

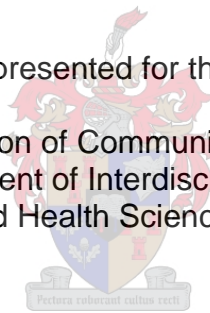
# Improving the quality of care for inpatient management of childhood pneumonia at the first level referral hospital: a country wide programme.

by

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Dissertation presented for the degree of PhD

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## Declaration

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

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## Summary

Pneumonia is the greatest single cause of mortality in children less than five years of age throughout the world causing more deaths than those due to AIDS, malaria and tuberculosis combined. Approximately 50% of all childhood pneumonia deaths occur in sub-Saharan Africa. Children in developing countries being treated for pneumonia frequently have one or more comorbid conditions which increases their risk of dying. The proper management of the child with severe or very severe pneumonia is essential to reduce case fatality. Standard case management (SCM) of pneumonia, has been shown to be an effective intervention to reduce deaths from pneumonia, but what is lacking is a means of delivering it in low-resource/high burden countries.

A major barrier to wide application of this intervention in low-income countries is weak health-care systems with insufficient human and financial resources for implementing SCM to a sufficient number of children at a level of quality and coverage that would result in a significant impact. The objective of this dissertation is to address this issue by investigating ways of improving delivery of standard case management of pneumonia in district hospitals throughout Malawi, a high HIV-prevalent country which would result in a decrease in the in-hospital case fatality rates (CFR) from pneumonia in children less than five years of age.

We reviewed the evidence base for SCM. Then we evaluated the development and implementation of a national Child Lung Health Programme (CLHP) to deliver SCM of severe and very severe pneumonia and a programme to provide uninterrupted oxygen supply in all paediatric wards at District Hospitals throughout Malawi. We demonstrated that it was feasible to implement and maintain both programmes country-wide.

Thirdly we evaluated the trend in case fatality rates in infants and young children (0 to 59 months of age) hospitalized and treated for severe and very severe pneumonia over the course of the implementation of the CLHP. The findings from this study showed that in the majority (64%) of cases, who were aged 2-59 months with severe pneumonia there was a significant effect of the intervention that was sustained over time whereas in the same age group children treated for very severe pneumonia there was no interventional benefit. No benefit was observed for neonates.

Fourthly we investigated factors associated with poor outcome reported in the previous study, in a subset of this cohort to determine the individual factors including demographics of the study population, recognised co-morbidities and clinical management that were associated with inpatient death. This study identified a number of factors associated with poor pneumonia-related outcomes in young infants and children with very severe pneumonia. They included co-morbidities of

malaria, malnutrition, severe anaemia and HIV infection. The study found that the majority of reported comorbid conditions were based on clinical signs alone indicating a need for more accurate diagnosis and improved management of these comorbidities that may lead to improved outcomes. Other identified factors included a number of potentially modifiable aspects of care where adjustments to the implementation of SCM are indicated. These included enhancing correct classification of the severity of the disease, the use of correct antibiotics according to standard case management, more extensive availability and use of oxygen together with oximetry to guide its use,.

Finally recommendations were made to address the identified reasons for poor outcomes and suggested future research.

## Opsomming

Pneumonie is die grootste enkele oorsaak van sterftes by kinders jonger as 5 jaar in die wêreld en veroorsaak meer kindersterftes as die menslike immuungebrekvirus (MIV), malaria en tuberkulose saam. Ongeveer 50% van kindersterftes van pneumonie kom in sub-Sahara-Afrika voor. Kinders in ontwikkelende lande, wie vir pneumonie behandel word, het dikwels een of meer bydraende toestande wat die doodsrisko verhoog. Kinders wie ernstige of baie ernstige pneumonie onderlede het moet korrek behandel word om sterfte te voorkom. Die standaard protokolle om kinderpneumonie korrek te behandel het getoon om effektief te wees om die sterftesyfers te verlaag. In lae inkomste lande bestaan die strategieë nie om die protokolle aan te wend nie.

'n Groot struikelblok in die aanwending van die pneumonie behandelingsprotokolle in lae-inkomste lande is die swak gesondheidsorgsisteme met onvoldoende menslike en finansiële hulpbronne. Die tekorte gee aanleiding tot die beperkte implementering van pneumonie protokolle wat die omvang en kwaliteit van die pneumonie protokolle beperk en daarom impakteer die protokolle nie op die kindersterftesyfer nie. Die doel van die verhandeling is om hierdie probleem aan te spreek deur navorsing hoe om die pneumonie protokolle landwyd in alle distrikhospitale in Malawi, 'n land met 'n hoë MIV prevalensie, aan te wend om sodoende die kindersterftesyfer (kinders jonger as 5 jaar) as gevolg van pneumonie te verlaag.

Ons het die getuienis van die pneumonie protokolle ondersoek. Hierna is 'n nasionale Kinderlong Gesondheidsprogram ontwikkel en landwyd geïmplementeer. Volgens die program is kinders met ernstige en baie ernstige pneumonie volgens Wêreldgesondheidsorganisasie (WGO) protokolle behandel. Ononderbroke suurstoftoevoer in alle pediatriesale in distrikhospitale in Malawi beskaf. Die navorsing het getoon dat die implementering en instandhouding van pneumonie behandelingsprotokolle is landwyd moontlik.

Verder het ons die tendens ondersoek of die kindersterftesyfer in babas en jong kinders (0 tot 59 maande) wat in die hospital opgeneem en behandel is vir ernstige en baie ernstige pneumonie tydens die implementering van pneumonie protokolle verminder het. Die bevindinge van hierdie verhandeling wys dat in die meerderheid (64%) van die kinders tussen 2 en 59 maande met ernstige pneumonie, en met die toepassing van die pneumonie protokolle, statistiesbetekenvol die sterfte syfer verlaag het. Die protokolle vir die behandeling van baie ernstige pneumonie het nie dieselfde wenslike effek gehad nie. In neonate (jonger as 2 maande) was daar ook geen verlaging in die sterftesyfer nie.

Laastens het ons die redes vir die swak uitkomstige ondersoek in 'n substudie en veral klem gelê op bydraende siektes en kliniese sorg tekorte geassosieer met pneumonie sterftes. Die studie het 'n aantal faktore geïdentifiseer wat bygedra het tot die sterftesyfer in kinders met baie ernstige pneumonie en in neonate. Die geïdentifiseerde bydraende faktore het malaria, wanvoeding, erge anemie en MIV-infeksie ingesluit. Voorkomende maatreëls moet vir die geïdentifiseerde faktore ingestel word. Aanpassings in die pneumonie protokolle is voorgestel.

Ten slotte word aanbevelings gemaak om die geïdentifiseerde redes vir swak uitkomstige aan te spreek en verdere navorsingidees word aanbeveel.

## **Dedication**

To the people of Malawi, especially the children and their mothers.

“Children are the living messages we send to a time we will not see.”

Neil Postman. *The Disappearance of Childhood*.

“Children are our greatest treasure. They are our future.” - Nelson Mandela

Also to my husband for his patience and support.

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## Chapter 1.

### Introduction

The millennium development goal four (MDG4) aimed to reduce childhood mortality by two-thirds by 2015 from levels in 1990. While substantial progress has been achieved, targets will not be reached in many high-mortality countries. By 2000, the gap in childhood mortality between industrialised and sub-Saharan African countries had increased from 20-fold in 1990 to 29-fold with the childhood under-five mortality rates in sub-Saharan Africa averaging 175 deaths per 1000 live births compared to six deaths per thousand live births in industrialised countries.[1] The mortality reduction targets were met in only 5 of 55 countries that had an under-five year mortality rate of 100 or more in 1990.[1]

At the beginning of the study, on which this dissertation is based, the global estimate in 2000 for child deaths was 10.8 million - 41% of these occurred in sub-Saharan Africa and 34% in Southern Asia.[2] The leading causes of death with uncertainty bounds were: diarrhoea 22% (14-30%), pneumonia 21% (14-24%), malaria 9% (6-13%), measles 1% (1-9%), AIDS 3%, neonatal causes 33% (29-36%) and 9% other causes.[2] In 2013 pneumonia remained the greatest single cause of mortality in children less than five years of age throughout the world despite the decrease in overall mortality rate.[3,4,5] Bhutta et al. reported that of the 6.9 million deaths in children younger than five years in 2011, pneumonia remained the number one cause of death (18.8%) in children one to 59 months. [5]

### Epidemiology

#### Morbidity

Developing countries have the highest number of episodes of pneumonia estimated at over 150 million cases (95%) worldwide annually with 7% to 13% requiring hospitalization.[4] The average number of episodes per child per year is 0.29 worldwide, and in sub-Saharan Africa and South Asia is 0.30 and 0.36 respectively.[6] Rudan et al. reported that there was an increase in the proportion of severe episodes requiring hospitalisation in the lower and middle-income countries.[6] In a recent meta-analysis of 62 studies from developing countries the pneumonia incidence was highest in neonates aged <28 days (68.6 episodes per 1000 per year, 95% CI 47.8–98.4); and infants aged 0–11 months (51.8 episodes per 1000 per year, 44.8–59.8).[7] There were approximately 20 episodes per thousand children per year requiring admission for severe pneumonia in children aged 0–59 months.[7] The high incidence of acute respiratory infections is a

considerable burden on health services globally and a major cause of hospital referral and admission in this age group.[7]

### **Mortality**

Nair et al. [7] estimated that in 2010 there were 11.9 million episodes of severe and 3.0 million episodes of very severe pneumonia in young children worldwide that required hospitalization with an estimated 265 000 (95% CI 160 000–450 000) in-hospital deaths, of which 99% of which occurred in developing countries. Afghanistan, Democratic Republic of the Congo, India, Nigeria and Pakistan together have the highest proportion (52%) of all pneumonia deaths.[8] Many published studies have used modeling to estimate pneumonia rates and deaths for countries in sub-Saharan Africa where it is estimated that approximately 50% of all childhood deaths occur but there is very little information available based on reliable sources to confirm this.[9,10,11,12] According to Black et al. [8] it is these high-burden/ low-resource countries that are the ones most in need of information that will allow them to target specific diseases and health-care services.

Of the 7.6 million deaths in children younger than five years in 2010 pneumonia remained the leading cause with an estimated 1.396 million deaths, 18.3% of total deaths (uncertainty range (UR) 1.189–1.642 million).[5] This included 4% of neonatal pneumonia deaths. Sepsis and meningitis are estimated to be responsible for a further 0.393 million (5.2%) neonatal deaths. In the 1-59 months age group diarrhoea was second and malaria third, 10.5% and 7.7% respectively of total deaths. AIDS deaths were an estimated 0.159 million (2%). The burden of mortality in children younger than five years varied widely across World Health Organization (WHO) regions in 2010, with the largest number of deaths seen in Africa (3.6 million) and South-East Asia (2.1 million). The proportion of deaths from pneumonia is dependent on the prevalence of malaria and Human Immunodeficiency Virus (HIV) which varies widely between regions, but even in regions where malaria and AIDS deaths are common pneumonia still accounts for up to 17% of deaths.[13] See Table 1 for regional causes of childhood deaths in 2010 due to infectious diseases.

### **Standard Case Management Strategy**

Despite the heavy burden of pneumonia on child morbidity and mortality, pneumonia has been neglected within the area of public health for many decades in developing countries. In the early 1980's childhood pneumonia was recognised as a major problem that needed to be addressed at a global level.[14] There were two schools of thought at this time as how best

Table 1.1. Regional causes of childhood deaths in 2010<sup>1</sup>

Region	Deaths/ millions	Child 1 – 59 months					Neonate 0-27 days	
		% of total deaths in region*					% of total deaths in region*	
	N=7.622	Pneumonia	Diarrhoea	Malaria	Meningitis	AIDS	Pneumonia	Sepsis or meningitis
Africa	3.552	14	11	15**	3	4***	3	4
SE Asia	2.096	15	10	1	2		7	7
Eastern Mediterranean	1.062	15	11	1	3		4	5
Western Pacific	0.467	14	4		2		2	3
Americas	0.284	8	4		1	1	2	5
Europe	0.161	9	4		1	1	3	4

\*Causes responsible for less than 1% of deaths are not shown.

\*\* 95.7% of global child deaths due to malaria

\*\*\* 89.5% of global child deaths due to AIDS

to address the issue. Scientists, especially epidemiologists and microbiologists supported the idea that the causative agents and risk factors should be identified before any intervention strategies were undertaken in the control of acute respiratory infections in children in developing countries. This school of thought is represented today in the Pneumonia Etiology Research for Child Health (PERCH) project whose aim is to provide data that reflect the epidemiologic situation in developing countries in 2015 and address differences in host, environmental, and/or geographic factors that might determine pneumonia aetiology relevant to pneumonia management in the 21<sup>st</sup> century.[15]

The other school of thought included experts, mainly paediatricians and community health specialists, who proposed that there was sufficient evidence available to define control strategies and that these could be implemented immediately.[16] During the 1980's, the WHO and United Nations International Children's Emergency Fund (UNICEF) main objective was to introduce an Acute Respiratory Infection (ARI) Programme based on standard case management (SCM) as it's central strategy to reduce mortality from pneumonia.[17]

<sup>1</sup> Adapted from Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379:2151-61.

**Case management defined [18]**


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Correct case management is the cornerstone of Programmes for the control of acute respiratory infections. Case management involves:

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- |                                                                                                                                             |                                                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| <p><b>1</b> Early recognition of pneumonia by health workers using signs of fast breathing and chest in-drawing.</p>                        | <p><b>3</b> Antibiotic treatment at home with recommended drugs, for cases of pneumonia which are not severe.</p>           |
| <p><b>2</b> Prompt referral to hospital for injectable antibiotic treatment and other intensive care, for severe and very severe cases.</p> | <p><b>4</b> Supportive home care for the vast majority of acute respiratory infections that do not require antibiotics.</p> |
- 

**Scientific basis for standard case management**

The ideal approach to the diagnosis of pneumonia and other lung diseases would be to identify the causative micro-organism(s) in each individual case so that appropriate treatment could be prescribed. However, the limitations of diagnostics at the time, which presently still exists, did not allow for such an approach.[19] A confirmed bacterial cause of pneumonia in children can usually only be established by culture of lung (or pleural fluid) aspiration or blood.[20] Blood cultures are positive in only a small portion of children even with severe pneumonia, and obtaining specimens from lung or pleural aspiration is usually not feasible in most routine situations as well as exposing the child to a risk of a serious complication.[20] Auscultation and radiological findings are unreliable means of determining the aetiology of pneumonia in children. Clinical information such as leucocyte count and the level or evolution of fever are imprecise in defining the bacterial or viral aetiology of pneumonia.[20] Due to the limitations of diagnostics a standard management approach for pneumonia in children including empirical use of antibiotics was adopted based on simple clinical signs.[20]

Faced with children presenting with cough or difficult breathing, especially in hospitals with diagnostic limitations, health workers must be able to distinguish those children that have pneumonia rather than the more common upper respiratory tract infection as well as determine severity of pneumonia in order to promptly treat potentially fatal cases. Standard case management includes classification of severity of pneumonia in children based on a limited number of clinical signs. It ensures that those requiring antibiotics receive the appropriate antibiotic at the appropriate dose. The use of empirical antibiotic therapy for pneumonia is a commonly accepted practice worldwide. In low-income countries, and especially in those with high infant mortality rates (IMR), as many as half of pneumonia cases in children attending health services may be of

bacterial origin and bacterial pneumonia is more likely to be fatal than pneumonia due to common respiratory viruses.[21] Simple clinical signs, without a chest x-ray or laboratory investigations, can diagnose almost all of these cases of pneumonia.

## Diagnosis

In the early 1980s research was undertaken to identify simple clinical criteria for detecting pneumonia.[22] These studies found that the presence of fast breathing and lower chest wall in-drawing in any child under five years of age presenting with cough or difficult breathing was highly predictive of pneumonia and the need for antibiotic treatment and hospitalization.

An increase in respiratory rate (rapid breathing) is one of the physiological responses to hypoxia and stiff lungs. However, it can also occur if a child is frightened, upset or feeding, so it is essential that the child be calm when the respiratory rate is measured. Since the normal respiratory rate in a young infant (less than 2 months) is higher than in older infants and children, a higher threshold for case detection is used in this age group. Furthermore, the greater variability in respiratory rate in this age group requires that the finding of an elevated rate be checked by a second count after an interval to ensure that the child is calm. Clinical studies carried out in the Gambia, [23] India, [24] and the Philippines [25] validated the use of clinical signs and refined the age-specific criteria used to diagnose pneumonia. The recommended upper limits of respiratory rates were defined as:  $\geq 60$  per minute for infants below 2 months;  $\geq 50$  per minute for infants aged 2—12 months;  $\geq 40$  per minute for children aged 12—59 months.

Stiff lungs (decreased lung compliance) resulting from severe pneumonia cause chest in-drawing during inspiration. Studies showed that children who present with lower chest in-drawing are more likely to have severe pneumonia than children without this sign.[21,22] As the respiratory rate can fall when pneumonia becomes more severe or the child is exhausted, the use of both signs results in detection of a higher proportion of severe pneumonia cases. Several clinical studies that have compared clinical signs with a chest radiograph have shown that fast breathing and chest in-drawing can very efficiently identify cases of pneumonia in young children with cough or difficult breathing who are not wheezing.[26]

The majority of studies [22-26] found that the presence of fast breathing and lower chest wall in-drawing in any child under five years of age presenting with cough or difficult breathing was highly predictive of pneumonia with a sensitivity  $\geq 80\%$  and specificity  $\geq 90\%$  for both.

The highest case-fatality rates occur in children who are either cyanosed and/or not able to drink – features that are used for the classification of very severe pneumonia. The presence of either of

these signs in children with cough or difficult breathing indicates an urgent need for admission and intensive therapy including oxygen and broad-spectrum parenteral antibiotics.[27,28] These findings provided the rationale for pneumonia case detection using clinical signs and symptoms without the need for auscultation or radiography: this forms the basis for empirical treatment of childhood pneumonia.[29]

Standard case management of community acquired pneumonia (CAP) in hospitalized children in developing countries was based on: 1) *Streptococcus pneumoniae* and *Haemophilus influenzae* being the most common causes of bacterial pneumonia, [30] 2) simple clinical signs having high sensitivity and specificity (in high mortality settings) for the diagnosis of pneumonia without the need for auscultation, radiology or laboratory investigations; [22] 3) effective, safe and cheap antibiotics being available to treat pneumonia both as an out- or inpatient.[31] These facts formed the basis for the empirical treatment of childhood pneumonia and became “the corner-stone of the current [WHO] case management strategy for the control of ARIs in children.”[32]

## **Treatment**

### **Aetiology and antimicrobials**

During the 1970s and 1980s studies carried out in developing countries on lung aspirates and blood cultures from hospitalized children with untreated community-acquired pneumonia showed that bacteria were present in more than 50% of cases and that *Streptococcus pneumoniae* and *Haemophilus influenzae* were the predominant bacteria, accounting for two-thirds of all bacterial isolates.[31,33-37] The BOSTID study findings published in 1990 of children admitted for pneumonia in sites in 5 countries found that a higher proportion was due to viral as opposed to bacteria infections with range 14% to 64%. Bacterial infection was found in 4.5% to 40% with *Streptococcus pneumoniae* and *Haemophilus influenzae* being the predominant bacteria.[38]

In 1990 the WHO published recommendations, based on these earlier findings for the standard antibiotic treatment for pneumonia using antimicrobials effective against these two bacteria.[39] The antibiotics of choice, for children two to 59 months, were amoxicillin or cotrimoxazole for non-severe pneumonia, benzylpenicillin for severe pneumonia and chloramphenicol for very severe pneumonia. The recommended treatment for infants less than two months was parenteral gentamicin and benzyl penicillin.

