Childhood pneumonia – the old and the new

Heather J Zar

School of Child and Adolescent Health
Red Cross War Memorial Children’s Hospital
University of Cape Town
South Africa

Correspondence:
Prof Heather Zar
5th floor ICH building
Red Cross War Memorial Children’s Hospital
Rondebosch, 7700
South Africa
Email: heather.zar@uct.ac.za
Tel: 021-658-5350
Fax: 021-689-1287
The development of antimicrobial therapy, effective vaccines and evolution of pneumonia management guidelines represent great progress in the prevention and management of pneumonia in children. However, pneumonia is currently the leading cause of death in children younger than 5 years in developing countries, accounting for approximately 20% of childhood deaths or 1.9 million deaths globally in children under five each year.\textsuperscript{1,2} Almost half of these deaths occur in Africa.\textsuperscript{1} Community acquired pneumonia also accounts for between 30-40% of paediatric hospital admissions with associated case fatality rates of 15-28%.\textsuperscript{3} This has been exacerbated by the human immunodeficiency virus (HIV) epidemic especially in sub-Saharan Africa as pneumonia is the commonest causes of illness, hospitalisation and mortality in HIV-infected children.\textsuperscript{3}

Besides directly causing childhood deaths, pneumonia is frequently an associated cause of mortality in children with other underlying conditions. Thus for every death directly attributable to pneumonia, 2 or 3 additional deaths associated with pneumonia may occur.\textsuperscript{1} Co-morbid conditions especially malnutrition, measles or immunosuppression increase the risk of mortality from pneumonia.\textsuperscript{1,3}

**Aetiology**

Childhood pneumonia is frequently due to mixed infections such as bacterial-viral or bacterial-mycobacterial pathogens.\textsuperscript{4} Children with polymicrobial pneumonia have a greater risk of dying than children in whom only a single organism is identified.\textsuperscript{4} Bacterial infections particularly *S. pneumoniae, H. influenzae* and *S. aureus* have remained the main causes of hospitalization and death from pneumonia in children in developing countries. *S. pneumoniae* is the most important bacterial pathogen.\textsuperscript{4-6} *M. tuberculosis* is also an important cause of acute pneumonia in children living in high TB prevalence areas.\textsuperscript{4,6,7}

Lack of sensitive assays for diagnosing bacterial pneumonia has led to an underestimation of the importance of bacterial co-infections in children with viral associated pneumonia. Mixed bacterial- viral infections occur frequently.\textsuperscript{4,8,9} Viruses
occur in 30-40% of acute respiratory infections in hospitalised children. Respiratory syncytial virus (RSV) predominates, accounting for 20-25% of such infections. Human metapneumovirus has recently emerged as an important respiratory pathogen, producing a spectrum of clinical illness similar to RSV. Almost a third of children with viral associated pneumonia may have concurrent S. pneumoniae infection in the absence of vaccination with pneumococcal conjugate vaccine.

A broader spectrum of pathogens causes pneumonia in HIV-infected children including gram negative bacteria and P. jirovecii. Methicillin-resistant S aureus (MRSA) has also increasingly emerged as a cause of community acquired pneumonia. HIV-infected children have a higher risk of severe pneumonia, bacteraemia and recurrent infections. Pneumonia due to M. tuberculosis is increasingly occurring in HIV-infected children living in high TB prevalence areas.

Management
The development of case management guidelines and broad spectrum, improved antimicrobials with paediatric formulations are important advances in treatment of childhood pneumonia. Pneumonia case management, as developed by the World Health Organisation (WHO) can significantly reduce overall and pneumonia-specific mortality in children. A meta-analysis of community-based studies found a reduction in all-cause mortality of 27% (95% CI 18-35%), 20% (11-28%), and 24% (14-33%) amongst neonates, infants, and children 0-4 years of age, respectively. In addition, pneumonia-specific mortality was reduced by 42% (22-57%), 36% (20-48%), and 36% (20-49%) amongst these three groups. The incorporation of pneumonia case management guidelines into the Integrated Management of Childhood Illness (IMCI) program has provided a more comprehensive approach to diagnosis, prevention and treatment of childhood pneumonia.

Paediatric formulations of antibiotics have enabled better therapy in children. Pencillin or ampicillin/amoxicillin remains the cornerstone of effective therapy of community-acquired pneumonia in children. Use of macrolides in older children may be required to
provide adequate coverage against *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. Short course (3 day) antibiotic therapy may be as effective as 5 days for ambulatory treatment of pneumonia. A study of 2000 children with non severe pneumonia in Pakistan found that the clinical efficacy of 3 days of oral amoxicillin was similar to 5 days of therapy. Rates of relapse (1%) and treatment failure (approximately 21%) were similar. More recently, in a study of Pakistani children with uncomplicated but severe pneumonia, home treatment with high dose oral amoxicillin was found to be as effective as hospitalization and treatment with parenteral ampicillin followed by oral therapy. This is consistent with a prior multicentre study that found that parenteral pencillin G had similar efficacy as oral amoxicillin for treatment of severe pneumonia. However, these results may not be applicable to children with other underlying illnesses or to those with complicated pneumonia.

