remain poorly understood. Different cellular components of the lung (mainly resident memory lymphocytes and innate lymphocytes) and reprogrammed responses from macrophages and epithelial cells (due to metabolic and epigenetic alterations) likely improve lung defense with age and need further elucidation. Dysregulation of lung-protective mechanisms is inferred to be responsible for microbial growth and

TABLE 1 | Consequences of early viral respiratory infections on immune and pulmonary phenotype – Knowledge gaps and opportunities.

Gap – Mechanisms by which insults to the developing fetus sculpt the immune trajectory during childhood

1. Better define the immunological niches where immune cells reside in the lungs
2. Elucidate how maternal-fetal environment and, later, perinatal environment determine the ontogeny of lung resident immune cells and developmental programming of the immune system
3. Better define how early-life insults disrupt stromal-immune cell communications in the niche and how such disruptions contribute to long-term deficits in host defense against viruses

Gap – Employing infant responses during pneumonia as a means to elucidate pathophysiology and improve outcomes in LRTI in infants

1. Better define the roles of immune cells in neonatal host defense, with a particular emphasis on *Reprogramming*, altered responses from the cells and *Remodeling, and the* impact of microbial and nonmicrobial insults on the cellular composition of the lung
2. Delineate elements of infant lung cellular and physiologic responses that are conserved or variant across different viral pathogens, such as response to RSV as compared to SARS-CoV2

Gap – Impact of viral infections on lung growth, development, and immune function

1. Identify signaling and transcriptomic mechanisms by which inflammation intercepts lung morphogenesis and influences regeneration
2. Role of parenchymal or immune memory in the persistence of low lung function in high-risk infants
3. Mechanisms by which immunity is linked to lung structure and function
4. Mechanisms that integrate lung growth with the immune system
5. Impact of environmental and commensal microbes on lung structure and pulmonary immune function

Gap – Assessment of growth and development of lung structure and function after early viral insults

1. Longitudinal studies investigating changes in lung function with viral respiratory infections during the first years of life
2. Development and validation of noninvasive modalities to sequentially assess lung growth and function
3. Immunologic correlates and biomarkers that help identify mechanisms impacting lung growth and development
4. Identify genes, environmental exposures, and their interactions that determine low lung function trajectories, starting in utero and during early postnatal life

Gap – Mechanisms of regeneration after infection

1. Developmentally appropriate studies of lung injury and regeneration in primates and other large animal models
2. Technologies to model injury and repair of the developing lung viral infection: organoids, lung on a "chip," and precision-cut lung slice cultures

Gap – Biomarkers and endotyping

1. Biomarker-based approaches for additional virus-specific respiratory phenotypes, predictors of outcome and to identify and test new phenotypic-specific treatments
2. Predictive biomarkers to enrich cohorts with subgroups of patients who are most likely to benefit from specific therapeutics
3. Integrating molecular biomarkers with comprehensive phenotyping of infants with viral respiratory infections to develop individualized and precision medicine approaches that prevent severe disease and long-term sequelae in all the subtypes of viral respiratory illnesses during early life.

(Continues)

physiological dysfunction in pneumonia. However, the identity and specificity of these pathways remain speculative. The distinction between invasive infection and colonization and the effects of viral-bacterial co-infections remains a diagnostic and scientific conundrum. Clinical studies of infants with pneumonia reveal heterogeneity in host responses during pulmonary infections [31–33]. Such heterogeneity can be leveraged to elucidate relevant immunological and physiological pathway alterations. Establishing molecular profiles that report variations in infant–host responses to pneumonia could guide research describing lung protection and resilience mechanisms. Although severe pneumonia has been generally associated with bacterial etiologies, significant studies conducted during the last decade in developed and low-middle-income countries (LMIC) have identified the prominent role respiratory viruses and viral-bacterial coinfections play in the etiology of pediatric pneumonia [34–36].