These recommendations were made prior to the HIV era and have since been shown to be not as effective in HIV positive children with pneumonia [40-42] and therefore the WHO introduced new recommendations in 2005.[43] For children with severe/very severe pneumonia who are HIV

positive or in whom HIV is suspected ampicillin plus gentamicin for 10 days is recommended. If the child does not improve within 48 hours then the recommendation is to change to ceftriaxone (80 mg/kg IV once daily over 30 minutes) if available. If not available then gentamicin plus cloxacillin is recommended.[43] Also recommended is high-dose cotrimoxazole (eight mg/kg of trimethoprim and 40 mg/kg of sulfamethoxazole IV every eight hours or orally three times a day) for three weeks.[43] Antibiotic treatment for severe pneumonia remained the same whereas that recommended for very severe pneumonia changed to ampicillin and gentamicin as well if available.[43]

Blood culture studies from tropical Africa have found that non-typhoidal *Salmonella* is a common isolate from children with a clinical diagnosis of pneumonia.[44-47] Other common causes are respiratory viruses, [48,49] pertussis and measles.[50] Pneumonia is a frequent and major complication of measles - the most frequent bacteria reported as cause of secondary infection are *Streptococcus pneumoniae* and *Staphylococcus S aureus*.[51] Herpes virus and adenovirus can cause measles-associated pneumonia.[51] Recommendations for treatment of measles-pneumonia is the same as above for very severe pneumonia.

With the introduction of conjugate vaccines that protect against *Haemophilus influenzae type b* (Hib) and common serotypes of *Streptococcus pneumoniae* over the last decade, there has been an impact on the incidence of bacterial pneumonia and meningitis.[52-54] The Hib vaccine, which is now routine in many countries has been shown to be highly efficacious – although less effective in HIV-infected children.[5] The pneumococcal conjugate vaccine (PCV) is also very effective [56-58] and since 2010 has been increasingly implemented in high burden settings in Africa. Even the recognised challenge of needing to cover a broader range of serotypes in the African region compared to the United States of America (USA) is being addressed with implementation of PCV 13 replacing the original PCV 7 valent vaccine.[59,60] The Global Alliance for Vaccines and Immunisation (GAVI) in their 2014 annual report for pneumococcal Advance Market Commitment (AMC) for vaccines stated that by the end of 2013 of the 73 AMC countries eligible and approved for support to introduce pneumococcal vaccines 40 had done so, eight had introduced PCV10, while 32 countries are using PCV13.[61]

A 2008 Cochrane review of 11 publications from six randomised clinical trials (RCTs) conducted in Africa, US, Philippines and Finland comparing PCV with placebo in children under two with invasive pneumococcal disease (IPD) found that PCV is effective in preventing IPD.[62] Efficacy all serotypes-IPD was 58% (95% CI 29% to 75%, P = 0.001). In X-ray defined pneumonia it was 27% (95% CI 15% to 36%, P < 0.0001) and in clinical defined pneumonia 6% (95% CI 2% to 9%, P =

0.0006). All-cause mortality was 11% (95% CI -1% to 21%, P = 0.08). Similar results were found in HIV-1 positive children.[62]

Although both Hib and PCV are safe and effective in the prevention of radiologically confirmed pneumonia in children, they only target selected pneumonia pathogens and are less than 100% effective. Therefore, they must be accompanied by both curative care and other preventative strategies.[63]

While both Hib and PCV have a lower efficacy in HIV-infected children [43,46], they do provide some coverage directly and indirectly through herd immunity and reduced carriage. Given the huge increased risk for bacterial pneumonia in the HIV-infected, even a reduced efficacy results in prevention of a large numbers of cases. Further, the risk of HIV-related pneumonia is falling in the region due to a declining risk of new HIV infections in babies, as well as protective effects of cotrimoxazole preventive therapy (CPT) and antiretroviral therapy (ART).

### **Co-morbidities influencing aetiology in high burden countries**

The aetiology of pneumonia in high-risk immunosuppressed children is different from that of immuno-competent children. *Streptococcus pneumoniae* and *Haemophilus influenzae* remain the primary cause of infection but there is a broader spectrum of pathogens found in the immunosuppressed child with pneumonia therefore antibiotic treatment recommendations need to be tailored to these high-risk groups.[64-67]

### **HIV**

An increase in paediatric HIV infection has had a substantial impact on childhood morbidity and mortality worldwide. HIV infection in children living in HIV endemic countries is due largely to mother-to-child transmission. Estimated transmission rates for developed countries are less than two per cent whereas in developing countries the range is 25 to 48% with interventions available to only 5%-10% of women.[68] It is estimated that there are currently more than 2.3 million children living with HIV worldwide of which 2 million (90%) live in sub-Saharan Africa.[69] These children become symptomatic in the first few years of life with >80% developing a respiratory disease at some point during the course of their illness.[70] A study in South Africa showed that the implementation of Prevention of Mother to Child Transmission (PMTCT) intervention of a single dose of Nevirapine (NVP) given to the mother at the onset of labour and to the baby within 72 hours of birth reduced MTCT of HIV significantly with lower rate of transmission at six weeks (8.7%) and 14 weeks (8.9%).[71] Another study from South Africa showed that the early HIV diagnosis and early



intervention with antiretroviral therapy reduced early infant mortality by 76% and HIV progression by 75%.[72]

In southern African countries it is estimated that between 35 to 65% of children admitted with severe pneumonia are co-infected with HIV and have a higher case fatality rate (CFR) (34%) than children with pneumonia who are HIV negative (9%).[73] Autopsy and clinical studies from the high HIV prevalent (>1% prevalence) setting have indicated that acute pneumonia in HIV-infected infants and children is caused by a wider range of pathogens than in those who are not HIV-infected.[64,74] In addition to bacteria, respiratory viruses and tuberculosis (TB), pneumonia associated with *Pneumocystis jirovecii* (PcP) and cytomegalovirus (CMV) are commonly reported. [41,46,65,75-79]

Most episodes of pneumonia in HIV-positive children have the same aetiology as in HIV-negative children and respond to the same treatment but there is a higher rate of failure due to a wider range of pathogens.[40,41,65] If the pneumonia does not respond to standard treatment and there is hypoxia that responds poorly to oxygen therapy then *Pneumocystis jirovecii pneumonia* should be considered.[46] Those most at risk are infants less than six months of age living in HIV-endemic regions.[80] See section on Aetiology and Antimicrobials for WHO recommendation for treatment of PcP.

### **Tuberculosis**

Chintu *et al.* reported that *Mycobacterium tuberculosis* was the third most common autopsy finding (18.8%) in Zambian children dying from pneumonia irrespective of their HIV status.[77] Prospective clinical studies of South African children hospitalized with severe pneumonia confirmed TB as the cause in 7-8% of admissions. [65,78] A more recent study of children admitted with severe/very severe pneumonia (WHO-defined) found that 15% had culture-proven TB.[41] A child with persistent fever and signs of pneumonia and those not responding to antibiotics, should be evaluated for tuberculosis such as by enquiring about recent close contact with a TB case.

### **Malnourished children**

Severely malnourished children are very immunosuppressed and have a higher incidence of pneumonia and related mortality. They have a broad spectrum of causative agents that includes bacterial infection with *S pneumoniae*, *H influenzae*, *Escherichia Coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, non-typhoidal *Salmonella species*, *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*. Viral pathogens include RSV, Influenza, Measles, Varicella and CMV, as well as fungal infections caused by *Pneumocystis jirovecii* and *Candida albicans*.[81] The treatment regimen recommended for these children includes cotrimoxazole prophylaxis on

admission if not acutely ill or a broad-spectrum injectable antibiotic such as chloramphenicol or ampicillin plus gentamicin if clinical pneumonia or sepsis is diagnosed.[43]

### **Young infants**

The WHO's multi-centred Young Infant Study (less than 2 months of age) on pneumonia, sepsis and meningitis found that the most common isolates from blood were *Staphylococcus aureus* (20.4%), *Streptococcus pneumoniae* (19.8%) and *Streptococcus pyogenes* (17.4%).[82] The gram-negative isolates were less frequent, *Escherichia coli* (11.4%), *Salmonella* species (10.2%), *Haemophilus influenzae* (4.2%) and *Klebsiella pneumoniae* (3.0%). *Streptococcus pyogenes*, *Staphylococcus aureus* and *Escherichia coli* were the most common organisms isolated in the first month of life and *Streptococcus pneumoniae* in both the second and third months of life. Group B *Streptococcus*, the most common pathogen found in neonates in developed countries was only found in 1.2% of all bacterial isolates. A recent study of young infants also found that *Staphylococcus aureus* was the most common organism isolated (43.4%) followed by Gram-negative bacilli (46.9%) with the most common organisms being *Escherichia coli* and *Klebsiella pneumoniae*. [83] The study also reported high levels of resistance to second and third generation cephalosporins and gentamicin. [83] In contrast, studies from Malawi and Kenya have found Group B *Streptococcus* to be the commonest isolate: 136 or 17% of 784 isolates from Malawian neonates. [84-86]

The recommended regimen for severe pneumonia or very severe pneumonia/disease in the infant less than two months is a combination of injectable ampicillin or benzylpenicillin plus gentamicin which covers the majority of these pathogens. If the response to treatment is poor, intramuscular or intravenous cefotaxime plus intramuscular ampicillin is recommended. [43]

### **Recent revisions to antibiotic recommendations**

In 2005, the WHO published recommendations based on new research. [87] For the treatment of non-severe pneumonia in children 2-59 months of age, oral amoxicillin or oral cotrimoxazole in low HIV-prevalent countries is recommended for a shorter period of three instead of five days. For severe pneumonia, in this age group the recommendation for hospitalized children remains unchanged but where referral and injectable antibiotic is not possible then the recommendation is oral amoxicillin in 45 mg/kg/dose twice daily for five days. For very severe pneumonia in children 2-59 months of age injectable ampicillin and gentamicin is now being recommended over that of injectable chloramphenicol. [88]

### **Factors influencing outcome of pneumonia:**

Several important environmental risk factors and endogenous (host) modifiers have been identified that influence the outcome of pneumonia in children.

### **Age**

Infection, particularly pneumonia, sepsis and meningitis are major contributors to high mortality rates in young infants less than two months of age in developing countries with the majority of pneumonia-related deaths occurring in infants less than 12 months of age.[86,89] A meta-analysis of studies carried out in 1992 on age-related fatality rate due to pneumonia showed that 20.8% of deaths occurred before one month of age, 57.8% between 1-11 months, and 21.5% at 12-59 months – no confidence interval (CI) reported.[90] More recent studies on age-related fatality rate due to pneumonia reported the following: McNally et al. found in-hospital mortality was highest in age <12 months OR=3.37 (95%CI 1.41-10.25).[40] Naheed et al. also reported in-hospital mortality was highest in age <12 months OR=2.0 (95%CI 1.3-3.2).[91] Sigauque et al. reported deaths by age groups: 12-23 months 28% OR=1, 2-11 months 60% OR=1.44 (95%CI 0.63-3.31) and <2 12% OR=1.48 (95%CI 0.86-2.54) – which again showed that children <12 months were at a higher risk of dying from pneumonia.[92]

### **Malnutrition**

Underweight children are at a higher risk of dying from infectious diseases with approximately 50% of all deaths being attributed to this factor.[93,94] There is a five-fold risk for pneumonia in children that are malnourished.[95] Malnutrition is estimated to contribute to 35% of child deaths globally as a common co-morbidity in child deaths reported as due to diarrhoea, pneumonia, measles and malaria.[95] The fraction of disease attributable to being underweight was 61% for diarrhea, 57% for malaria and 53% for pneumonia.[95] Caulfield et al. reported that the risk of dying from pneumonia was highest in those with >three SDs malnutrition RR=8.09 (95%CI 4.36-15.01) and a RR=4.03 (95%CI 2.67-6.08) with -2 to -3 SDs.[96] Nantanda et al. reported that children with severe malnutrition and pneumonia also had a higher risk of dying OR=16.5 (95%CI 4.2-65.5).[97] Naheed et al found mortality was higher in malnourished children admitted with pneumonia OR=4.6 (95%CI 2.9-7.4).[91] Chisti et al. reported similar findings in his review of malnourished compared to well-nourished children with moderate malnutrition and pneumonia RR= 4.03 (95%CI 2.67-6.08) and severe malnutrition and pneumonia RR=8.09 (95%CI 4.36-15.01).[81]

### **Micronutrient deficiency**

Findings from a pooled analysis of randomized controlled trials of zinc supplement for children in developing countries showed that the pneumonia incidence was significantly reduced in those children receiving zinc (OR 0.59, 95% CI 0.41 - 0.83). [98] Aggarwal et. al. in a meta-analysis

found that there was a significant reduction in the incidence of pneumonia in children receiving zinc as opposed to a placebo (RR 0.80, 95% CI 0.70 - 0.92).[99] A Ugandan study found that zinc reduced case-fatality in HIV-infected children with severe pneumonia.[100] A systematic review carried out by The Lancet Diarrhoea and Pneumonia Interventions Study Group reported that zinc supplementation resulted in a 28% reduction in pneumonia-specific mortality (RR 0.72, 95% CI 0.23–2.09), a 50% reduction in hospital admissions for pneumonia (0.50, 0.18–1.39), and an observed 23% reduction in pneumonia prevalence (0.77, 0.47–1.25).[101] Another study on the number of pneumonia interventions reported that zinc supplement reduced the incidence of pneumonia by 14–25% (90% CI: 8–30).[102] Bryce, et al. in a study of the 20 countries with the highest rates of under nutrition, reported that only four countries were implementing zinc supplementation, two implementing nation-wide and two implementing it in selected districts only.[103]

Supplementation of vitamin A has been shown to have no direct effect on pneumonia incidence or mortality but there are indirect benefits in that the risk of mortality and morbidity from measles, diarrhoea, HIV and malaria decreases.[104] Bryce, et al in 2006 found that 56 out of 60 priority countries reviewed had a national vitamin A supplementation programme - but that only 46% had coverage of  $\geq 70\%$  and that 12.5% had rates of  $\leq 40\%$  with 26.8% of countries having no data.[105]

### **Low birth weight**

Low birth weight is associated with reduced lung function [106] and infants whose birth weight is below 2.5 kilograms are at a higher risk (1.69  $p < 0.005$ ) of admission for pneumonia [107] and 50% more likely to die from pneumonia during the first year of life than infants with normal weight at birth.[108]

### **Breast feeding:**

Sub-optimal breast-feeding increases the risk of developing pneumonia OR 3.1 (1.91-5.01). [108] Infants not being exclusively breastfed had a 17 times increase of requiring hospitalization for pneumonia (95% CI 7.7 - 36.0), and the younger the age the higher the relative risk especially for infants below 3 months of age: RR 61 (19.0 - 195.5) subsequently decreasing to RR 10 (2.8 to 36.2).[109] In a population with a high prevalence of HIV infection there is a major risk of transmission of HIV-1 from a positive mother to her infant through breastfeeding – approximately 40% of HIV infected infants acquired the disease via this route.[110] However, the benefits of breast-feeding still far outweigh the risk of not breast feeding the young infant, especially now in the era of PMTCT and maternal ART programmes only a small proportion of HIV-exposed infants will become infected by this route. The introduction of PMTCT intervention that start HIV+ pregnant women on life-long

ARTs regardless of CD4 cell count has shown a significant reduction of the risk of transmission through breast milk (0.5% - 0.7%).[80,111]

## **HIV**

There are a number of strategies that could potentially reduce the burden of HIV-related lung disease.[112] These include reducing antenatal HIV prevalence and prevention of mother-to-child HIV transmission. According to the Joint United Nations Programme on HIV/ Acquired Immune Deficiency Syndrome (UNAID) 2013 report the expansion of programmes for PMTCT and the use of more effective ART regimens helped prevent more than 800 000 children from becoming newly infected between 2005 and the end of 2012.[113]

A study by Chintu et al. on cotrimoxazole preventive therapy (CPT) reported pneumonia was more frequent in the placebo group as opposed to the treatment group as was the mortality rate - 35 out of 112 deaths in the placebo group with 13 of 74 deaths in the treatment group ( $p=0.04$ ).[114] The WHO recommends that CPT be provided for all HIV-infected children as a randomized-controlled trial reported improved survival with a significant decrease in death and hospitalization by 43% and 23% respectively.[115] CPT should also be provided to all HIV-exposed and infected infants from birth as it prevents PcP which is common in this age group.[116]

The most significant intervention is the early introduction of ARTs which has been demonstrated, in regions where this has been implemented, to decrease the incidence, [117] overall and pneumonia specific mortality rates.[72] Violari et al. compared early versus deferred antiretroviral therapy in HIV-infected infants 6 to 12 weeks of age with a CD4 lymphocyte percentage of 25% or more.[72] They reported that early HIV diagnosis and early antiretroviral therapy reduced HIV progression by 75% - 26% in the deferred-therapy group versus six per cent of infants in the early-therapy group - hazard ratio for disease progression, (0.25; 95% CI, 0.15 to 0.41;  $P<0.001$ ). In pneumonia adverse events, grade three or four, in infants in the early-therapy group there was 25 cases (12.2%) versus 25 (26.5%) in the deferred-therapy group - in pneumonia grade one or two there were 66 (32.1%) and 56 (59.4%) cases respectively. Early infant mortality was reduced by 76% - overall death rate per 100 person-years in the deferred-therapy group was 21.2% (95% CI 13.0–32.7) and in infants in the early-therapy group 4.9% (95% CI 2.3–9.0) - hazard ratio for death,(0.24; 95% CI, 0.11 to 0.51;  $P<0.001$ ). Of the four in-hospital pneumonia deaths all occurred in the deferred-therapy group.[72] ART is still not readily available for all eligible HIV-infected children with only 29%-36% receiving treatment.[118]

## **Indoor Air Pollution**

Approximately 50% of all people globally, most living in low-income countries, rely on solid fuel for cooking, lighting and heating.[119,120,121] More than 75% of the population in India, China and nearby countries, and 50–75% of people in parts of South America and Africa continue to cook with solid fuels such as dung, wood, agricultural residues or coal.[122] Cooking indoors in a poorly ventilated room leads to high levels of indoor air pollution due to biomass particles and smoke.

There is an increased incidence in pneumonia in relation to the amount of time-spent daily exposed to this type of pollution. The risk of pneumonia in young children is increased by exposure to unprocessed solid fuels by a factor of 1.8 [123] with 56% of global deaths attributed to indoor smoke in children less than five years of age [124] - this translates into deaths due to pneumonia among children under five years of age as nearly 800 000; 358 000 in Africa, and 288 000 in South-East Asia.[125]

Many studies have been carried out on the effects of indoor air pollution (IAP) on child lung health but to date only one intervention study has examined the impact of introducing an alternative way of cooking/heating in relation to reduction in childhood pneumonia.[126] Additional research is required before recommendations, as to what intervention is the most cost-effective or efficient, can be made.