Antibiotic coverage should be broadened to include gram negative pathogens in HIV-infected children hospitalized with pneumonia. In addition, empiric treatment with cotrimoxazole and corticosteroids should be initiated if there is a clinical suspicion of PCP. Although there are no randomized trials of the efficacy of corticosteroids for PCP in children, adult data and paediatric studies using historical controls indicate that early use of steroids significantly reduces PCP-associated mortality. The risk of cytomegalovirus associated pneumonitis in association with steroid use is unclear; CMV pneumonitis co-infection has been reported in post-mortem studies of children dying from respiratory causes.

Mortality from pneumonia is frequently due to hypoxemia, which requires oxygen therapy. The development of low flow methods using nasal prongs, nasal catheter or nasopharyngeal catheter has enabled efficient and cost-effective options.

**Prevention**

General preventative measures including improved nutrition, micronutrient supplementation with vitamin A and zinc, reduction of indoor biomass fuel exposure and passive smoke exposure may reduce pneumonia incidence and severity. Vitamin A
supplementation is effective for reducing the severity of respiratory complications of measles but there is no clear evidence for protection against non-measles pneumonia. Daily prophylactic elemental zinc may substantially reduce the incidence and duration of pneumonia, particularly in malnourished children.\(^\text{16}\)

Global immunization programs through the Expanded Program of Immunization (EPI) have produced a decline in measles pneumonia and childhood pertussis. The availability and demonstrated efficacy of new conjugate vaccines as *H influenzae* type b (Hib) and pneumococcal vaccine (PCV) have great potential to reduce the burden of childhood pneumonia. Hib conjugate vaccine reduces the incidence of invasive disease including meningitis and sepsis, and radiologically confirmed pneumonia.\(^\text{17}\) However, the efficacy of this vaccine for protection against invasive disease is reduced in HIV-infected children not receiving anti-retroviral therapy, (44% in HIV-infected compared with 96% in uninfected children).\(^\text{18}\)

Pneumococcal conjugate vaccine (PCV) is highly effective against serotype specific invasive pneumococcal disease (IPD) in studies from USA, Africa and in high risk paediatric populations.\(^\text{19-24}\) A study in USA evaluating a 7 valent vaccine (PCV7) reported a 94% reduction in IPD from vaccine strains.\(^\text{19}\) Studies evaluating a 9-valent PCV in South Africa and the Gambia observed a 72-77% reduction in vaccines-serotype specific IPD among vaccinated children.\(^\text{20,21}\) Although the efficacy against invasive disease was lower in HIV infected (65%) than HIV uninfected children (83%) in South Africa, the absolute burden of disease prevented by vaccination was greater because of the higher underlying burden of pneumococcal pneumonia in HIV infected children.\(^\text{20,22}\) In Alaskan children and Australian Aboriginal children rates of invasive pneumococcal disease have fallen dramatically since the introduction of PCV7.\(^\text{23,24}\) The incidence of radiologically confirmed pneumonia is also reduced by vaccination (even though chest Xrays under estimate the burden of pneumonia).\(^\text{19-21}\) PCV also reduces antimicrobial-resistant pneumococcal disease.\(^\text{20}\) PCV can also reduce childhood mortality especially in children with poor access to health care as evidenced by a Gambian study in which vaccination reduced all-cause childhood mortality by 17%.\(^\text{21}\) However, PCV is
unavailable or unaffordable to most children in developing countries, where it potentially may have the largest impact on childhood morbidity and mortality.

Chemoprophylaxis is highly effective for primary prevention of PCP in HIV-infected children, but requires early identification of HIV-infected infants and infrastructure and resources for implementation. The most effective prophylactic agent is oral trimethoprim-sulphamethoxazole (cotrimoxazole, TMP-SMX). A randomised controlled study of TMP-SMX prophylaxis in HIV-infected Zambian children reported that this reduced hospitalisation by 23% and mortality by 43%. The impact on mortality occurred in children of all ages. The WHO has issued revised guidelines for TMP-SMX prophylaxis, recommending more liberal and widespread use of prophylaxis for HIV-infected children and HIV-exposed infants from 4-6 weeks of age. Lastly, treatment of HIV-infected children with antiretroviral therapy may prevent much of the morbidity and mortality from HIV-associated pneumonia.

Effective interventions for prevention and treatment of childhood pneumonia exist but the challenge is to achieve widespread implementation and high coverage rates globally. Access to the new vaccines especially pneumococcal conjugate vaccine for all children should be a global health priority.

References
