Targeted strategies are needed to prevent childhood asthma

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Strategies that effectively target specific bronchiolitis endotypes will lead to better treatment modalities and bring us closer to our ultimate aim of childhood asthma prevention https://bit.ly/3IxcqcB

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In this issue of *European Respiratory Journal*, RAITA *et al.* [1] examined nasopharyngeal samples from 244 infants less than 1 year of age who were hospitalised with first-time respiratory syncytial virus (RSV) bronchiolitis in the USA and their association with asthma development by 5 years. The authors measured RSV (the most common viral pathogen causing bronchiolitis) and human rhinoviruses (RV) and examined metatranscriptomic profiles to determine whether specific endotypes of bronchiolitis may be associated with later development of asthma. This is an important research priority, as bronchiolitis represents a major cause of infant hospitalisation and mortality worldwide. Most recent estimates suggest that there are more than 3 million cases of RSV hospitalisations and approximately 60 000 deaths in children less than 5 years of age each year [2]. Moreover, there is significant phenotypic variation in bronchiolitis presentation [3] and there are no objective clinical markers to indicate which children may be at increased risk of asthma. This is important as it would guide future management options and surveillance strategies. The interactions between viruses (such as RSV and RV) and resident bacteria might also influence asthma risk. As societies emerge from the COVID-19 pandemic and associated public health measures, a reduction in transmission of other respiratory pathogens such as RSV has resulted in primary infection occurring at an older age [4]. The longer term immunological effects of this and the potential impact on asthma outcomes are yet to be determined. A recent study showed that asthma risk was higher in children whose first RSV infection occurred at 6–23 months, as compared to 0–6 months [5]. Despite the global burden of RSV, no vaccines are currently widely available and treatment options remain limited. Studies that provide a framework to develop novel strategies to combat this common paediatric problem are therefore urgently needed.

Using an integrated omics approach, the authors identified five biologically distinct profiles in the upper respiratory tract of children with bronchiolitis, each associated with different levels of asthma risk. All profiles were RSV-positive (as expected from a bronchiolitis cohort), and two profiles were found to be associated with the highest asthma risk: the first, RSV with *H. influenzae* (adjusted OR 2.81, 95% CI 1.11–7.26) and the second, RSV with *S. pneumoniae* (adjusted OR 2.49, 95% CI 1.10–5.87). These findings support previous data in children showing an association between these common pathogens and asthma [6]. Whilst not directly comparable, a recent meta-analysis of 2624 children <18 years of age across 20 different studies linking individual participant microbiome data with acute and chronic paediatric respiratory disease found a non-specific signature dominated by *H. influenzae* and *S. pneumoniae* [7]. Importantly, the current study extends this knowledge by identifying bronchiolitis endotypes during early life that are associated with the later development of childhood asthma. This is a critical time period when the microbiome and infant immune system is rapidly maturing in response to a multitude of environmental exposures.

Asthma is a heterogenous condition with several clinical phenotypes and likely distinct mechanistic drivers [8]. A *Lancet* commission on asthma recently highlighted this heterogeneity and the limitations of the "one-size-fits-all" approach to asthma management currently used [9]. Interventions to prevent asthma are urgently needed. Severe RSV infection in early life may play a role in asthma pathogenesis; however, the

aetiopathological mechanisms remain elusive. The identification of novel asthma endotypes would facilitate the development of more targeted preventative interventions and therapeutic strategies. This would assist in identifying, at an early age, those at higher risk of asthma that warrant early surveillance and in guiding treatment approaches. Significant research has been invested in this area but has not yielded much success to date. The findings by RAITA *et al.* [1] on the identification of distinct metatranscriptome "endotypes" of severe bronchiolitis associated with asthma development offers much promise and will facilitate precision medicine [10]. The ability to target these metatranscriptomic profiles at an individual level to predict disease severity and/or later development of clinical phenotypes, such as wheezing illness and asthma, would be a major breakthrough. Many questions have been raised from this research which will hopefully lead to better defined strategies to protect our most vulnerable infants.

The role of the microbiome in the pathogenesis of chronic diseases is well recognised. Much of this evidence comes from the gut microbiome but emerging data also suggests that the respiratory microbiome plays an important role in maintaining the balance towards health or disease [11, 12]. The metatranscriptome profiles identified in the current study provide the necessary impetus and justification for future studies investigating novel respiratory microbiome interventions. One such example of this approach is the use of oral bacterial lysate preparations in infants which have been shown to be effective in reducing recurrent wheeze episodes and asthma exacerbations [13]. Another interesting finding from the study by RAITA *et al.* [1] was that a metatranscriptome profile dominated by the bacterium *M. nonliquefaciens* was associated with a non-significantly lower risk of asthma development by 5 years of age (adjusted OR 0.47, 95% CI 0.10–1.65). It is tempting to speculate that while interventions focusing on this bacterium might be beneficial for asthma, the pathogen has also been associated with rare but life-threatening invasive disease [14]. This highlights the delicate balance of viral and bacterial organisms in the nasopharynx and their complex interactions with host immune responses. In a related publication by the same authors, amongst infants with RSV bronchiolitis, an endotype associated with a co-dominance of *H. influenzae* and *S. pneumoniae* and high interferon-mediated inflammatory responses was associated with a higher risk of developing asthma (OR 6.00, 95% CI 2.08–21.9; p=0.002) [15], which is suggestive of potential synergy between pathogens.

