# Childhood pneumonia – looking beyond mortality

H J Zar

## Introduction

Pneumonia remains a major cause of morbidity and mortality in children globally despite a substantial decline in the incidence in the last decade.[1–3] Advances in immunisation, improvements in socio-economic status, and effective HIV preventative and treatment strategies have reduced the burden of childhood pneumonia and severe disease.[4] However, recent estimates are that globally pneumonia still causes approximately 15% (or just under 1 million deaths) of an estimated 6.3 million deaths annually in children under five years of age.[1] This burden is disproportionately high in Africa, where almost 50% of deaths in children under 5 years occur, despite African children comprising only 25% of live births globally.[1] Of concern, this proportion is estimated to increase by 2030, when African children are projected to account for 50% of global under-five mortality.[1] Pneumonia is the main cause of death in African children outside the neonatal period, accounting for approximately 18% of deaths in children under five years. Among African countries, Nigeria and the Democratic Republic of Congo (DRC) have an especially high burden of childhood pneumonia. Pneumonia incidence and severity is highest in the first year of life, especially in the first six months.[3]

## Why is the burden and severity of childhood pneumonia so high in African children and what are the possible interventions to address this?

Five factors will be considered in the following discussion. Firstly, risk factors that may make a child vulnerable to pneumonia or to severe disease may be especially prevalent in some African countries. Paediatric HIV is largely confined to sub-Saharan Africa, where 90% of HIV-infected children reside; HIV infection is an important risk factor for pneumonia, severe disease, and mortality, with HIV-infected children having a six-fold higher risk of developing severe pneumonia compared with uninfected children and a six-fold higher risk of death.[5] Other risk factors for pneumonia and for severe disease that are prevalent in African populations include smoke exposure, lack of breastfeeding, chronic underlying disease, prematurity or low-birth weight, low socio-economic status, crowded living conditions, or malnutrition.[6,7] HIV-exposed but uninfected children, who are born to an HIV-infected mother, are emerging as another important vulnerable group who have a higher risk of pneumonia than HIV-unexposed infants.[8]

Secondly, lack of good access to care and unavailability of effective management strategies is a further factor making African children more at risk of developing severe disease and of mortality. Use of case management guidelines, with effective use of antibiotics has been shown to substantially reduce pneumonia and all-cause under-five mortality.[9] Community-based interventions, including use of case management guidelines by community workers has also been found to effective for reducing pneumonia mortality.[10] Use of oxygen for hypoxic disease is an effective intervention and is life saving.[11] However, almost 50% of African children with pneumonia are not taken to a health facility. Furthermore, the availability and affordability of some essential drugs including oxygen in many African countries is sub-optimal.[12]

Thirdly, there is limited coverage and affordability of effective preventive interventions for childhood pneumonia in Africa. Vaccination is one of the most effective strategies for reducing childhood pneumonia, but coverage for childhood immunisations, especially the newer conjugate vaccines, is also suboptimal in several African countries. New conjugate vaccines against Streptococcus pneumoniae (PCV) and Haemophilus influenzae type b (Hib) have substantially reduced the burden of childhood pneumonia in vaccinated children.[13] Data from six studies of the effectiveness of Hib conjugate vaccine in low- and middle-income countries (LMICs) indicates a reduction of 18% in radiological pneumonia, of 6% in severe pneumonia, and of 7% in pneumonia-associated mortality.[13] While PCV reduces severe invasive pneumococcal disease and bacteraemia, prevention of non-bacteraemic pneumococcal pneumonia is almost 20-fold greater compared with that of bacteraemic pneumonia.[14] Furthermore, the overall burden of disease prevented in HIV-infected children is much greater because of their susceptibility to disease. PCV has also led to a decline in hospitalisation and death for adult pneumonia due to indirect protection through reduction in circulating pneumonia causing pneumococci serotypes.[15] However, a South African study found that even with high coverage for the 13-valent PCV, the incidence of pneumonia remained high, especially in the first six months of life.[8] PCV may also have considerable impact on reducing mortality, as demonstrated by a randomised controlled trial of 9-valent PCV in the Gambia, in which PCV9 reduced childhood mortality by

