Respiratory Syncytial Virus and Asthma Inception: Cause and Effect, or Shared Susceptibility?

RSV and asthma inception – cause and effect or shared susceptibility?

Helen E Groves[1,2],

Michael D Shields[1,2]

1. **Wellcome Wolfson Centre for Experimental Medicine, Queens University Belfast**
2. **Royal Belfast Hospital for Sick Children, Belfast**

For many asthma patients, the natural history of the disease starts with an initial presentation in infancy and early childhood. Episodes of recurrent wheeze in infancy are very common. For instance, the international study of wheezing in infants identified 45% of infants under one year of age had at least one episode of wheezing and 20% reported recurrent episodes of wheeze.[1] For most these episodes do not persistent beyond early childhood, but for some wheezing episodes progress into later childhood and adolescence with the development of the classical asthma phenotype. Research in this early age group is challenging in view of the important limitations of performing bronchoscopy and studies of airway structure in young infants. While it is well established that a range of allergens, infections and even exercise can contribute to exacerbations and progression of asthma,[2–4] the mechanisms responsible for inception of the asthma phenotype are less clear.

In recent years there has been increased emphasis on the potential role of viral respiratory tract infections (RTIs) in asthma inception. It is recognized that viral RTIs in early life are associated with greater risk of recurrent wheezing in infancy and the subsequent development of asthma. In particular, severe bronchiolitis is a strong predictor for later development of asthma and there is now a large body of emerging evidence linking both rhinovirus (RV) and respiratory syncytial virus (RSV) bronchiolitis and asthma inception.[5] In infants diagnosed with RSV related lower RTI, the odds of later developing asthma ranges from 2 to 13 and in infants with RV related lower RTI, the odds of later developing asthma ranges from 2 to 10.[5–8] The VINKU-study demonstrated RV and allergic sensitization were significantly associated with recurrent wheezing in later infancy and RV-associated wheeze episodes in the first two years of life occurred more commonly in infants aged over six months.[9] Interestingly the TABS study showed that birth four months before the winter virus peak, which correlates strongly with peak RSV bronchiolitis infection, carried a higher risk of later asthma development compared to birth twelve months prior to the peak, suggesting younger age of bronchiolitis infection may correlate with subsequent asthma risk.[10]

In the same issue of this journal, a study conducted by Homaira and colleagues on a large population in New South Wales has also demonstrated that severe RSV disease is associated with an increased risk of subsequent asthma hospitalization in early childhood.[11] This study adds a novel perspective, showing that the increased risk in this cohort was age related, being at least 2-7 fold greater in infants whose first episode of severe RSV disease was after six months of age compared to children whose first RSV hospitalization occurred in the first six months of life. While this study was limited to capturing only subsequent asthma hospitalizations and not primary or ambulatory care attendances, it none-the-less adds new and important data on this subject. Interestingly, the authors also noted a dose-response relationship showing greater rates of asthma hospitalization in later childhood with greater age of first severe RSV disease. Homaira and colleagues postulate a number of possible explanations for this unexpected finding, including waning maternal antibody levels in older infants and greater capacity for modification and airway remodeling in infants under 6 months of age. They also speculate that children developing severe RSV related disease in later infancy may already have begun to manifest an underlying susceptibility that is later evidenced by the subsequent development of asthma.[11]