### **Environmental tobacco smoke**

Children exposed to second-hand tobacco smoke have an increased incidence of pneumonia, which is associated with the number of people who smoke within the household. [127,128] A USA meta-analysis on respiratory effects in children exposed to environmental tobacco smoke (ETS) concluded that there was sufficient evidence to infer a causal relationship between ETS exposure and an increased risk of lower respiratory tract infections (LRTIs), such as bronchitis and pneumonia and an increased severity of asthma. The risk increases when the mother smokes.[129]

### **Lack of access to oxygen**

In children with severe/very severe pneumonia, hypoxaemia is common and associated with mortality, increasing the risk of dying five-fold.[130,131] Hospitals have very limited access to oxygen throughout the developing world, [132] and when oxygen is available the equipment required to deliver it is often lacking.[133,134] Pulse oximetry is also not widely available, making staff dependent on clinical signs to diagnose hypoxaemia. There are published technical guidelines for oxygen therapy in the management of childhood pneumonia in low-income countries, covering the indications for use, sources and equipment for the administration of oxygen.[135] In the absence of pulse oximetry these guidelines recommend a combination of clinical signs to

diagnose hypoxaemia. An implementation study in five district hospitals in Papua New Guinea showed that the introduction of oximetry, oxygen therapy and training reduced pneumonia-related mortality in children by one-third. [136]

### **Inadequate immunization coverage**

Immunization dramatically reduces the incidence of common childhood diseases such as pertussis, diphtheria, tetanus, poliomyelitis and measles. Vaccination has had an important effect on measles incidence and mortality, and in the past measles was a major cause of pneumonia-related deaths. Global measles vaccine coverage is >75% but several regions, particularly South Asia and sub-Saharan Africa have a much lower rate.[137] Measles can cause deaths due to pneumonia either directly or more commonly indirectly as it is complicated by secondary bacterial pneumonia such as due to *Staphylococcus*. Bryce et al. found only 10 out of 60 priority countries were on track for achieving 90% coverage of DPT3 and measles vaccines by 2015.[105]

As noted above, the implementation of the Hib vaccine and the widening coverage of the PCV is preventing bacterial pneumonia and deaths in many high-burden settings. Bhutta et al. reported that measles vaccine was 85% (95% CI 83–87) effective in prevention of measles in infants <12 months which affects the risk of subsequent complications, including secondary bacterial infections; Hib vaccines reduction in severe pneumonia was six per cent (RR 0.94, 95% CI 0.89–0.99) with a seven per cent (0.93, 0.81–1.07) reduction in pneumonia mortality. Pneumococcal vaccines resulted in an 11% (0.89, 0.81–0.98) reduction in severe pneumonia with an 18% (0.82, 0.44–1.52) non-significant reduction in pneumonia mortality.[101]

### **Lack of access to quality health care and trained staff**

Weak health systems that are chronically underfunded result in many health workers being poorly paid, or in some cases not paid at all, leading to high attrition rates (8% to 60%) with many migrating. [138] Bryce et al. found that <10% of health workers providing care to children had been trained in SCM of childhood pneumonia and that the attrition rate of trained staff was as high as 40% within 2 years of their receiving training.[139]

In many developing countries, especially in sub-Saharan Africa, this lack of human resources necessary to deliver the most basic health care is a major problem. Fourteen percent of the world's population lives in Africa, they bear a quarter of the global burden of disease but only have 1.3% of global health workers.[140] The HIV/Acquired Immunodeficiency Syndrome (AIDS) epidemic, especially in sub-Saharan Africa, has put a further strain on already over-burdened, under-funded and under-staffed health systems and is further reducing the workforce from AIDS related death. According to the 2002 UNAIDS Report the rising incidence of HIV-positive health workers led to more

absenteeism, reduced productivity and higher training and recruitment costs with some countries experiencing five- to six-fold increases in health-worker illness and death rates.[141]

Malawi experienced a six-fold increase in mortality of health workers from AIDS-related diseases between 1985 (0.5%) and 1997 (3.0%) - other sub-Saharan African countries reported similar trends – especially South Africa.[138] In 2007 Malawi health service vacancy levels remained static at 46% due to a high attrition rate and deaths which alone represented 50% of all trained staff losses.[142] The human resource (HR) capacity of the MOH to implement the Sector Wide Approach (SWAp) and to deliver the Essential Health Package (EHP) is still limited even with an increase of 53% of health personnel between 2004 to 2010 there are still significant vacancies for priority Health Care Workers mainly nurses, physicians, clinical officers, environmental health officers, laboratory and pharmacy technicians.[142] According to the Malawi Health Sector Strategic Plan (HSSP) for 2011 to 2016:

*“The human resource challenges remain both acute and complex and HR projections show that at current output levels it will take many years to come anywhere near the numbers of health staff needed to provide minimum standards of service delivery.”*[142]

Poor pay, lack of motivation and the perception that they are under-valued often leads to health workers failing to staff health facilities, as many open private practices to replace their lack of government salaries.[132,134] Underfunded health systems result in many facilities having few or no antibiotics and supplies to treat those children accessing care. Often health centres are lacking supervision, referral systems and transport. In these circumstances mothers lose confidence in the health care system.[143] A household survey carried out in 2000 in Malawi reported that 54% of child deaths occur in the community (at home) and that 24% of those children dying had not been to the hospital/had contact with a health worker for the disease that caused their deaths.[144]

Standard case management of pneumonia, as well as other relatively inexpensive child survival interventions are readily available but global coverage is less than 50% for most of them - with universal coverage of these interventions it is calculated that 63% of child deaths can be prevented.[145] Treatment of pneumonia remains low as reported In the Countdown 2015 report for 2012 - of the 45 countries who had data on antibiotic treatment the median coverage was 39% (range 3%-88%).[146]

## **Effectiveness of SCM of pneumonia at the primary level**



A meta-analysis of nine community-based trials to evaluate case management has been reported.[147] It included four studies in countries in South-East Asia, one Western-Pacific country, one Eastern Mediterranean country and one country in Africa. The overall reduction in mortality, in three age-groups (neonates, infants <1 year and children 0-4 years), was 27%, 20% and 24% respectively, while in the same three age groups pneumonia specific mortality reduction was 42%, 36% and 36% respectively. Theodoratou et al. 2010 review of the effect of case management with antibiotic treatment of pneumonia at the community level reported the pneumonia mortality rate reduction of children 0–5 years old was 35% (95% CI 18–48%).[148]

The Integrated Management of Childhood Illness (IMCI) strategy includes case management of pneumonia, diarrhoea, malaria and measles, as well as malnutrition at the primary level of care. By 2002, IMCI had been introduced into most developing countries worldwide. In the 2004 report, it was reported that the evaluation team had great difficulty finding countries where IMCI was sufficiently implemented to allow any degree of assessment of “reasonable change” mainly due to weak health systems unable to support such a horizontal approach.[149] Two exceptions are Tanzania [150] and Bangladesh [151] that demonstrated significant changes in the quality of care and decrease in mortality following implementation of IMCI at primary level facilities. A survey carried out by Marsh et al. of 57 high burden countries on community case management (CCM) of pneumonia found only 50% (27/57) reported some implementation of CCM for pneumonia, most on a small scale. Information was received from 33 of the 35 highest mortality countries of which only 14 reported implementation of CCM of pneumonia.[152]

### **Inpatient care of children with severe pneumonia**

The majority of studies reviewed by Theodoratou et al. on inpatient management of pneumonia focused on the effect/outcome of various antibiotic regimens.[148] Very few studies have examined the quality of curative care at first level referral hospitals in developing countries for children with common, serious diseases that are referred by primary-level IMCI. Studies that have been undertaken, identified similar problems leading to poor quality of care.[132,134,153] The main ones being poor case management including inadequate triage and assessment, over or under diagnosis of severe illness, and lack of implementation of appropriate guidelines for managing severe illness. Other identified problems were over, under or inappropriate treatment with antibiotics, fluids and oxygen and lack of ongoing assessment/monitoring of the severely ill child. Problems identified within health systems included lack of appropriately trained health workers at all levels, insufficient level of staffing, poor supervision of staff, lack of quality assurance monitoring and insufficient supplies, drugs and equipment.[154,155]

The SCM intervention strategy has been shown to be efficacious. It works, and is relatively affordable. The problem is that in most low-income countries the health services are unable to deliver these interventions to a sufficient number of children at a level of quality and coverage that would result in a significant impact.[139,156,157]

### **Study justification**

There are three research approaches that can be followed to reduce the incidence of and the case fatality from childhood pneumonia. The first approach focuses on research into the causative agents and risk factors to provide data that reflect the epidemiologic situation in developing countries and address differences in host, environmental, and/or geographic factors that might determine aetiology relevant to pneumonia management in the 21<sup>st</sup> century. This approach focuses on the change of organisms causing pneumonia after the introduction of conjugate pneumococcal and Haemophilus influenzae vaccine and determining optimal treatment of children with severe pneumonia. These studies concentrate on what would be the optimal treatment rather than on the delivery of the treatment.

The second approach focuses on decreasing the number of children developing pneumonia through specific preventive interventions – this includes research into effects of breast-feeding (15%-23% incidence reduction in infants), micronutrients such as zinc (14%-25% incidence reduction), indoor air pollution (75% incidence reduction in specific settings) and immunization (PCV and Hib incidence reduction 23%-35% and 22%-34% respectively).

Neither of these interventions addresses the present needs of children presenting to health facilities with acute pneumonia. The third approach focuses on improving the access to care and delivery of correct management of children presenting with pneumonia based on the proven effective intervention that is presently available – SCM. For children living in the developing world the implementation of SCM of pneumonia reduces the CFR at community level by 34%-50% and facility based level by 29% -45%.[102] This is an operational based research model which analyses the delivery of public health interventions, determines present limitations and strives to correct these limitations. The advantage of this approach is that access-to-services are improved, standardised interventions of known efficacy made available throughout a country and the effect of the intervention measured.

Most research on facility based management of pneumonia has focused on the effect of different antibiotic regimens on pneumonia outcomes as opposed to research into the SCM strategy that

can enhance the quality, coverage, effectiveness and performance of the programme in which the research is being conducted. No studies have been published describing the challenges of a country wide introduction of SCM of pneumonia and the effect of SCM on case fatality rates. The research of this dissertation is designed to evaluate the existing knowledge (papers one and two) and to describe operational research to evaluate practice in implementation in a specific setting (papers three to seven).

The process utilized to carry out the research was a stepwise approach with specific aims.

- 1) To examine the published evidence of effectiveness of SCM in HIV infected children with severe or very severe childhood pneumonia (paper one).

This aim is addressed in chapter two.

- 2) To describe the utility of oxygen therapy for treatment of children with severe and very severe pneumonia (paper two).

These aims are addressed in chapter three.

- 3) Identify the challenges relating to the implementation of SCM of pneumonia in all first-level referral hospitals throughout Malawi, a high-burden/low-resource country (paper three).

This aim is addressed in chapter four.

- 4) To evaluate the steps in the development and implementation of a national Child Lung Health Programme (CLHP) to deliver SCM of severe and very severe pneumonia in all paediatric inpatient wards in all first-level referral hospitals throughout Malawi (paper four). The diagnosis of pneumonia was based on SCM protocol clinical signs and symptoms only and was made by paramedical health workers i.e. Clinical Officers and Medical Assistants. To describe the process of providing uninterrupted oxygen supply in all paediatric wards in first level hospital throughout Malawi at District Hospitals for children with severe and very severe pneumonia (paper five).

This aim is addressed in chapter five.

- 5) To evaluate the trend in pneumonia specific case fatality rate over time following the implementation of a Child Lung Health Programme (CLHP) within the existing government health services in throughout Malawi to improve delivery of pneumonia case management (paper six).

This aim is addressed in chapter six.

6) To investigate the influence of management and co-morbidities on pneumonia CFR in children less than five years admitted with severe and very severe pneumonia to district hospitals in Malawi (paper seven).

This aim is addressed in chapter seven.

For papers four to seven, the research outline was as follows:

### **Research question**

Will improved delivery of standard case management of pneumonia in district hospitals throughout Malawi be accompanied by a decrease in the in-hospital case fatality rates (CFR) from pneumonia in children less than 5 years of age?

### **Research hypothesis**

Improved SCM of pneumonia in district hospitals throughout Malawi is associated with a decrease in the in-hospital CFR from pneumonia in children less than 5 years of age.

### **Primary outcome**

The primary outcome of the study is in-hospital CFR in children less than 5 years of age in facilities that have improved the delivery of SCM of pneumonia.

### **Study setting**

All district hospitals throughout Malawi prior to and over the course of improving SCM of pneumonia through the implementation of the CLH Programme.

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## Chapter 2

### **The influence of HIV infection on pneumonia standard case management**

In southern African countries it is estimated that between 35% to 65% of children admitted with severe pneumonia are co-infected with HIV and have a higher case fatality rate (34%) than children with pneumonia who are HIV negative (9%).

Further, the number of pneumonia deaths may be underestimated in malaria-endemic and HIV-endemic countries because of the common problem of clinical overlap.

**Penny M Enarson, Robert P Gie, Donald A Enarson, Charles Mwansambo, Stephen M Graham. Impact of HIV on standard case management for severe pneumonia in children. *Expert Rev. Resp. Med.* 4(2), 211–220 (2010).<sup>2</sup>**

This review describes how HIV infection is likely to have a major impact on current WHO recommendations for the standard case management of pneumonia in children. The identified studies indicated an overall six fold (range 2.5–13.5-fold) increase in pneumonia-related fatality in HIV-infected compared with HIV-uninfected African infants and children and that are more likely to have disease due to mixed infection and from a wider range of pathogens including *Pneumocystis jiroveci*, *Mycobacterium tuberculosis* and cytomegalovirus.

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**EXPERT  
REVIEWS**

# Impact of HIV on standard case management for severe pneumonia in children

*Expert Rev. Resp. Med.* 4(2), 211–220 (2010)

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It is estimated that 2 million children under 5 years of age die from pneumonia each year and that half of these deaths occur in sub-Saharan Africa. Over 85% of the more than 2.3 million children living with HIV worldwide reside in sub-Saharan Africa. HIV infection is likely to have a major impact on current recommendations for the standard case management of pneumonia in children and is the rationale for undertaking this review of published studies. The studies identified indicate an overall sixfold (range 2.5–13.5-fold) increase in pneumonia-related fatality in HIV-infected compared with HIV-uninfected African infants and children. They are more likely to have disease due to mixed infection and from a wider range of pathogens including *Pneumocystis* pneumonia, TB and cytomegalovirus. Scaling-up of the implementation of strategies that prevent HIV and *Pneumocystis* pneumonia remains an important strategy to reduce the burden of HIV-related pneumonia in the region. Research is urgently required to address the most effective pneumonia case management strategy in HIV-infected infants and children.

**KEYWORDS:** child • developing country • HIV • pneumonia • standard case management

Overall, 50% of deaths from pneumonia in children less than 5 years of age occur in just six low-income countries; 90% occur in 42 countries [1]. The highest case–fatality rates (CFRs) due to child pneumonia are reported from the sub-Saharan African region and it is estimated that approximately half of all pneumonia-related deaths in children occur in this region [2]. This is also the region most affected by the epidemic of HIV, with high rates of mother-to-child transmission [3]. Of the estimated greater than 2.3 million children living with HIV worldwide, approximately 2 million (>85%) live in sub-Saharan Africa [4]. Most of these children develop a respiratory disease at some point during the course of their illness and respiratory disease is a major cause of death [5,6].

Autopsy and clinical studies from the high HIV-prevalent (>1% prevalence) setting have indicated that acute pneumonia in HIV-infected infants and children is caused by a wider range of pathogens than in those who are not HIV-infected [7,8]. In addition to bacteria, respiratory viruses and TB, pneumonia associated with *Pneumocystis jirovecii* (*Pneumocystis* pneumonia [PcP]) and cytomegalovirus (CMV) is commonly reported [9–16].

The incidence of bacterial pneumonia and TB are greatly increased in HIV-infected African children, and pneumonia in HIV-infected children, including that caused by common respiratory viruses, is more likely to be fatal [17–19]. Coinfection is particularly common in HIV-infected children and bacterial pneumonia appears to be caused by a broader spectrum of pathogens than in HIV-uninfected children. The degree of immunosuppression associated with HIV disease will influence the incidence of pneumonia and severity of disease. The wider range of bacterial and non-bacterial pathogens, as well as an increased rate of coinfection and the high CFR, pose a substantial challenge to standard case management (SCM) guidelines that focus on the treatment of bacterial pneumonia and hypoxia.

The aim of this article is to review the impact of HIV infection on the effectiveness of SCM for African children with severe or very severe childhood pneumonia.

## Methods

A search of electronic databases was undertaken using PubMed, the Cochrane Central Register of Controlled Trials and Google Advanced Scholar search engine, limited to Medicine,



Pharmacology and Veterinary Science fields, for all articles in English on childhood pneumonia published between 1990 and 2009 using the following key words: pneumonia, child, standard case management, HIV-infected, HIV-uninfected and developing country. Other sources accessed were WHO documents, both hard copies and electronically accessed copies, the first authors' personal archives of references and references given to the first author by experts in this field. Hand searches were also carried out on reference lists of retrieved articles (see FIGURE 1).

Inclusion criteria for the review were as follows: original articles that included and compared data of HIV-infected and HIV-uninfected children less than 5 years of age admitted to hospital with WHO-defined severe or very severe pneumonia and managed according to WHO-recommended SCM regimens.

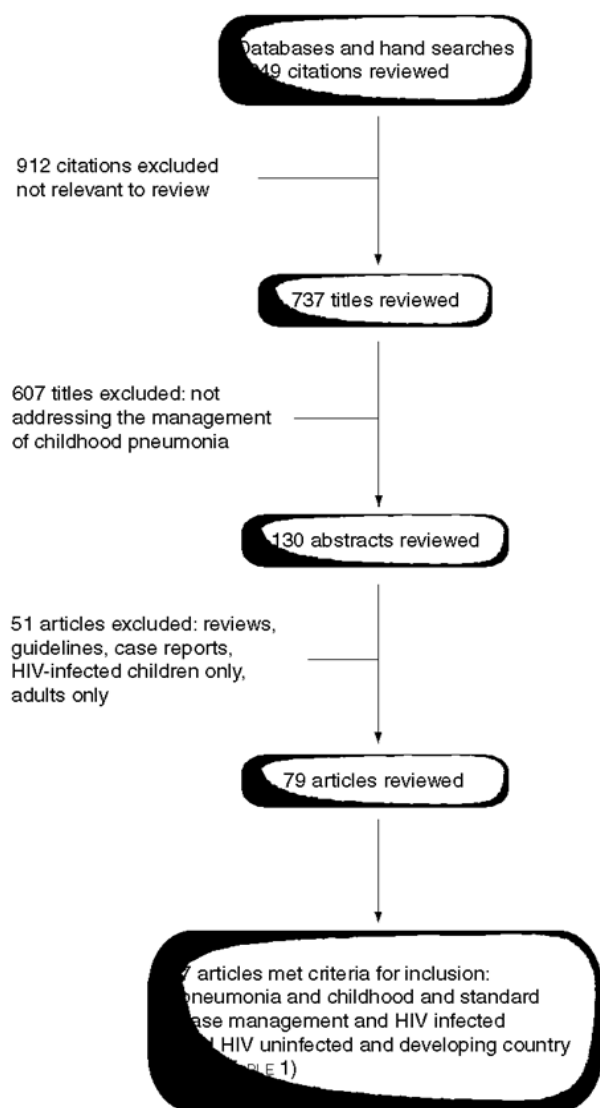


Figure 1. Search results.

### Background to SCM for child pneumonia

Acute respiratory infection (ARI) is very common in children worldwide and pneumonia (or lower respiratory tract infection) represents the less common but more severe end of the clinical spectrum of ARI. Pneumonia is the leading single cause of death in children under 5 years of age worldwide. It is particularly common in low-income countries and is estimated to cause approximately 2 million deaths globally each year [20–23]. The majority (estimated 95%) of pneumonia cases occur in developing countries, with 7–13% requiring hospitalization [24]. The average number of pneumonia episodes per child-year in sub-Saharan Africa and South Asia is 0.30 and 0.36, respectively [23]. Pneumonia incidence is greatest among infants (less than 1 year of age) and decreases steadily with age during childhood [25].

The WHO recognized the 'epidemiological magnitude' of childhood pneumonia and introduced the WHO ARI Control Program in 1984. Central to the program's recommended approach was the classification of ARI on the basis of two key clinical signs that could be widely used, including in resource-limited settings: fast breathing (age-specific rates) and chest indrawing [26]. This empirical approach based on clinical signs meant that of all children presenting with ARI, the majority that had no evidence of pneumonia did not receive unnecessary antibiotics, while those with nonsevere pneumonia (fast breathing only) could be identified for home-based management with antibiotics and those with severe pneumonia (chest indrawing) should receive appropriate antibiotics and be hospitalized [27].

### Scientific basis for SCM

The work of Shann and others [26] provided a logical basis for SCM and became the cornerstone of the current WHO case management strategy for the control of ARI in children [28,29]. Research in the 1980s identified simple clinical signs (fast breathing and chest indrawing) that could predict those cases with pneumonia (requiring antibiotics) and could predict severe pneumonia cases and those patients at risk for death (requiring hospitalization and possibly oxygen) [30–39].

