Epidemiology and aetiology of community-acquired pneumonia in children: South African Thoracic Society guidelines (part 1)

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Background. Pneumonia remains a major cause of morbidity and mortality among South African (SA) children. Improved immunisation regimens, strengthening of HIV programmes, better socioeconomic conditions and new preventive strategies have influenced the epidemiology of pneumonia. Furthermore, sensitive diagnostic tests and better sampling methods in young children improve aetiological diagnosis.
Objectives. To summarise current information on childhood community-acquired pneumonia (CAP) epidemiology and aetiology in children as part of the revised South African Thoracic Society guidelines.
Methods. The Paediatric Assembly of the South African Thoracic Society and the National Institute for Communicable Diseases expert subgroup on epidemiology and aetiology revised the existing SA guidelines.The subgroup reviewed the published evidence in their area; in the absence of evidence, expert opinion was accepted. Evidence was graded using the British Thoracic Society (BTS) grading system, and the relevant section underwent peer review.
Results. Respiratory viruses, particularly respiratory syncytial virus, are the key pathogens associated with hospitalisation for radiologically confirmed pneumonia in HIV-uninfected children. Opportunistic organisms, including *Pneumocystis jirovecii*, are important pathogens in HIV-infected infants, while non-typable *Haemophilus influenzae* and *Staphylococcus aureus* are important in older HIV-infected children. Co-infections with bacteria or other respiratory viruses are common in hospitalised children. *Mycobacterium tuberculosis* is common in children hospitalised with CAP in SA.
Conclusions. Numerous public health measures, including changes in immunisation schedules and expansion of HIV prevention and treatment programmes, have influenced the epidemiology and aetiology of CAP in SA children. These changes have necessitated a revision of the South African Paediatric CAP guidelines, further sections of which will be published as part of a CME series in *SAMJ*.

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Community-acquired pneumonia (CAP) forms part of a broad spectrum of acute lower respiratory tract illness (LRTI) in children. This terminology recognises that LRTI is a spectrum of illness ranging from airway to parenchymal disease, dependent on the pathogen/s and the host response.[1] As prevention and management strategies for childhood pneumonia have been strengthened, so reductions in pneumonia incidence, severity and shifts in aetiology have occurred. Besides the impact on under-5 mortality, pneumonia in early childhood may reduce lung function, setting a trajectory for long-term impairment of lung health including the development of asthma or chronic obstructive pulmonary disease (COPD) in adulthood.

In South Africa (SA), with socioeconomic improvements, reduction in perinatal HIV transmission, increasing numbers of

HIV-exposed uninfected (HEU) children, effective combination antiretroviral therapy (ART) programmes, and improved immunisation, the epidemiology and aetiology of childhood pneumonia is changing. In addition, improved diagnostic methods have highlighted the importance of multiple pathogens contributing to co-infection in the aetiology of respiratory illness, and the importance of organism interactions. Current treatment and preventive strategies for childhood pneumonia therefore require revision.

Epidemiology

Pneumonia is one of the most common causes of morbidity and mortality in SA children, despite improvements in immunisation and HIV management programmes. In 2017, there were ~320 000 pneumonia episodes and 4 100 deaths in SA children aged <5 years.[2] The incidence of pneumonia in children <5 years old in SA has declined by ~50% from 2000 to 2015, including an estimated 71% reduction in children living with HIV (CLWH).[3] The roll-out of interventions to prevent mother-to-child transmission (PMTCT) of HIV and increased provision of ART to HIV-infected individuals has contributed to the decline in pneumonia cases.[4] Furthermore, following introduction of pneumococcal conjugate vaccine (PCV) into the SA public immunisation programme in 2009, PCV immunisation was estimated to have reduced under-5 hospitalisations for all-cause pneumonia by 33% and 39% in HIV-uninfected and HIV-infected children, respectively, by 2014.[5] Invasive pneumococcal disease has also declined by 69% among children <2 years, including an 89% reduction in PCV7 serotypes and a 57% reduction in PCV13 serotypes in 2012.[6] Despite these reductions, pneumonia remains one of the most important causes of death in SA children <5 years of age and is a major cause of healthcare utilisation and morbidity.[7,8] There are several determinants of pneumonia severity and mortality. The case fatality risk among children hospitalised with pneumonia in 5 SA hospitals was 2% from 2009 to 2012,[8,9] with HIV infection an important risk factor for hospitalisation and in-hospital mortality.[10] HEU infants have an increased risk of hospitalisation compared with HIV-unexposed infants and an increased risk of in-hospital death, predominantly in the first 6 months of life.[11,12] Increased risk of hospitalisation in HEU infants has also been found for specific pathogens such as pneumococcus, respiratory syncytial virus (RSV) and influenza virus.[10,11,13] Additional risk factors for severe pneumonia include infancy (particularly those <4 months), premature birth, incomplete immunisation, maternal smoking or household tobacco smoke exposure, indoor air pollution, low birthweight, malnutrition, lack of exclusive breastfeeding and overcrowding.[9,14,15]

