## PRACTICE REVIEW

# Childhood pneumonia – progress and challenges

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Remarkable progress has been made in the development of antimicrobial therapy, effective vaccines and pneumonia management guidelines in the past 50 years. 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. This article reviews changes in the epidemiology, management and prevention of childhood pneumonia in developing countries, specifically in Africa and South Africa, and addresses future challenges.

*Main findings.* The HIV epidemic has sharply increased the incidence, severity of, and mortality due to, childhood pneumonia. Bacterial infection remains a major cause of pneumonia mortality. Additional pathogens such as *Pneumocystis jirovecii* and Gram-negative bacteria are found in HIV-infected children, associated with a high mortality. *Mycobacterium tuberculosis* is an important cause of acute pneumonia in both HIV-infected and uninfected children. Use of case management guidelines can substantially reduce neonatal, infant and under-5 mortality and pneumonia-specific mortality. General preventive interventions including micronutrient supplementation with zinc and vitamin A, and immunisations can substantially reduce the burden of childhood pneumonia. Despite a lower efficacy in HIV-infected children, vaccination protects against disease in a significant proportion of children.

In South Africa, new advances over the past 50 years have included greater access to primary health care for children, the use of Integrated Management of Childhood Illness guidelines in primary care, development of guidelines for diagnosis and management of childhood pneumonia and adoption of an expanded immunisation programme that includes coverage for *Haemophilus influenza*e type b. The pneumococcal conjugate vaccine recently licensed in South Africa also has the potential to significantly reduce the burden of childhood pneumonia. Recent rollout of the national antiretroviral programme can reduce the incidence and severity of HIV-associated pneumonia through the prevention of HIV infection, use of co-trimoxazole prophylaxis and treatment with antiretrovirals.

*Conclusion.* Available, effective interventions for prevention and treatment of childhood pneumonia exist; the challenge is to achieve widespread implementation and high coverage rates in developing countries. Greater access to newer vaccines and to antiretroviral therapy and co-trimoxazole prophylaxis in HIV-infected children is necessary to further reduce the burden of childhood pneumonia and the discrepancies in global child lung health.

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In the past 50 years, major progress has occurred in the fields of molecular biology and vaccinology and in the development and use of antimicrobials. These have contributed to greater understanding of childhood pneumonia and resulted in improved management and intervention strategies. Pneumonia nevertheless remains a major cause of childhood morbidity and mortality in developing countries.[1-4] Acute respiratory infections (ARIs), principally pneumonia, account for approximately 1.9 million (95% confidence interval (CI) 1.6 - 2.2 million) deaths globally in children under 5 years of age each year,[4] 90% of which occur in the developing world.[1,4] This has

been exacerbated by the human immunodeficiency virus (HIV) epidemic, especially in sub-Saharan Africa, as pneumonia is the commonest cause of illness, hospitalisation and mortality in HIV-infected children.[5] This article reviews changes in the epidemiology, management and prevention of childhood pneumonia in developing countries with emphasis on Africa and South Africa.

## Epidemiology of childhood pneumonia

Pneumonia constitutes a major proportion of the global burden of childhood disease, being responsible for around 20% of childhood deaths, the majority of which occur in developing countries.[1-4] Annually, almost half of the 1.9 million deaths due to acute respiratory tract infections in children under 5 years of age occur in Africa.[6] Childhood community-acquired pneumonia accounts for between 30% and 40% of hospital admissions with associated case fatality rates of between 15% and 28%.[7,8] Studies from South Africa have estimated the proportion of under-5 deaths due to pneumonia to range from

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8% to 22%.[9,10] These studies, done during the apartheid era, found marked differences in pneumonia-specific mortality between ethnic groups with the highest rates for black African children and the lowest rates for Caucasians. A study investigating childhood pneumonia deaths from 1968 to 1985 reported high rates in all population groups, ranging from 7 to 270 times those in developed countries, and highlighted the large differences in rates by ethnic group.[9] This is consistent with the observation that the proportion of children dying from pneumonia is related to the general under-5 mortality rate, declining as the under-5 mortality rate diminishes.[4] In South Africa, under-5 mortality for 2003 was reported as 66 per 1 000, representing a 1.3% increase from 1995 to 1999 and a 1.6% increase from 2000 to 2003.[6] Moreover, in South Africa there is wide variation in under-5 mortality rates accord-ing to geographical and socio-economic factors.[9-11] 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.[4] Co-morbid conditions, especially malnutrition, measles or immunosuppression, increase the risk of mortality from pneumonia.[1,5,12]