The rationale for recommended choice of antibiotics was based on studies carried out in developing countries using lung aspirate and/or blood culture from hospitalized children with untreated community-acquired pneumonia. These studies consistently showed that bacteria were present in more than 50% of cases, and that *Streptococcus pneumoniae* and *Haemophilus influenzae* were the predominant bacteria, accounting for two-thirds of all bacterial isolates [40–45]. In 1990, the WHO published recommendations for the standard antibiotic treatment for pneumonia using antimicrobials effective against these two bacteria [46]. For children 2–59 months of age, amoxicillin or cotrimoxazole were recommended for nonsevere pneumonia, benzylpenicillin for severe pneumonia and chloramphenicol for very severe pneumonia. The recommended treatment for infants less than 2 months of age was gentamicin and benzylpenicillin.

Other important causes of child pneumonia were also recognized. These include those potentially preventable by immunization (e.g., pertussis and measles) [47] and common respiratory

viruses (e.g., respiratory syncytial virus and influenza) [48,49]. Recommended second-line antibiotics were targeted at relatively less common pathogens, such as *Staphylococcus aureus* and Gram-negative enteric bacteria [29]. *Mycobacterium tuberculosis* was not recognized as an important cause of acute severe pneumonia, although most studies were carried out in regions where confirmation by culture was unavailable.

A meta-analysis by Sazawal and Black of nine studies of community-based trials to evaluate SCM of pneumonia in non-HIV-endemic settings found that the overall reduction in mortality in three age groups (neonates, infants <1 year and children 0–4 years of age) was 27, 20 and 24%, respectively, while in the same three age groups the pneumonia-specific mortality reduction was 42, 36 and 36%, respectively [50].

The WHO has recently revised its recommendations based on a limited number of studies comparing antibiotic regimens and outcomes [51–56]. Amoxicillin is now preferred to cotrimoxazole for the treatment of nonsevere pneumonia in children 2–59 months of age. For severe pneumonia in HIV-uninfected infants and children (2–59 months of age), the recommendation for hospitalized children remains unchanged, but where referral and injectable antibiotic is not possible, then the recommendation is oral amoxicillin twice daily for 5 days. For very severe pneumonia, injectable ampicillin (or penicillin) and gentamicin is now preferred to chloramphenicol. It is important to note that the HIV-infection status of African children will often not be known at the time of presentation to health services, and so many HIV-infected children with pneumonia will be managed (at least initially) according to such guidelines.

### Influence of HIV on SCM for childhood pneumonia

Our search strategy identified seven published studies that reported outcomes in HIV-infected and HIV-uninfected children with WHO-defined severe and very severe pneumonia using the SCM strategy [9,10,14,16,57–59]. The impact of HIV on the CFR is summarized in TABLE 1. Four of the studies were from South Africa, all representing large urban-based hospitals in Johannesburg, Cape Town and Durban. The other published studies were from elsewhere in HIV-endemic sub-Saharan Africa, including urban (Malawi) and rural district hospitals (Zambia and Mozambique). One additional study from urban Blantyre in Malawi is included as it provides relevant data submitted for publication in 2009 [GRAHAM SM, UNPUBLISHED DATA]. Combined, the studies represent 2880 infants and children (2–59 months of age) from high HIV-endemic settings who were hospitalized with severe pneumonia, with 74% of study participants from studies of South African children.

HIV prevalence is particularly high in the urban settings. All studies show a marked and significant increase in risk of death associated with HIV infection. There is marked variability in CFR for studies that included cases with WHO-defined severe and very severe pneumonia in both groups, with a range of 2–14% for HIV-uninfected and 13–36% for HIV-infected children. The one study that included only children with severe pneumonia and did not include children with very severe pneumonia reported the lowest CFR in both groups [58]. Combining outcome data from

the eight studies, overall in-hospital CFR was 16.8% (221 deaths) in 1313 HIV-infected children compared with 3.4% (54 deaths) in 1567 HIV-uninfected children (odds ratio [OR]: 5.67; 95% CI: 4.17–7.71).

The studies listed are all hospital-based and not likely to represent all cases of severe pneumonia in these HIV-endemic communities. Furthermore, not all studies included consecutive cases of pneumonia admitted to hospital and may represent a biased sample of children with more severe disease. This may in part explain the high reported CFR. Nevertheless, the same selection criteria were applied to HIV-infected and HIV-uninfected children within the context of each study and HIV status was not known until after children had been enrolled in the study. Therefore, direct comparison of outcomes remains valid.

There are no data of impact of HIV in a number of common scenarios. First, there have been no reported studies of the impact of HIV on etiology or outcome among children with nonsevere pneumonia. Recommendations for infants and children with nonsevere pneumonia have recently been reviewed and published but the lack of data for HIV-infected children is highlighted [53]. It is recommended that HIV-infected children with nonsevere pneumonia already receiving cotrimoxazole preventive therapy (CPT) should receive an alternative antibiotic, such as amoxicillin, for nonsevere pneumonia [60]. These recommendations are logical but do not have an evidence base. Furthermore, HIV-infected children are an important 'at-risk' group, similar to severely malnourished children or neonates – groups for which home-based management of pneumonia is not advised. While it may be prudent to refer and hospitalize some HIV-infected children with WHO-classified 'nonsevere' pneumonia, the potential benefit would need to be weighed against the high risk of nosocomial infection [53,61]. Again, there is no evidence to inform best practice in this scenario. Second, there are no studies of etiology or impact on outcomes of HIV infection in infants of less than 2 months of age with pneumonia. This is a group likely to be particularly vulnerable to invasive disease due to bacteria and mycobacteria (including bacillus Calmette–Guérin disease) but there are no data of incidence, etiology or outcome and impact of HIV on neonatal pneumonia. Finally, the studies listed were mainly in children not receiving recommended HIV-related interventions, such as CPT or antiretroviral therapy (ART). It is highly likely that increasing implementation of these interventions will change the disease spectrum and outcome. For example, the prevalence of PcP would be lower and therefore pneumonia-related mortality reduced if CPT for HIV-exposed infants was widely implemented, and the incidence of pneumonia is reduced in HIV-infected children receiving ART [62,63].

### Factors associated with poorer outcome using SCM in HIV-infected infants & children

There are a number of important reasons as to why HIV-infected infants and children might be at higher risk of pneumonia and death than HIV-uninfected children. These include host factors such as: HIV-related immunosuppression and malnutrition,

**Table 1. Impact of HIV infection on case–fatality rate in African children managed according to recommended standard case management for severe or very severe pneumonia.**

Site and year	Number in study	Number HIV-infected (%)	WHO-defined pneumonia included in study	Antibiotic regimen	Case–fatality rate (%)		Ref.
					HIV-uninfected	HIV-infected	
South Africa urban hospital 1998	1165	548 (47%)	Severe and very severe	Physician directed and high-dose cotrimoxazole when PcP suspected	2	13	[9]
Malawi urban hospital 1996	150	93 (62%)	Severe and very severe	WHO guidelines and high-dose cotrimoxazole when PcP suspected	9	30	[10]
South Africa urban hospital 1998	250	151 (60%)	Severe and very severe	Physician directed and high-dose cotrimoxazole when PcP suspected	8	20	[14]
South Africa urban hospital 2001–2002	358	242 (68%)	Severe and very severe	WHO guidelines and high-dose cotrimoxazole for all infants	2.5	21	[16]
Zambia rural hospital 1995	132	14 (11%)	Severe and very severe	WHO guidelines	14	36	[57]
South Africa urban hospital 1999–2001	366	82 (22%)	Severe only	WHO guidelines: either amoxicillin or penicillin	0.7	3.6	[58]
Mozambique rural hospital 2004–2006	195	49 (25%)	Severe and very severe	Penicillin and gentamicin or chloramphenicol	2	27	[59]
Malawi urban hospital 2006	264	134 (51%)	Severe and very severe	WHO guidelines and high-dose cotrimoxazole when PcP suspected	3	13	[GRAHAM SM, UNPUBLISHED DATA]

PcP: *Pneumocystis pneumonia*.

which are known risk factors for death; susceptibility to a wider range of pathogens and coinfections including those that are not effectively treated by antibiotics aimed at pathogens such as PcP, CMV and TB; and the greater likelihood of underlying recurrent and chronic lung disease. The heterogeneity of methodology and reporting of studies from the region does not allow a comprehensive or quantitative analysis of risk factors.

There are limited data comparing the degree of immunosuppression with outcomes from high HIV-prevalence settings. A study of South African children reported that treatment failure was more common in HIV-infected children even with mild or asymptomatic HIV disease than in HIV-uninfected children [64]. PcP was only described in HIV-infected children classified with severe HIV-related disease but the diagnosis of PcP is itself part of the clinical definition [9]. One study compared CD4 cell counts

and percentage in HIV-infected children with severe pneumonia and did not find a significant difference between those with PcP and those without [65]. The impact of malnutrition *per se* is difficult to establish as HIV-infected children are more likely to be malnourished [GRAHAM SM, UNPUBLISHED DATA] [9,14,16,58,59].

Studies that report CFR by age show that age is an important risk factor for death, with most of the increased HIV-related mortality with pneumonia occurring in infants [GRAHAM SM, UNPUBLISHED DATA] [10,16,59,60]. A South African study reported that outcome in HIV-infected children was only significantly worse in those of less than 12 months of age, and a separate study from the same group found that being less than 1 year of age was a significant risk factor for poor outcome on multivariate analysis [16,58]. These are similar to findings in two studies of Malawian children [GRAHAM SM, UNPUBLISHED DATA] [10]. Young age and hypoxia are well-recognized

as risk factors for a fatal outcome in childhood pneumonia. In addition, the predominance of deaths in infants is likely to reflect HIV-related etiology [10,14,16].

The causes of pneumonia in HIV-infected infants and children in high HIV-endemic settings have been reviewed recently [7,8]. The relative importance varies with age and HIV status (TABLE 2). PcP and CMV are particularly common in infants, often as a coinfection. A prospective clinical study of HIV-infected and -uninfected South African infants and children with pneumonia found that PcP was the only independent risk factor for mortality [65]. Other clinical studies have also noted that PcP is a major contributor to mortality [10,16]. Furthermore, autopsy studies from a number of sites in the region have shown that bacterial pneumonia, PcP, TB and CMV are commonly found in the lungs of HIV-infected infants and children dying from pneumonia [11,13,66–68]. Autopsy studies are useful in that they give information on causes of pneumonia-related death; however, they do not give any information on the incidence or burden of various causes and no information about specific bacterial causes.

Standard case management recommendations for first-line antibiotic treatment of pneumonia rely on knowledge of the common bacterial causes and resistance patterns. Data on the causes of bacterial pneumonia in HIV-infected African infants and children are very limited. Studies rely on blood culture to identify causes, which has poor sensitivity and a potential bias against the identification of the more fastidious organisms when antibiotic use prior to hospitalization is common. The largest clinical study to report on bacterial etiology found that, while HIV-infected children are at a much higher risk of bacterial pneumonia than HIV-uninfected children, the spectrum of bacterial pathogens was similar between the two groups [9]. HIV-infected African infants and children are susceptible to pneumonia due to the common bacterial pathogens, such as pneumococcus, as well as to other bacteria such as *S. aureus* and Gram-negatives such as *Klebsiella pneumoniae* [GRAHAM SM, UNPUBLISHED DATA] [9,10,14,16].

The spectrum of bacterial pneumonia causes is likely to be affected by the uptake of bacterial conjugate vaccines, although bacterial conjugate vaccines have been found to be less effective in HIV-infected South African children [69,70] and cases of pneumonia due to *H. influenzae* are described in HIV-infected children who have been vaccinated with the *H. influenzae* type b conjugate vaccine. In addition to pneumococcus, urban-based studies from South Africa have consistently found that *S. aureus* is a common isolate from the blood of HIV-infected infants and children with pneumonia [9,14,16]. By contrast, in tropical Africa, nontyphoidal Salmonellae along with pneumococcus are commonly isolated from blood culture in children with pneumonia in rural and urban settings, but data in HIV-infected children are limited [GRAHAM SM, UNPUBLISHED DATA] [10,71]. HIV-infected infants and children are at risk of colonization and disease with antibiotic-resistant pathogens,

probably owing to increased exposure to antibiotics and episodes of hospitalization. The low numbers and poor sensitivity of culture for confirming cases of bacterial pneumonia make it difficult to compare outcomes for bacterial pneumonia in relation to HIV and the impact of antibiotic resistance on outcomes. One study did note that bacteremia did not have an impact on mortality in HIV-infected infants, in contrast to the major effect of PcP [16].

Clinical studies have also identified TB and opportunistic pulmonary infections such as PcP and CMV as important [6,16,72]. PcP and CMV often occur as a coinfection, are particularly common in infants and are associated with a very high CFR [73]. Coinfection is common in HIV-infected children and is a major contributor to the high mortality. McNally *et al.* studied treatment failure on standard antibiotic regimens for severe and very severe pneumonia in infants and children who were HIV infected, exposed-uninfected and uninfected [16]. They found that 70% of children had two or more mixed organisms and that polymicrobial disease was a strongly significant predictor for poor treatment outcomes. Using the 2003 WHO guidelines for SCM of severe/very severe pneumonia in HIV high-burden low-resource countries [74], 42% of infants failed treatment by 48 h. Madhi *et al.* have reported a greater risk of death in HIV-infected children with viral pneumonia due to common respiratory viruses than in HIV-uninfected children [9], and this risk may relate to secondary bacterial coinfection [17,19]. Uncertainties remain about the role of CMV in the pathogenesis of severe pneumonia but it is often identified in fatal cases and in infants with PcP who have a poor response to treatment.

### Recommended adaptation of antibiotic regimens in high-HIV-burden countries

Recognition of the problem of high HIV-related CFRs and especially the problem of PcP prompted the WHO to convene a workshop in Harare (Zimbabwe) that drafted a SCM approach for high HIV-endemic settings [74]. The main changes to the existing recommendations were to broaden antibiotic cover for severe pneumonia cases in HIV-infected children to include treatment for Gram-negative pathogens and to treat presumptively for PcP with high-dose cotrimoxazole in all HIV-infected infants and children (2–59 months of age) with very severe pneumonia and all HIV-infected infants (2–12 months of age) with

**Table 2. Predominant causes of pneumonia by age and HIV status.**

HIV-uninfected children	Additional organisms in HIV-infected children
For children 2–12 months of age: <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Staphylococcus aureus</i> Gram-negative bacteria Viruses	For children 2–12 months of age: <i>Pneumocystis jiroveci</i> Cytomegalovirus <i>Mycobacterium tuberculosis</i> Coinfections
For children 12–59 months of age: <i>S. pneumoniae</i> <i>H. influenzae</i> <i>S. aureus</i> Viruses	For children 12–59 months of age: <i>M. tuberculosis</i> Gram-negative bacteria Coinfections

severe pneumonia. A number of studies have attempted to implement this approach but HIV-related mortality has remained stubbornly high [16,60]. PcP is still a major cause of death and is particularly associated with severe hypoxia and young age, both known risk factors for death. These recommendations [74] are currently under review and some changes are likely. For example, it is recognized that presumptive treatment for PcP in children 12–59 months of age is not supported by evidence as PcP is rare in this age group.

The particular problem of PcP highlights the fact that it may not be adjustments to SCM that reduce CFRs due to pneumonia in HIV-endemic settings, but rather the increased uptake of effective preventive strategies such as preventing mother-to-child transmission [75], CPT for all HIV-exposed infants [76] and early ART for HIV-infected infants [77]. All of these interventions are currently recommended by the WHO [78–80] – the challenge is implementation. It also remains important to consider TB as a cause of treatment failure in infants and children with acute pneumonia [13]. TB is curable, drugs are available and so a careful contact history is especially useful [81].

### Expert commentary

In HIV-endemic African countries, children with severe pneumonia are commonly coinfecting with HIV and these HIV-infected children have a much higher CFR than children with pneumonia who are HIV-uninfected. The highest risk group are infants. PcP and coinfections are important reasons for an increased risk of poor treatment response to SCM in HIV-infected infants and children. HIV testing should be routine for all children with severe pneumonia in HIV-endemic communities. Confirmation of HIV infection can be problematic in resource-limited settings but virological testing is increasingly available.

Unfortunately, very little attention has been directed specifically towards the impact of HIV on SCM of childhood pneumonia in countries with a high prevalence of HIV. Studies undertaken consistently show that the outcome of pneumonia is much worse if the child is HIV-infected and also identify the challenge of improved SCM in HIV-infected children. There needs to be an improved evidence base from randomized controlled trials to direct the most effective antibiotic regimens supported by data of bacterial etiology and resistance patterns from different regions. An effective SCM will also need to address other pathogens and the problem of coinfections. Research is required to measure the impact of early treatment for PcP and CMV in HIV-infected infants.

Preventive strategies are already available and these would substantially reduce the burden of HIV-related lung disease in children; these include reducing antenatal HIV prevalence in women, prevention of mother-to-child HIV transmission, ART and CPT. The ideal would be a 'downstream' approach where effective ARV regimens would be made available to all HIV-infected women during pregnancy, delivery and for the duration of breastfeeding – to substantially reduce the risk of mother-to-child transmission and improve maternal survival. Another problem requiring greater attention is the need to screen HIV-infected pregnant

women for TB to reduce the risk of TB disease in mothers and infants. Such strategies place even greater demands on both human and financial resources and are still not readily available for all HIV-infected African mothers and children.

### Five-year view

With the scaling-up of implementation of preventive strategies, such as universal availability of mother-to-child transmission prevention, CPT and treatments such as early ART, there should be a reduced burden of HIV-related pneumonia and death, particularly in infants. Another significant result of the widespread routine use of CPT for HIV-exposed infants will be a major reduction in the prevalence of PcP in this high-risk age group. The increased availability of ART treatment for HIV-infected children will result in an increase in their survival rate, which will subsequently increase the burden of children with HIV-related chronic lung disease. The SCM approach to pneumonia in HIV-infected infants and children needs to be informed by clinical trials that aim to improve the outcome of bacterial pneumonia, PcP and CMV. One area that continues to be a challenge is that of conducting bacterial etiology and resistance studies to inform antibiotic recommendations for the empirical SCM approach including populations with high coverage of the *H. influenzae* type b and pneumococcal conjugate vaccine.

Specific research required includes:

- Impact of HIV on etiology and outcomes (treatment failure) in infants and children (2–59 months of age) with nonsevere pneumonia;
- Etiology of bacterial pneumonia in HIV-infected infants and children (2–59 months of age) with severe and very severe pneumonia;
- Importance of TB as a cause of pneumonia and SCM treatment failure;
- Impact of HIV on the etiology and outcomes of HIV-infected neonates and infants less than 2 months of age with pneumonia and sepsis;
- Impact of HIV on the etiology and outcomes of school-aged children and adolescents (>5 years of age) with pneumonia;
- Impact of early CPT and ART on the incidence and outcome of pneumonia in infants;
- Impact of specific treatment for CMV (e.g., ganciclovir) on outcomes of HIV-infected infants with severe pneumonia;
- Impact of *in vitro* cotrimoxazole resistance in *P. jirovecii* on the effectiveness of CPT in the prevention of PcP.

### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

*No writing assistance was utilized in the production of this manuscript.*

## Key issues

- In HIV-infected children, pneumonia is usually the presenting condition on first contact with health services and is the most common cause of death.
- The effect of HIV on pneumonia standard case management (SCM) has not been widely addressed in different settings and in different age groups.
- The range of pathogens causing pneumonia is wider in HIV-infected than in HIV-uninfected children.
- Treatment failure and death is common on standard first-line antibiotics for severe pneumonia, especially for HIV-infected infants.
- Common causes of severe pneumonia in HIV-infected infants associated with a high case-fatality rate are *Pneumocystis* pneumonia and coinfections, including cytomegalovirus.
- Randomized controlled trials aimed at informing more effective SCM of pneumonia in HIV-infected infants and children are urgently required.
- Severe pneumonia due to pulmonary TB appears to be common in HIV-infected children.
- Cotrimoxazole preventive therapy should be provided to all HIV-exposed infants and HIV-infected children.
- Screening for HIV and TB in pregnant women and implementation of recommended strategies has great potential for reducing HIV and HIV-related pneumonia in children.

