Childhood pneumonia: The Drakenstein Child Health Study

Advances in immunisation, improvements in socioeconomic status and effective HIV prevention and treatment strategies have reduced the population burden of childhood pneumonia and severe disease.[1] However, pneumonia remains the major single cause of death in children outside the neonatal period, causing approximately around 1 million deaths annually, or 15% of an estimated 6.3 million deaths in children aged <5 years.[2,3] This burden is disproportionately high in low- and middle-income countries (LMICs) and in Africa, where almost 50% of deaths in children aged <5 years occur, despite African children comprising only 25% of live births globally.[3,4] The incidence and severity of pneumonia are highest in the first year of life, especially in the first 6 months.[2,5]

New conjugate vaccines against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* (PCV) can substantially reduce the burden of childhood pneumonia in vaccinated children. Data from six studies of the effectiveness of Hib conjugate vaccine in LMICs reported reductions of 18% in radiological pneumonia, 6% in severe pneumonia and 7% in pneumonia-associated mortality.[6] The impact of PCV in reducing pneumonia hospitalisation, mortality, bacteraemic disease and clinical disease in children has been reported in several studies.[7-11] PCV immunisation of children has also led to a decline in hospitalisation and death due to pneumonia in adults as a result of indirect protection through reduction in circulating vaccine-type pneumococcal serotypes.[7]

Defining pneumonia epidemiology and aetiology in the context of strong immunisation programmes is an ongoing priority for child health. South Africa (SA) was the first African country to implement PCV immunisation in the national immunisation programme; 7-valent PCV was introduced for infants at 6 and 10 weeks and 9 months in 2009 and replaced with 13-valent PCV (PCV13) in 2011. In the context of relatively strong immunisation and primary healthcare programmes, it is important to understand the changing epidemiology and aetiology of childhood pneumonia.

The Drakenstein Child Health Study is an SA birth cohort study of 1 000 mother-child pairs that investigates the epidemiology, aetiology, risk factors and long-term outcome of childhood pneumonia and determinants of child health.[12] This study takes place at two primary healthcare clinics and one hospital in the Drakenstein subdistrict in Paarl, a periurban area outside Cape Town. Women enrolled during pregnancy are followed through childbirth, and mother-child pairs are followed until children are at least 5 years of age. Children receive primary healthcare and immunisation at clinics. Continuous pneumonia surveillance is undertaken.[13] Although the prevalence of HIV infection in pregnant women in the cohort was around 25%, only 2 children were HIV-infected, a reflection of the strong mother-to-child HIV-prevention programme. To assess pneumonia aetiology, a nested case-control study was done and respiratory specimens (nasopharyngeal swabs and induced sputum) were tested using a multiplex polymerase chain reaction to identify up to 33 potential respiratory organisms.[14]

We found that pneumonia remains a major cause of illness (incidence 0.27 episodes per child year) and hospitalisation, particularly in the first 6 months of life, despite excellent immunisation coverage including PCV13.[14] Several viruses, most strikingly respiratory syncytical virus (RSV, the most frequently detected pathogen), were strongly associated with pneumonia.[14] *Bordetella pertussis* was strongly associated with pneumonia, but occurred in a small number of children; *H. influenzae* (other than type b) was less strongly associated with pneumonia, but was common. Multiple potential pathogens were identified at each pneumonia episode, adding to evidence that childhood pneumonia may be due to infection with multiple organisms, particularly in the case of severe disease. Induced sputum provided an increased yield for potential pathogens compared with nasopharyngeal specimens, notably for *B. pertussis* and several viruses, suggesting that induced sputum can be used to improve diagnostic strategies even in very young infants.[14]

The high burden of childhood pneumonia may partly reflect high exposure to potential pathogens and to risk factors that may make a child vulnerable to pneumonia. Smoke exposure, lack of breastfeeding, prematurity or low birth weight, low socioeconomic status, crowded living conditions, or HIV infection or exposure are important risk factors for childhood pneumonia that were common in this setting and in LMIC settings generally.[2,4] Despite the high incidence of pneumonia and of severe disease, there was a low case fatality rate, attesting to good access to care and a strong primary healthcare programme including use of case management guidelines, antibiotics, oxygen, timely referral and access to hospital.[14]