Summary: Epidemiology

1. Pneumonia incidence in children has declined by around 50% from 2000 to 2015, with an estimated 70% reduction in episodes in HIV-infected children.
2. A reduction in vertical transmission of HIV, increased provision of ART, and PCV have contributed to this reduction.
3. Pneumonia remains a major cause of morbidity and death in SA children.
4. Risk factors for pneumonia hospitalisation include: HIV infection, HIV exposure (predominantly in infants), young age (particularly those <4 months), premature birth, incomplete immunisation, maternal smoking or household tobacco smoke exposure, indoor air pollution, low birthweight, malnutrition, non-exclusive breastfeeding and overcrowding.

Aetiology of pneumonia in children

A wide spectrum of pathogens, ranging from viral and bacterial to fungal and parasitic organisms, is implicated in pneumonia pathogenesis, and disease may be due to multiple organisms (evidence level Ia). If children are hospitalised with pneumonia, bacterial-viral co-infection is often the norm (evidence level Ib).[16,17] In the current era of conjugate vaccines targeting *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae*, there has been a shift in the spectrum of pathogens causing pneumonia, with viruses contributing to a greater proportion of severe LRTI episodes (evidence level Ib) and non-typable *H. influenzae* and *S. aureus* emerging as important bacterial pathogens.[18-24]

Bacterial organisms

The Drakenstein Child Health Study and the Pneumonia Etiology Research for Child Health (PERCH) case-control studies indicate that non-typable *H. influenzae* and *S. aureus* are now the leading bacterial causes of severe pneumonia in SA children (Supplementary Table 1; http://samj.org.za/public/sup/14997.docx) (evidence level Ib).[21,25,26]

Children presenting with empyema or pleural effusion, confluent dense consolidation or pneumatocoele on chest X-ray associated with high-grade pyrexia and elevation of acute-phase reactants (e.g. C-reactive protein), or those with features of suppurative lung disease, are highly likely to have a bacterial cause (evidence level Ib).[27,28] The most frequently isolated bacteria are *S. aureus,* non-typable *H. influenzae*, *S. pneumoniae* and *S. pyogenes* (group A Streptococcus).[27,29]

Gram-negative enteric organisms, particularly *Klebsiella pneumoniae*, *Escherichia coli, Enterobacter cloacae* and Salmonella spp. are important pneumonia pathogens in HIV-infected and malnourished children in sub-Saharan Africa (evidence level Ib).[30-32] In the Child Health and Mortality Prevention Surveillance (CHAMPS) programme, a study designed to establish the infectious aetiology of fatal illness in children dying in hospital, *K. pneumoniae* was identified in 16% of CAP deaths, and the most common organism isolated in death from hospital-acquired infection in Soweto.[33] Non-fermenting Gram-negatives, such as *Moraxella catarrhalis* or *Pseudomonas aeruginosa,* are increasingly recognised as contributors to bacterial pneumonia in children (evidence level II).

Bordetella pertussis is an important cause of pneumonia in young infants who are unimmunised or incompletely immunised. In Cape Town, *B. pertussis* prevalence among young children hospitalised with pneumonia was 16% in CLWH, 11% in HEU and 5% in HIV-unexposed children.[34] In the PERCH study, *B. pertussis* was detected in 2% of HIV-uninfected and 1% of HIV-infected children hospitalised with severe or very severe pneumonia.[25,26]

Tuberculosis

Mycobacterium tuberculosis is increasingly recognised as an important pathogen in acute pneumonia in settings with a high burden of tuberculosis and HIV (evidence level Ib). In SA, 43 - 85% of children with culture-confirmed tuberculosis presented with acute cough (<14 days) (evidence level Ib).[32,35-37] In the Drakenstein study, the incidence of tuberculin skin test (TST) conversion was 12 per 100 child years, and that of pulmonary tuberculosis 2.9 per 100 child years (evidence level Ib).[38] In the PERCH study, 3% of SA children hospitalised with World Health Organization-defined severe pneumonia had microbiologically confirmed tuberculosis (evidence level Ib).[39] Given the suboptimal sensitivity of mycobacterial culture, the proportion of SA paediatric pneumonia cases associated with *M. tuberculosis* is likely to be in the region of 7 - 15% (evidence level IVa).[25,26,38]

If pulmonary tuberculosis is diagnosed, the child must be notified and treatment should be initiated in accordance with the South African Guidelines for the Management of Tuberculosis in Children (2013) (https://health-e.org.za/2014/06/10/guidelines-management-tuberculosis-children/https://health-e.org.za/wp-content/uploads/2014/06/National-Childhood-TB-Guidelines-2013.pdf).