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## Chapter 3

### Oxygen an essential medicine

Hypoxia is common in children with respiratory disease and is associated with significant morbidity and mortality. Recent work has shown that improved management of hypoxia can markedly reduce pneumonia-related mortality. While the mechanism is clear, the real challenge is implementation of improved hypoxia management systems in many health facilities in resource-limited setting. This includes more accurate detection of hypoxia using oximetry as well as effective delivery of oxygen. This article challenges the following misconceptions about the use of oxygen therapy in low income/resource countries: The burden of hypoxaemia is small and does not justify its inclusion as a public health issue; oxygen therapy is too expensive or too complicated to implement; it is palliative and does not improve rates of cure; there is a lack of evidence of effectiveness; and it is not cost-effective.

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Improving access to oxygen and pulse oximetry has demonstrated a reduction in mortality from childhood pneumonia by up to 35% in high-burden child pneumonia settings and is an entry point for improving the quality of care.

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## Oxygen is an essential medicine: a call for international action

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### SUMMARY

Hypoxaemia is commonly associated with mortality in developing countries, yet feasible and cost-effective ways to address hypoxaemia receive little or no attention in current global health strategies. Oxygen treatment has been used in medicine for almost 100 years, but in developing countries most seriously ill newborns, children and adults do not have access to oxygen or the simple test that can detect hypoxaemia. Improving access to oxygen and pulse oximetry has demonstrated a reduction in mortality from childhood pneumonia by up to 35% in high-burden child pneumonia settings. The cost-effectiveness of an oxygen systems strategy compares favourably with other higher profile child survival interventions, such as new vaccines. In addition to its use in treating acute respiratory illness, oxygen treatment is re-

quired for the optimal management of many other conditions in adults and children, and is essential for safe surgery, anaesthesia and obstetric care. Oxygen concentrators provide the most consistent and least expensive source of oxygen in health facilities where power supplies are reliable. Oxygen concentrators are sustainable in developing country settings if a systematic approach involving nurses, doctors, technicians and administrators is adopted. Improving oxygen systems is an entry point for improving the quality of care. For these broad reasons, and for its vital importance in reducing deaths due to lung disease in 2010: Year of the Lung, oxygen deserves a higher priority on the global health agenda.

**KEY WORDS:** oxygen; hypoxaemia; pneumonia; lung disease; health systems

HYPOXAEMIA is a major cause of morbidity and mortality associated with acute and chronic lung disease in children and adults. Hypoxaemia is a low level of oxygen in the arterial circulation and, in lung disease, results from impaired alveolar exchange of oxygen from inspired air into the pulmonary circulation. Tissue hypoxia is the consequence of arterial hypoxaemia. Hypoxaemia is a constant in the pathogenesis that leads to death due to lung disease irrespective of age, sex, aetiology, geographic region or clinical presentation of the patient. As we commemorate World Pneumonia Day this month, in 2010: Year of the Lung, it is timely and important to emphasise the potential of oxygen treatment to reduce deaths due to lung disease globally. Oxygen treatment is also critical for the effective management of many other

diseases where the primary pathology is not in the lung (severe sepsis, severe malaria, status epilepticus), and oxygen treatment is an essential part of surgical (including trauma and obstetric) care and anaesthesia.

Oxygen was discovered by Joseph Priestley in 1774, and has been available as treatment for hypoxaemia and used with significant clinical benefit for over a century,<sup>1</sup> predating antibiotics for pneumococcal pneumonia or pulmonary tuberculosis (TB). It is therefore remarkable that oxygen treatment is still not widely available in low- and middle-income settings that bear by far the greatest burden of death due to lung disease.<sup>2–5</sup> There are a number of common misperceptions as to why this is the case (see Table): the burden of hypoxaemia is small and does not justify its inclusion as a public health issue; oxygen therapy is too expensive or too complicated to implement; it is palliative and does not improve rates of cure; there is a lack of evidence of effectiveness; and it is not cost-effective. This paper aims to challenge such misperceptions. It will emphasise the importance of reliable and low-cost sources of oxygen to treat hypoxaemia and

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**Table** Misperceptions about oxygen treatment in developing countries and evidence to address these

Misperceptions	The truth and supportive evidence
The burden of hypoxaemia is minimal and does not justify emphasis as a public health issue	The global burden of hypoxaemia is very large: the median hypoxaemia prevalence in 21 studies of children with severe pneumonia was 13.3%. This corresponds to at least 1.5–2.7 million annual cases of hypoxaemic pneumonia presenting to health care facilities <sup>6</sup>
Oxygen therapy is only needed by a narrow group of patients	Hypoxaemia is common in almost all serious illnesses in all age groups Hypoxaemia occurred in 19.1% of 2464 neonates in 4 studies; <sup>6</sup> hypoxaemia occurred in 2.9–17.1% in 4 studies of malaria, 2.7–14.6% in 3 studies of meningitis, and 1.8–8.3% in 4 studies of malnutrition <sup>6</sup> Oxygen therapy is essential for the treatment of common adult illnesses and emergencies and for emergency obstetric care <sup>7</sup>
There is a lack of evidence of effectiveness of oxygen	More than 50 years' experience with oxygen in the treatment of seriously ill patients indicates that oxygen is an essential life-saving therapy
Oxygen is palliative and does not improve rates of cure	In a developing country setting, improving oxygen systems has resulted in a 35% reduction in case-fatality rate for childhood pneumonia <sup>8</sup>
Oxygen therapy is too expensive and not affordable in low-income countries where prevention with vaccines is better	Oxygen therapy is comparable in cost-effectiveness to other interventions being proposed to reduce the global burden of pneumonia deaths, including conjugate pneumococcal vaccine. Improving oxygen systems cost US\$51 per DALY, and US\$1673 per additional life saved in one study <sup>8</sup>
Oxygen therapy is too complicated to implement	Oxygen therapy, based on oxygen concentrators and including pulse oximeters in some countries, has been successfully introduced and sustained in district hospitals in many low-income countries <sup>8–13</sup>

the use of pulse oximetry to detect hypoxaemia for effective care of lung disease and other conditions in health facilities. Like universally accepted and far-reaching treatments such as antibiotics, oxygen is a life-saving therapy in many critical serious illnesses that can and should be widely available.

### DEFINITION OF HYPOXAEMIA AND WHEN TO GIVE OXYGEN

Definitions of hypoxaemia have been established from studies using pulse oximetry.<sup>14</sup> The normal range for arterial oxygen pulsed saturation (SpO<sub>2</sub>) at sea level is 94–100%. Because of the lower partial pressure of oxygen in arterial blood at higher altitudes, the normal range of SpO<sub>2</sub> is lower in populations living in mountainous regions.<sup>14,15</sup> However, the lower limit of the normal range for a population is not necessarily the optimal point at which supplemental oxygen therapy is indicated. Changing the level of SpO<sub>2</sub> at which oxygen is given will result in a major variation in the amount of oxygen used.<sup>16</sup>

In practice, most studies of hypoxaemia prevalence and oxygen effectiveness have adopted a threshold at which to give oxygen of SpO<sub>2</sub> < 90%.<sup>6,17</sup> An SpO<sub>2</sub> of 90% corresponds to the beginning of the steep part of the haemoglobin–oxygen dissociation curve and represents a safe margin for error where oxygen supplies are sufficient. Conditions such as severe anaemia, severe heart failure, severe sepsis, brain injury and postoperative care require oxygen therapy at thresholds of SpO<sub>2</sub> > 90%. In these conditions, oxygen delivery from the lungs to body tissues is seriously impaired, or vital organs may be particularly susceptible to low oxygen levels, and many clinicians recommend giving oxygen at SpO<sub>2</sub> < 94%. On the other hand, the therapeutic target range of SpO<sub>2</sub> in pre-term infants at risk of oxygen toxicity, particularly to the retina and lungs, should be lower, at 85–90%.<sup>18</sup>

### ESTIMATING THE GLOBAL BURDEN OF HYPOXAEMIA

Every year, nearly 9 million children die mostly from preventable or treatable diseases, and more than 95% of these deaths occur in developing countries.<sup>19</sup> Pneumonia is the leading cause of death in children aged <5 years, responsible for an estimated 18% of all deaths in this age category.<sup>20–22</sup> Hypoxaemia is a major fatal complication of pneumonia, and the risk of death increases with increasing severity of hypoxaemia.<sup>23,24</sup> In a recent systematic review of more than 16 000 children with acute pneumonia or other lower respiratory tract infections, the median hypoxaemia prevalence of children with severe pneumonia requiring hospitalization was 13.3% (interquartile range of studies 9.3–37.5%).<sup>6</sup> On the basis of an estimated 11–20 million children admitted to hospital with pneumonia each year,<sup>21</sup> this corresponds to 1.5–2.7 million cases of hypoxaemic pneumonia presenting to health facilities; countless more do not make it to the health facilities.

Hypoxaemia also occurs in children with illnesses that are not primarily due to lower respiratory tract infection, such as acute sepsis, meningitis, severe malaria and acute asthma.<sup>6</sup> For example, of 491 sick neonates and children presenting to a provincial hospital in the highlands (1600 m above sea level) of Papua New Guinea (PNG), 257 (52%) were hypoxaemic. Hypoxaemia was present in 73% of the neonates and children with pneumonia, and also in 32% of those with non-pneumonia illnesses, including meningitis, septicaemia, severe malnutrition, low birth weight, birth asphyxia and congenital syphilis.<sup>25</sup> Even conditions that are infrequently complicated by hypoxaemia, such as malaria (where 3–5% of all hospitalised cases have hypoxaemia), contribute substantially to the global hypoxaemia burden because they are so common.<sup>6</sup> Of 13 183 children aged 60 days or more admitted to a district hospital in rural coastal

Kenya, 5.3% were hypoxaemic; the most frequent final diagnoses among hypoxaemic children were malaria (35%), pneumonia (32%), malnutrition (10%) and gastroenteritis (7%).<sup>17</sup> Hypoxaemia also occurs in acute asthma, an increasing problem in low- and middle-income settings.<sup>26</sup> One study found that 26% of 51 children presenting to an emergency department in India with asthma had hypoxaemia.<sup>27</sup>

Among newborns, in addition to pneumonia, conditions such as respiratory distress syndrome, birth asphyxia, transient tachypnoea of the newborn and sepsis may lead to hypoxaemia.<sup>25,28</sup> Apnoea and hypoventilation occur in otherwise healthy premature babies (usually <32 weeks gestational age) due to immature respiratory drive, and in babies of any gestational age with sepsis, asphyxia, seizures or hypoglycaemia. Judicious oxygen therapy is often necessary for these common conditions that are the cause of a large proportion of the neonatal deaths occurring globally each year.<sup>29</sup> In the abovementioned Kenyan study, 8% of 991 children admitted aged 7–59 days were hypoxaemic, with the most frequent diagnoses being pneumonia (47%) and sepsis (32%).<sup>17</sup> Of 1105 neonates admitted at <1 week of age, 19% were hypoxaemic, and the most common diagnoses were sepsis (54%), birth asphyxia (30%) and prematurity (24%). Hypoxaemia was strongly associated with in-patient mortality (age-adjusted risk ratio 4.5, 95% confidence interval [CI] 3.8–5.5) in all age groups.<sup>17</sup>

The predominant causes of hypoxaemia in adults are chronic obstructive pulmonary disease, acute asthma and pneumonia. Hypoxaemia also occurs in sepsis, shock, major trauma, anaphylaxis, acute heart failure, pulmonary embolism, pleural effusion, pneumothorax, lung fibrosis, carbon monoxide poisoning, obstetric and surgical emergencies and in sickle cell crises.<sup>7</sup>

Oxygen therapy should also be available for maternal care, especially for the management of complications associated with delivery. Obstetric emergencies associated with hypoxaemia include amniotic fluid embolus, eclampsia and antepartum or postpartum haemorrhage. Supplemental oxygen is also indicated for women with underlying hypoxaemic conditions, such as heart failure, during labour.<sup>7</sup> Oxygen therapy is a core requirement for safe surgery and anaesthesia.<sup>7</sup>

The morbidity and substantial mortality associated with the outbreak of avian influenza in South-East Asia, and the more recent H1N1 influenza pandemic, have increased attention to deaths due to respiratory infections in adults. Part of pandemic preparedness is to ensure that health facilities have effective oxygen systems.<sup>2</sup>

### OXYGEN IS AN ESSENTIAL MEDICINE

Oxygen is included on the World Health Organization (WHO) list of essential medicines.<sup>30</sup> Although it

is listed under anaesthetic agents, oxygen has broad indications and should be in a class of its own, perhaps the only drug with no alternative agent. In its guidelines, the WHO emphasises the importance of oxygen within the necessary package of providing care for seriously ill children,<sup>31</sup> and for emergency, anaesthesia and surgical services in district and provincial hospitals.<sup>32,33</sup> Administration of oxygen at the point of care requires a source, such as an oxygen concentrator or cylinder, and equipment for delivery, such as tubing, face mask or nasal prongs. Although it is a treatment that is a basic requirement to save the lives of seriously ill patients, oxygen is rarely available in primary care facilities and is often lacking in district hospitals.<sup>2,34,35</sup> Health authorities should ensure that oxygen equipment is available and included in their health planning budget for any health facility where seriously ill patients may present.

### IMPROVED AND CHEAPER TECHNOLOGY FOR MEASURING HYPOXAEMIA

Hypoxaemia can be detected using clinical signs, blood gas analysis or pulse oximetry. Examining for more than one clinical sign is usually more sensitive for detecting hypoxaemia than a single sign, but increased sensitivity is at the price of lower specificity, so that misdiagnosis of the presence or absence of hypoxaemia using clinical signs is common.<sup>17,23,36–38</sup> Cyanosis has poor sensitivity: the lack of cyanosis despite severe significant central nervous system symptoms from hypoxaemia was recognised by J S Haldane in 1920.<sup>1</sup> Blood gas analysis is expensive, invasive and provides a single measure in time only. Pulse oximetry measures oxygen saturation of haemoglobin in the arterial blood by comparing absorbance of light of different wavelengths across an illuminable part of the body. When used correctly, pulse oximetry can provide reliable monitoring with little or no distress to the patient, and is the accepted standard for detecting hypoxaemia (Figure).<sup>39</sup> Pulse oximetry can correctly identify 20–30% more children with hypoxaemia than using clinical signs alone.<sup>25,40,41</sup>

Pulse oximetry can ensure the most efficient use of oxygen therapy, which is especially important in resource-limited settings. As not all patients with signs associated with hypoxaemia (such as the inability to drink in children) will have hypoxaemia, the use of oximetry can also reduce unnecessary oxygen use. A highly cost-effective intervention in hospitals that care for large numbers of children with acute respiratory disease,<sup>8</sup> pulse oximetry technology is robust and becoming increasingly affordable as the price of oximeters decreases. The reliability, durability and replacement costs of oximeter sensors has been a limiting factor in pulse oximetry being sustained as a clinical tool in resource-poor health facilities, but there are now many examples of achieving sustainability and measuring effect on clinical outcomes.<sup>8,40</sup>



**Figure** Oxygen systems require a reliable method for detecting hypoxaemia and an uninterrupted supply of oxygen. Illustration by David Woodroffe, David Woodroffe Digital Illustration, UK.

Monitoring with pulse oximetry is included in the WHO Surgical Safety Checklist, launched in 2008 as part of the WHO project to improve safety in operating rooms worldwide.<sup>32,42</sup> The checklist is simple, and can be completed in less than 2 minutes. However, monitoring with pulse oximetry is not currently achievable in many operating rooms around the world.<sup>43,44</sup> The Global Pulse Oximetry Project, a partnership including the WHO and the World Federation of Societies of Anaesthesiologists, aims to address this by making available for purchase or donation low-cost pulse oximeters and replacement parts, including low-priced probes, to hospitals in low-income settings.<sup>45</sup>

There is a wide range of oximeters on the market: from handheld, disposable battery-operated oximeters, costing about US\$100, to desktop oximeters with rechargeable batteries and technology to reduce movement artefact, costing about US\$1000. Reusable sensors cost around \$150–200, and should have a guaranteed life-span of at least 12 months. More detail on the technical aspects and use of pulse oximetry in paediatric care in developing countries can be found in a recent review.<sup>41</sup>

### IMPROVED AND CHEAPER SYSTEMS FOR OXYGEN THERAPY

Oxygen supplies are limited in many health facilities. Oxygen cylinders—the standard storage form of oxygen in most poorly resourced or remote health facilities—are expensive, difficult to transport and require regular replenishment. Oxygen concentrators are a less expensive and more reliable alternative for providing oxygen treatment, as long as there is a reliable power supply (Figure). Oxygen concentrators take air from the environment and push it through a sieve bed that allows oxygen to pass freely through

while retaining nitrogen. Bedside portable oxygen concentrators can provide a reliable source of oxygen at a maximum rate in the range of 5–10 l/min. Good quality machines cost between US\$600 and \$1200, and run for many years with minimal service and maintenance.<sup>46,47</sup> Concentrators can supply oxygen to multiple patients, depending on patient size and oxygen requirements, by using additional equipment to divide the flow of oxygen from the concentrator.<sup>46</sup>

There is growing experience in the clinical, organisational, biomedical technology and training aspects of setting up and sustaining oxygen concentrators in hospitals and small health facilities in developing countries. Concentrators are now successfully supplying oxygen needs in hospitals in many developing countries, including Egypt, Malawi, PNG, The Gambia, Nigeria and Nepal.<sup>8,9,11,13,48–50</sup> Concentrators have also been used successfully to supply oxygen to anaesthetic machines in Malawi and other African countries.<sup>51,52</sup> Oxygen concentrators have recently been reviewed, including up-to-date models, their specifications, use and effectiveness.<sup>46,47</sup>

### COST-EFFECTIVENESS OF OXYGEN THERAPY

There is strong evidence that the use of pulse oximetry and the availability of reliable oxygen sources in district and provincial hospitals can reduce death rates from pneumonia by one third.<sup>8</sup> An implementation field trial of an improved system for detecting hypoxaemia and giving oxygen in five hospitals in PNG, which included more than 10 000 children with pneumonia, demonstrated a 35% overall reduction in case-fatality rate from pneumonia. This system for detection and treatment of hypoxaemia using pulse oximetry and oxygen concentrators cost just over US\$1670 per additional life saved, and US\$50 per disability adjusted life years (DALY) averted.<sup>8</sup>

The Malawi Child Lung Health project introduced a comprehensive strategy to improve case management of pneumonia in infants and children in district hospitals. This included the introduction of oxygen concentrators where they were not already available. The project followed over 40 000 children and reported a fall in pneumonia case-fatality rates from 18.6% to 8.4%, and estimated that the average cost of treatment for a hospitalised case of pneumonia was \$136.<sup>53</sup> These cost-benefit data compare favourably with other interventions that are already accepted and recommended to be universally available to reduce mortality from pneumonia, such as pneumococcal conjugate vaccines (estimated at US\$100 per DALY averted and US\$4500 per life saved in moderate and high mortality countries).<sup>54</sup>

### BARRIERS TO GLOBAL OXYGEN THERAPY

The current barriers to achieving effective oxygen therapy for sufferers of hypoxaemia exist on several levels. At the policy level, both internationally and

locally, the aforementioned misperceptions that oxygen therapy is not a necessity, is too expensive, and does not improve rates of cure can be squarely refuted with evidence (Table). Such arguments against oxygen therapy would never be accepted in industrialised countries. The rich-poor disparity in the availability of this important treatment must be addressed by moving oxygen up the international health agenda. Pneumonia has been an overlooked disease, but the momentum exemplified through World Pneumonia Day shows that this is changing. The barrier of ineffective health systems may also be cited by sceptics, but this holds true with many other effective treatments, and country examples are now available that demonstrate the effectiveness and impact of oxygen systems in remote settings with limited resources.<sup>46</sup> Technological solutions to oxygen concentrators in settings without a reliable power source are being explored.<sup>46</sup> These include solar-powered systems (currently a capital-intensive option),<sup>12</sup> storing power in batteries to provide energy when mains power is unavailable, and more energy efficient concentrators that run on direct current.