The HIV pandemic has resulted in a large increase in the incidence, severity and outcome of childhood pneumonia in developing countries. Globally, there are approximately 2.3 million HIV-infected children, living predominantly in sub-Saharan Africa.[13] Approximately 540 000 children are infected with HIV annually, the majority in developing countries where few interventions to prevent perinatal HIV acquisition are available and where access to antiretroviral agents is extremely limited.[13] Thus infant, under-5 and pneumonia-specific mortality rates have increased in sub-Saharan Africa. Studies have reported that 26 - 59% of HIV-infected African children die within the first years of life while under-5 mortality rates exceed 60% in some countries.[8] Moreover, respiratory disease has been reported to be the dominant cause of hospitalisation and death in HIV-infected African children.[7,14-16]

The impact of the HIV epidemic on childhood pneumonia has been compounded by poor access and unavailability of preventive strategies and limited availability of highly active antiretroviral therapy (HAART) for African HIV-infected children. As a result, HIV-associated lung disease is a major cause of childhood morbidity, hospitalisation and mortality in sub-Saharan Africa with 90% of HIV-infected children developing a respiratory illness during the course of their HIV disease.[5,8]

## The impact of HIV on childhood pneumonia in Africa

The HIV epidemic poses a threat to many of the gains made in child health over the last few decades in sub-Saharan

Africa. Besides the impact on the epidemiology and outcome from childhood pneumonia, HIV has changed the spectrum of pathogens responsible for childhood pneumonia and their antimicrobial susceptibility. Opportunistic infections, especially *Pneumocystis jirovecii* pneumonia (PCP), have become an important cause of mortality among HIV-infected infants.[5,17-20] In sub-Saharan Africa, a dual HIV and tuberculosis (TB) epidemic has resulted in a large increase in TB incidence, with impact on the epidemiology and severity of childhood TB. HIV infection has also been associated with an increase in the antimicrobial resistance patterns of common bacterial pathogens.[21] Changes in the microbial pathogens and susceptibility patterns have implications for the choice of empirical antibiotic therapy for childhood pneumonia. Furthermore, although respiratory viruses are identified less frequently in HIV-infected children hospitalised for pneumonia (15%) compared with HIV-negative children (45%), the absolute burden of hospitalisation for viral associated pneumonia is 2 - 8-fold greater in HIV-infected children. HIV-infected children in whom respiratory viruses are identified have a more prolonged hospital stay and a higher case fatality rate than HIV-uninfected children.[22]

The reliability of diagnostic methods for childhood pneumonia including clinical assessment differ in HIV-infected and uninfected children. Diagnosis of specific infections such as pulmonary TB is more difficult in HIV-infected children because of nonspecific clinical signs, other HIV-associated illnesses and the development of anergy. The efficacy of usual management strategies such as choice of empirical antibiotic therapy or duration of therapy differs for HIV-infected children. The efficacy of preventive measures such as immunisation is reduced in HIV-infected children particularly if they are not receiving antiretroviral therapy.[23]

Pneumonia is the commonest reason for hospitalisation among African HIV-infected children.[7,14-16] Pneumonia-specific mortality rates are higher in HIV-infected children with case fatality rates consistently reported as 3 - 6 times those of HIV-negative patients.[21,22,24] Therefore, the HIV-epidemic has increased the demand for health care resources with more children requiring ambulatory treatment, hospital admission and intensive care for pneumonia. This also raises important ethical considerations for allocation of resources.