3.1 | The Lifelong Trajectory of Pulmonary Mucosal Immunity Is Established During Development

Macrophages within the airway lumen (alveolar and airway macrophages, AM) are long-lived cells derived from embryonic progenitors colonizing the airways soon after birth and self-renew under homeostatic conditions [37, 38]. AMs are distinguished from tissue-dwelling interstitial macrophages (IM) via their particular repertoire of surface receptors [39–41]. Additional populations of monocyte-derived macrophages are recruited to the lung during inflammatory conditions [42] and contribute to improved survival in Influenza A virus-infected juvenile mice [43]. Macrophages represent the lung's first line of defense and maintain pulmonary immune homeostasis via

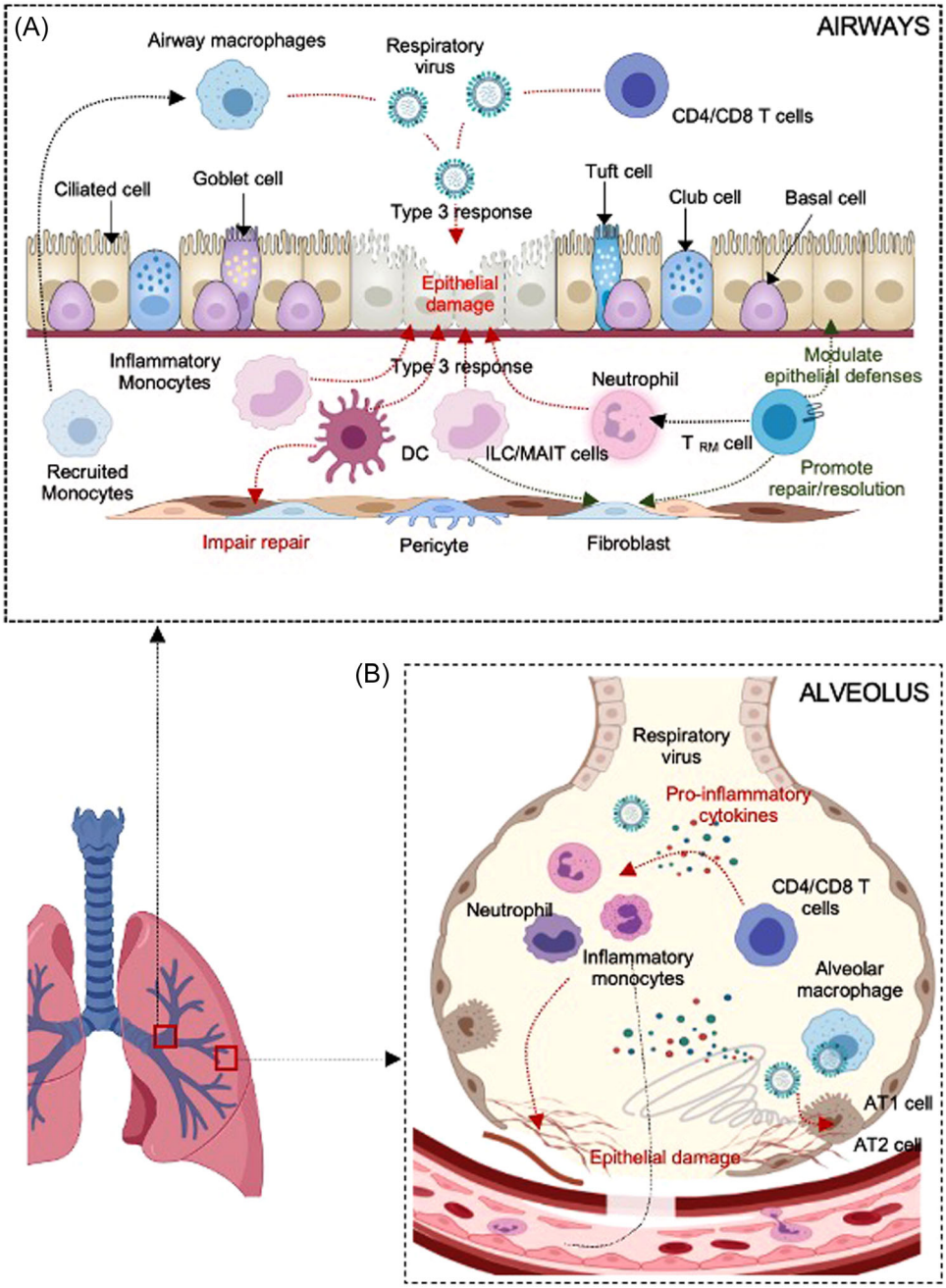

FIGURE 1 | Immune response to respiratory viruses. Complex crosstalk between epithelial cells and stromal cells and resident and recruited immune cell populations in either (A) airways or (B) Alveolus. This figure provides specific examples and is not exhaustive. AT1, alveolar epithelial type 1 cells; AT2, alveolar epithelial type 2 cells; DC, dendritic cell; MAIT cell, mucosal-associated invariant T cell; T_{RM} cell, tissue-resident memory T cell. [Color figure can be viewed at wileyonlinelibrary.com]

close interactions with lung parenchymal cells. Homeostatic interactions are driven by activation (TLR 2, 4, 6; IL-1R, IFNγR, and TNFR) and suppression (CD200R, SIRPα, mannose receptor, TREM2, IL-10R, TGFβR) [44] signals. In addition, in mice, the local pulmonary environment provides critical phenotypic cues for bone-marrow-derived macrophages transplanted into the lung to transform into an AM phenotype [45].