### IMPROVING QUALITY OF CARE AND STRENGTHENING HEALTH SYSTEMS

Improving access to oxygen treatment should already be a priority—we should not have to debate the provision of adequate oxygen in hospitals or any health facility with high workloads, and its benefits to the overall system should further boost support for broader availability. Programmes that emphasise the use of oxygen concentrators and pulse oximetry are an entry point for improving the overall quality of health care.<sup>41,46</sup> Benefits of a functioning oxygen system cut across various programmes involving several disciplines: internal medicine, paediatrics, obstetrics, anaesthesia, surgery, trauma and burns. To implement and maintain oxygen concentrators requires strengthening of health systems and building of capacity and collaboration among clinicians, administrators and technicians.

Training for clinicians and technicians is necessary for the implementation of an effective oxygen system. Clinical training includes indications for and how to give oxygen therapy, supportive care for seriously ill children, screening and monitoring using pulse oximetry, and simple maintenance and cleaning of oxygen equipment.<sup>31,55</sup> Such training was provided along with the installation of oxygen concentrators in Malawi and PNG, and reinforced with regular review of the oxygen systems by a National Oxygen Team.<sup>8,9,46</sup> The designation of a 'high-dependency' area for seriously ill children within the children's ward, close to the nurses' station, improved the recognition of hypoxaemia and other complications.<sup>35</sup> Building capacity among local biomedical engineers and technicians

has resulted in timely servicing and maintenance of equipment, and reduced the sense of isolation felt by hospital technicians in rural hospitals.<sup>9</sup>

In scaling up oxygen systems, we urge that more prospective data on cost, challenges and patient outcomes from different settings be collected through implementation or operational research. These data will help to advance the argument for further improving oxygen therapy systems while also providing a unique opportunity to examine the integration of appropriate technology into patient care.

### TECHNICAL RESOURCES

The Oxygen Systems Working Group of the International Union Against Tuberculosis and Lung Disease (The Union) has compiled a set of resources on the Union website that freely provides information relating to the identification and management of hypoxaemia: <http://www.theunion.org/news/saving-lives-of-children-with-hypoxaemic-pneumonia.html> (or [http://www.rch.org.au/cich/links/index.cfm?doc\\_id=699](http://www.rch.org.au/cich/links/index.cfm?doc_id=699)). These resources include published literature as referred to in this article, and focus particularly on providing technical assistance for implementation of an effective oxygen system. The group aims to keep this set of resources updated as new, relevant information emerges. The WHO has produced a handbook, *The Clinical Use of Oxygen*,<sup>35</sup> a working draft of which is downloadable free from the websites. Free consultancy is available from members of the group with practical experience in the planning and provision of local and national oxygen systems.

### CONCLUSION

The evidence is compelling that oxygen therapy is a highly effective intervention for positively impacting global mortality. We call for international health policy makers, funders and implementers to grasp the opportunity to ensure that it is available to all who need it.

### Acknowledgements

The authors thank D Phillips, PATH, Seattle, WA, USA, for reviewing an earlier draft of the manuscript and providing helpful comments.

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## R É S U M É

Dans les pays en développement, l'hypoxémie est habituellement en association avec la mortalité, mais des techniques réalisables et d'un bon taux de coût-efficacité pour faire face à l'hypoxémie ne bénéficient que d'une attention limitée ou nulle au sein des stratégies mondiales actuelles en matière de santé. L'oxygénothérapie a été utilisée en médecine depuis près de cent ans, mais dans les pays en développement, la plupart des nouveau-nés, enfants et adultes gravement malades n'ont pas accès à l'oxygène ou à un test simple de détection de l'hypoxémie. Il a été démontré qu'améliorer l'accès à l'oxygène et à l'oxymétrie de pouls entraîne une réduction de la mortalité par pneumonie de l'enfant jusqu'à 30% dans les contextes à fardeau élevé de pneumonie infantile. Une stratégie d'administration d'oxygène systématique se compare favorablement à d'autres interventions de profil plus élevé pour la survie de l'enfant, tel de nouveaux vaccins. À côté de son utilisation dans le traitement des

maladies respiratoires aiguës, l'oxygénothérapie est indispensable pour une prise en charge optimale d'un grand nombre d'autres conditions chez les adultes et les enfants et est essentiel pour la sécurité de la chirurgie, de l'anesthésie et des soins obstétricaux. Les oxyconcentrateurs représentent la source d'oxygène la plus régulière et la moins coûteuse dans les services de santé où la fourniture de courant électrique est fiable. Il est possible de maintenir des oxyconcentrateurs dans les contextes des pays en développement si l'on adopte une approche systématique impliquant les infirmières, les médecins, les techniciens et les administratifs. L'amélioration des systèmes d'oxygène est un point d'entrée pour l'amélioration de la qualité des soins. Vu ces importantes raisons et vu son importance vitale dans la réduction des décès par maladies pulmonaires, l'oxygène mérite une priorité élevée dans l'agenda mondial de la santé au cours de cette Année du Poumon : 2010.

## R E S U M E N

La hipoxemia se encuentra con frecuencia asociada a la mortalidad en los países en desarrollo y sin embargo, las estrategias sanitarias mundiales vigentes desatienden o prestan muy poca atención a los métodos viables y rentables que existen para tratarla. La oxigenoterapia se ha utilizado en medicina durante casi 100 años, pero en los países en desarrollo los recién nacidos, los niños y los adultos más gravemente enfermos no cuentan con acceso al oxígeno ni a la prueba más sencilla que permite detectar la hipoxemia. Se ha demostrado que cuando mejora el acceso a la oxigenoterapia y a la oximetría de pulso, la mortalidad por neumonía en los niños disminuye hasta un 35% en los medios con una alta carga de morbilidad. La rentabilidad de una estrategia de sistemas de oxígeno es superior a la rentabilidad de otras intervenciones más complejas que favorecen la supervivencia de los niños, como la introducción de nuevas vacunas. Además de su aplicación en el tratamiento de las enfermedades respi-

ratorias agudas, la oxigenoterapia es necesaria en el manejo de muchas otras enfermedades de los adultos y los niños y es esencial en la seguridad de las cirugías, la anestesia y la atención obstétrica. Los concentradores de oxígeno constituyen la fuente de oxígeno más constante y menos costosa en los establecimientos sanitarios que cuentan con un suministro eléctrico fiable. En medios con recursos limitados, los concentradores de oxígeno son sostenibles cuando se adopta una estrategia sistemática en la cual participa el personal de enfermería, los médicos, los técnicos y el personal administrativo. El progreso en los sistemas de aprovisionamiento de oxígeno representa un punto de entrada a una mejor atención de salud. Por estas razones generales y por su importancia decisiva en la disminución de la mortalidad por enfermedades respiratorias, se justifica atribuir al oxígeno una mayor prioridad en los programas mundiales de salud, en este 2010: Año del Pulmón.

## Chapter 4

### **The challenges to improving standard case management at inpatient level**

Up to 20% of children assessed at primary level Integrated Management of Childhood Illnesses (health centres) require referral to the next level for admission with severe/very severe pneumonia/disease. A number of studies have identified that there are major problems at these facilities including lack of triage, poor assessment and knowledge of standard case management strategies, late or missed treatment, inadequate supplies of drugs and oxygen and little if no regular monitoring or reassessment of severely ill children. If we are to achieve the MDG 4 then these deficiencies in the quality of inpatient paediatric care in resource poor countries must be addressed.

**Stephen M Graham, Mike English, Tabish Hazir, Penny Enarson, Trevor Duke. Challenges to improving case management of childhood pneumonia at health facilities in resource-limited settings. Bulletin of the World Health Organization 2008;86:349–355.<sup>4</sup>**

This review focuses on the major challenges and uncertainties relating to case-management guidelines in a variety of settings; and the issue of implementation in resource-limited settings. It highlights issues relating to pneumonia management at health facilities that require further evidence to improve effectiveness of case-management guidelines in different settings. It addresses the particular challenges encountered in regions of high case-fatality rate where bacterial pneumonia is common in young infants and where comorbidities such as HIV infection and malnutrition are common. The review concludes that even in such settings, implementation of SCM guidelines can substantially reduce pneumonia-related mortality because many health facilities still lack the basic needs for effective case management: evidence-based training, facilitated referral, antibiotics and oxygen.

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## Public health reviews

# Challenges to improving case management of childhood pneumonia at health facilities in resource-limited settings

Stephen M Graham,<sup>a</sup> Mike English,<sup>b</sup> Tabish Hazir,<sup>c</sup> Penny Enarson<sup>d</sup> & Trevor Duke<sup>a</sup>

**Abstract** Effective case management is an important strategy to reduce pneumonia-related morbidity and mortality in children. Guidelines based on sound evidence are available but are used variably. This review outlines current guidelines for childhood pneumonia management in the setting where most child pneumonia deaths occur and identifies challenges for improved management in a variety of settings and different “at-risk” groups. These include appropriate choice of antibiotic, clinical overlap with other conditions, prompt and appropriate referral for inpatient care, and management of treatment failure. Management of neonates, and of HIV-infected or severely malnourished children is more complicated. The influence of co-morbidities on pneumonia outcome means that pneumonia case management must be integrated within strategies to improve overall paediatric care. The greatest potential for reducing pneumonia-related deaths in health facilities is wider implementation of the current guidelines built around a few core activities: training, antibiotics and oxygen. This requires investment in human resources and in equipment for the optimal management of hypoxaemia. It is important to provide data from a variety of epidemiological settings for formal cost-effectiveness analyses. Improvements in the quality of case management of pneumonia can be a vehicle for overall improvements in child health-care practices.

Bulletin of the World Health Organization 2008;86:349–355.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

## Introduction

Pneumonia is the leading cause of death in children worldwide and the great majority of these deaths occur in resource-limited settings.<sup>1</sup> WHO developed a case-management strategy in the 1980s aiming to reduce pneumonia-related deaths. This was a cornerstone of the acute respiratory infection (ARI) programme and was later incorporated into the Integrated Management of Childhood Illness (IMCI) guidelines which include primary care and hospital-based case management. The basis for the case-management strategy was that:

1. Almost all ARI-related deaths were in children with pneumonia.
2. Children with pneumonia need assessment by a trained health worker.
3. Pneumonia could be distinguished from other respiratory tract infection by the use of simple clinical

signs such as respiratory rate and chest indrawing.<sup>2</sup>

4. Many pneumonia deaths were caused by bacteria, usually *Streptococcus pneumoniae* or *Haemophilus influenzae*.<sup>2</sup>
5. Children with a cough but who do not have pneumonia should not receive antibiotics, reducing selection pressure for antimicrobial resistance.
6. Hypoxaemia is common and associated with increased risk of death.<sup>3,4</sup>

Clinical definitions of severity of pneumonia were proposed and are still used.<sup>5</sup> The evidence on clinical assessment and severity classification of pneumonia has been reviewed recently.<sup>6</sup> Studies show that clinical definitions of severity correlate with case-fatality rate.<sup>7–9</sup> While non-severe pneumonia is far more common than severe pneumonia,

most deaths occur in children with severe pneumonia.

Effectiveness of community-based implementation of the WHO ARI case-management strategy was reviewed by meta-analysis. In communities where previously there had been no antibiotics or case-management strategy, the strategy reduced pneumonia-specific mortality by 35–40%.<sup>10</sup> The provision of training in case management in the hospital setting also improved outcomes and reduced unnecessary antibiotic use.<sup>11</sup> Implementation of the case-management strategy remains a challenge in resource-limited settings.

This review aims: (1) to highlight challenges and uncertainties relating to current case-management guidelines in a variety of settings; and (2) to address the issue of implementation in resource-limited settings. The review

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doi:10.2471/BLT.07.048512

(Submitted: 11 October 2007 – Revised version received: 16 January 2008 – Accepted: 1 February 2008)

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will focus on case management after presentation to a health facility, the management of childhood pneumonia outside this context being the focus of another review in this issue of the *Bulletin*.<sup>12</sup>

### Methods

Information for this review involved a search of PubMed and authors' personal archives of references. Keywords for the search included "child", "pneumonia", "case management", "hypoxia", "implementation", "cost-effectiveness" and "programmes." The most recent reviews, including Cochrane reviews of topics, were referenced wherever possible rather than original articles due to such a large subject matter. Over 200 references were retrieved, with most focusing on efficacy of treatment strategies and relatively few on programme implementation.

### Current issues for case management

The relative importance of the issues listed below will vary between regions.

#### Clinical overlap

It is important to make the correct diagnosis. The case-management strategy assumes that the presentation of fever and cough with fast breathing means that the child has pneumonia and requires an antibiotic. This simple clinical definition can overlap with that of other diseases that do not require an antibiotic.

Studies of non-severe pneumonia from Asia report that a large proportion of antibiotic treatment failure for pneumonia has been in children with wheeze.<sup>13,14</sup> WHO now recommends a trial of rapid-acting bronchodilator in children with wheeze and fast breathing before making a diagnosis of pneumonia even though nebulizers are not available to health workers in the community.<sup>15</sup> Further, infants with wheeze usually have viral bronchiolitis and so bronchodilators are often ineffective.<sup>16</sup> A separate management algorithm is needed for children with wheeze. Teaching health workers what constitutes an effective response to bronchodilators will be important for diagnosis and further management.

Clinical presentation and appropriate management is more complicated in regions that are endemic for HIV,

malnutrition, tuberculosis or malaria. *Plasmodium falciparum* malaria can sometimes cause cough and fast breathing and can be rapidly fatal in children if untreated.<sup>17,18</sup> For this reason, any febrile child in a high-risk area should be treated with an effective antimalarial whatever the alternative or comorbid conditions. Such guidance is appropriate for health workers who direct outpatient management with no laboratory support. Overlap between conditions and the common presence of comorbidities in the sickest children emphasizes the need for integrated strategies for case management.<sup>5</sup>

#### Referral for inpatient management

Clinical deterioration due to pneumonia is often rapid, especially among young infants. Septicaemia and hypoxaemia are likely to be the major mechanisms leading to deterioration and death. The health facility for initial presentation of even the sickest child is usually a primary health-care centre with limited options for case management. Accurate recognition of the child with severe pneumonia, supported by a mechanism that allows prompt referral to a facility for parenteral antibiotics and oxygen, is critical but currently inadequate in resource-limited settings. Inadequate referral had a significant independent effect on poor outcomes in Mexican children with pneumonia.<sup>19</sup>

#### Antibiotic choice and duration

Antibiotics are required to treat pneumonia. WHO recently revised recommendations on the basis of evidence from studies comparing antibiotic treatment for pneumonia<sup>15</sup> and provided guidelines for management of children with pneumonia and HIV in resource-limited settings.<sup>20</sup> The evidence from these studies was recently reviewed.<sup>6,21</sup>

Important issues regarding antibiotics and pneumonia are listed:

1. "Treatment failure" has been used as an endpoint in trials assessing the clinical effectiveness of antibiotics, but the term has a variety of definitions.
2. What proportion of children with fast breathing will benefit from antibiotic therapy in populations where respiratory viruses cause most cases of non-severe pneumonia and an increasing proportion of severe pneumonia? A recent study from Paki-

stan reported radiological evidence of pneumonia in only 14% of children with WHO-defined non-severe pneumonia.<sup>22</sup>

3. In vitro intermediate resistance of *S. pneumoniae* to penicillin is common worldwide and more broad-spectrum antibiotics such as cephalosporins are increasingly available and preferred as first-line therapy as they are perceived to be more effective.<sup>6</sup> However, intermediate resistance of pneumococcus may not affect response to recommended high dosages of penicillin for pneumonia.<sup>23</sup>
4. Health workers often do not make a distinction between severe and very severe pneumonia and tend to treat all hospitalized children according to the guidelines for very severe pneumonia.<sup>24</sup>
5. Increasing global coverage of effective vaccines against *H. influenzae* type b (Hib) and pneumococcus means that these bacteria are becoming, or are likely to become, less important causes of pneumonia.<sup>25,26</sup>
6. Nontyphoidal salmonellae are a common isolate from children with features of severe pneumonia in tropical Africa but are not well covered by current recommendations.<sup>9,27</sup>
7. Pulmonary tuberculosis is increasingly recognized as a common cause of acute pneumonia especially in children in tuberculosis-endemic countries.<sup>8,28</sup> It is difficult to confirm diagnosis and so to differentiate from bacterial or viral pneumonia. Therefore it is hard to estimate the real burden.
8. HIV-infected children and severely malnourished children with severe pneumonia should receive broad-spectrum antibiotics but the most effective duration of antibiotics in these children is unknown.
9. *Pneumocystis jiroveci* pneumonia is common and often fatal in HIV-infected infants but treatment response is poor in resource-limited settings.<sup>8,29</sup>

#### Management of hypoxaemia

Hypoxaemia occurs in around 20% of children presenting to health facilities with pneumonia, although there are marked geographical differences in prevalence.<sup>30</sup> Hypoxaemia is associated with a marked increased risk of mortality

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from pneumonia.<sup>3,4</sup> There is still some debate about the definition of hypoxaemia, particularly as altitude increases,<sup>4</sup> but it is generally considered that oxygen saturation of arterial haemoglobin measured by pulse oximetry (SpO<sub>2</sub>) <90% at sea-level represents hypoxaemia requiring treatment.<sup>5,28</sup> Detecting hypoxaemia presents another challenge. Many studies have demonstrated variability in the predictive value of clinical signs.<sup>31</sup> Pulse oximetry is the optimal approach to determining the need for and response to oxygen therapy and is the “standard of care” in higher income countries. The technique is robust and can be readily used in resource-limited settings but is moderately expensive.<sup>32</sup>

#### Value of micronutrients

Vitamin A is well established as an effective treatment for measles, significantly reducing pneumonia and the case-fatality rate.<sup>33</sup> The value of zinc in children with severe pneumonia is less certain and may depend upon the prevalence of zinc deficiency in the community. A randomized controlled trial (RCT) in Bangladeshi children with severe pneumonia found that daily zinc was associated with a shorter duration of severe pneumonia, hypoxia and hospital stay compared to placebo, while a similar study in India did not find any effect.<sup>34,35</sup>

#### Management of treatment failure

It is important to define or standardize treatment failure for the purpose of RCTs that compare therapeutic efficacy and for assessment of guidelines. Recent studies have used various definitions of treatment failure, based on failure to improve on different clinical criteria, measured 2–5 days after beginning treatment,<sup>6,8</sup> and revising current WHO case definitions of treatment failure can substantially reduce observed treatment failure rates.<sup>36</sup> In clinical practice, most clinicians would expect that a child with pneumonia would show some evidence of clinical improvement on antibiotics by 48 hours at the latest – and if not would consider a change of antibiotics or an alternative diagnosis. However, what comprises “some evidence of clinical improvement” remains the critical issue.

There are many risk factors for treatment failure and some of the more common are young age, viral pneu-

monia, wheeze, poor adherence to treatment, immunosuppression (e.g. HIV or malnutrition), development of empyema, prior antibiotic use, antibiotic resistance or alternative diagnosis (e.g. malaria, foreign body). Most of the treatment failures and deaths are in infants and this high-risk group could be categorized separately. It is important to distinguish between “benign” treatment failure such as due to viral infection and “true” treatment failure indicating worsening pneumonia or developing complications. It may be more helpful to use objective signs of clinical severity and pulse oximetry rather than persistence of tachypnoea.<sup>37</sup>

#### Management of “at-risk” groups

##### Neonatal pneumonia

Pneumonia is common in young infants (< 2 months) and is always classified as severe as they are at higher risk of hypoxaemia, apnoea and mortality than older children with pneumonia. Neonatal pneumonia is responsible for a large proportion of pneumonia deaths but is more difficult to define, as clinical presentation is even less specific than in children.<sup>38</sup> There is clinical overlap with “neonatal sepsis” and with non-infective conditions causing respiratory distress. Important pathogens identified from limited studies in developing countries include streptococci and a wide range of Gram-negative bacteria such as *Escherichia coli* or *Klebsiella* spp.<sup>38,39</sup> The current recommendation of penicillin or ampicillin plus gentamicin is appropriate. A major case-management problem for neonatal pneumonia is the difficulty of providing adequate supportive care such as hydration, nutrition and oxygen in resource-limited settings.