With increasing uptake of PCV in LMICs, the proportion of lower respiratory tract infections (LRTIs) due to viruses, particularly RSV, may be expected to increase.[15,16] RSV was the commonest identifiable organism, and was associated with severe disease but not with mortality. This is consistent with global and African data preceding PCV that reported RSV to be the commonest pathogen in children with LRTI.[17] Globally RSV was estimated to cause approximately 34 million episodes of acute lower respiratory tract infections (ALRIs) in children aged <5 years, or 22% of all ALRIs; 10% of episodes resulted in severe illness and hospitalisation, and 99% of deaths occurred in LMICs. Further studies in African children preceding the availability of PCV,[18,19] and several recent case-control studies in children well vaccinated with PCV13, mostly from high-income countries, have reported RSV to be a predominant pathogen in children hospitalised with pneumonia.[20,21] Consistent with other studies, RSV occurred in young infants with the peak incidence under 6 months.[22] Maternal immunisation against RSV during late pregnancy may therefore be an attractive novel strategy to prevent disease in young infants.[23] In addition, *B. pertussis* occurred in young infants, and mostly before completion of the primary series of three immunisations; in turn, immunisation of pregnant women with *B. pertussis* may also be an effective strategy to prevent this burden.[24]

As health systems are strengthened, it is crucial to consider the impact of childhood pneumonia beyond acute disease in childhood or mortality. This is especially relevant as health systems are challenged to address the Sustainable Development Goals for 2030. Chronic sequelae from early childhood pneumonia such as bronchiectasis are increasingly recognised; one review reported chronic sequelae following severe pneumonia to occur in ~15% of children.[25] Early childhood pneumonia has increasingly been associated with the development of chronic non-communicable respiratory diseases into childhood and adulthood, such as asthma or chronic obstructive airways disease (COPD),[26] of which SA has one of the highest global prevalences. Accumulating evidence from several cohort studies has shown that lung health is established early in life and that lung function follows a set trajectory into adulthood, implying that the roots of adult lung disease such as COPD lie in early exposures including childhood pneumonia.[27]

For many African countries or LMICs, challenges remain in implementing available effective, preventive and management strategies

for childhood pneumonia.[28] However, the Drakenstein Child Health Study shows that even in LMIC settings with strong health programmes, pneumonia remains a major concern for child health. The strengthening and implementation of available effective preventive and management interventions, such as available immunisations and use of case management, have the potential to substantially reduce pneumonia burden and under-5 mortality.[6] Strategies to reduce risk factors, such as optimising nutrition, promoting breastfeeding, preventing HIV transmission through mother-to-child prevention programmes and reducing exposure to biomass or cigarette smoke, must be strengthened, particularly in Africa. However, our findings show that despite good application of these in this area and the low prevalence of HIV in children, there is a large residual burden of pneumonia, for which novel strategies are required.

While attention to reducing risk factors and strengthening health systems to deliver effective preventive and management strategies are a priority in LMICs, novel strategies are needed to reduce pneumonia incidence, especially looking beyond pneumonia mortality to the considerable associated morbidity and development of chronic disease. This is a key lesson from the Drakenstein Child Health Study, where despite good primary healthcare, high coverage with vaccines contained in the SA national immunisation programme, very low prevalence of HIV infection in children and good access to care, pneumonia remains a major cause of childhood illness.[14] Given the considerable burden of LRTI due to RSV and the young age of infants most vulnerable to disease and to developing severe LRTI, the development of several new RSV vaccine candidates is a promising development.[23] A novel strategy to immunise pregnant women in the third trimester of pregnancy to protect against RSV disease in their infants in the first few months of life has recently been developed.[23] This will probably need to be coupled with additional vaccination of infants to provide extended protection until children are 2 years of age. The challenge for African and other LMICs will be to ensure that such new strategies are accessible and affordable, if effective.

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