Determining the aetiology of lower respiratory tract illness in children

Acute lower respiratory tract infection (LRTI) is one of the leading causes of mortality in children aged <5 years, globally and especially in Africa.[1,2] Infants are at the highest risk of requiring hospitalisation and developing the most severe disease. Further specific environmental and host risk factors are associated with more severe disease, such as exposure to tobacco smoke, indoor air pollution, prematurity, malnutrition, and HIV infection or HIV exposure in infants. Besides the acute illness, LRTI, especially severe disease, may be associated with long-term morbidity including chronic lung disease and lung function impairment.[3] Timely identification of the cause of LRTI is therefore crucial to initiate appropriate therapy while preventing overuse of unnecessary treatment, especially in the era of antibiotic resistance. In addition, accurate diagnosis is important for epidemiological data, for informing new vaccines and interventions that may be needed, and for guiding cohorting of patients and infection control measures. The development of highly effective conjugate vaccines against *Haemophilus influenzae* type b and 10- or 13-valent pneumococcal conjugate vaccines against *Streptococcus pneumoniae* has led to a shift in the spectrum of pathogens causing pneumonia, with a reduced proportion of bacterial infections, while viruses contribute to a greater proportion of severe LRTI episodes.[4,5]

In this issue of *AJTCCM*, Marafungana *et al.*[6] describe viral pathogens in children with LRTI admitted to King Edward VIII Hospital, Durban, South Africa, from January 2018 to June 2020. Clinical and viral data were retrieved from inpatient files and laboratory records. Multiplex polymerase chain reaction testing was used for detection of viruses on different respiratory samples. The cohort represents children at high risk of severe LRTI, with a young age (median 5 months), and almost 50% being HIV exposed and a third malnourished. Adenovirus was the most commonly detected virus, followed by parainfluenza virus and respiratory syncytial virus (RSV). No seasonal pattern was identified for adenovirus-associated LRTI, in contrast to RSV- or parainfluenza-associated LRTI. However, viral data were only available in 16% of children admitted with LRTI over this time, and no data on bacterial or mycobacterial pathogens were obtained.

Globally, viral pathogens have been identified as a common cause of LRTI in children aged <5 years, with RSV being the most common cause of severe viral LRTI in infancy.[7] In a large case-control study of severe and very severe pneumonia in children hospitalised in seven low-and-middle-income countries including SA, the Pneumonia Etiology Research for Child Health (PERCH) Study, RSV was also the most common pathogen, identified in almost a third of cases.[8,9] Identification of adenovirus-associated LRTI may not be straightforward because detection of adenovirus is not invariably associated with LRTI, as adenovirus can be detected in the nasopharynx of children with upper respiratory tract infection as well as in healthy asymptomatic children.[8] A case-control approach would therefore be valuable in attributing aetiology. Further typing of adenovirus isolates may be helpful, as specific variants are associated with disease and long-term morbidity,[10] but these were not undertaken in the study by Marafungana *et al.*[6]

Determining the aetiology of LRTI may be challenging, especially in young children. Samples are often taken from the upper respiratory tract, such as nasopharyngeal aspirates or swabs, as these are relatively easy to obtain and have a high yield for PCR-based testing. However, testing of samples obtained from the upper respiratory tract may not discriminate between colonising and pathogenic organisms, making it difficult to attribute aetiology, unless the organism is invariably pathogenic, such as *Bordetella pertussis*, RSV or *Mycobacterium tuberculosis.* Use of a case-control design with healthy age-matched children enrolled during a similar time period serving as controls would be helpful in attributing aetiology. Multiplex PCR testing is highly sensitive for viral detection, allowing for multiple viral pathogens to be detected, even when these are colonising organisms. Obtaining samples of induced sputum may provide more accurate data on pathogens in the lower respiratory tract, and may be especially important for detection of *M. tuberculosis*.[11]

The role of co-infections in LRTI pathogenesis has also been increasingly appreciated. Co-infection including viral-bacterial co-infection and viral-mycobacterial infection is common, especially in severe LRTI. HIV exposure and malnutrition are well-recognised risk factors for LRTI in infants, as shown in this cohort. Among such vulnerable infants, additional pathogens such as *M. tuberculosis* and Gram-negative bacterial organisms including *Klebsiella pneumoniae* have also been found to be important pathogens.[12,13] Finally, the study also included a period of the COVID-19 pandemic in SA and the national lockdown that impacted on LRTI hospitalisations and circulation of viral pathogens, which were significantly reduced during this time, globally and in SA.[14]

Detection of adenovirus as a cause of LRTI may have important implications for long-term morbidity, as adenovirus LRTI may result in post-infectious bronchiolitis obliterans and bronchiectasis, requiring long-term follow-up.[15] However, the impact of all-cause LRTI on long-term health in children through adulthood is increasingly appreciated, including in the development of chronic obstructive pulmonary disease.[16,17] Data indicate that early-life LRTI is associated with reduced lung function and an increased risk of all-cause premature or respiratory mortality.[3,16] These findings underscore the importance of strategies to reduce risk factors, including nutritional support, avoidance of tobacco smoking and indoor air pollution exposure from the antenatal period through childhood, HIV prevention and control, tuberculosis preventive strategies, and optimal immunisation coverage.

The study highlights the increasing importance of viral pathogens in the pathogenesis of severe LRTI in children, including those with underlying comorbidities. Stronger strategies to prevent or ameliorate comorbidities are needed and new interventions to prevent viral LRTI are essential, as have recently been developed for RSV in infants.[18] Finally, the study highlights the need for long-term follow-up of children with severe LRTI who may have subsequent morbidity, to optimise their future health.

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