##### HIV-related pneumonia

HIV prevalence is now greater than 50% in children hospitalized with very severe pneumonia in some settings in sub-Saharan Africa.<sup>8,29</sup> HIV-related pneumonia has been reviewed recently.<sup>29</sup> Studies provide consistent data but are mainly from large urban-based referral hospitals. Incidence of pneumonia, including bacterial pneumonia, is much higher for HIV-infected children than for HIV-uninfected children. The common causes of bacterial pneumonia are similar but the range of bacterial pathogens is wider. Oppor-

tunistic infections such as *P. jiroveci* and cytomegalovirus are common and associated with poor outcome. Pulmonary tuberculosis is common in HIV-infected infants and children presenting with severe pneumonia in tuberculosis-endemic regions.<sup>40</sup> Mixed infections and treatment failure are common.<sup>8</sup> Case-fatality rates are reported to be 3–8 times higher than in HIV-uninfected children even when current guidelines are applied.<sup>8,29</sup> This emphasizes the potential of prevention of mother-to-child transmission, co-trimoxazole preventive therapy and antiretroviral therapy to reduce the burden and case-fatality of pneumonia in HIV-endemic countries.<sup>29</sup> Improved survival means that an increasing proportion of pneumonia presents in school-aged children and guidance is needed for case-management of children aged 5–15 years, both HIV-infected and uninfected.

##### Severely malnourished children

Many of the issues already outlined for neonates and HIV-infected children apply to severely malnourished children. Pneumonia is more common and more fatal than in well nourished children and is caused by a wider range of bacteria and opportunistic pathogens.<sup>41</sup> Clinical presentation is less specific and overlaps with septicaemia.<sup>42</sup> There are also difficult management issues regarding supportive care, especially nutrition. Cover for Gram-negative bacilli is included in first-line antibiotics for severely malnourished children with pneumonia, and pulmonary tuberculosis should be considered if they do not respond. HIV testing should be routine.

#### Implementation

For the purposes of training and implementation, it is important to achieve consensus and to define “best practice” based on available evidence. Summarizing and presenting this evidence and suggesting standards is a major role of WHO. Most critical to success, however, and more challenging, is transforming policy (or guidelines) into widespread practice. The most effective intervention to reduce pneumonia-related deaths for the majority would be improved access to early care where simple, appropriate interventions are provided, including referral where necessary. To do this requires adequate health worker numbers, training and

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support, and ready availability of antibiotics and oxygen.<sup>43,44</sup>

The impact of training in ARI case-management was first described by Qazi et al. in Pakistan.<sup>11</sup> In addition to reducing ARI-related case-fatality, there was a marked reduction in antibiotic use for outpatient management over the study period. However, it is not only the quality of training that matters but also the coverage. Many children with pneumonia seek care from private practitioners or health workers who have not undergone training in case management.<sup>1</sup> Effective practice must be promoted in all sectors and from the community level upwards. There also needs to be political will and involvement of leading health professionals. There are many other issues that may need to be addressed such as integration into present service delivery, health-seeking behaviour, barriers to accessing health services, quality and extent of training, health-care worker retention, supervision, secure antibiotic supply, continued supervision and in-service training, maintenance and repair of equipment and clinical audit.<sup>32,44</sup> A comprehensive strategy in Malawi, an HIV-endemic country with an established ARI programme, markedly reduced pneumonia-related case-fatality at district hospitals.<sup>45</sup> Implementation of an effective oxygen system in Papua New Guinea reduced severe pneumonia mortality in one hospital by 40%<sup>3</sup> and, when this was extended to five other hospitals, there was an overall pneumonia case-fatality rate reduction of 35% (unpublished data, T Duke).

**Adequate equipment and “best practice”**

The issue of hypoxaemia identification and management raises important issues. What should be considered minimal “best practice” in resource-limited settings where most children with pneumonia die? When resources are limited, what are the most cost-effective interventions to prioritize for pneumonia management? These questions reflect fundamental moral and ethical issues encompassed in a child’s right to health in a global setting where the average amount of money spent on management of an equivalent episode of illness may vary more than 100-fold between high- and low-income countries.<sup>46</sup>

Data from district hospitals illustrate that there is much that can be done to improve the quality of care of pneumonia and other common illnesses in district-level hospitals in developing countries. Evidence-based practice, training, support and equipment are often neglected in low-income settings, but can be achieved at low cost.<sup>24,30,47,48</sup> A survey of 21 hospitals in seven less-developed countries found inadequate knowledge and practice for managing pneumonia among 56% of doctors and nurses.<sup>48</sup> Of 14 district hospitals in Kenya, none had an oxygen saturation monitor and 11 had an inadequate oxygen supply.<sup>24</sup> In five hospitals in Papua New Guinea, oxygen was not available on the day of admission for 22% of 1300 children (range between hospitals 3–38%) with the worst situation in remote rural district hospitals.<sup>30</sup> Oxygen is even less available in primary health care clinics than in hospitals in developing countries but is often required for sick children while awaiting referral and during transport to a district hospital. In Kenya, government primary health-care clinics are not routinely provided with oxygen (unpublished observation, M English).

It is possible to provide oxygen systems in resource-limited settings but the challenge is to incorporate and sustain oxygen technology into clinical care. Oxygen concentrators were successfully introduced into small hospitals in Egypt and the importance of support for training and maintenance was highlighted.<sup>49</sup> More recently, pulse oximeters and oxygen concentrators were introduced into hospitals in Papua New Guinea, improving outcomes using a multidisciplinary approach to provide technical and training support. In Papua New Guinea, in the first 2.5 years, 5 of 15 concentrators and 2 oximeters malfunctioned but all were easily repaired.<sup>32</sup>

**Importance of cost and implementation data**

It is expensive to treat children with pneumonia especially as inpatients.<sup>50,51</sup> In Pakistan, the average cost to treat a child with pneumonia as an outpatient was estimated by activity-based costing as US\$ 13.44, representing 82% of annual health expenditure per person at the time. In comparison, inpatient

costs were estimated as US\$ 71 and US\$ 235 for pneumonia and severe pneumonia respectively.<sup>50</sup> These are consistent with estimates from Africa and south-east Asia.<sup>51</sup> This emphasizes the potential of studies that compare effectiveness of oral to parenteral antibiotics or shorter-course therapy to that currently recommended. Parenteral antibiotics that require only once-daily administration such as gentamicin or ceftriaxone are less costly in terms of equipment and staff-time than those requiring multiple injections. Potential cost savings for the patient and health system are also substantial when unnecessary antibiotic use is reduced.<sup>11</sup> In Pakistan, antibiotics constitute the highest proportion of cost incurred for a family in childhood pneumonia management.

Cost-effectiveness has been compared to other child-survival strategies.<sup>51</sup> It was estimated that case management of pneumonia, together with oral rehydration therapy and measles immunization, achieved the largest health gains by an individual intervention. The average cost-effectiveness ratio was US\$ 47 and US\$ 70 per DALY (disability-adjusted life year) averted for sub-Saharan Africa and south-east Asia respectively. Cost-effectiveness data will become increasingly important to help prioritize future case-management strategies, including human resource costs. Oxygen therapy is potentially a costly intervention. The proportion of children presenting to health facilities with hypoxaemia varies widely and is influenced by referral patterns and admission criteria, level of health facility, age and altitude. The demand for oxygen therefore varies widely between institutions, a fact rarely considered in facility resource planning.

There is a need for more data not just to measure cost-effectiveness but also potential cost-savings. It has already been stated that more rational use of antibiotics may lead to substantial cost-savings for families. Although moderately expensive, oximetry may be cost-effective, not just because of improved outcomes compared to the use of clinical signs,<sup>3</sup> but also because of potential cost savings by more rational use of oxygen. Interventions that aim to improve the management of children with pneumonia should be encouraged to collect and publish comprehensive

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data relating to cost and behaviour change as well as outcome.

There is also a need for more research on health systems and implementation, to address the provision of available interventions more effectively to the children who need them most. A model for setting research priorities has been developed to shift the emphasis from the generation of new knowledge and publication to potential public health outcomes.<sup>52</sup> It is recognized that implementation research is methodologically challenging but measuring the impact of delivery at different levels of health facilities and cost will provide the important data needed for political support.

### Conclusion

This review has highlighted issues relating to pneumonia management at health facilities that require further evidence to improve effectiveness of case-management guidelines in different settings. This is a particular challenge in regions of high case-fatality rate where bacterial pneumonia is common in young infants and where comorbidities such as HIV infection and malnutrition are common. Even in these settings, implementation of current guidelines can substantially reduce pneumonia-related mortality because many health facilities still lack the basic needs for effective case management: evidence-based train-

ing, facilitated referral, antibiotics and oxygen. ■

### Acknowledgements

Steven Graham recently worked for the Malawi-Liverpool-Wellcome Trust Programme of Tropical Clinical Research and the Department of Paediatrics, College of Medicine, University of Malawi, Blantyre, Malawi, from where he gained much of the experience relating to this review. He was supported by a Wellcome Trust-funded core grant 074124/Z/04/Z.

**Competing interests:** None declared.

### Résumé

#### Difficultés pour améliorer la prise en charge des cas de pneumonie chez l'enfant dans les établissements de soins des pays à ressources limitées

La prise en charge efficace des cas joue un rôle important dans la réduction de la morbidité et de la mortalité dues à la pneumonie. Des recommandations reposant sur des éléments factuels solides sont disponibles, mais sont appliquées diversement. Le présent article expose dans leurs grandes lignes les recommandations actuelles pour la prise en charge de la pneumonie chez l'enfant dans les pays où interviennent la plupart des décès d'enfants par pneumonie et identifie les difficultés pour améliorer cette prise en charge dans divers pays et chez différents groupes « à risque ». Ces recommandations concernent notamment le choix d'un antibiotique adapté, le recouvrement clinique avec d'autres pathologies, l'orientation rapide et appropriée vers des soins hospitaliers et la prise en charge des échecs thérapeutiques. La prise en charge des nouveau-nés et des enfants infectés par le VIH ou gravement dénutris est plus complexe. L'influence

des comorbidités sur l'issue de la pneumonie implique que la prise en charge de cette maladie doit s'intégrer dans des stratégies d'amélioration des soins pédiatriques en général. Le plus fort potentiel de réduction de la mortalité par pneumonie dans les établissements de soins réside dans l'élargissement de l'application des recommandations actuelles, élaborées autour de quelques interventions centrales : formation, antibiotiques et oxygène. Cet élargissement nécessite des investissements en ressources humaines et en équipements pour une prise en charge optimale de l'hypoxémie. Il est important de fournir des données provenant de divers contextes épidémiologiques pour établir des analyses coût/efficacité formelles. L'amélioration en termes de qualité de la prise en charge de la pneumonie pourrait servir de moteur à des améliorations globales des pratiques de soins pédiatriques.

### Resumen

#### Retos para mejorar el manejo de los casos de neumonía en la niñez en los centros sanitarios en los entornos con recursos limitados

Un manejo de casos eficaz constituye una estrategia importante para reducir la morbilidad y la mortalidad por neumonía en la niñez. Las directrices basadas en la evidencia de que se dispone se utilizan en diversa medida. En el presente análisis se describen las directrices actuales para el tratamiento de la neumonía en la niñez en las circunstancias que rodean la mayoría de las muertes por neumonía en la infancia y se señalan los retos que deben superarse para mejorar el tratamiento en diversos contextos y diferentes grupos en riesgo. Entre ellos cabe citar la elección apropiada del antibiótico, el solapamiento clínico con otras dolencias, la derivación rápida y apropiada para dispensar atención hospitalaria, y el manejo de los casos de fracaso terapéutico. El tratamiento de los recién nacidos y de los niños infectados por el VIH o malnutridos es más complicado. Dada

la influencia de posibles comorbilidades en la evolución de la neumonía, el tratamiento de los casos de esa enfermedad debe integrarse en estrategias orientadas a mejorar la atención pediátrica en general. Las mayores posibilidades de reducir las defunciones relacionadas con la neumonía en los centros de salud son las que se derivan de una más amplia aplicación de las directrices actuales centradas en unas cuantas actividades básicas: capacitación, antibióticos y oxígeno. Eso exige invertir en recursos humanos y en equipo para manejar óptimamente la hipoxemia. Es importante aportar datos procedentes de diversos entornos epidemiológicos para poder realizar análisis formales de costo-eficacia. Las mejoras de la calidad del tratamiento de casos de neumonía pueden brindar la ocasión para introducir otras mejoras más generales en las prácticas de salud infantil.

## ملخص

## التحديات التي تواجه تحسين معالجة الأطفال المصابين بالالتهاب الرئوي في المرافق الصحية في المواقع المحدودة الموارد

الوخيم بمزيد من التعقد. ويتضح من تأثير المراضة المشتركة على حصيلة الإصابة بالالتهاب الرئوي، ضرورة إدماج معالجة حالات الالتهاب الرئوي في استراتيجيات مناسبة لتحسين الرعاية الشاملة للطفولة. وتتمثل أكبر الإمكانات للحد من الوفيات ذات الصلة بالالتهاب الرئوي، التي تحدث في المرافق الصحية، في توسيع نطاق تنفيذ الدلائل الإرشادية الحالية التي تركز على عدد قليل من الأنشطة الرئيسية، وهي: التدريب، والمضادات الحيوية، والأكسجين. ويستلزم هذا الأمر الاستثمار في الموارد البشرية وفي المعدات، من أجل تحقيق المعالجة المثلى لنقص تأكسج الدم. ومن المهم توفير البيانات من مواقع وبائية متنوعة، لإجراء تحليل رسمية للمردودية. ومن الممكن أن يكون تحسين جودة معالجة حالات الالتهاب الرئوي وسيلة للتحسين الشامل لممارسات الرعاية الصحية للأطفال.

نُعد المعالجة الفعالة لحالات الالتهاب الرئوي استراتيجية هامة في الحد من الوفيات والمراضة ذات الصلة بالالتهاب الرئوي بين الأطفال. وتتوافر في هذا الصدد دلائل إرشادية مرتكزة على بيئات سليمة، ولكن تتفاوت درجة الاستفادة منها. وتقدم هذه الدراسة نبذة عامة عن الدلائل الإرشادية المتاحة حالياً لمعالجة الالتهاب الرئوي لدى الأطفال في الأماكن التي تحدث فيها معظم وفيات الأطفال بسبب هذا المرض، كما تحدد الدراسة التحديات التي تواجه تحسين سبل المعالجة في أماكن مختلفة وبين مجموعات مختلفة معرضة للمخاطر. وتشمل هذه الدلائل الإرشادية الاختيار السليم للمضادات الحيوية، والتشابه السريري مع حالات أخرى، والإحالة الفورية والمناسبة لتلقي الرعاية داخل المستشفيات، وتغيير حالات فشل المعالجة. وتتمس معالجة الولدان والأطفال المصابين بفيروس الإيدز أو بسوء التغذية

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## Special theme – Prevention and control of childhood pneumonia

### Case management of pneumonia in resource-limited settings

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## Chapter 5a

### **Development and Implementation of a National Programme for the Management of Severe and Very Severe Pneumonia**

More attention and support need to be given to actions to improve hospital care for children. Improving hospital systems that deliver better care for children will have an impact more widely on other hospital services, support first-level IMCI services and strengthen links with local communities, all of which should result in better utilization of health services at all levels. The challenges remain to bring these and other strategies to scale and to support research into their use, impact and sustainability in different environments. This relatively inexpensive intervention (SCM) is effective and with universal coverage it is calculated that 65% of pneumonia deaths can be prevented but this approach has not been implemented on a large scale and the effect of this intervention accurately evaluated. The problem is that in most low-income countries – Malawi for example - the health service delivery mechanism was unable to deliver this intervention to a sufficient number of children at a level of quality and coverage that would result in a significant impact. A distinction needs to be drawn between the interventions for child survival that are known to be effective (e.g. SCM for pneumonia) and the “delivery strategy” by which to deliver these strategies to the child at risk.

**Enarson PM, Gie R, Enarson DA, Mwansambo C (2009) Development and Implementation of a National Programme for the Management of Severe and Very Severe Pneumonia in Children in Malawi. PLoS Med 6(11): e1000137. doi:10.1371/journal.pmed.1000137 Published November 10, 2009.**

This article describes the development and scaling-up of a country-wide delivery strategy of SCM for pneumonia in children in Malawi. Expansion was designed to achieve the widest possible access to the CLHP in the shortest time whilst maintaining quality. By the end of the fourth year, all twenty two district and three central hospitals had been included. Between 1 October 2000 and 31 December 2005 they reported 48,702 pneumonia cases admitted. During this period the proportion of children dying of pneumonia fell from 18.6% to 8.4%, a reduction of 54.8% over the baseline.

# Development and Implementation of a National Programme for the Management of Severe and Very Severe Pneumonia in Children in Malawi

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## Background

The reduction of child mortality by two-thirds from its 1990 level by 2015 the fourth United Nations Millennium Development Goal is a major challenge. Pneumonia accounts for much ( $\geq 20\%$ ) of this mortality in poor countries, but standard case management (SCM) of pneumonia [1] has the potential to reduce overall child mortality. A recent meta-analysis estimated that SCM of pneumonia could reduce overall mortality in neonates, infants under 1 y old, and children aged 0–4 y, respectively, by 27%, 20%, and 24%, and pneumonia-specific mortality by 42%, 36%, and 36% in the same age groups [2].

However, even proven intervention strategies cannot function without an effective “delivery strategy” [3]. For example, although the World Health Organization (WHO)/United Nations Children’s Fund has developed an Integrated Management of Childhood Illness (IMCI) strategy to reduce child mortality, of the 100+ low- and middle-income countries that introduced IMCI in the 1990s, only 48% had scaled up coverage by the end of 2002. Weak health systems were the main cause of this failure with the poorest countries doing worst [3].

We describe here the development and scaling-up of a country-wide delivery strategy of SCM for pneumonia in children in Malawi, a country where more than 200 children per thousand die before they are 5 y old.

## The Health Service Delivery Model

The International Union Against Tuberculosis and Lung Disease (The Union)

The Health in Action section is a forum for individuals or organizations to highlight their innovative approaches to a particular health problem.

previously pioneered an effective delivery model for antituberculosis services [4] for patients in poor countries. The approach used in this framework, which is one of the most cost-effective health interventions [5] devised so far, was incorporated into the WHO Stop TB Strategy and, by 2005, it had been successfully introduced into 190 countries [6]. Its principles include political commitment, standardized diagnosis and treatment, training, logistics, recording and reporting, supervision, and evaluation of services.

The Union has adapted this model to improve the management of severe and very severe pneumonia in children admitted to first-level (district) hospitals, institutions that are accessible to the whole population but where care is often deficient [7–9]. The framework allows accurate accounting of services, materials, and training, facilitates the calculation of outcome per unit of cost, and permits the management of supplies to avoid disruption of essential materials.

The model focuses on strengthening district hospitals and their associated health centres the basic management unit. Thus, it should facilitate the management of pneumonia in institutions that are peripheral enough to promote access but central enough to facilitate monitoring and evaluation.

The core elements of this approach for the delivery of SCM for pneumonia are:

- Political commitment of the government for countrywide implementation within existing health systems and the support of a donor partner to assist until the programme is self-sustaining. This element implies that there is/are:
  - an existing structure for delivering the services;
  - access for all patients to the services;
  - financial resources to sustain activities.
- Diagnosis and treatment based upon SCM (Table 1) with a system of quality control.
- Training of clinical staff in SCM.
- Logistics to purchase and distribute uninterrupted supplies of standardized drugs.
- Recording and reporting of clinical outcomes of pneumonia.
- Supervision and evaluation of the services.

