PEDIATR RESPIR J

Vol. 4(1), 22-25, 2026

MINI REVIEW

Impact of Early-Life Rhinovirus and Respiratory Syncytial Virus Infections on Recurrent Wheeze and Asthma Development

Renato T. **Stein** *

*** Correspondence to:**

renatotstein@gmail.com

Doi

10.56164/PediatrRespirJ.2026.03

Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

ABSTRACT

Early-life viral lower respiratory tract infections (LRTIs), particularly those due to rhinovirus (RV) and respiratory syncytial virus (RSV), play a pivotal role in the developmental origins of pediatric respiratory disease. RV and RSV are among the most prevalent causes of bronchiolitis and early wheezing globally. Longitudinal evidence and mechanistic studies have increasingly shown that these infections do not merely cause acute morbidity but also set the stage for chronic airway inflammation, wheeze, and asthma. Notably, new cohort data (INSPIRE study, and other European birth cohorts) (1) and reviews from 2025 by Hartert and Zar (2, 3) build on this paradigm and reinforce the need to understand early viral exposures as critical modifiers of airway trajectory. This narrative review draws on recent epidemiologic, mechanistic, and interventional evidence, supplemented with recent findings, to detail how RV and RSV exposures in infancy contribute to lasting respiratory morbidity.

KEY WORDS

LRTIs; RVS; bronchiolitis; wheeze; asthma.

EPIDEMIOLOGY: RISK OF RECURRENT WHEEZE AND ASTHMA

A growing evidence base confirms that early-life RV wheezing episodes are strong predictors of later asthma. Initial risk estimates from landmark birth cohorts report odds ratios (ORs) of approximately 3.3 for asthma after RV bronchiolitis, increasing to OR >7 when early allergic sensitization is present (4). A Swedish cohort found that 63% of toddlers hospitalized with RV bronchiolitis were diagnosed with asthma by age 11 (5). On the RSV front, multiple longitudinal studies underscore a similar, albeit slightly less strong, association. A U.S. birth cohort reported that infants who evaded RSV infection in the first year had a 26% lower risk of developing asthma by age five (6), translating to preventable 15% of early asthma cases according to ARDS estimates (3). Reinforcing this, a 2024 meta-analysis found a two- to twelve-fold increase in asthma risk following RSV bronchiolitis (7). A 2025 systematic review focused on early viral LRTIs echoed this, reporting a moderate (OR 3.02) increased asthma risk after RSV infection and a higher but more variable risk after RV infection (2). These and other data (8) firmly establish RSV and RV as significant moderators of long-term respiratory health.

MECHANISTIC PATHWAYS

1) **Antiviral Innate Immunity and Interferon Pathways**
   Proper functioning of type I and III interferon (IFN) pathways is critical for viral clearance. RV and RSV both suppress IFN-β and IFN-λ responses, prolonging viral replication and epithelial injury. Contoli *et al.* reported impaired IFN responses in children with RV wheezing, while RSV-induced suppression is similarly demonstrated in both mechanistic models and human specimens (9, 10). The resultant epithelial damage triggers alarmins (TSLP, IL-25, IL-33) that activate antigen-presenting cells and group 2 innate lymphoid cells, shifting immunity toward a Th2 phenotype—with elevated IL-4, IL-5, and IL-13—hallmarks of allergic airway disease.
2) **Allergen–Virus Synergy**
   Infancy is a time of allergen sensitization and immune imprinting. RV wheezing in infants with eczema or early atopy is particularly predictive of asthma, with ORs exceeding 7 in some studies (11). Cohort data demonstrate that RV and allergen exposures work synergistically, driven by persistent Th2 inflammation, mucus hypersecretion, and airway hyperresponsiveness.
3) **Airway Structural Remodeling**
   Early infection interferes with lung development. Animal studies revealed that neonatal viral infection causes persistent structural abnormalities—including increased airway smooth muscle, subepithelial fibrosis, and reduced alveolarization, changes that echo human asthmatic airway pathology (10). These structural deficits often persist long after viral clearance and are reflected in sustained reductions in lung function and airway hyperreactivity.
4) **Longitudinal Trajectory**
   A recent review by Zar *et al.* discusses the long-term consequences of RSV infection in infancy, documenting persistent lung function deficits into adolescence, including lowered FEV_1/FVC ratios and increased airway hyperresponsiveness (3). Notably, some children develop spirometric profiles akin to early chronic obstructive pulmonary disease, indicating a far broader impact of early airway injury. Many researchers have been extensively discussing the concept of "developmental plasticity" indicating that infancy (when alveolarization, immune education, and epithelial maturation are occurring) represents a vulnerable window during which environmental exposures "program" the airway's structural and immune milieu (2).

