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Childhood Pneumonia in Low and Middle Income Countries: Burden, Prevention and Management

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Abstract: *Background:* Pneumonia is the leading cause of morbidity and mortality in children under five years of age worldwide. The burden of childhood pneumonia occurs predominantly in low or middle income countries. Despite recent advances in management and preventative strategies, high rates of treatment failure and case fatality continue to occur in children in such countries.

Aim: To review the current evidence on the epidemiology and management of childhood pneumonia in low and middle income countries

Methods: Direct search of Medline database from 1995 to date through Pubmed was conducted. Search terms included: (pneumonia OR lower respiratory tract infections OR lower respiratory infections OR ARI) AND child. Search was restricted to English articles. In addition reference lists of selected studies were reviewed for relevant information.

Findings: Major findings accounting for the high burden include delayed health seeking, poor access to health care, poorly resourced health care systems, inadequate immunisation programs and lack of availability of oxygen delivery systems. The burden of pneumonia deaths has also been increased by the paediatric HIV epidemic in sub-Saharan Africa. Effective preventive interventions include exclusive breastfeeding, optimizing nutrition, reduction of indoor air pollution and immunisations. Wider availability of new immunisations particularly pneumococcal conjugate vaccine can substantially reduce pneumonia incidence. Prophylactic trimethoprim- sulphamethoxazole and antiretroviral therapy are important strategies to prevent pneumonia in HIV infected children, and wider implementation of these is still needed. The most effective treatment strategy remains case management guidelines as contained in the Integrated Management of Childhood Illness program. Case management efficacy is dependent on timely access to health facilities, on health worker ability to recognise and treat pneumonia or severe pneumonia and on availability of appropriate antibiotics and functioning referral pathways. In areas of high HIV prevalence, guidelines must be adapted to broaden antimicrobial coverage including treatment for *Pneumocystis jirovecii* pneumonia. Monitoring of hypoxia with pulse oximetry and appropriate oxygen delivery systems are still not widely available and should be prioritized in pneumonia management programs.

Conclusions: Improved access to preventive and management strategies is urgently needed to reduce the burden of childhood pneumonia in resource limited settings. Further research on childhood pneumonia is needed to delineate the burden of specific pathogens, to develop better diagnostic tests and to improve current management and preventive strategies.

Keywords: Pneumonia, children, burden, prevention, management.

BURDEN OF CHILDHOOD PNEUMONIA

Pneumonia remains the leading cause of death in children under 5 years in low and middle income countries despite the introduction of case management guidelines and the development of new preventative strategies including effective vaccines [1]. Pneumonia currently accounts for 18% of annual deaths in children under five worldwide, 20% in low income countries compared to only 4.3% in high income countries [1]. The global incidence of clinical pneumonia cases has been estimated to be 0.29 events per child year, which equates to 150 million new episodes annually worldwide [2]. The burden of childhood pneumonia remains disproportionately represented in low and middle income countries; 74% of new pneumonia cases occur in just 15 countries and more than half in just 6 countries: India, China, Pakistan, Bangladesh, Indonesia and Nigeria [3]. The estimated clinical pneumonia incidence expressed as events per child year is highest in South East Asia (0.36), then Africa (0.33), followed by the Eastern Mediterranean (0.28) [3]. In addition severe pneumonia requiring hospitalization makes up a significant proportion of these pneumonia episodes, accounting for 7-13% of cases [3]. Severe respiratory infections in childhood may be associated with an increase in long term respiratory morbidity and an added health burden [4-6].

Childhood pneumonia is caused by a combination of host and environmental factors. In low and middle income

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countries pneumonia is frequently caused by bacterial pathogens, in contrast to high income countries where viral pathogens predominate. The main bacterial causes of childhood pneumonia are *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* [7-10]. Pneumococcal disease is the most common cause of vaccine preventable deaths [11]. In 2000 there were an estimated 13.8 million cases of pneumococcal pneumonia, causing 741 000 deaths in children under 5 years, 82 700 in HIV positive and 658 000 in HIV negative children. Most cases of pneumococcal pneumonia occurred in South East Asia (38.6%), Africa (27.6%) and the Western Pacific region (17%) [11]. Similarly *H. influenzae type b* (Hib) infection, still contributes substantially to the global burden of childhood pneumonia; recent estimates are 7.9 million cases of H influenzae pneumonia annually in children under 5 years worldwide, causing 292 000 deaths, 6 400 in HIV positive children and 286 000 in HIV negative children [12]. An important cause of bacteraemic pneumonia in tropical Africa is non-typhoidal salmonellae [13-15]; this is not treated by current recommended first line antibiotic for childhood pneumonia [16]. The main viral cause of childhood pneumonia in children admitted to a rural Kenyan hospital was respiratory syncytial virus (RSV), with *Human coronavius,* influenza type A, Parainfluenza type 3, Human adenovirus and human metapneumonvirus being less frequent but important pathogens[1]. RSV was associated with severe disease[1]. Childhood pneumonia is frequently caused by multiple pathogens – these include combinations of bacterial, viral, mycobacterial or fungal infections. Recent studies have shown that prognosis is exponentially worse as the number of causative pathogens increases [17].

