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EDITORIAL

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The emerging role of viral and bacterial co-infection in early childhood

Key words: asthma, infection and inflammation, paediatric lung disease, viral infection

The upper airway becomes colonised with niche-specific bacterial communities early in life to create the respiratory microbiome. This is well established by about 12 months of age, with the historical concept of a sterile lower respiratory tract being supplanted by evidence of site-specific bacterial species colonising different levels of the respiratory tract[1]. Newer molecular techniques such as 16S ribosomal RNA sequencing have led to an appreciation of the complexity and dynamic nature of this process. Exposure to bacteria early in life plays a crucial role in the development of an effective immune response. The "hygiene hypothesis" proposes that lack of sufficient exposure to diverse microbial species predisposes to the development of asthma and atopy. The respiratory tract microbiome is most recognised in the nasopharynx, which is colonised by a variety of bacteria including potentially pathogenic microorganisms (PPMs) such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moxarella catarrhalis*. These PPMs generally do not cause clinical disease in the nasopharynx but when they move from this location, particularly into the lower respiratory tract they may induce acute respiratory infection (ARI).

Viral infection, both symptomatic and asymptomatic, is prevalent in childhood and interacts with the bacteria of the respiratory microbiome. This has been proposed to occur in two ways: directly, by viral binding to a bacterial cell or utilisation of a bacterial product; or more commonly, indirectly, where the viral infection increases host susceptibility to bacterial infection. The most recognised interaction is acute viral infection leading to bacterial infection of the lower respiratory tract. The influenza A virus (IAV) pandemic of 1918 caused at least 50 million deaths; a large proportion of which were probably due to complicating bacterial pneumonia[2]. An example of indirect interaction, viral neuraminidase exposes bacterial receptors by cleaving respiratory epithelial sialic acid[3]. Mallia *et al* infected a cohort of patients with COPD with rhinovirus (RV) and found that 60% of this cohort developed acute bacterial airway infection as determined by bronchoscopy[4]. In addition, the respiratory microbiome also influences the severity of viral infection[5].

Respiratory syncytial virus (RSV) is a ubiquitous seasonal infection in early childhood with universal exposure by 3 years of age. Most ARIs are mild or asymptomatic, however RSV causes approximately 200 000 deaths a year, mainly in developing nations[6]. RSV infection is also an important risk factor for the development of asthma, which may occur via modulation of the developing immune response. Recently it has been proposed that an interaction between RSV and the microbiome is an important factor in the pathogenesis of asthma; and this may also represent a therapeutic target[7]. Similarly, lower respiratory tract

infection (LRTI) with RV has been associated with later chronic wheeze in children with early atopy.[8]

Brealey *et al* studied the relationship between RSV infection and *S. pneumoniae* colonisation[9]. Sixty young children who presented with symptoms of an acute ARI to an emergency department, had nasopharyngeal aspirates taken. Quantitative PCR was used to screen for respiratory viruses and bacterial pathogens. This study found a significant association between the detection of RSV and *S. pneumoniae*. Interestingly, convalescent samples demonstrated significant reductions in the loads of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Similarly, in a prospective cohort study examining bacterial and viral nasopharyngeal microbiota, Teo *et al* demonstrated an association between *Moraxella* species and RSV in febrile LRIs. These data add to recently published studies on the entity of viral and bacterial co-infection in early life [8, 10].

The literature describes strong associations between viral infection and the detection of PPMs in the upper airway. This data is primarily associative and reflects the unique challenges in studying young children. At this stage, it is not clear if the bacterial findings from the nasopharynx reflect the lower airways or only represent localised expansion in unwell individuals[7]. The work by Brealey *et al*[9] builds on previous studies by showing that the combination of RSV and *S. pneumoniae* is associated with more severe ARIs. Further defining the entity of viral and bacterial infection will require longitudinal studies with control subjects and ideally imaging/sampling of the lower respiratory tract as well as

relevant animal models. Candidate antenatal vaccines against viral respiratory pathogens (such as RSV) are currently in phase III clinical trials; these may also offer insights as 'vaccine probe' experiments in observing how early immunity may affect microbiome development in children.

The studies of viral-bacterial co-infection in young children are currently at an early stage. However, this work may potentially have major implications for the management of young children with ARIs as the field develops. It may be useful in determining whether hospital admission is required and direct the appropriate use of antibiotics. Tantalisingly, it may also be a pathway to understanding factors involved in the development of asthma and new pathways of immunomodulation.

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