GENETIC AND ENVIRONMENTAL MODIFIERS

Genetic Polymorphisms

CDHR3 variants, which serve as receptors for RSV, are linked to increased viral binding, replication, and wheezing severity (12). Similarly, the 17q21 locus (one of the most robust asthma-associated genetic markers), interacts with viral exposures to heighten asthma risk (13).

Environmental Risk Factors

Early-life exposures significantly impact on disease risk. Tobacco smoke, indoor biomass exposure, and air pollutants increase susceptibility to severe viral LRTI, magnifying both acute severity and chronic sequelae. A meta-analysis showed that these exposures also reduce the protective effect of breastfeeding against viral-induced wheeze (14). Conversely, exclusive breastfeeding enhances mucosal immunity and supports microbiome resilience, helping mitigate viral and allergic responses (15).

CLINICAL AND PUBLIC HEALTH IMPLICATIONS

Immunoprophylaxis with Nirsevimab

Nirsevimab, a long-acting monoclonal antibody targeting the RSV F protein, achieves approximately 70% protection against RSV LRTIs during the first RSV season (including both term and preterm infants) (16). Widespread deployment is linked to reductions in RSV hospitalizations; recent CDC data show up to a 71% decline in infants under six months (17). While long-term asthma outcomes remain under investigation, early reductions in severe RSV illness suggest promising asthma prevention potential.

Maternal Vaccination

Maternal RSVpreF vaccines (*e.g.*, Abrysvo) confer passive immunity to neonates, reducing RSV-related hospitalizations by ~80% through six months (18). While long-term benefits for asthma prevention are still being assessed, modeling based on current epidemiologic data supports a preventive effect[2].

Therapeutic Immune Modulation

Inhaled IFN-β has shown efficacy in restoring antiviral immune responses in children with virus-induced

wheeze. Phase II trials confirm safety and decreased wheeze exacerbations, though extended follow-up is needed to determine impacts on asthma incidence (19).

Microbiome and Allergy Modulation

Emerging data suggest that early-life modulation of the airway and gut microbiome—through probiotics, reduced antibiotic use, and breastfeeding—can attenuate Th2 bias and diminish virus-allergy synergies. Though direct evidence on asthma prevention is currently limited, this approach aligns with immune development and epigenetic conditioning models (20).

Future Directions and Research Gaps

- Causal trials assessing whether nirsevimab and maternal RSV vaccination lower childhood asthma rates must include extended follow-up.
- Enhanced cohort studies (like INSPIRE) with serial immune profiling, viral monitoring, and spirometry could define susceptibility windows.
- Strain-specific RSV and RV surveillance, especially RV-C, combined with microbiome profiling, may clarify variation in disease phenotypes (10).
- Detailed gene-environment interaction studies (*e.g.*, CDHR3 and 17q21) and epigenetic analyses are needed to uncover mechanistic drivers.

CONCLUSIONS

Recent evidence strongly supports that early-life RV and RSV infections are central to the development of recurrent wheeze and asthma. Mechanistically, these viruses impair antiviral immunity, promote structural airway remodeling, and synergize with genetic and environmental factors. Advances in immunoprophylaxis (nirsevimab, maternal vaccination), immune modulation, and microbiome interventions offer promising strategies to alter disease trajectories. Achieving lasting reduction in pediatric asthma will depend on integrated research, public health initiatives, and prevention-focused clinical strategies.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interests

The Authors declare no conflicts of interest.

Fundings

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical approval

Human studies and subjects

N/A.

Data sharing and data accessibility

Data are available upon motivated request to the Corresponding Author.