The HIV epidemic has increased the burden of childhood pneumonia in high HIV prevalence areas. Paediatric HIV is essentially a disease of children in sub-Saharan Africa where more than 90% of the approximately 2 million HIV-infected children under 15 years reside [18]. Pneumonia is the commonest cause of hospitalization and death in HIV-infected children [17, 19-21]. Pneumonia related mortality is 6 fold higher in HIV infected compared to HIV uninfected children[2]. Increasing evidence suggests that HIV exposed uninfected children also have a higher risk of severe pneumonia and poorer outcome as compared to HIV unexposed infants [17]. In addition, there has been an exponential increase in tuberculosis (TB) prevalence in areas of high HIV prevalence. In the WHO African region TB incidence has increased from 168 per 100 000 population per year in 1990 to 363 cases per 100 000 population per year in 1997[3]. Tuberculosis contributes to the burden of acute and chronic lung disease in children.

Prioritizing the prevention and appropriate management of childhood pneumonia is essential to meet the Millennium Development Goal 4 of decreasing under 5 child mortality by two thirds from 1995 by 2015. In response to this the WHO and UNICEF have developed the Global Action Plan for Prevention and Control of Pneumonia (GAPP) to highlight pneumonia as a major cause of death in children and to assist in scaling up of interventions with proven benefit [22].

PREVENTION OF CHILDHOOD PNEUMONIA

All children should be protected against pneumonia through promoting a healthy environment and access to effective preventive and treatment measures. Strategies for reducing childhood pneumonia (Table **1**) include.

Table 1. Prevention Strategies for Childhood Pneumonia

Strategies to Reduce Childhood Pneumonia
General Strategies
Nutrition and micronutrient supplementation • Exclusive breastfeeding for 6 months in HIV-uninfected mothers • Adequate nutrition • Vitamin A supplementation • Zinc supplementation
Environmental factors • Avoidance of indoor air pollution • Hand washing
Specific Strategies
Immunisation • Measles • Haemophilus influenzae type B • Pneumococcal • Pertussis
Antibiotic prophylaxis • Cotrimoxazole for HIV infected or exposed children • Isoniazid for mycobacterial disease
Prevention of HIV infection in children • Upscaling mother to child transmission programs
HAART in HIV-infected children early

Nutritional Interventions

Exclusive Breastfeeding

Exclusive breastfeeding for the first 6 months of life and continued from 6-11 months significantly decreases infant mortality, early neonatal sepsis, acute respiratory infections and diarrhoea [23-26]. In a prospective observational birth cohort study in Dhaka, Bangladesh, infants who received partial or no breastfeeding compared with infants who were exclusively breastfed in the first few months of life had a 2.2 fold higher risk of death in infancy and a 2.4 fold higher risk of acute respiratory infections [23]. An estimate of exclusive breastfeeding coverage in 2000 amongst the 40 countries with 90% of child deaths was only 39% [27]. Pneumonia incidence could be reduced by 15-23% with universal exclusive breastfeeding [28]. In addition universal coverage of exclusive breastfeeding could reduce child deaths by 13% [27]. This estimate took into account that exclusive breastfeeding in HIV infected mothers could result in the infant becoming infected. The estimated reduction in child

[1]Berkley JA, Munywoki P, Ngama Mwanajuma, *et al*. Viral etiology of severe pneumonia among Kenyan infants and children JAMA 2010; 303(20): 2051-7.

[2]Enarson PM, Gie RP, Enarson DA, *et al*. Impact of HIV on standard case management for severe pneumonia in children Expert Rev Respir Med 2010; 4(2): 211-20.

[3]WHO: World Health Statistics. Geneva. In.; 2009.

deaths would have been 15% if this were not the case [27]. However, specific issues regarding breastfeeding in HIV-infected mothers must be considered, including the availability of an alternative safe milk supply, the potential for HIV transmission, the social and environmental circumstances and maternal preference.