Respiratory viruses

Respiratory viruses are the leading cause of pneumonia and of hospitalisation in young children (evidence level Ia).[9,20,40] Respiratory virus-related illness follows predictable seasonal shifts; in SA this season is between March and September (autumn to early spring) (evidence level II).[41,42] RSV causes 18 - 31% of pneumonia episodes (evidence level Ia).[43] Other viruses associated with pneumonia include influenza, para-influenza, human metapneumovirus (HMPV), human rhinovirus and adenovirus (Supplementary Table 2; http://samj.org.za/public/sup/14997.docx) (evidence level Ib).[9,21,24]

Respiratory viruses are diverse, continually adapting and prone to causing intermittent epidemics and pandemics, particularly when adapting from animal reservoirs to the human host. Numerous pandemic influenza events occurred in the 20th century,[44] and the pandemic 2009 H1N1 influenza strain was implicated in the first influenza pandemic of the 21st century. Coronaviruses, too, have been associated with epidemics in recent decades.[45-48] Highly virulent influenza and coronavirus outbreaks may be associated with considerable case fatality risk, and it is for this reason that all cases of severe acute respiratory syndrome in which no alternative aetiological diagnosis is made be investigated for novel respiratory viruses. Such cases constitute a Category 1 Notifiable Medical Condition in SA (https://www.nicd.ac.za/wp-content/uploads/2017/06/NMC-list_2018.pdf) and as such should be notified within 24 hours of diagnosis.

Although novel COVID-19 infection appears to affect children mildy, with most developing asymptomatic or mild illness,[49] children with acute lower respiratory illness requiring hospitalisation should be tested for SARS-CoV-2 through the epidemic. Evidence on COVID-19 in children is rapidly evolving and current management of paediatric cases should defer to recommendations from the National Department of Health (https://www.nicd.ac.za/diseases-a-z-index/covid-19/covid-19-guidelines/). Children infected with SARS-CoV-2 may present with non-respiratory illness including multisystem inflammatory disease; and so, where resources permit, hospitalised children may be screened for infection, especially if there is a history of contact with a positive adult.

Viral-viral co-infections and viral-bacterial co-infections are increasingly recognised in the pathogenesis of severe pneumonia (evidence level Ib).[50] Preceding respiratory viral infection may prime the respiratory tract for new acquisition of bacterial colonisation, and increase in density of colonisation, or vice versa (evidence level Ib).[51-53]

Measles and varicella-zoster virus occasionally cause severe, or fatal, pneumonia in the context of outbreaks or epidemics (evidence level II). Typically, malnourished or immunocompromised children tend to develop the most severe forms of pneumonia related to these organisms.[54,55] Children hospitalised with measles or varicella-zoster virus-associated pneumonia frequently develop superimposed bacterial pneumonia (primarily *S. aureus* and *S. pyogenes*) and require treatment with broad-spectrum antibiotic therapy (evidence level IVa).[56-58]

Opportunistic organisms

Pneumocystis jirovecii, either alone or as a co-pathogen with cytomegalovirus (CMV), is a leading infection in CLWH not on ART in SA (evidence level Ib).[26,59-62] Typically, pneumocystis pneumonia (PCP) affects young infants, between 6 weeks and 6 months of age; presentation is with severe hypoxia, dyspnoea, low-grade fever and normal chest auscultation (evidence level Ib).[63] However, *P. jirovecii* also commonly colonises the airways in infants.

The association of CMV alone with severe childhood pneumonia in HIV-infected and HEU children is contentious (evidence level II),[64,65] although histological evidence of CMV pneumonia is frequently seen in HIV-infected children dying of pneumonia.[66] Fatal disseminated disease associated with CMV is also well described in children who are solid organ or bone marrow transplant recipients.[67,68]

Atypical bacteria

Chlamydophila pneumoniae, *Chlamydia trachomatis*, *Mycoplasma pneumoniae* and Legionella spp. are infrequently associated with pneumonia in SA children (evidence level II),[21,25,26,69] but should be considered in the differential diagnosis in children with progressive respiratory failure, despite broad-spectrum antibiotic cover (evidence level IVa). Age <5 years of age and HIV infection were associated with hospitalisation for severe *M. pneumoniae* in SA.[70]

Summary: Aetiology

Co-infections are common in pneumonia pathogenesis.