Variations in developmental origins, tissue residency, and environmental influences create a rich diversity of pulmonary macrophages with distinct functions and responses [37, 38, 46]. At the same time, macrophages from the yolk sac or fetal liver recolonize the empty pulmonary niches and develop into functional tissue-resident AM. Mature macrophages from other tissue sites do not serve as AM progenitors [47], highlighting the importance of the local tissue environment in establishing innate immunity. After birth, fetal monocytes infiltrating the murine lungs during the embryonic period differentiate into AMs. This process is dependent on the expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) by lung epithelial cells, which is upregulated during the first days of life, the stimulus for which is unknown [37]. Maturation of AMs and other $CD11c^+$ cells can be achieved by intranasal administration of a mixture of microbial extracts

[48], indicating that exposure to airway microbiota could assist in the maturation of these cells. AMs have a crucial role in the first-line defense against various inhaled antigens. In healthy animal fetuses, these monocytes are relatively quiescent; however, intra-amniotic exposure to endotoxin or other inflammatory mediators induces rapid maturation and differentiation even before birth [49]. Thus, innate immune cells colonize the lung early during fetal development and react to intrauterine inflammation.

While epithelial cells and AM cooperate to facilitate the clearance of apoptotic cells and debris, recent studies highlight the ability of macrophage signals to influence phagocytosis by epithelial cells [50]. Secretion of insulin-like growth factor (IGF-1) from macrophages follows exposure to inflammatory cytokines and during phagocytosis of apoptotic cells. The binding of IGF-1 to IGF-1 receptors expressed on nonprofessional antigen-presenting epithelial cells inhibited the engulfment of apoptotic cells in human and mice sera [51]. Disruption of IGF-1 signaling in the epithelium in infants with bronchopulmonary dysplasia (BPD) [52] is associated with enhanced allergic airway inflammation, underscoring the regulatory role of the airway macrophage in modulating epithelial function [53].

$CD11b^+$ conventional dendritic cells (DCs) constitute a large proportion of pulmonary immune cells during the first 2 weeks of life in mice [54] and have unique activation profiles compared with adults. Neonatal $CD11b^+$ DCs are potent in processing antigens and inducing Th2-type immune responses. The microbiota influences the activation profiles of DCs during the neonatal period. The functionality of neonatal pulmonary DCs has been tested in various animal models. Murine and ovine models identified similar capacities of neonatal and adult pulmonary DCs to take up and process antigens and stimulate T-cell responses [55, 56]. However, the antigen-presenting capacity of neonatal DCs in response to granulocyte-macrophage colony-stimulating factor is reduced in comparison to adult DCs.

In contrast to tissue-resident innate cells, adaptive immune cells in the lung of neonates are scarce and exhibit limited functionality. T cells are found in low frequencies in the neonatal mouse lung [56]. They are predominantly comprised of naive T cells [57], which show an intrinsic bias towards producing Th2 cytokines and transcription factors when stimulated in vitro [56]. Thus, neonates' susceptibility to viral lung infections could be driven by insufficient or inappropriate T-cell responses, driven by an insufficient environment to prime these T cells [58]. Human and mouse regulatory T cells (Tregs) accumulate inside the neonatal lung [54, 57], and their accumulation is linked to the microbial exposure [54, 57]. Notably, the Treg compartment in neonates is dominated by natural thymus-derived Tregs (nTreg) cells [54]. Peripherally induced Treg (iTreg) cells are found in the murine lung later in life, and their appearance is initiated by microbiota in a PD-L1-dependent manner [54]. Taken together, immune cells slowly accumulate in the lung during the postnatal period, which is a period of rapid lung growth, alveolar remodeling, and colonization by microbiota.