## Aetiology of childhood pneumonia

Bacterial infections, particularly *Streptoccocus pneumoniae, H. influenzae* type b and *Staphyloccocus aureus,* have remained the major reasons for hospitalisation and causes of death from pneumonia in children in developing countries. *S. pneumoniae* is the most important bacterial pathogen in HIV-infected and uninfected children.[21,24] HIV-infected children are at increased risk for severe pneumonia, bacteraemia and recurrent infections. A Zambian study of children dying of respiratory

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disease reported that pyogenic pneumonia, occurring in 41% and 50% of HIV-infected and uninfected children respectively, was most common and frequently occurred with other non-bacterial respiratory pathogens.[20] *M. tuberculosis* is also an important cause of acute pneumonia in children living in high TB and high HIV prevalence areas, accounting for approximately 8% of pneumonia cases.[21,24,25] In a Zambian postmortem study, TB occurred in 18% of HIV-infected and 26% of HIV-uninfected children and was the second most commonly identified cause of death in children older than 1 year.[20]

Viruses occur in 30 - 40% of acute respiratory infections in hospitalised children; among viral pathogens, respiratory syncytial virus (RSV) predominates, accounting for 20 - 25% of such infections.[22] A newly described paramyxovirus, human metapneumovirus (hMPV), is emerging as a respiratory pathogen second to RSV in children; this has been identified in 11% of South African HIV-uninfected children hospitalised for lower respiratory tract infections.[26,27] This virus produces clinical illness similar to RSV.[26-28] 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. Data from Gambia indicate that mixed bacterial and viral infections may occur in 8 - 40% of cases of childhood pneumonia.[29,30] Recent data from South Africa indicate that in at least 31% of children, viral-associated pneumonia may be due to concurrent infection with *S. pneumoniae* in the absence of vaccination with pneumococcal conjugate vaccines.[26,31]

A broader spectrum of pathogens causes pneumonia in HIV-infected children including Gram-negative pathogens, such as *Escherichia coli* and *Salmonella* spp. as well as *P. jirovecii*.[21,24] While *P. jirovecii* was recognised as a cause of pneumonia in malnourished infants in the 1940s, it has re-emerged as a major pathogen in HIV-infected infants, causing severe pneumonia. Postmortem studies have detected PCP in 16 - 67% of HIV-positive children dying of respiratory illness,[20,32] while in-hospital case-fatality rates for PCP have ranged from 20% to 63%.[17-19] The prevalence of PCP among HIV-infected children hospitalised with pneumonia in Africa has varied from 10% to 49%.[17-19,33] The management of pneumonia in HIV-infected children is further complicated by the presence of complex pneumonia resulting from multiple simultaneous bacterial, viral and fungal infections. In addition, HIV-exposed children may be at increased risk for PCP even if they are HIV-uninfected.[19,34]

## Management

Important advances in the management of childhood pneumonia have occurred in the past 50 years, including the development of case management guidelines and production of broad-spectrum, improved antimicrobials with paediatric formulations. In addition, in South Africa in the last decade, improved access to health care for children has resulted from the policy of free care for children and an emphasis on primary health care.

Pneumonia case management was first developed by the World Health Organisation (WHO) as an acute respiratory infection (ARI) guideline and subsequently as part of the Integrated Management of Childhood Illness (IMCI) programme.[35] The pneumonia case-management strategy developed by WHO was based on the assumptions that: (*i*) bacterial pneumonia was largely responsible for ARI mortality in developing countries; (*ii*) antibiotic treatment could reduce case fatality; and (*iii*) a simple algorithm based on clinical signs could reliably detect children with pneumonia. The cornerstone of the ARI case management strategy depends on two key clinical signs – lower chest indrawing and respiratory rate. Based on these signs, children presenting with cough or difficult breathing are categorised into three groups: those with lower chest indrawing are defined as having severe pneumonia, children with tachypnoea are defined as having pneumonia while those without tachypnoea or chest indrawing are considered to have an upper respiratory tract infection. These signs, based initially on work done by Shann *et al.*,[36] have been validated by many subsequent studies and confirmed as having good sensitivity for the diagnosis of pneumonia.[37-39] Children defined as having severe pneumonia require hospital referral, those with pneumonia based on the presence of tachypnoea require oral antibiotics, while those with an upper respiratory tract infection are treated symptomatically.