Optimizing Nutrition

Stunting, underweight and micronutrient deficiency have been identified as risk factors for childhood pneumonia and for more severe pneumonia [3, 29, 30]. Malnutrition is associated with a poor outcome in children with pneumonia, consequently efforts to reduce poor nutrition are likely to reduce the burden and severity of pneumonia [29, 31]. However there is a lack of interventional research in this area. Jones *et al.* estimated a 6% reduction in child mortality with complimentary feeding in children 6 -23 months of life [27].

Micronutrient Supplementation

Zinc deficiency is common in low and middle income countries [32]. Zinc is important in skin and mucous membrane maintenance, leukocyte function and cytokine expression [33]. Supplemental zinc given either daily or as a weekly dose has been shown to decrease the incidence of pneumonia in young children in zinc deficient areas [34-36]. In a randomized controlled trial in Bangladesh children under 2 years given zinc 70 mg once weekly for 12 months had a reduced pneumonia incidence [199/809 children receiving zinc versus 286/812 children receiving placebo developed pneumonia (RR 0.83; 95%CI 0.73 to 0.95)] [34]. This translates into a 17% reduction in pneumonia incidence and a 49% reduction in severe pneumonia in children receiving zinc supplementation. Zinc appears safe in HIV infected children [35]. Food supplementation with zinc has the potential to reduce pneumonia incidence by 14-25% (90% CI 8-30) [28]. The role of zinc in the treatment of pneumonia is less clear. One controlled trial assessing the effect of zinc administered during a severe episode of pneumonia showed improvement in all severe pneumonia indicators and a shortened duration of hospital stay in zinc-supplemented children. However other studies have not confirmed these findings or have reported worsening of acute hypoxia [37, 38]. Results from ongoing trials in Nepal, Tanzania and Bangladesh are awaited.

Vitamin A significantly reduces the severity of measles associated pneumonia, reducing pneumonia associated morbidity and mortality by half (RR 0.51; 95%CI 0.35 to 0.74) [39]. However, Vitamin A supplementation has no impact on non-measles pneumonia incidence or pneumonia related mortality [29]. There is little evidence for the effect of supplementation with other micronutrients for preventing pneumonia in children.

Indoor Air Pollution

Indoor air pollution produced by the use of solid fuels such as wood, dung, crop waste and coal has been identified as a potentially modifiable risk factor for childhood pneumonia [40] Solid fuels are used by over 3 million people worldwide [28]. A recent meta-analysis of exposure to indoor air pollution showed an increased risk of pneumonia in young children exposed to unprocessed solid fuels (OR 1.78; 95% CI 1.45 to 2.18), with a similarly increased risk of severe pneumonia [41]. Two interventions for reducing indoor air pollution have been investigated: switching to cleaner gaseous fuels (liquefied petroleum gas, kerosene or ethanol) in the household or improved combustion and ventilation through high-quality, well maintained biomass stoves. Using these interventions could reduce pneumonia incidence by 22-46% [28].

Handwashing

Handwashing with soap reduces the risk of acute respiratory infections and diarrhoea [42]. In a randomized controlled trial in Pakistan, neighbourhoods received handwashing education and then were randomly provided with plain or antibacterial soap. Control neighbourhoods received neither education nor soap. Children <5 years from the household who received soap had a 50% reduction in pneumonia episodes (95%CI -65 to -34) [42]. There was no difference between the households that used plain or antibacterial soap [42]. Widespread implementation of handwashing when used together with improved water and sanitation has been estimated to reduce child deaths by 3% [27].

Immunisation

Development of vaccines against the common respiratory pathogens has been a major advance in reducing the global burden of childhood pneumonia. Pertussis and measles immunisation, as part of the global Expanded Program on Immunisation (EPI), have significantly reduced childhood deaths in low and middle income countries [43, 44]. Conjugate vaccines against two of the common bacterial causes of childhood pneumonia, *H. influenzae* type b (Hib) and *S. pneumoniae*, are now available with widespread coverage in high income countries. However, these vaccines have not yet been widely incorporated into the EPI of most low and middle income countries.

Measles vaccine is part of the EPI schedule. Widespread coverage of the measles vaccine has been highly effective for reducing measles associated pneumonia and deaths, averting 11 million measles deaths from 2000-2007, representing a decrease of 74% in measles associated mortality [43]. A recent review of vaccine coverage in 45 low and middle income countries estimates measles vaccine coverage to be 74% (IQR 58-83). However, only 54% of children had received their initial measles vaccine by 12 months of age [45]. With improved vaccine coverage to above 90%, a decrease in under 5 mortality by around 1% could be achieved [27],

Pertussis vaccine had been part of the EPI since 1974. In 2003 pertussis vaccination prevented over 38 million cases of pertussis and 607 000 pertussis related deaths [44]. However, in the same year there were still an estimated 279 000 deaths related to pertussis pneumonia, 90% of which occurred in low income countries. The greatest burden of pertussis related mortality is in the first 6 months of life. The recommended pertussis vaccine schedule is three doses at 6, 10 and 14 weeks. Recent estimates of pertussis vaccine coverage in low and middle income countries are 84% coverage of 1st dose and 63% coverage of the 3rd dose [45]. However, dose timing was markedly delayed with only 57% of 1st doses given by 12 weeks and only 27% of 3rd doses

given by 5 months [45]. Improvement in vaccine timing and higher vaccine coverage may reduce the burden of mortality due to pertussis in low and middle income countries.