1. The most frequently isolated bacterial pathogens following PCV and Hib immunisation are non-typable *H. influenzae* and *S. aureus*.
2. *B. pertussis* is implicated in severe pneumonia aetiology in those with incomplete immunisation.
3. *M. tuberculosis* is an important pathogen in settings with a high burden of tuberculosis.
4. Gram-negative bacteria are important pathogens in HIV-infected and malnourished children.
5. Respiratory viruses, particularly RSV, are responsible for most pneumonia episodes. Influenza, para-influenza, adenovirus and human bocavirus, HMPV and rhinovirus are common, although not always pathogenic.
6. In HIV-infected children not on ART, *P. jirovecii* either alone or as a co-pathogen with CMV, is an important opportunistic infection.

Special circumstances: HIV infection or exposure

HIV infection rates in children have declined significantly with the advent of effective PMTCT interventions, from 30% to 1 - 3% in SA.[71] There is subsequently a large population of children born to HIV-infected mothers who are HEU.[71] HEU infants have an increased risk of pneumonia, particularly in the first 6 months of life (evidence level Ib).[10] The exact mechanisms of vulnerability in HEU infants may involve *in utero* exposure to HIV viral proteins, exposure to ART, lack of effective protective maternal antibodies, or abnormalities in immunological responses (evidence level III).[71,72]

Prior to the ART roll-out, CLWH had a 4 - 6-fold increased risk of developing severe pneumonia,[14,73] and a 4 - 6-fold increased risk of death once hospitalised for pneumonia (evidence level II).[9,73] However, widespread use of ART has markedly reduced this burden, with a decline in mortality rates among children on ART from 7.1 per 100 person-years to 0.6 per 100 person-years in a multicentre prospective cohort study from the USA.[74]

HIV-infected infants not on ART, especially those with viral load ≥100 000 copies/mL and CD4 <15%, are at greatest risk of developing severe disease (evidence level Ib).[75] Additional risk factors for severe disease include poor nutritional status and anaemia (evidence level Ib).[73]

Aetiology of pneumonia in HIV-infected children

In the era of ART, the aetiology of pneumonia is similar among CLWH, HEU and HIV-unexposed children (Supplementary Tables 1 and 2; http://samj.org.za/public/sup/14997.docx).[76] However, in HIV-infected infants, *P. jirovecii* is still the leading cause of hospitalisation.[26]

M. tuberculosis should be considered in HIV-infected children with pneumonia, as evidence suggests an increased risk for tuberculosis (evidence level Ib).[73] HIV-infected infants not on ART have a 20-fold higher risk of developing culture-confirmed tuberculosis compared with HIV-uninfected infants (evidence level 1b).[77] This risk declines with the introduction of ART.[78]

Summary: HIV infection or exposure

1. A broader range of pathogens is responsible for pneumonia in CLWH, encompassing opportunistic infections such as PCP and CMV, *S. aureus* and Gram-negative organisms (evidence level Ib).
2. *M. tuberculosis* should be considered in CLWH and HEU children, as there is an increased risk for tuberculosis in these populations (evidence level Ib).

Conclusions

Updated evidence on the epidemiology and aetiology of paediatric CAP in SA children is presented in this CME article. Epidemiological shifts in pneumonia burden have occurred, primarily through improvements in coverage for Hib and pneumococcus in the SA Extended Programme on Immunisation, as well as expansion of the ART roll-out and PMTCT programmes. Success in preventing HIV infection in SA infants has resulted in a growing population of HEU infants who themselves are at increased risk for CAP hospitalisation, however. Case-control studies of hospitalised childhood pneumonia conducted in SA during the past decade have highlighted the role of respiratory viruses in the aetiology of hospitalised pneumonia in young children; however, bacterial-viral or viral-viral co-infections may be more common in children with severe disease. *M. tuberculosis* is an important pathogen to consider in our high-burden setting. Although great progress has been made in widening access to ART for CLWH and in HIV prevention programmes, PCP is still the most important condition precipitating hospitalisation in HIV-infected infants.

Updated guidance on diagnosis, treatment and prevention of childhood pneumonia, based on current knowledge of pneumonia aetiology, are presented in parts 2,[79] 3[80] and 4[81] of the SA paediatric pneumonia guidance CME articles.

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