This point underscores one of the greatest challenges in discerning the role played by early life viral RTIs and asthma inception. Certainly, as discussed, the evidence of a link is strong. However, it remains unclear whether the occurrence of severe viral RTIs in infancy causes structural and functional changes that later manifest as asthma, if the association is due to shared innate susceptibility to both viral RTIs and asthma, or indeed if these early viral RTIs are simply the initial appearance of asthma.[5] Specifically in relation to RSV RTI, a number of genetic polymorphisms associated with both RSV and asthma have been identified, many of which are involved in immune responses, raising the possibility of individual immune susceptibility.[5] However, there is also an increasing body of evidence regarding a possible causality relationship. RSV infection leads to a number of long-term changes in immune developments and in animal models has been shown to cause pathophysiological changes similar to those noted in asthma.[12,13] The importance of this debate, as eluded to by Homaira and colleagues, is entwined with the potential development of a new RSV vaccine or specific therapy to prevent severe RSV infection. If achieved, such interventions might represent an opportunity to modify subsequent asthma development. However, it is important to note, as discussed by Feldman *et al* In their very thorough review on this topic, that in all likelihood viral RTIs do not constitute the sole causative agent for asthma inception and indeed multiple risk factors, many of which may yet remain unidentified, likely play a role.[5] On the other hand, given that the majority of infants are infected with RSV during the first year of life and it has been estimated that on a population level, 13% of asthma is associated

with infant bronchiolitis during RSV season,[14] RSV prevention is a tantalizing target. Interestingly, a report this year from a single-blind extension of the MAKI trial (ISRCTN73641710) looking at the effect of RSV immunoprophylaxis in late preterm infants on later asthma development did show decreased parental report of current asthma in the RSV prevention group compared to placebo (absolute risk reduction 7.4%, 95% CI 1.5 to 13.2).[15] However, these results should be interpreted cautiously given that the proportion with current physician-diagnosed asthma was similar and indeed the authors suggest results reflect a common predisposition for RSV-related RTI and asthma rather than causation.[16]

Therefore, the debate regarding the role of RSV in initial asthma inception continues. Further work on associated immunological mechanisms, such as that by Turi *et* al who recently identified distinct clusters of nasal immune-response pathways present at first RSV or RV infection which were associated with subsequent development of wheezing,[17] may help more clearly define this relationship. We echo the recent call by Ramilo *et al.* for larger prospective cohort studies to carefully delineate virological and immunological parameters that underpin RSV disease severity and determine the subsequent development of recurrent wheeze.[18] This exciting era of potential novel RSV therapeutic and vaccine strategies may provide an opportunity to modify the severity of RSV disease and, with the possibility of impacting post RSV-wheezing phenotypes and ensuing asthma inception, surely that is an aim worth pursuing. One strategy being pursued for RSV prevention is the development of a maternal RSV vaccine to boost antibody protection in the newborn. Several candidate vaccines are being developed and results of a recent phase three trial of the Novavax maternal RSV F vaccine candidate are anticipated within in the next year.[19] It is important to note that the decay of maternally transferred antibodies can occur by four months of age.[20] Therefore, a maternal RSV vaccine may provide protection against severe RSV-related lower RTI in children under this age but effectiveness could be less for infants over six months of age. Accordingly, the work by Homeria *et al.* is very timely and highlights that there may be an additional need for an efficacious RSV vaccine in infants aged over six months if indeed RSV plays a causative role in asthma inception.