The ***H. influenzae*** **type b (Hib)** conjugate **vaccine** has been available for almost 20 years and is highly effective in both high and low income settings [46-53]. Hib reduces the incidence of bacteraemic pneumonia by more than 80% and radiologically confirmed pneumonia by 22-55% in immunocompetent children [46, 47, 54]. In addition the vaccine reduces asymptomatic nasopharyngeal carriage protecting unvaccinated people through development of herd immunity [55-57]. The Hib vaccine has reduced protection against invasive disease in HIV infected children not on antiretroviral therapy, but protects against the development of pneumonia or severe disease in a substantial proportion due to the increased susceptibility of immunocompromised children to such illness [58]. Hib vaccine is a cost effective intervention to reduce childhood pneumonia and mortality [59]. 61 of 72 GAVI-eligible countries have already included Hib into their routine immunization schedule in 2009 [22]. However, improved vaccine coverage in high burden countries not yet using Hib could reduce global pneumonia mortality by a further 22-34% [28].

The **pneumococcal conjugate vaccine (PCV)** has large potential to reduce the burden of childhood pneumonia and mortality. *S. pneumoniae* is consistently reported to be the commonest aetiological agent in childhood pneumonia in low and middle income countries accounting for 13.8 million cases of pneumonia a year globally, 94% in low and middle income countries [11]. In addition the HIV epidemic has considerably increased the burden and severity of pneumococcal pneumonia [60, 61]. PCV7 is a highly effective vaccine, reducing the incidence of bacteraemic pneumonia, radiologically confirmed pneumonia (by 13-37%) and clinical pneumonia [62, 63]. However the sensitivity of chest radiographs in detecting pneumococcal pneumonia is low and hence the burden of pneumonia prevented is likely to be much higher. A reduction in all cause pneumonia of 61% was reported in a North American study [64]. As many of the vaccine serotypes associated with antimicrobial resistance are included in the vaccine, PCV has also reduced antibiotic resistant disease [62, 65]. In a rural setting in the Gambia, PCV9 reduced childhood mortality by 16%, translating into 7 deaths prevented per 1000 children immunized [63]. PCV7 is immunogenic in HIV infected children [66, 67]. Although there is decreased efficacy in HIV-infected compared to uninfected children, the overall burden prevented is much higher in HIV infected children due to their susceptibility to severe disease [68]. Concern about replacement disease with non-vaccine serotypes due to an increase in non-vaccine serotype disease in communities with wide vaccine coverage has been raised [69-71]. However, a sustained and substantial reduction in invasive pneumococcal disease has occurred overall in populations with widespread use of PCV7. Cost effectiveness analysis shows that PCV is cost effective in low and middle income countries, especially due to the development of herd immunity [72]. Comprehensive PCV coverage could reduce childhood pneumonia mortality by 23-35% [28].

Antibiotic Prophylaxis

Pneumocystis jirovecii Pneumonia (PCP) Prophylaxis

Prophylaxis against PCP with oral trimethoprim-sulphamethoxazole (TMP-SMX), is effective to prevent primary and secondary infection with PCP in HIV-infected children. This requires timely identification of HIV infected mothers and children, and infrastructure and resources for implementation [73]. In countries where routine prophylaxis has been instituted, a dramatic reduction in PCP has occurred. In the only randomized controlled trial of PCP prophylaxis in HIV-infected children, a Zambian study found a 43% reduction in mortality and a 23% reduction in hospitalizations in children taking prophylaxis [74]. As PCP has been reported in HIV-exposed uninfected children, TMP-SMX prophylaxis may be considered in these infants, until 6 months of age. Current WHO guidelines recommend use of TMP-SMX prophylaxis in HIV-exposed and HIV-infected children from 4-6 weeks of age [75]. Prophylaxis may be discontinued if the child's HIV status is confirmed to be negative and breast feeding has ceased for at least 6 weeks or in HIV-infected children older than 18 months when there is sustained immune reconstitution on HAART. The recommended dose of TMP-SMX is 5mg/kg of TMP component (maximum dose 80mg TMP), given daily. If TMP-SMX is not tolerated alternatives include dapsone 2mg/kg once daily, parenteral pentamidine 4mg/kg every 2 to 4 weeks or aerosolized pentamidine, 300mg *via* Respigard II inhaler if the child is older than 5 years of age [76].