The pulmonary parenchyma contains a diverse resident lymphoid cell population, including memory T cells, innate lymphoid cells, regulatory T cells, and γδT cells. Immune responses are coordinated by the interaction of tissue-resident lymphoid cells and macrophages to initiate effector responses, mediate repair and resolution, and ultimately restore homeostasis. Specialized subsets of T cells are recruited to the adult lung following antigen exposure, such as antigen-specific Th2 cells, in response to chemokine receptors CCR4 and CCR8 [59, 60]. These memory T cells are retained in the lung following the initial encounter with an antigen. Such resident memory T cells (T_{RM}) are sufficient to generate local inflammation even in the absence of memory T cells from secondary lymphoid organs [61]. $CD4^+$ and $CD8^+$ T_{RM} are present even in healthy human lungs, expressing CD69 and a diverse TCR repertoire [62, 63]. T_{RM} are an essential component of immunity at barrier surfaces and provides rapid protective immune responses during recall infections with respiratory pathogens such as influenza, RSV, or pneumococcus. In mice infected with influenza, lung $CD4^+$ T_{RM} offers superior protection compared to systemic memory $CD4^+$ T cells with identical antigen specificity [29]. In human studies, airway $CD8^+$ T_{RM} abundance correlates with reduced disease severity in RSV infection [64]. In mice infected with pneumococcus, lung $CD4^+$ T_{RM} hasten neutrophil recruitment and pulmonary defense by enhancing chemokine expression by epithelial cells [65]. The ability of T_{RM} to eliminate pathogens even in the absence of antibodies can be exploited to generate more effective vaccines [66]. T_{RM} also influences immune responses to inhaled allergens. Following influenza infection in mice, pulmonary $CD8^+$ memory cells can be reactivated in an antigen-independent fashion [67]. IFN-γ antagonizes subsequent Th2 responses and protects mice from allergic airway inflammation [68]. Allergen-specific Type 2 memory cells persist in the murine lung after exposure to house dust mites [69].

Innate lymphoid cells (ILC) lacking lineage markers are enriched at barrier surfaces and are thought to be vital for regulating immunity, tissue repair, and homeostasis [70]. ILCs are further delineated into various subtypes, including natural killer (NK) cells, lymphoid tissue-induced cells (LTI), ILC1, ILC2, and ILC3. They respond to injury through cytokine signaling and are considerably enriched in human fetal lungs compared to other developing organs [71, 72]. ILC2s and ILC3s are localized within the murine lung parenchyma. Similar to the developmental trajectories of pulmonary macrophages, ILCs traffic to the tissue during fetal development. The second wave of immigration and expansion of tissue ILC pools occurs around birth [73]. Concurrently, both fetal and perinatally-seeded ILCs develop their effector phenotypes under the control of tissue factors. Murine lung resident ILC pool sizes are maintained locally via self-renewal during homeostatic conditions and augmented by recruitment from extrapulmonary sources during inflammation [73, 74] and infection [75]. In mice, pulmonary epithelial-derived cytokines, IL-33, and TGF-β enhance the accumulation of ILC2s within the lung, particularly after the allergen challenge [76, 77]. Similarly, alveolar fibroblast-derived IGF-1 supports the expansion and functional maturation of the ILC3s [75]. ILC3s have a crucial role in the first-line defense against various respiratory pathogens. Although newborns have a higher risk of establishing pulmonary infections, ILC3s from newborn animals have an adult-like response to the LPS challenge [78]. Therefore, the composition of the lung ILC pool is dynamic and influenced by the environment.

Nevertheless, how the balance between pathogenic and protective ILC response is patterned during development and maintained thereafter is unclear. Such an understanding is critical as the initial over-representation of ILC3s (pathological) relative to ILC2s (protective) may favor the development of the inflammatory immunopathology [79]. For example, lack of ILC3s results in underdeveloped secondary lymphoid organs and dysfunctional adaptive immune response in the mouse gut [80]. Because ILC3s stimulate mesenchymal cells to create the lymphoid niche, the size of the lymph node and niche for adaptive lymphocytes depends on the ILC3 population [81]. Thus, the relative ratios of one group of ILCs may impact effector outputs and have long-lasting effects on lung immunity and repair [79].

Lung resident or roving regulatory T cells (Tregs) maintain immune tolerance to airborne particles [82]. Depleting naturally occurring $CD4^+CD25^+FoxP3^+$Tregs enhances allergic responses, while their transfer mitigates allergic responses via IL-10 [83, 84]. Resident pulmonary Tregs are present from birth, and their maturation is influenced by local microbiota and cues from the local lung environment [54]. For example, in mice, the generation of inducible Tregs is linked with PD1-PDL1 expression induced by exposure to microbes [54]. Crosstalk between AMs and T cells represents a potential mechanism for generating inducible Treg cells [85] in infants. Respiratory pathogens, such as RSV, can shape Treg homeostasis. Loss of Tregs due to early-life RSV infection can contribute to Th2-mediated pathology during childhood [86].