References

1. Mallol J, García-Marcos L, Solé D, et al. International prevalence of recurrent wheezing during the first year of life: Variability, treatment patterns and use of health resources. *Thorax*. 2010;65(11):1004-1009. doi:10.1136/thx.2009.115188.
2. Platts-Mills T. Allergen avoidance in the treatment of asthma and allergic rhinitis - UpToDate. 2017:207-208.
3. Wark PAB, Gibson PG. Asthma exacerbations · 3: Pathogenesis. *Thorax*. 2006;61(10):909-915. doi:10.1136/thx.2005.045187.
4. Dougherty RH, Fahy J V. Acute exacerbations of asthma: Epidemiology, biology and the exacerbation-prone phenotype. *Clin Exp Allergy*. 2009;39(2):193-202. doi:10.1111/j.1365-2222.2008.03157.x.
5. Feldman AS, He Y, Moore ML, Hershenson MB, Hartert T V. Toward Primary Prevention of Asthma Reviewing the Evidence for Early-Life Respiratory Viral Infections as Modi fi able Risk Factors to Prevent Childhood Asthma. 2015;191(1):34-44. doi:10.1164/rccm.201405-0901PP.
6. Escobar GJ, Ragins A, Xu Li S, Prager L, Masaquel AS, Kipnis P. Recurrent Wheezing in the Third Year of Life Among Children Born at 32 Weeks' Gestation or Later. *Arch Pediatr Adolesc Med*. 2010;164(10):915-922.
7. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *AmJRespirCrit Care Med*. 2000;161(5):1501-1507. doi:10.1164/ajrccm.161.5.9906076.
8. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing Rhinovirus Illnesses in Early Life Predict Asthma Development in High-Risk Children. *Am J Respir Crit Care Med*. 2008;178:667-672. doi:10.1164/rccm.200802-309OC.
9. Jartti T, Lehtinen P, Vuorinen T, Ruuskanen O. Age and Previous Wheezing Episodes Are Linked to Viral Etiology and Atopic Characteristics. *Pediatr Infect Dis J*. 2009;28(4):311-317. doi:10.1097/INF.0b013e31818ee0c1.
10. Wu P, Dupont WD, Griffin MR, et al. Evidence of a Causal Role of Winter Virus Infection during Infancy in Early Childhood Asthma. *Am J Respir Crit Care Med*. 2008;178:1123-1129. doi:10.1164/rccm.200804-579OC.
11. Homaira N, Briggs N, Oei J, et al. The Journal of Infectious Diseases Association of age at first severe RSV disease with subsequent risk of severe asthma : a population-based cohort study. *J Infect Dis*. 2018.
12. Kim EY, Battaile JT, Patel AC, et al. Persistent activation of an innate immune axis translates respiratory viral infection into chronic lung disease. *Nat Med*. 2008;14(6):633-640. doi:10.1038/nm1770.Persistent.
13. Peebles RS, Sheller JR, Johnson JE, Mitchell DB, Graham BS. Respiratory syncytial virus infection prolongs methacholine-induced airway hyperresponsiveness in ovalbumin-sensitized mice. *J Med Virol*. 1999;57(2):186-192. doi:10.1002/(SICI)1096-9071(199902)57:2<186::AID-JMV17>3.0.CO;2-Q.
14. James K, Gebretsadik T, Escobar G, et al. Risk of Childhood Asthma Following Infant Bronchiolitis During RSV Season. *J Allergy Clin Immunol*. 20143;132(1):227-229. doi:10.1016/j.jaci.2013.01.009.Risk.
15. Scheltema NM, Nibbelke EE, Pouw J, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. *Lancet Respir Med*. 2018;6(4):257-264. doi:10.1016/S2213-2600(18)30055-9.
16. Scheltema NM, Nibbelke EE, Pouw J, et al. RSV prevention in infancy and asthma in later life –

Authors' reply. *Lancet Respir Med*. 2018;6(7):e33. doi:10.1016/S2213-2600(18)30232-7.
17. Turi KN, Shankar J, Anderson LJ, et al. Infant Viral Respiratory Infection Nasal-Immune-Response Patterns and Their Association with Subsequent Childhood Recurrent Wheeze. *Am J Respir Crit Care Med*. 2018;198(8):1064-1073. doi:10.1164/rccm.201711-2348OC.
18. Ramilo O, Mejias A. Respiratory Syncytial Virus – induced Acute Disease Severity and Long-Term Wheezing Uncovering the Unexpected. *Am J Respir Crit Care Med*. 2018;198(8):984-986. doi:10.1164/rccm.201805-0908ED.
19. Novavax. A Study to Determine the Safety and Efficacy of the RSV F Vaccine to Protect Infants Via Maternal Immunization. Available at: https://clinicaltrials.gov/ct2/show/NCT02624947. Accessed November 15, 2018.
20. Wu P, Hartert T V. Evidence for a causal relationship between respiratory syncytial virus infection and asthma. *Expert Rev Anti Infect Ther*. 2011;9(9):731-745. doi:10.1586/eri.11.92. Evidence.