Prevention of Mycobacterial Disease

Isoniazid (INH) has been used successfully as preventive therapy in HIV uninfected children at risk of TB disease [77]. All children under 5 years exposed to a household TB contact should receive INH prophylaxis (10mg/kg) daily for six months to prevent primary infection. HIV-infected children exposed to a household contact should receive prophylaxis irrespective of age.

In HIV-infected adults with a positive tuberculin skin test, prophylaxis reduces the risk of TB disease by 36% [78]. A randomized control trial of INH prophylaxis versus placebo conducted in South African HIV-infected children not on HAART living in an area of high TB prevalence showed a significant reduction in TB incidence and mortality. INH reduced the incidence of TB by 72% and mortality by 54% [79]. Thus INH may be an effective public health intervention for HIV-infected children living in high TB prevalence areas. However further study of the long term protective efficacy, the optimal duration of prophylaxis, and the efficacy in HIV-infected children on HAART is needed. Potential concerns with using INH prophylaxis are the need to exclude TB disease in children before initiating this and the impact on mycobacterial drug sensitivity [80]. Long term INH prophylaxis appears to be safe in HIV-infected children [79, 81].

Highly Active Antiretroviral Therapy (HAART)

The use of HAART has decreased the incidence and severity of HIV associated pneumonia, and mortality, especially when initiated early in life. Comparative incident

ratios of opportunistic infections in HIV-infected children in the HAART era and pre-HAART era have reported a more than 5 fold reduction in the incidence of bacterial pneumonia and respiratory opportunistic infections [82, 83]. A recent South African study showed a 76% reduction in all cause mortality in infants less than 12 weeks who were randomized to receive HAART at HIV diagnosis irrespective of CD4 count or clinical staging compared to the use of deferred HAART (when CD4 counts fell below 20% or 25% or clinical criteria were met). Although the cause of death was unknown in many children, infections were the commonest cause of death in those dying in hospital [84]. The WHO has revised their recommendations to recommend early initiation of HAART in infants as soon as they are confirmed to be HIV-infected [85].

MANAGEMENT OF CHILDHOOD PNEUMONIA IN LOW AND MIDDLE INCOME COUNTRIES

Case Management of Childhood Pneumonia

The WHO developed case management guidelines for childhood pneumonia based on the premise that most fatal pneumonia was caused by bacterial infections, that these could be treated effectively with antibiotics, that children could access health care facilities and that a combination of clinical signs that could be taught to health care workers would identify most pneumonia cases. These were later incorporated into the IMCI guidelines. The guidelines aim to ensure prompt recognition and appropriate treatment of pneumonia in an accessible community based setting and to identify children at risk or with severe pneumonia who should be referred to health care facilities (Table **2**). The guidelines use cough or difficulty in breathing as the entry criteria; increased respiratory rate above age norm or lower chest wall indrawing are used to diagnose pneumonia or severe pneumonia. Additional signs such as decreased feeding, lethargy, convulsions or persistent vomiting are used to diagnose very severe pneumonia. This algorithm can be successfully taught and used by community health workers [86-88].

Although these guidelines are sensitive for identifying children with pneumonia, they lack specificity. This may be particularly problematic in children presenting with wheezing [89] who may have asthma or viral bronchiolitis and in children with malaria who may present with tachypnoea [90]. In addition clinical management of children living in areas with high HIV and TB prevalence or with high rates of malnutrition is more complicated, requiring adaptation of management guidelines. The clinical overlap of co-morbid diseases must be considered in local case management strategies.

Case management has been shown to be effective in decreasing pneumonia related child mortality [86]. A meta-analysis estimating the impact of case management indicated a reduction of 24% in total child mortality and 36% reduction in pneumonia related mortality in children under 5 years [86]. However challenges still exist in implementing effective case management. Only half of the countries with the highest pneumonia mortality surveyed in a recent review reported implementing community based case management [91]. Of these many reported very limited scale of implementation, covering less than 10% of the child population [91]. Delayed care seeking is an important risk for fatal childhood pneumonia and is commonly reported [92]. In 2004 only 29% of Ugandan children with symptoms of pneumonia reported to have used first or second line antibiotics during their illness [90]. In a recent review of care seeking in children with fatal pneumonia, carers waited a median of 2 days from recognition of illness before seeking care outside of home. Most care givers (57%) had used self-prescribed antibiotics before consulting health providers, leading to delayed care seeking [93]. Insufficient dosing with low quality drugs is common in low income countries [90] and a challenge that needs to be addressed.