Thus, lung development and maturation of pulmonary mucosal immune responses are closely linked [87]. Their contemporaneous development enables the lung to "instruct" rapidly maturing pulmonary mucosal defenses. This convergence in the timing of lung growth and immune maturation ensures robust lung protection while restricting damage to the organ's critical gas exchange machinery. A potential consequence of this coupling is that injury during development, for instance, premature birth and BPD, can interrupt the developmental trajectory of lung resident macrophages and ILCs and contribute to an increased risk of respiratory infections and chronic inflammatory disorders that may persist beyond infancy into adolescence. Similarly, fetal inflammation disrupted lung development and delayed the maturation of pulmonary mucosal immunity [88]. Thus, infants exposed to fetal inflammation may be predisposed to chronic respiratory disorders during childhood.

3.2 | Critical Times in Pulmonary Immune Maturation: A Window of Opportunity

The postnatal period of lung growth and alveolarization is vital for long-term pulmonary health. Infants are exposed to successive waves of commensal bacteria and infections with commonly occurring pathogenic microbes. Healthy and complex microbiota are necessary for immune development in the newborn [89]. Factors such as Cesarean delivery, no exposure to breast milk, diet, antibiotics, intubation, and stress decrease the abundance of beneficial bacterial species and increase the overgrowth of pathogenic ones [90, 91]. Perturbations in microbial composition and function, termed dysbiosis, disrupt tissue and immune homeostasis and are associated with diverse inflammatory diseases in the lung and gut [91].

Further insights into the pathogenesis of poor or impaired lung growth/development trajectories will be derived from an increasing understanding of lung and immunity, which begin in utero and become more active after birth when the infant is exposed to a diversity of microbiota microbial pathogens and environmental toxins (Figure 2).

3.3 | Persistent Deficits in Lung Function Due to Developmental Insults in Infancy

Severe viral LRTI in childhood is associated with decreasing lung function in adulthood, increasing the risk of asthma and COPD [92]. Prematurity, BPD, malnutrition, immune defects, and genetic or acquired pulmonary disorders during infancy predispose to increased severity of viral LRTI in childhood and asthma later in life [93]. The relative contributions of early life conditions and exposures to long-term pulmonary health remain unresolved, as do the critical causal mechanisms.

When considering how growth abnormalities affect pulmonary outcomes, defining "normal" lung function is essential. Advances in MRI provide detailed anatomic information regarding airway structure and lung parenchyma, enabling estimation of lung volumes, perfusion, and alveolar structure [94]. Young children are highly susceptible to viral LRTI. Novel methodologies demonstrate that infants who develop symptomatic viral LRTI and wheeze have pre-existing "low lung trajectories" [95].

In a prospective study, neonates with significant airflow deficit [96] were ~1.5 times more likely to develop asthma by age 7. Their airflow obstruction progressed during childhood, suggesting that airway abnormalities were present at birth. A recent study [97] found that airway obstruction and asthma-associated bronchial hyperreactivity were fixed traits from 1 month to 13 years of age and neither deteriorated nor improved with asthma remission. The Tucson Children's Respiratory Study followed 1246 children to early adulthood. Children with lower trajectories had lower maximal expiratory flow at FRC during infancy and at 6 years of age. They were likelier to have a history of maternal asthma, prior RSV infections, and physician-diagnosed asthma in adulthood [98]. Collectively, these data support the concept that airway obstruction and bronchial hyperreactivity are inherent traits that increase the risk of developing airway inflammation and childhood asthma [97]. Early identification of infants at risk for low lung trajectories and elucidation of the pathogenic mechanisms are needed to develop strategies to preserve and maximize lung function later in life.