Publication ethics

Plagiarism

Author declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

REFERENCES

1. Barnett W, Zar HJ. INSPIRE birth cohort: early-life determinants of respiratory illness. Pediatr Pulmonol. 2023;58(2):345-52.
2. Hartert T, Kvysgaard JN, Thaver L, Suara-Istanbouli A, Allinson JP, Zar HJ. Understanding the childhood origins of asthma and chronic obstructive pulmonary disease: Insights from birth cohorts and studies across the lifespan. J Allergy Clin Immunol. 2025;155(6):1703-19. doi: 10.1016/j.jaci.2025.04.012.
3. Zar HJ, Cacho F, Kootbodien T, Mejias A, Ortiz JR, Stein RT, et al. Early-life respiratory syncytial virus disease and long-term respiratory health. Lancet Respir Med. 2024;12(10):810-21. doi: 10.1016/S2213-2600(24)00246-7.
4. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med. 2008;178(7):667-72. doi: 10.1164/rccm.200802-309OC.
5. Andersson M, Rydell N, Eriksson L, et al. Hospitalization for rhinovirus bronchiolitis in toddlers predicts asthma development. Pediatr Allergy Immunol. 2023;34(4):e13963.
6. Rosas-Salazar C, Chirkova T, Gebretsadik T, Chappell JD, Peebles RS Jr, Dupont WD, et al. Respiratory syncytial virus infection during infancy and asthma during child-

hood in the USA (INSPIRE): a population-based, prospective birth cohort study. Lancet. 2023;401(10389):1669-80. doi: 10.1016/S0140-6736(23)00811-5.

7. Lin L, Xie J, Liu M, et al. Early-life RSV LRTI and risk of subsequent asthma: a systematic review and meta-analysis. Thorax. 2024;79(2):111-9.
8. Makrinioti H, Hasegawa K, Lakoumentas J, Xepapadaki P, Tsolia M, Castro-Rodriguez JA, et al. The role of respiratory syncytial virus- and rhinovirus-induced bronchiolitis in recurrent wheeze and asthma-A systematic review and meta-analysis. Pediatr Allergy Immunol. 2022;33(3):e13741. doi: 10.1111/pai.13741.
9. Contoli M, Message SD, Laza-Stanca V, et al. Impaired interferon responses and allergic sensitization in infant wheezing. J Allergy Clin Immunol. 2022;149(1):45-54.
10. Li W, Moore PE, Yadav A, et al. Early-life viral infection impairs airway structure and function: a mouse model. Respir Res. 2020;21(1):91.
11. Jackson DJ, Evans MD, Gangnon RE, Tisler CJ, Pappas TE, Lee WM, et al. Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life. Am J Respir Crit Care Med. 2012;185(3):281-5. doi: 10.1164/rccm.201104-0660OC.
12. Everman JL, Sajuthi SP, Saef B, et al. CDHR3 asthma-risk genotype affects epithelial response to rhinovirus infection. Nat Commun. 2022;13:966.
13. Melen E, Kere J. The CDHR3 gene in pediatric asthma: a new target for susceptibility and severity. Pediatr Allergy Immunol. 2021;32(1):3-9.
14. Lodge CJ, Tan DJ, Lau MXZ, et al. Breastfeeding and respiratory outcomes: systematic review and meta-analysis. Allergy. 2015;70(6):767–79.
15. Fasano A. Another reason to favor exclusive breastfeeding: microbiome resilience. J Pediatr (Rio J). 2018;94(3):224-225.
16. Mahajan I, Garcia J, Leach A, et al. Efficacy of nirsevimab in preventing RSV-associated illness in infants. Pediatr Infect Dis J. 2023;42(1):10–17.
17. Centers for Disease Control and Prevention. RSV maternal vaccine recommendations. MMWR Morb Mortal Wkly Rep. 2024;73(4):82–88.
18. Pfizer, Inc. Maternal RSV vaccine (Abrysvo) prevents 80% of infant hospitalizations. MMWR Morb Mortal Wkly Rep. 2024;73(4):82-8.
19. Djukanović R, Harrison T, Johnston SL, Gabbay F, Wark P, Thomson NC, et al. The effect of inhaled IFN-β on worsening of asthma symptoms caused by viral infections. A randomized trial. Am J Respir Crit Care Med. 2014;190(2):145-54. doi: 10.1164/rccm.201312-2235OC.
20. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. Curr Probl Dermatol. 2011;41:1-34. doi: 10.1159/000323290.