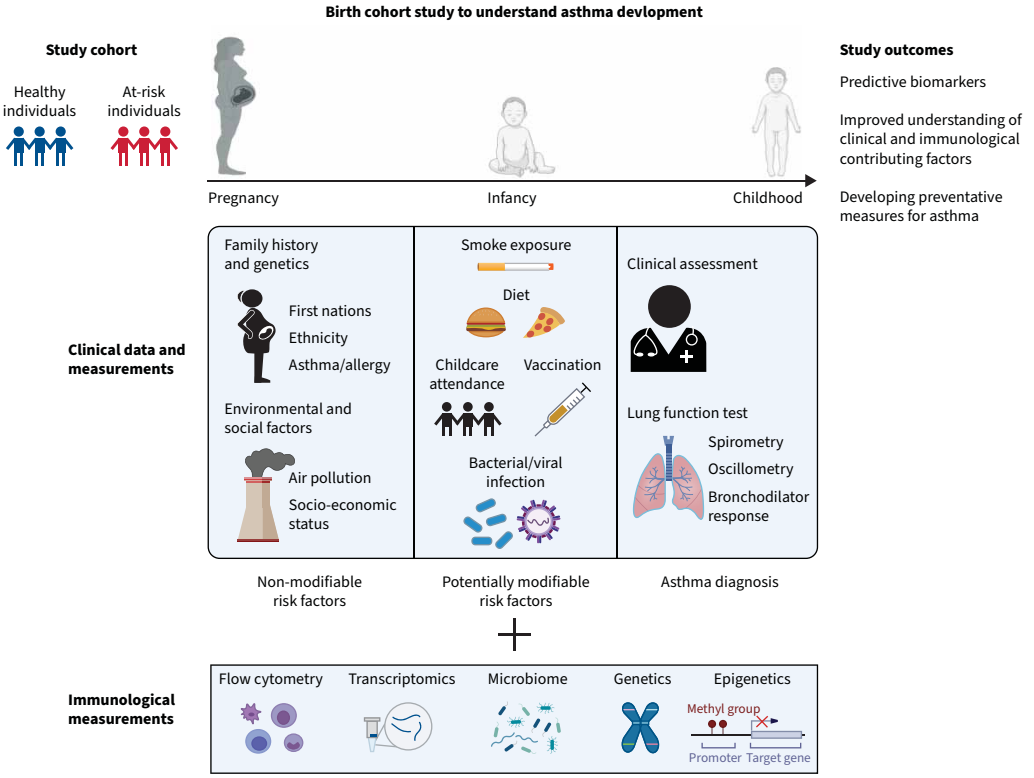

FIGURE 1 Ideal birth cohort study. A schematic describing the key features and advantages of a birth cohort study to determine the role of potentially modifiable and non-modifiable risk factors in the development of childhood asthma.

Taking a broader view, this research has sharpened the focus on bronchiolitis as a disease endpoint and RSV as the major causative pathogen. RSV-bronchiolitis is responsible for a major proportion of paediatric hospitalisations worldwide. Given that a high proportion of these hospitalisations occur in low- and middle-income country (LMIC) settings, this number is likely to be significantly underestimated. Primary prevention of RSV infection represents an extremely important public health priority. There is an urgent need for effective and safe vaccines to prevent RSV infection. This is likely to be a combination of maternal vaccination and monoclonal antibody-based immunoprophylaxis for infants [16]. Such interventions may have profound effects on the early life trajectory to asthma in susceptible populations.

Validating this study's findings in larger and geographically diverse cohorts is a necessary next step. For example, it is not yet known whether these or different metatranscriptomic profiles are observed in LMIC settings. Many factors are likely to influence microbiome profiles and asthma risk which likely differ from the USA, where the current study was conducted. One key difference is that pneumococcal carriage rates are much higher in LMIC settings [17] due to limited access to pneumococcal conjugate vaccines and this will likely affect the interactions with viruses such as RSV. Another factor that was not considered in the present study was the role of preterm birth, as this was an exclusion criteria. In many LMICs, preterm births are increasingly common and are a well-known risk factor for RSV bronchiolitis and chronic lung disease [18]. Importantly, preterm infants have distinct microbiome and immune system profiles which in turn may have important effects on the development of wheezing and asthma [19]. Different approaches to study these relationships should be considered. One approach that would allow careful examination of viral effects on host immune responses would be a human challenge study. However, as these are largely conducted in healthy adults [20, 21], the results may not be generalisable to high-risk infant populations who are most susceptible. An ideal study design would be a well-conducted, adequately powered birth cohort study (figure 1). Longitudinal follow-up of participants with evaluation of early life exposures (risk factors and effect modifiers) will inform the mechanisms that drive RSV bronchiolitis and asthma pathogenesis. In a LMIC setting where the burden of RSV disease is substantial, such a study could be feasible in the context of sample size and study power to detect meaningful differences in clinical outcomes. To undertake such studies requires significant motivation and investment on the part of funders (both government and philanthropic) and researchers.

In conclusion, Raita *et al*. [1] provide novel data that extend our understanding of the complex interplay between RSV, the upper airway microbiome and the host immune response. The finding that specific metatranscriptome profiles were associated with the subsequent development of asthma has important implications for future research and brings us one step closer to our goal. Strategies to effectively target these specific endotypes will lead to better treatment modalities and bring us closer to our ultimate aim of asthma prevention.

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