3.4 | Regenerating the Pulmonary Parenchyma After Viral LRTI

Strategies for protection and optimal treatment of LRTI are essential goals but remain inadequate. Early-life infections (RSV) can lead to significant long-term disease in childhood and adulthood [98]. In addition, longitudinal studies support

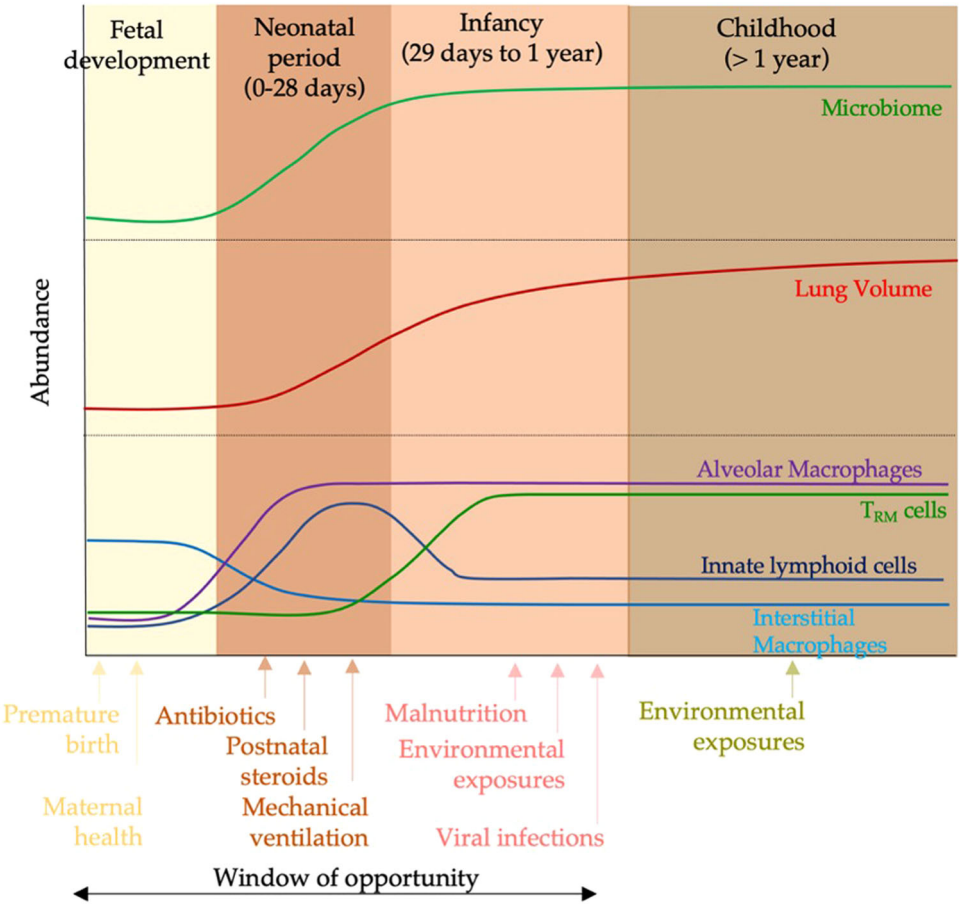

FIGURE 2 | Neonatal window of opportunity: Ontogeny of pulmonary immune development, increase in lung volume and colonization by the gut microbiome. Insults during the developmental window, for example, premature birth, poor maternal health, antibiotic use during the neonatal period, mechanical ventilation, environmental exposures, and viral infections interrupt the programmed increase in pulmonary immune cells, maturation of lung function, contributing to durable, consequences for child health and morbidity. [Color figure can be viewed at wileyonlinelibrary.com]

the "fetal origins of lung disease" hypothesis, which posits that physiological stresses in early life predispose to disease risks in later life.

LRTI in early infancy coincides temporally with pulmonary alveologenesis, by which AT1 cells form in close apposition to specialized alveolar-capillary cells, creating the efficient gas-exchange structure of the alveoli [99, 100]. Viral injury, as in influenza infection, disrupts this association, leading to significant alveolar damage. Extensive rebuilding of the epithelial [101] and the endothelial [102] compartments is required to regenerate the alveolar-capillary interface. Severe lung injury in preterm infants causes alveolar simplification, reducing the gas-exchange surface [88], a hallmark finding in BPD. The discovery of mechanisms supporting alveolar growth, septation, and regeneration will likely provide the framework to optimize lung protection and therapies for LRTI in infants.

Studies of the regenerative mechanisms of the developing lung and the anatomical and functional consequences of recurrent viral injury are needed to better understand lung regeneration in the pediatric population. While observational evidence supports a connection between early-life viral exposure and subsequent inflammatory and tissue responses, we need a clearer understanding of how each exposure influences lung immune and parenchymal responses. In addition, while regenerative and fibrotic responses following severe viral injury are well established in rodent models [103], little data currently exists to address the mechanisms that distinguish regenerative processes in the adult and developing lungs.