The use of case-management guidelines for treatment of childhood pneumonia can significantly reduce overall and pneumonia-specific mortality in children.[40,41] A meta-analysis of community-based studies found all-cause mortality was reduced by 27% (95% CI 18 - 35%), 20% (11 - 28%), and 24% (14 - 33%) among neonates, infants, and children 0 - 4 years of age, respectively.[41] In addition, pneumonia-specific mortality was reduced by 42% (22 - 57%), 36% (20 - 48%), and 36% (20 - 49%) among these three groups.[41] These reductions in mortality associated with antibiotic use are consistent with estimates of the proportion of childhood deaths attributable to bacterial pneumonia. The incorporation of ARI case-management guidelines into the IMCI guidelines has provided a more comprehensive approach to diagnosis, prevention and treatment. However, current IMCI guidelines require adaptation to include management of HIV-associated respiratory illness. The IMCI programme has been adapted for use in South Africa and has increasingly become part of the management of children in primary care settings.[42] In addition, South African guidelines for the diagnosis and management of community-acquired pneumonia in children at primary, secondary or tertiary care facilities have recently been published.[43]

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The development of paediatric formulations of antibiotics has enabled better therapy in children. Pencillin or ampicillin/amoxicillin remain the cornerstone of effective and rational antibiotic treatment of community-acquired pneumonia in children. Recently, short-course antibiotic therapy was reported to be as effective as conventional 5-day treatment for ambulatory treatment of pneumonia. A study in Pakistan of 2 000 children with pneumonia reported that the clinical efficacy of 3 days of oral amoxicillin (15 mg/kg/dose) was similar to 5 days of therapy.[44] Rates of relapse (1%) and treatment failure (approximately 21%) were similar in both groups. However, these results may not be applicable to HIV-infected children in whom longer duration of therapy may be needed. For severe pneumonia, oral therapy may be effective in children who are able to tolerate oral antibiotics. A multicentre study reported that parenteral pencillin G had similar efficacy to oral amoxicillin for treatment of severe pneumonia.[45]

Despite increasing *in vitro* resistance to beta-lactam antibiotics, favourable pharmacodynamic and pharmacokinetic properties of these antibiotics still make them the treatment of choice when managing pneumonia, even when due to pneumococcal isolates with low or intermediate resistance to the beta-lactam antibiotics.[45,46]

For HIV-infected children hospitalised with severe pneumonia, antibiotic coverage should be broadened to include Gram-negative pathogens.[43] Frequently this involves either the selection of a third-generation cephalosporin or the addition of an aminoglycoside to a beta-lactam antibiotic. Use of macrolides in older children may be required to provide adequate coverage against *Mycoplasma pneumoniae* and *Chlamydia* spp., although the importance of these pathogens in South Africa remains to be elucidated.

In addition, empirical treatment for PCP with co-trimoxazole and corticosteroids should be considered, particularly in HIV-infected infants who are not taking co-trimoxazole prophylaxis or in high HIV prevalence settings in infants with severe pneumonia if their HIV status is unknown.[5,8,43] Although there are no randomised trials of the efficacy of corticosteroids for PCP in children, adult data and paediatric studies using historical controls indicate that timely use of steroids significantly reduces PCP-associated mortality. This however requires further study in Africa, where the risk particularly of cytomegalovirus (CMV)-associated pneumonitis may differ from that in developed countries. Concurrent CMV pneumonitis has been identified in 30 - 40% of postmortem studies in the presence of other causes of respiratory mortality.[20,47]

Mortality from pneumonia is frequently due to hypoxaemia, which can be effectively treated with oxygen. The development of low-flow methods using nasal prongs, nasal catheter or nasopharyngeal catheter has enabled efficient and cost-effective options.[43,48]

## Prevention

Effective tools for preventing much of the burden of childhood pneumonia are available. General measures include improved nutrition, micronutrient supplementation with vitamin A and zinc, and attention to indoor environments, particularly avoidance of exposure to passive smoke.[23] Vitamin A supplementation is effective for reducing the severity of respiratory complications of measles[49] but there is no evidence for protection against non-measles pneumonia. Daily prophylactic elemental zinc may substantially reduce the incidence of pneumonia, particularly in malnourished children.[50] A pooled analysis of randomised controlled trials of zinc supplementation in children in developing countries found that zinc-supplemented children had a significant reduction in pneumonia-incidence.[51]

Global immunisation programmes through the Expanded Program of Immunization (EPI) have produced a decline in measles pneumonia and childhood pertussis. Cost is however a major challenge to the adoption of the new generation of childhood conjugate bacterial vaccines into the EPI schedules in developing countries. Furthermore investment is required to ensure that the most vulnerable children have access to vaccines by development of the infrastructure and resources required for a successful immunisation programme. In many African countries coverage even for the EPI programme is poor.[6] In South Africa, relatively high coverage rates for diptheria-pertussis-tetanus (DPT) (94%) and measles (83%) immunisation have been reported.[6] The availability and demonstrated efficacy of new immunisations such as *H. influenzae* type b (Hib)[52-54] and pneumococcal[55-58] conjugate vaccines have great potential to substantially reduce the burden of childhood pneumonia.