A further challenge is improving case management at the health facility of first contact. Poor quality care in district hospitals has been reported to be problematic [94, 95]. Using facility based case management guidelines correctly and assuming access to resources such as antibiotics and oxygen has the potential to reduce children pneumonia mortality by 29-45% [28]. Most pneumonia deaths occur in children with severe pneumonia [17, 96], hence identifying and appropriately managing children with severe pneumonia is critical and may lead to timely use of alternative effective treatments when indicated.

National implementation of such guidelines can be effectively done, as has been recently described in Malawi, which resulted in a more than 50% reduction in paediatric pneumonia deaths [97].

MANAGEMENT OF PNEUMONIA IN THE COMMUNITY

The WHO has recently updated the guidelines for management of pneumonia (Table **3**) [85]. **Pneumonia**, defined as rapid breathing should be treated with oral

Table 2. WHO and IMCI Guidelines for Assessment of Severity of Pneumonia in Children [16, 133]

WHO Classification	IMCI Classification	Clinical Signs	Management
No pneumonia	Cough or cold	No signs of pneumonia or very severe disease	Symptomatic treatment, advise carer when to return immediately, follow up in 5 days if not improving
Non-severe pneumonia	Pneumonia	Fast breathing*	Give oral antibiotics for 3 days, advise the carer when to return immediately, follow up in 2 days
Severe pneumonia	Severe pneumonia or very severe disease	Chest indrawing	Give first dose of antibiotic Refer urgently to hospital
Very severe disease		Any general danger sign#	Give first dose of antibiotic Refer urgently to hospital

*< 2 months, 60 breaths per min, child 2-12 months: >50 breaths per minute; Child 12-59 months: >40 breaths per minute.
Lethargy, inability to feed, convulsions, vomiting everything.

Table 3. Current Antibiotic Guidelines Based on Updated WHO and IMCI Recommendations for Community Acquired Pneumonia in Children [98]

	Drug	Route	Dose	Frequency	Duration
Pneumonia	**Amoxicillin** Or **Trimethoprim-sulphamethoxazole****	Oral Oral	15mg/kg or 30mg/kg 4mg/kg trimethoprim component	3 times daily 2 daily 2 daily	5 days 3 days 3 or 5 days
Severe pneumonia	**Beta lactam antibiotic**: Benzyl penicillin Ampicillin	 Intravenous	 50 000units/kg 25 mg/kg	 4 times daily 3 times daily	Until child improves then change to oral amoxicillin, total 5 days
Very severe pneumonia	**Beta lactam antibiotic**: Benzyl penicillin or Ampicillin AND **Gentamicin**	Intravenous Intravenous Intravenous	50 000units/kg 50mg/kg 7.5mg/kg	4 times daily 3 times daily 1 daily	10 days[#] 10 days[#] 10 days[#]

**Not recommended in a child on TMP-SMX prophylaxis.
[#]Until child improves, then continue oral antibiotic 3 times daily to complete 10 days.

antibiotics. Previous WHO recommendations of amoxicillin (15mg/kg) three times a day or trimethoprim-sulphamethoxazole (TMP-SMX) (4mg/kg TMP component) have recently been updated [98]. Amoxicillin 30mg/kg may be given twice a day. A recent study comparing the pharmacokinetics of 15mg/kg amoxicillin given three times a day with 25mg/kg amoxicillin given twice a day to children aged 2-59 months, found the two regimens comparable [99], suggesting that the twice daily regimen is as effective and may result in better adherence. There is no established link between resistance to co-trimoxazole and response to non-severe pneumonia treatment [100, 101]. A large randomized controlled trial in Pakistan, that compared the clinical efficacy of twice daily oral amoxicillin with twice daily TMP-SMX found them to be equally effective for pneumonia [101]. A second study of children with severe pneumonia, comparing amoxicillin with co-trimoxazole showed amoxicillin to be more effective than cotrimoxazole [102]. However, because of the high rate of background antibiotic resistance, amoxicillin should preferably be used as first line treatment for non-severe pneumonia in HIV infected children.