3.5 | Imprinting, Epigenetic Control of Inflammation Following Viral LRTI

The acquisition of antiviral immunity starts in early infancy and is influenced by the generation of humoral and cellular immunologic memory [104, 105]. The global burden of severe viral LRTI is linked to RSV, influenza, and now COVID-19; therefore, advances in modulating host–pathogen interactions in these diseases provide an opportunity to impact childhood health. Immunologic memory of viruses is acquired by infection and vaccination; however, current influenza vaccines may not be as effective due to "immunologic imprinting" [106]. Questions remain regarding the immunologic basis for imprinting, including whether it applies to first exposures or is modified by subsequent life exposures, vaccinations, asymptomatic infections, or vertical transfer of maternal antibodies [107]. These

questions are being addressed in maternal-infant cohort studies that capture prenatal and infant viral infections, vaccinations, and host immune responses through viral surveillance and serological testing [108]. The concept of immunological imprinting needs to be investigated in common respiratory pathogens (e.g., RSV, rhinovirus) other than influenza. Evidence indicates that not all respiratory viral infections have similar long-term consequences. Early-life RSV or rhinovirus infections significantly increase the risk of subsequent wheezing and pulmonary sequelae, but infections with influenza viruses do not. Thus, the type of initial viral infection and infant age significantly affect subsequent immunologic and pulmonary trajectories. These studies have implications for defining the mechanisms mediating the origins of chronic respiratory conditions.

3.6 | Microbe–Host Interactions Relating to LRTI in Infancy

Studies indicate that the respiratory and intestinal microbiota is established in early life and influence susceptibilities to viral respiratory infection and asthma [109–114]. Analyses of immune cell populations during early human development indicate that bacterial dysbiosis may alter the development of protective immune responses [104]. Since analyzing pulmonary immune and parenchymal cells are challenging, studies of epithelial cells isolated from nasal brushings may provide insights into the interactions among microbes and immune and epithelial cells in infants. Longitudinal studies are needed to define the maturational trajectories of airway epithelial immunity in children.

Modifications of microbial exposures (e.g., antibiotic use) may shape airway immune responses during early life. Experimental models offer a shorter timespan to understand longitudinal development but may not accurately reflect the human host response. Animals and primate models are needed to study age-dependent responses to viral exposures in the presence of commensal bacteria. They may offer better insights into lung structure and immunity [115, 116]. Small amounts of bacterial DNA are present in the airways of preterm and term infants at birth, indicating exposure to the airway microbiome before or immediately after birth [117], which may modulate lung inflammation and repair [118]. At present, evidence of an airway virome at birth is lacking, and whether a similar antenatal "priming" of the immune system occurs with viruses is unknown. The interplay between respiratory viruses and the infant's immune response is complex. Viral type, genotype, and load, as well as age, microbiome, and maternal antibodies, are likely to influence disease severity [119–121]. Infants with mild RSV infections had significantly higher viral loads, less nasopharyngeal colonization by *H. influenzae* and *S. pneumoniae*, and enhanced systemic expression of IFN-stimulated genes (ISGs) compared with children with severe disease [119–121]. Complex interactions among respiratory viruses, host immunity, and resident microbiota have led to early-life interventions such as bacterial lyophilizes to mitigate wheezing after LRTI [119, 122, 123] (trial number: NCT02148796).

3.7 | Advances in Biomarkers and Molecular Endotyping of LRTI in Infants and Children

New physiologic, imaging, cellular, and genetic markers of pulmonary injury and regeneration provide many opportunities to identify factors contributing to susceptibility to LRTI. Club cell secretory protein (CC16) is a signature product of club cells and other non-ciliated airway epithelial cells that increases in peripheral circulation from birth to adulthood, providing robust intra-subject tracking across all ages [124–126]. Surfactant protein D (SP-D), both in serum and respiratory samples, is used as a biomarker in chronic lung diseases, such as idiopathic pulmonary fibrosis [127] and pulmonary alveolar proteinosis [128], and may be applied to pediatric patients. Clinical trials are underway using recombinant SP-D to mitigate lung inflammation in preterm infants at risk for BPD [129]. The ability of SP-D to bind and neutralize influenza, COVID-19, and other respiratory viruses is also being considered in clinical applications [129, 130].