*Heather J Zar, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital and MRC Unit on Child & Adolescent Health, University of Cape Town, South Africa. Correspondence to: Professor Heather J. Zar, Dept of Paediatrics and Child Health, 5th Floor, ICH Building, Red Cross War Memorial Children's Hospital, Cape Town, South Africa.*
*Email: heather.zar@uct.ac.za*

15%.[16] Early use of antiretroviral therapy and cotrimoxazole prophylaxis in HIV-infected infants is also effective for reducing pneumonia incidence and severity in children,[17] but coverage for these is still sub-optimal in some areas of sub-Saharan Africa.

Fourthly, African children may have high exposure to infectious diseases compared with children in high-income countries, as well as higher exposure to particular pathogens. For example Mycobacterium tuberculosis (TB) has now been well described to occur commonly in children with acute pneumonia living in high TB prevalence areas, with up to 8% of children presenting with pneumonia found to have culture-confirmed TB.[18] Children living in households in which a member is HIV-infected may be especially exposed to infectious risks and so are more vulnerable to developing pneumonia from a variety of pathogens.

Lastly, the large burden of childhood pneumonia in African children may reflect a young population in which children constitute 25–60% of the total population. However, the burden of pneumonia in African children is disproportionate to the childhood population, with a much higher incidence in African children compared with those in high-income countries.

## Discussion

Importantly, the impact of childhood pneumonia extends beyond acute disease in childhood. 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 approximately 15% of children.[19] In addition, 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 airway disease (COPD).[20–22] Early respiratory syncytial virus (RSV) or rhinovirus-associated lower respiratory tract infection has been associated with the development of asthma in childhood in high-income populations.[23,24] 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.[25]

Effective strategies to prevent and manage pneumonia in African children must be urgently strengthened given the substantial burden of disease, impact on mortality and the accumulating evidence of the association with development of chronic lung disease and respiratory non-communicable diseases (NCDs). The strengthening and implementation of available effective interventions, such as available immunisations and use of case management have the potential to substantially reduce pneumonia burden and under-five mortality.[13] Further 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.

In addition, new strategies are needed to address the residual burden of pneumonia once available vaccines have been well implemented and to develop effective interventions for pathogens for which there are limited strategies. In children well vaccinated with available vaccines including PCV13, viruses can be expected to form an increasing proportion of pneumonia caseload.[26] Among these, RSV is clearly the most prominent pathogen for which there are very limited, affordable interventions available to prevent or treat disease. In 2005, RSV was estimated to cause approximately 34 million episodes of acute lower respiratory tract infection (ALRI) in children under five years or 22% of all ALRI; 10% of episodes resulted in severe illness and hospitalisation and 99% of deaths occurred in LMICs.[27] Furthermore, studies in African children preceding the availability of PCVs[28–30] 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.[31,32] Most episodes of severe RSV pneumonia occur in the first few months of life. Therefore the development of several new RSV vaccine candidates is a very promising development. Recently, a novel strategy to immunise pregnant women in the third trimester of pregnancy, enabling transplacental transfer of antibody and potential protection against RSV disease in their infants in the first few months if life has been proposed with the first multicenter trial of RSV vaccination of pregnant women currently underway. This will most likely need to be coupled with additional vaccination of infants to provide extended protection until children are two years of age. The challenge for African countries will be to ensure the availability and affordability of new strategies such as maternal immunisation against RSV, if they are to be effective. Implementation and access to effective vaccines to prevent childhood pneumonia have been much slower in Africa than in high-income countries, but the potential to reduce disease burden is much higher in Africa. For the future, timely access and implementation of such strategies for all children and mothers who need this treatment must be ensured.

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