Recent studies have shown shorter course (3 day) antibiotic therapy for immunocompetent children with pneumonia to be as effective as a 5 day course [103]. Two large randomized trials found 3 days of amoxicillin to be equivalent to 5 days [103, 104]. The first study randomized 2000 children in outpatient departments in seven hospitals in Pakistan to either 3 or 5 days of amoxicillin 15mg/kg every 8 hours. Rates of treatment failure at five days were similar in the 2 groups [209 (21%) *vs* 202 (20%), (95% CI -1.8 to 3.2)]. The disease relapse rates were also similar in the groups [12 (1%) *vs* 13(1%) (95% CI-0.6 to 0.8)] [103]. The second study randomized 2188 children from 7 outpatient sites in India to either 3 or 5-days of amoxicillin at 30-50mg/kg/day. Clinical cure was achieved in 980 (89.5%) in the 3-day group and 983 (89.9%) in the 5 day group (95% CI -2.1 to 3.0). Rates of relapse were also similar in both groups [5.3% *vs* 4.4% (95% CI -1.0 to 3.0)] [104]. Shorter course therapy has the advantages of being more cost effective, improved adherence and less development of antimicrobial resistance. However, these results are not generalisable to high HIV prevalence areas.

In addition, with the increased use of Hib and pneumococcal conjugate vaccines, other bacteria such as S aureus and viruses will become increasingly important in the aetiology of childhood pneumonia [105]. Future research to monitor and accurately diagnose the aetiology of childhood pneumonia is needed.

Children with no pneumonia (normal respiratory rate and no chest indrawing) often have an upper respiratory tract infection and should be treated symptomatically.

MANAGEMENT OF PNEUMONIA AT HEALTH FACILITY

The WHO classification of pneumonia severity into severe and very severe categories has debatable clinical relevance and has been recently reviewed elsewhere [106]. Moreover many health workers do not make this differentiation clinically and treat all children with WHO classified severe and very severe pneumonia according to guidelines for very severe pneumonia [94]. For the purpose of this review the management of severe and very severe pneumonia has been combined into management of severe pneumonia requiring hospitalization.

The clinical signs used in the case management guidelines have high sensitivity to identify severe disease but not to detect hypoxia requiring oxygen therapy [107-110]. Hypoxemia in children with severe pneumonia is common; a recent meta analysis reported that 13% of children admitted to hospital with severe pneumonia had hypoxemia [111]. This analysis did not include many children who do not present at a health facility and hence underestimates the true burden of hypoxemic pneumonia. Hypoxemia is associated with more severe disease and is a risk factor for death [111, 112]. Clinically signs such as cyanosis, respiratory rate >60 breaths per minute, nasal flaring, inability to drink, head nodding, chest wall indrawing and altered mental state are not sensitive measures of hypoxia [113-117]. Up to 20% of children with WHO severe pneumonia (without clinical signs of hypoxia such as cyanosis or drowsiness), were found to be hypoxic [111]. Pulse oximetry is the most reliable method for identifying hypoxia in children. Where pulse oximetry is not available respiratory rate >60 breath per minute and altered mental state are the most reliable

clinical indicators [118]. Routine screening of hypoxia with pulse oximetry and improved oxygen delivery systems have been shown to have a significant reduction in mortality [119-121]. Improved oxygen delivery systems in 5 hospitals in Papua New Guinea reduced the risk of death for a child with pneumonia by 35% (risk ratio 0.65; 95% CI 0.52-0.78) [119]. Identifying hypoxemia accurately has the potential to improve treatment and outcome in childhood pneumonia in low income countries by improving identification of severe disease and guiding treatment and monitoring.

Children with severe pneumonia and hypoxia or general danger signs (lethargy, decreased feeding) should be treated with intravenous or intramuscular antibiotics and oxygen and referred to hospital. Until recently WHO guidelines recommended a combination of benzyl penicillin and gentamicin or chloramphenicol [122, 123]. However, a recently published randomized controlled trial conducted in seven middle and low income countries in Asia, Africa and South America compared the clinical efficacy of intravenous ampicillin (50mg/kg four times a day) and gentamicin (7.5 mg/kg once a day) with chloramphenicol (25mg/kg three times a day) [124]. There was a higher treatment failure rate in the chloramphenicol group at 5 days (16% versus 11%; relative risk 1.43; 95% CI 1.03-1.97), at 10 days (19% versus 14%; relative risk 1.37; 95% CI 1.03-1.83) and 21 days (22% versus 16%; relative risk 1.34; 95%CI 1.02-1.75). Bacteremia was associated with a higher treatment failure rate in the chloramphenicol group [124]. Consequently hospitalised children with severe pneumonia should initially be treated with a B-lactam antibiotic and gentamicin. An alternative would be a second or third generation cephalosporin used alone especially if allergy or toxicity precludes use of the former combination.

Beta-lactam antibiotics have excellent penetration into respiratory secretions. No correlation between antibiotic resistance and treatment failure has been shown [125]. A recent study investigating the effect of *in vitro* beta-lactam resistant pneumococci on clinical outcome in children with severe pneumonia, showed excellent response to treatment with either Penicillin G (200 000units/kg/day) intravenously or ampicillin (150mg/kg/day) intravenously even in the presence of penicillin resistant pneumococci [125]. Antibiotic choice should be modified according to the culture results and antimicrobial sensitivities once available.