Molecular biomarkers can also be used to phenotype viral LRTI in infants, often lumped together as "viral bronchiolitis" [131]. Distinct bronchiolitis phenotypes and endotypes have been identified based on the heterogeneity of clinical presentations, molecular immune signatures, and clinically relevant outcomes [132–134]. Studies showed that matrix metalloproteinase (MMP)−9 airway levels correlate with disease severity in children with critical RSV infection [122, 123]. Azithromycin has anti-inflammatory properties targeting MMP-9 [135, 136]. A pilot trial in children mechanically ventilated for severe RSV LRTI showed that high-dose azithromycin reduced endotracheal MMP-9 levels and the duration of hospitalization [137]. Another study showed that azithromycin treatment during RSV bronchiolitis reduced upper airway IL-8/CXCL-8 concentrations and overall respiratory morbidity over 1 year [138]. Subsequently, two clinical trials suggested that azithromycin might initially reduce the likelihood of asthma-like symptoms in young children, with no significant effects over the following 2-4 years [139, 140].

3.8 | Opportunities to Strengthen Maternal and Infant Immunity

To date, the strategies to prevent viral LRTI in young children have been limited to influenza and prophylactic antibodies (palivizumab) to reduce RSV LRTI in high-risk infants. Although the influenza vaccine is indicated for children only after 6 months of age, maternal influenza immunization significantly benefits early child health outcomes [141]; similar approaches are being developed for other respiratory viruses such as RSV and COVID-19. Considerable knowledge gaps remain in our efforts to prevent respiratory viral infections. These include the identification of conserved highly immunogenic epitopes to facilitate universal influenza vaccine design with improved protection [142]. Another relates to immune imprinting as the initial exposure to influenza shapes the antibody response upon subsequent exposures [143]. Defining the mechanisms for virus-induced immune imprinting is a high priority.

There has been a renaissance in developing preventive strategies for RSV infection related to improved knowledge of the

structure of the RSV fusion (F) protein in its preF and postF conformations. The F protein induces the production of potent neutralizing antibodies, especially in its preF conformation [144]. The most plausible approach to protect young infants < 6 months of age will be via passive immunization with either maternal immunization with stabilized preF vaccines [145] or through prolonged half-life preF monoclonal antibodies (mAb) administered to the infant. This strategy should be followed by active immunization in children > 6 months of age with live attenuated vaccines administered intranasally [146] or virus vector vaccines expressing the preF protein alone or with other proteins.

3.9 | Overarching Priority Areas in Neonatal and Pediatric Pulmonary Research

There are many unanswered questions regarding LRTI in children from a developmental and clinical perspective. First, should we try to prevent viral respiratory infections prenatally and in childhood, or should we seek to reduce their severity? Is the concept of a "viral hygiene hypothesis" plausible? Second, nearly all infants and young children develop viral respiratory infections, but only a subset are critically ill or suffer long-term consequences. What is the role of lung development in this risk, and how does viral LRTI impact lung development? Finally, how do we improve short- and long-term respiratory outcomes? We need to know which outcomes are clinically meaningful, measurable, and modifiable, their public health and social impact, the correlates of protection (mucosal vs. systemic), and if the intervention(s) are cost-effective. Addressing these knowledge gaps will require developing carefully followed birth cohorts that incorporate comprehensive analytical tools with longitudinal follow-up to adulthood.

Deciphering responses to infection unique to children will rationally guide studies related to predictive tools, endotyping, and host-directed therapies. Approaches that mitigate airway damage caused by an overly robust inflammatory response and mucus production while favoring viral clearance in young children are needed. Masks, social distancing, and hand hygiene should not be overlooked. An important aspect to study would be whether these nonpharmacological preventive strategies, which may delay "normal" acquisition of viral infections, lead to downstream immunologic and pulmonary effects that impact development and vulnerability to future infections. Addressing these knowledge gaps and others highlighted by this Workshop will provide new opportunities for discriminating which subjects are at risk for accelerated decline in pulmonary function and who will benefit from interventions to prevent such complications. We encourage the scientific community to view these challenges in clinical care on pulmonary health trajectories and disease burden not as a window of susceptibility but as a window of opportunity.

4 | Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed for articles published from January 1971 to June 2023, by use of the terms "Pulmonary Immune Ontogeny," "Pulmonary development," "Viral LRTI," "severity," "window of opportunity," and "COVID-19". Articles from these searches and relevant references cited in those articles were reviewed.

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Disclosure

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the US Department of Health and Human Services.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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