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Growing up with your airway microbiota: a risky business.

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Childhood is a critical time for respiratory health with environmental and infectious exposures being linked to future respiratory disease and susceptibility[1,2]. Respiratory microbiome research has introduced a new context for these exposures due to the presence of a pre-existing microbial community in both the upper and lower respiratory tract in healthy children[3-5]. Variation in community composition has been observed in chronic lung diseases[6,7] and particular microorganisms or combinations of organisms in infants have been associated with future disease development. Thus deviation from a healthy microbiota in early life appears to play an important role in disease development with changes evident by one week of age[8]. The dynamics of the infant airway microbiota and its relationship to disease development has therefore been the focus of increasing attention.

Acute respiratory infections are common in children under five years of age[9] and indications suggest that susceptibility might be, at least partly, determined by the microbiota[5,8]. Toivonen and colleagues have conducted the largest study of the respiratory microbiome in infants to date, obtaining a nasal swab at 2 months of age from 839 infants and parent recorded data on respiratory infections until 24 months of age to look at incidence of acute respiratory infections (ARI).

The study was conducted, described and controlled, taking into account many of the methodological issues that can arise when using the 16S rRNA gene sequencing approach for the microbiota[10].

There are clear and reproducible differences between sampling types and areas of the respiratory tract. Choices have to be made during study design as to the method and area most appropriate for the question and, pragmatically, one that can be obtained at scale[11,12]. In Toivonen and colleagues' Finnish cohort, nasal swabs were collected. Nasal swabs can be expected to represent the upper respiratory tract nasal microbiota and infections that start or are restricted to the nasopharynx. Although, the relationship with the lower respiratory tract may be less well represented; the necessary sampling for this would likely be prohibitive in a cohort of this size.

The authors stratified the infants according to their nasal microbiota, with each of the five resulting groups represented by a particular dominant organism. Of these the highest reported incidence rate of respiratory infections was in the *Moraxella*-dominant group and lowest rate in the Corynebacteriaceae group. These results echo that of previous, smaller longitudinal studies of the nasopharyngeal microbiota in infancy and add further evidence of a potentially pathogenic role for *Moraxella* and protective role of *Corynebacterium* in the risk of developing ARIs[8]. *Moraxella* has also been associated with respiratory disease in a range of different contexts, such as asthma[1] and chronic obstructive pulmonary disease[13]. It should be noted that although rigorous statistical methods have been applied, there is quite a large difference in numbers of infants in each of these groups and a future study might corroborate these findings by the targeted recruiting of equal numbers of study participants in each organism dominated group and recording ARI incidence. The lack of a

Haemophilus-dominated microbiota group is surprising as this was identified in a previous infant cohort as a risk for ARIs[5] and *Haemophilus* is an organism associated chronic lung diseases in childhood such as asthma[1] and primary ciliary dyskinesia[14]. This could be a feature of this cohort or might represent methodological differences and is worthy of additional exploration.

As Toivonen *et al* correctly state association does not prove causality. In this study a higher rate of respiratory viral detection was observed in the *Moraxella*-dominated group. Viral infections are recognised as a common cause of ARIs in infancy. The authors of this study were unfortunately unable to assess the inflammatory effects of different microbiota profiles. Although viral infections were adjusted for in their analyses, the interactions between viruses, the microbiota and host inflammation were not explored. *In vitro* work looking at interactions within and between microbes and the host may help us to better understand the causal mechanisms for these differences and determine therapeutic targets for promotion of lung health.

As the authors continue to follow-up these children longitudinally, it will be interesting to observe the impact of different microbiota profiles on later respiratory health and whether the children sampled stay within the same groups. Recurrent ARIs in the first year of life have been shown to be a significant risk factor for both reduced lung function at one year of age and hospitalisations with respiratory symptoms, particularly asthma, at three years of age in two large population based studies in children in South Africa[15] and Australia respectively[16]. Surprisingly, Toivonen *et al* did not find an association with microbiota profiles and recurrent wheezing, although this may reflect the low incidence of recurrent wheezing in this cohort, and the long term implications of this study on future lung health remain unknown. Nonetheless, there is a growing body of evidence that interventions to reduce the severity and frequency of ARIs in infancy could improve lung health.

What such interventions should entail, however, is debatable. Given the pathogenic role of *Moraxella* in promoting neutrophilic airway inflammation[17] and disease susceptibility, an argument could be made for aggressive antibiotic treatment for *Moraxella*-dominated communities. In an era of increasing antimicrobial resistance, caution should be taken when advocating such an approach in the absence of evidence of causation between *Moraxella* and lung disease. The current study reported greater use of systemic antibiotics in the *Moraxella* and *Streptococcus*-dominated groups before 2 months of age. It is unknown if the need for early antibiotic treatment is a result of or risk factor for development of a *Moraxella*-dominated community as such further longitudinal investigation into the development of the microbial community in early life is required.

The microbiota throughout the body has consistently been shown to be highly individual[18]. Personalised treatments based on risk-stratification by the dominant organism in the microbiota, similar to that used in this study, may prove beneficial. Such strategies have yet to be evaluated in paediatric cohorts

in whom the greatest window of opportunity exists to prevent abberant development of the microbiota and influence long-term respiratory health.

The insights afforded by this large, well-conducted study by Toivonen *et al* provide growing evidence that some microbiota profiles, potentially those dominated by *Moraxella*, may be related to an increased risk of future lung disease. Future work in this area exploring mechanisms of causation and longitudinal outcomes will help to determine if these microbiota profiles in infancy are truly risky or innocent bystanders in children with increased risk of ARIs.

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