Admission to hospital and use of intravenous antibiotics has resource implications, requires intravenous access and may be a risk for nosocomial infection. Recent evidence suggests that oral amoxicillin is equally as efficacious as intravenous antibiotics in children admitted to hospital with severe pneumonia [126, 127]. A multicentre study in eight low and middle income countries in Africa, Asia and South America compared the efficacy of oral versus intravenous antibiotics in children admitted to hospital with severe pneumonia [126]. Children aged 3-59 months were randomized to receive either oral amoxicillin (15mg/kg/dose three times a day) or intravenous penicillin (50 000IU/kg four times a day) for 48 hours, after which, if symptoms improved, they were discharged home with a 5 day course of oral therapy amoxicillin. Treatment failure at 48 hours in each group was similar [19% in the amoxicillin group *vs* 19% in the penicillin group (95% CI -4.2 to 3.3)] [126]. In another recent study at seven sites in Pakistan in children 3-59 months with severe pneumonia, five days of high dose amoxicillin (80-90mg/kg per day) given as outpatient therapy was compared with intravenous ampicillin (25mg/kg four times a day) for 48 hours followed by three days oral amoxicillin (80-90mg/kg per day in two doses). The number of children who failed treatment in the 2 groups was similar [7.5% in ambulatory *vs* 8.6% in the hospital group at day 6 (95% CI -1.3 to 3.5)] [127]. However these results are not applicable in areas with high HIV prevalence. In addition extrapolation of these results to areas of high pneumonia associated mortality may not be possible as the mortality rate was only 0.2%, which is lower than that in many other studies [127]. The use of pulse oximetry to identify children with hypoxia may however be an excellent tool to screen children for outpatient treatment.

Failure to respond adequately to antibiotic treatment is a challenge in childhood pneumonia. Treatment failure rates have been reported to range from 9 to 21% [17, 102, 103, 126, 128]. Identifying children with severe pneumonia who are likely to fail treatment may lead to timely switch to alternative effective treatment and hence decrease mortality. Recent research has included identifying risk factors for treatment failure in children with pneumonia in low and middle income countries [17] and developing clinical tools that could be used in resource limited settings to improve management of at risk children. Fu *et al.* recently showed that using clinical signs at presentation and after 24 hours could be used to predict clinical failure of oral amoxicillin therapy [129]. Using oxygen saturations had equal predictive value at 12hrs [129]. Young age, increased initial respiratory rate and baseline hypoxia were all associated with increased risk of treatment failure [129]. In another study, lack of exclusive breastfeeding, overcrowding and chest radiographic signs of pneumonia were related to failure of first line therapy [130]. Others have also documented association between chest radiographic pathology and disease severity [131]. Mamtani *et al.* developed a clinical tool using simple clinical parameters to predict risk of treatment failure: age of child, excess age-specific respiratory rate at baseline and at 24hr of hospitalization, with a 66-70% predictive accuracy for treatment failure [132]. It is possible that monitoring of simple clinical signs at presentation and after 12 hours together with routine monitoring of oxygen saturation with pulse oximetry could reliably identify those children that require hospitalization and consideration of alternative therapy.

RESEARCH PRIORITIES

More research on childhood pneumonia is needed to better understand the burden and to develop more effective and cost effective preventative and treatment strategies. Specific areas of importance include:

- Development of better tools for pneumonia diagnosis
- Development of rapid, reliable methods for aetiological diagnosis
- Study of the changing burden of disease in the post Hib, post PCV era
- Assessment of the efficacy of preventative strategies in HIV-infected children with limited access to HAART and in the era of HAART

- Improved preventative strategies including development of new and combination vaccines
- Improved treatment strategies including shorter course therapy and oral therapy in HIV-infected and uninfected children
- Monitoring of the development of antimicrobial resistance and impact on treatment interventions
- Cost efficacy analysis of specific preventative and therapeutic interventions

SUMMARY

Childhood pneumonia continues to be the major cause of mortality in low and middle income countries. Implementation of preventive strategies must be intensified, particularly immunisation with Hib and PCV. For treatment, case management strategy must be more widely implemented at the community level, with attention to operational and educational aspects. Better access to oxygen delivery systems is needed. Treatment and preventative strategies require adaptation in high HIV prevalence areas to include interventions that are specific for HIV-infected children. Further research to develop better diagnostic tests, preventative and treatment strategies is needed, especially when high coverage with Hib and PCV has been achieved.

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