Use of the Hib conjugate vaccine may potentially reduce Hib invasive disease by 46 - 93% in vaccine recipients.[53] However, the efficacy of this vaccine for protection against invasive disease is reduced in HIV-infected children not receiving antiretroviral therapy (44% in HIV-infected compared with 96% in uninfected children).[54] South Africa is the only African country which funds, since 1998, the inclusion of Hib conjugate vaccine in its EPI programme. However, the Hib conjugate vaccine has in the past few years become more available in other African countries through donor-funding support. The potential of Hib conjugate vaccine to reduce childhood pneumonia morbidity was first shown in Gambia, where in addition to reducing meningitis and sepsis, vaccination was associated with a 21% reduction in radiologically confirmed pneumonia.[52]

Further potential strides in preventing bacterial pneumonia have been observed with the conjugate pneumococcal vaccines. Unlike the polysaccharide pneumococcal vaccines, which are ineffective in children less than 5 years of age, conjugate pneumococcal vaccines are immunogenic, safe and effective

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in children immunised as early as 6 weeks of age onwards. A recent South African trial found that the use of a nine-valent pneumococcal conjugate vaccine reduced invasive pneumococcal disease caused by vaccine serotypes by 65% and 83% in HIV-infected and uninfected children respectively, while the incidence of radiologically confirmed pneumonia was reduced by 13% and 20% in these two groups respectively.[55] Although the efficacy of the conjugate pneumococcal vaccine was lower in HIV-infected compared with uninfected children, the overall burden of pneumonia prevented in HIV-infected children was 9.7-fold greater, mainly because of the higher underlying burden of pneumococcal pneumonia in HIV-infected children.[56] A different formulation of the vaccine, which is more limited in the number of serotypes included in the vaccine to those studied in South Africa, has recently been licensed in South Africa. Because of cost constraints, this vaccine has however not as yet been included in the EPI and hence remains inaccessible to the majority of South African children. The need for advocacy to include a conjugate pneumococcal vaccine into EPIs in developing countries is supported by a study in The Gambia.[57] In addition to reducing the incidence of radiologically confirmed pneumonia by 37%, the vaccine was also found to reduce all-cause childhood mortality by 17%.[57]

Chemoprophylaxis is highly effective for primary prevention of PCP in HIV-infected children, but requires timely identification of HIV-infected infants and infrastructure and resources for implementation. The most effective prophylactic agent is oral trimethoprim-sulphamethoxazole (co-trimoxazole, TMP-SMX), a widely available, well-tolerated and inexpensive drug.[23] A randomised controlled study of TMP-SMX prophylaxis in HIV-infected Zambian children reported that this reduced mortality by 43% and morbidity, including hospitalisation, by 23%.[58] The impact on mortality was noted in children of all ages. As a result of this study, the WHO 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.[59] Early identification of HIV-infected infants to initiate this therapy however remains a challenge and probably undermines the potential of this intervention to reduce childhood pneumonia morbidity and mortality in South African children. Similarly, widespread implementation of the WHO guidelines remains a considerable challenge in other sub-Saharan African countries, dependent on timely identification of HIV-infected mothers and their babies.

Prevention of childhood HIV infection by preventing mother-to-child transmission and treatment of HIV-infected children with antiretroviral therapy may prevent much of the morbidity and mortality from HIV-associated pneumonia. The use of antiretroviral therapy in HIV-infected children has dramatically reduced the incidence and severity of pneumonia in the developed world; however, such therapy is currently unaffordable and unavailable to most children in developing countries. Recent rollout of the national antiretroviral programme in South Africa has the potential to reduce HIV-associated pneumonia incidence and severity through the prevention of HIV infection, use of TMP-SMX prophylaxis and treatment of HIV-infected children with antiretroviral therapy. However, in South Africa and other sub-Saharan countries, there remain large operational, cost and educational challenges to expanding the availability of antiretroviral therapy to all children who need it.

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