## Implementation of a Child Lung Health Programme

In 1999 the Government of Malawi asked The Union to assist it in the development and implementation of a Child Lung Health

**Citation:** Enarson PM, Gie R, Enarson DA, Mwansambo C (2009) Development and Implementation of a National Programme for the Management of Severe and Very Severe Pneumonia in Children in Malawi. *PLoS Med* 6(11): e1000137. doi:10.1371/journal.pmed.1000137

**Published:** November 10, 2009

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**Funding:** Funded by the Bill & Melinda Gates Foundation grant ID#: 413 (<http://www.gatesfoundation.org/Pages/home.aspx>). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing Interests:** The authors have declared that no competing interests exist.

**Abbreviations:** CLHP, Child Lung Health Programme; IMCI, Integrated Management of Childhood Illness; SCM, standard case management.

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## Summary Points

- More than 20% of child mortality in poor countries is due to pneumonia.
- Standard case management of pneumonia has the potential to reduce overall child mortality, provided it can be delivered effectively.
- The government of Malawi recently introduced a national programme for the delivery of standard case management for pneumonia in children in Malawi with the help of technical and donor partners.
- This Health in Action article describes the development, scale-up, and achievements of this national programme, which is based on a successful antituberculosis service delivery model, and discusses the challenges facing the implementation of this adapted service delivery model.

Programme (CLHP) to manage children under 5 y old hospitalized with severe/very severe pneumonia. The government identified the following problems: (1) inadequate health-worker skills in district hospitals; (2) inadequate supplies of antibiotics and equipment to administer oxygen therapy; (3) deficient use of strategic information.

The resultant CLHP was incorporated into the existing paediatric wards and outpatient departments in first-level government hospitals and implemented solely by the personnel within these services. It was coordinated with existing policies for the treatment of acute respiratory infections (ARI) and for the implementation of the IMCI strategy and centrally managed by the ARI/IMCI team.

As part of the existing health system [6], the national Ministry of Health (MOH) contributed 70.8% of the CLHP's running costs; these costs paid for facilities and human resources. The donor (The Bill and Melinda Gates Foundation) provided the remaining costs (a total of US\$1.93 million over a 6-y period); 21% of these costs were used for investment and 79% covered operating costs.

CLHP implementation was carried out in four "work-packages" that identified activities for each year and set a framework for preparing budgets (see Table 2). Implementation across the country was done step-wise to ensure that the policies were adapted to

local circumstances; expansion used previously developed sites as training facilities.

## The CLHP in More Detail

### Signing a Formal Agreement

In 2000, The Union and the Government of Malawi signed a formal agreement outlining the government's commitment to the CHLP [10].

### Situation Analysis

A standardized evaluation of the epidemiology of childhood lung disease, the nature of the health services available to deal with them, and the efficiency, equity, and accessibility of these services was carried out [11].

### Developing a Plan of Action

A 5-y plan designed to achieve country-wide CLHP coverage was prepared on the basis of available documents and the situation analysis. The plan included a manual of policies and procedures, a calendar of activities, a budget, a description of the responsibilities of the parties involved in implementation, an evaluation mechanism, and the procedures to be followed.

### Establishing Initial Implementation Sites

Initial implementation sites (administrative districts) were selected according to

the following criteria: presence of a functioning ARI and/or IMCI programme; commitment of the District Health Officer to the CLHP; availability of a designated health worker who, in addition to normal activities, assumed responsibility for implementation; and a catchment area of approximately 100,000 population. A plan for regular monitoring was then developed.

### Training Health Management Personnel

The programme manager and staff at each implementation site participated in intensive training to enhance their management skills and the computer skills needed to efficiently manage information.

### Training Inpatient and Outpatient Health Care Workers in Case Management

A CLHP training manual and modules were adapted to local conditions and used as a standard operating and reference manual. The training curriculum for health care workers, although focused on SCM of childhood lung diseases (pneumonia, tuberculosis, asthma, and HIV-related lung disease), also included case management of other major childhood illnesses (malnutrition, diarrhoea, malaria, anaemia, and meningitis) because children frequently presented with comorbid conditions. Annual training courses focused on theoretical and practical case management using local paediatric facilities and initially relied on an international course faculty. Local faculty gradually took on more responsibility for these courses. One-day follow-up training sessions took place 4–6 wk after the annual course plus ongoing in-service training.

### Monitoring Progress

Information routinely collected to provide patient care formed the core of the CLHP monitoring activities. Information

**Table 1.** Pneumonia SCM.

Diagnosis	Presenting Signs and Symptoms	Recommended Treatment Regimens
<b>Very severe pneumonia</b>	Respiratory rate: $\geq 50$ aged 2–11 mo; $\geq 40$ aged 12–59 mo; Lower chest wall in-drawing; Cyanosis; unable to drink; reduced level of consciousness; grunting (infants)	Chloramphenicol 25 mg/kg 8 hourly; or ampicillin 50 mg/kg IM four times daily plus gentamicin 7.5 mg/kg once daily; or if ampicillin unavailable, benzylpenicillin 50,000 units/kg every 6 h plus gentamicin 10 d antibiotic treatment
<b>Severe pneumonia</b>	Respiratory rate: $\geq 50$ aged 2–11 mo; $\geq 40$ aged 12–59 mo; lower chest wall in-drawing	Benzylpenicillin 50,000 units/kg every 6 h; or if injectable penicillin unavailable or referral is not possible, then oral amoxicillin 25 mg/kg twice daily for 5 d
<b>Nonsevere pneumonia</b>	Respiratory rate: $\geq 50$ aged 2–11 mo; $\geq 40$ aged 12–59 mo	Cotrimoxazole (trimethoprim 4 mg/kg-sulphamethoxazole 20 mg/kg) twice daily for 5 d; or amoxicillin 25 mg/kg twice daily 3 d antibiotic treatment

IM, intramuscularly; SCM, child aged 2–59 mo.  
doi:10.1371/journal.pmed.1000137.t001

**Table 2.** Key activities within each work package.

Coordination	Training	Monitoring/Evaluation	Supply
Planning/budgeting; training/supervision; recording/reporting; supply management; sSectoral coordination <sup>a</sup> : define sectoral stakeholders; develop sectoral mechanisms; define stakeholders in other sectors; outline mechanism for inter-agency coordination	Standard operating manuals development; training materials development; training courses; training follow-up; supervision; describe frequency by level <sup>b</sup> ; define procedures; standardize forms; outline reporting mechanisms	Describe frequency by level <sup>b</sup> ; define procedures; develop standardized forms; outline reporting mechanisms; analyze progress toward targets; prepare routine reports; establish peer review processes; establish quality assurance processes	Outline core requirements; define procurement plan; describe logistics system; monitor order/delivery; inspect/audit stock

<sup>a</sup>Coordination of CLHP with other sectors involved in health services.

<sup>b</sup>The frequency of training and monitoring/evaluation of regions and districts by more central bodies.

doi:10.1371/journal.pmed.1000137.t002

was gathered using standard forms [12]. These documents were simple, clear, and kept to the absolute minimum required for adequate patient care and for monitoring and evaluating the CLHP. Monthly reports were generated on the number of pneumonia admissions by age and severity, treatment outcomes by age, and severity and monthly supply requirements.

This information was used for managing materials, for monitoring the quality of care, and for epidemiological surveillance. It was also used to assess health service utilization, the efficiency of the services provided, and the transparency of management procedures.

#### Focusing Services on Vulnerable Children

The target group of the CLHP was vulnerable children with severe/very severe pneumonia who were at greatest risk of dying and who required hospital care.

#### Managing Supplies and Materials

Uninterrupted supply of appropriate antibiotics was assured by using the routine reports to complete order forms to obtain annual supplies. To avoid “rupture of supply,” there was a “reserve” stock of medications (equivalent to 100% of the previous year’s order) within the country. The information system was crucial for accurate planning of drug requirements.

#### Evaluating the Services

The monthly reports on diagnosis, treatment, and outcomes provided the information needed to monitor the CLHP. They were also used to evaluate output and to advocate for resources. Systematic review identified and corrected problems in implementation. Completeness of the records was routinely evaluated.

Technical support by external experts twice a year focused on maintaining quality. Unit managers also met regularly to review their work and their problems.

In addition, an independent review undertaken during the third year of the implementation period provided in-depth evaluation of the services and of the role of all the collaborators in the agreement.

#### Scaling Up

Expansion was designed to achieve the widest possible access to the CLHP in the shortest time whilst maintaining quality. Five district/central hospitals were enrolled in October 2000 with five, six, and eight more enrolling in each subsequent year. By the end of the fourth year, all 22 district hospitals and two of the four central hospitals in Malawi had implemented the CLHP. Another central hospital was enrolled in the programme in 2004.

See Text S1 for further discussion on the framework and why this approach was chosen.

#### Results Achieved

From October 2000 to December 2005, 312 health workers (approximately one-quarter of all nurses, clinical officers, and medical assistants working in government hospitals) participated in 5-d training courses.

- The 22 district and three central hospitals reported 48,702 cases between 1 October 2000 and 31 December 2005. The annual number of pneumonia admissions increased from 3,673 in the first full year (2001) to 7,516, 13,149, 10,134, and 13,674 in the subsequent years. Although this annual increase was partly due to the addition of new sites, for individual districts the mean yearly increase of admissions varied between 61.8% and 68.6%. The most likely explanation for this increase is that increasing confidence of the health care workers and community members in the CLHP resulted in more children being brought for treatment.

- The average cost per case managed in hospital was US\$136 of which the investment cost for the international donor was US\$8.34 per case.
- 10% of children treated were aged <2 mo, 52% were aged 2–11 mo, and 37% were aged 12–59 mo.
- In children aged 12–59 mo, 2% of cases were nonsevere pneumonia, 62.8% were severe pneumonia, and 25.2% were very severe pneumonia; in infants, 10.0% of cases had severe/very severe pneumonia.
- The proportion of children dying of pneumonia fell from 18.6% to 8.4%, a reduction of 54.8% over the baseline.

#### Challenges

The major challenge facing the implementation of the CLHP in Malawi has been a shortage of health care workers. In particular, the attrition rate of trained workers has been high because of recruitment to the private sector, transfer of trained staff to other government hospitals, and deaths from HIV/AIDS. To address this problem, regular in-service and on-the-job training has been introduced and participation in the annual CLHP training course extended. The MOH has also increased the intake to nurses’ training institutes and restarted the Medical Assistant training programme.

A second challenge has been continuing high case fatality rates in some districts due to aggravating factors such as malaria, malnutrition, anaemia, and HIV/AIDS. Case management of these conditions has now been introduced into the CLHP training course.

A third challenge has been a lack of equipment. To deal with this challenge, the CLHP has funded vehicles, computers, and other electronic equipment to improve supervision and communication. Oxygen concentrators have been provided at each site [13].

A final challenge facing the CLHP has been sustaining the programme beyond the cycle of foreign assistance. Following the programme's success, the MOH has included the CLHP in the Essential Health Package, which is funded through the Sector Wide Approach [14]. The CLHP has now been maintained for 3 y since the end of external project funding and is currently being expanded to nongovernment hospitals [15].

## Conclusions

The implementation of the CLHP in Malawi demonstrates the feasibility and

effectiveness of a model programme based on the principles of the successful model for tuberculosis control to reduce case fatality in children hospitalized for pneumonia within first-level referral hospitals. The experience shows that while external funding is required to introduce the CLHP, the other key elements of the model are also necessary. Although it has not been possible to compare this approach, which has a substantial vertical component, with a locally integrated approach, the experience in Malawi suggests that this model could help the world achieve Millennium Development Goal 4.

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## Supporting Information

**Text S1** Discussion on framework/why this approach was chosen.  
Found at: doi:10.1371/journal.pmed.1000137.s001 (0.11 MB DOC)

## Author Contributions

ICMJE criteria for authorship read and met: PME RG DAE CM. Wrote the first draft of the paper: PME. Contributed to the writing of the paper: PME RG DAE CM.

## Text S1

### 1. Discussion on framework/why this approach was chosen

The MOH adopted the policies of the WHO/UNICEF-promoted programme on Integrated Management of Childhood Illness (IMCI) in 1992. In 2000 only 4 districts – those with the highest Infant Mortality Rate (IMR) in the country were in the process of implementing IMCI. The focus of the IMCI programme is the integrated case management of sick children at outpatient services from district hospital outpatient departments up to the most peripheral health post. At the time the IMCI programme did not include the care of referred children for further evaluation (chronic cough, persistent fever, wheeze) or for admission into hospital (severely ill children).

Since 1985 there had been an upsurge both in numbers and notification of TB cases and an increase in HIV related morbidity and mortality. The increased load on health care services and hospital capacity was of major concern.

The economic situation at this time made it difficult for the government of Malawi (GOM) to increase its health care expenditure to match the population growth and increased disease burden as described above and at the same time to sustain health programmes whose strategic components depended on the one hand on imported materials (drugs and laboratory supplies), and on the other hand on activities that required regular supervision.

In 2000 the main causes of morbidity and mortality in children <5 years of age were malaria, pneumonia and anaemia. Endemic malnutrition contributed largely to both morbidity and mortality. The management of severe and very severe pneumonia at inpatient level was not following international guidelines for developing countries.

There was no severity classification (standardized case definition) of pneumonia and no clear policy for the use of second line antibiotic regimens for treatment of the different categories. Oxygen was not available in most paediatric wards at district hospitals. The clinical overlap between pneumonia and malaria was problematic as the use of blood film examination for malaria parasites was infrequently used to clarify diagnosis. The HIV status of almost all children admitted with acute or chronic respiratory problems into district hospitals was unknown.

Less than 10% of staff involved in the care of sick children at the District Hospital level had been trained in standard case management of acute respiratory illness. Past child health training initiatives without follow up supervision have been largely ineffective at changing case management practices. Supervision was carried out very infrequently due to budgetary and other practical problems. Maternal education was inadequate.

There was a major problem identified with shortages of antibiotics at the district level mainly due to Central Medical Stores stock-outs.

The existing information system (tally card records) of Outpatient Department attendances and inpatient registrations were not sufficiently detailed or complete for the purposes of the CLH project. Also there were no standard MOH patient records at inpatient level.

## Box 1. Main findings of situation analysis

### Macroeconomic Situation:

- Percent of population living in poverty 65.3%
- GDP per capita \$160
- Economically in the lower quartile of Southern African Development Community (SADC)
- Contributing factors, floods, drought, global and others

### Demographics/health indicators:

- Life Expectancy at birth
 

Male	41.4 years
Female	44.6 years
- Infant Mortality Rate (<1 year) 134/1000 live births
- Child Mortality Rate (<5 years) 234/1000 live births
- Maternal Mortality Ratio: 1120/100,000 live births
- NACP estimates 14% of population are HIV+ rates higher in the urban areas (26%)
- HIV sero-positivity in pregnant women varied from 10% in rural areas, close to 30% in urban areas
- Upsurge in numbers and notification of TB cases - increases in smear negative and extra pulmonary TB - cure rates had fallen from 80% to 60%

### Main causes of morbidity/mortality in children <5 years of age:

- Malaria +/- anaemia
- Pneumonia – hospital case fatality rate  $\geq$  26%
- Pneumonia + malaria
- Severe malnutrition (50% stunted, 4% severe malnutrition)
- Gastroenteritis

### Health services:

- Chronic under-funding
- Only 1 MOH hospital per district regardless of population size
- Doctor/population 1/110000
- Acute shortage of all health personnel
- Very few staff involved in the care of sick children at district hospital level – at 1 hospital 0.5 nurse to >80 patients
- Less than 6% staff trained in ARI standard case management
- Chronic shortage of drugs/supplies at central level
- No regular supply of oxygen available on paediatric wards
- No regular supervision from central level
- No patient records kept or regular reporting system in place

## 2. Recording and reporting

An Inpatient Recording Form originally developed primarily as an information collection tool. This underwent many revisions over the early months of 2000 and was then piloted in one of the DHs. The transition from being merely a data collection tool to a “patient treatment record” was at the request of the CLH Programme Manager, as at the time many of the DHs did not have any generic type forms to record ongoing treatment for inpatients. The form is constructed in such a way that the majority of information gathered only requires a tick so reducing the time required to complete it.

The information routinely collected formed the basis for materials management, in that supplies were ordered based on the needs reflected in the routine reports of activities. Besides providing the data for the planning of material requirements it also provided important information on quality of patient care and epidemiological surveillance. The extent of the problem (health services utilization), the efficiency of the services provided and the transparency of the management procedures was also derived from the data. This assisted the programme managers in annual planning discussions at which priorities for government spending are established and advocacy within the Ministry of Health and other governmental ministries.

Successful implementation of an information system required that indicators be identified, that they be routinely evaluated, and that the recording and frequency of reporting be optimal. Well defined epidemiological and operational indicators were established for measuring targets that were deemed measurable, valid, reliable and readily interpretable. The indicators used were: 1) type of patient, 2) type of treatment and 3) treatment outcomes.



Each district hospital CLHP Coordinator was expected to complete monthly reports on cases and treatment outcomes and submit to central level management unit. To assist with this activity and reduce amount of time required (average time 1-1.5 hrs/month) Epi-Info software was loaded onto each district hospital's computer, where possible, for use by the CLHP designated focal person who attended workshops on how to use these programmes prior to their installation.

Systematic computer data entry and tabulation were essential for the regular accounting of services and supplies and generating data to feed back to the district hospitals and to the MOH. As of December 2005 2260 of the 2274 (99.4%) expected reports had been submitted.

The CLHP Coordinators analyse their own data and present their findings regularly at peer review meetings. A number have carried out operational research with the assistance of Central Level staff.

At Central Level a form for entering and checking data accuracy was developed on Excel by which to detect and correct mistakes.

The information system allowed close monitoring of activities, evaluation of outcomes and regular estimates of the needs and consumption of oral drugs as well as supplies for parenteral medications.

At the beginning of the programme there was already a data entry/management clerk at Central Level who entered the monthly reports into a Central Level computer. Analysis of this information allowed close monitoring of activities, evaluation of outcomes and regular estimates of the needs and consumption of oral drugs as well as supplies for parenteral medications.

To address the issue of rupture in drug supplies the CLHP maintained a "reserve" stock of medications (100%) within the health services system. In this way, every patient could be assured of receiving all the medications necessary for the treatment of pneumonia. Also the numbers of cases of pneumonia presenting for treatment showed a marked seasonality making it even more important to maintain a 12 month "reserve" at Central Level to control for varying levels of disease throughout the year. By implementing this system no rupture in supplies at the national level occurred during the first five years of operation. The data is also integrated into the HMIS system.

### **3. Costs**

The MOH services are entirely financed by the government and external donors. The latter provide most of the development expenditure and finance a large percentage of the recurrent costs of preventive and promotive services. Free medical care for children less than 5 years of age in government-run facilities is the policy throughout the country.

Being part of the existing health system<sup>6</sup> the national Ministry of Health (MOH) contributed 69.0% of the running costs comprising facilities and human resources. The donor (The Bill and Melinda Gates Foundation) provided 31.0% of the costs (a total of US\$1.93 million over a five-year period) of which 21% was investment and 79% operating costs. See Figures 1 and 2 below.

**Sustaining the programme beyond the cycle of foreign assistance**

At the end of the Gates funding cycle the MOH included the CLHP in the Essential Health Package (EHP) which is funded through the Sector Wide Approach (SWAp).<sup>i</sup> The CLHP Management Team worked with the DHOs to identify what activities needed to be included within the SWAp budget to maintain CLH services. According to the MOH annual report for the work of the Malawi health sector for the period July 2007 to June 2008 the ARI/CLH programme has continued functioning successfully with a further decrease in pneumonia CFR reported at 6.3 for year under review. It is now being expanded to non-government hospitals.<sup>ii</sup>

Figure 1 Breakdown MOH contribution

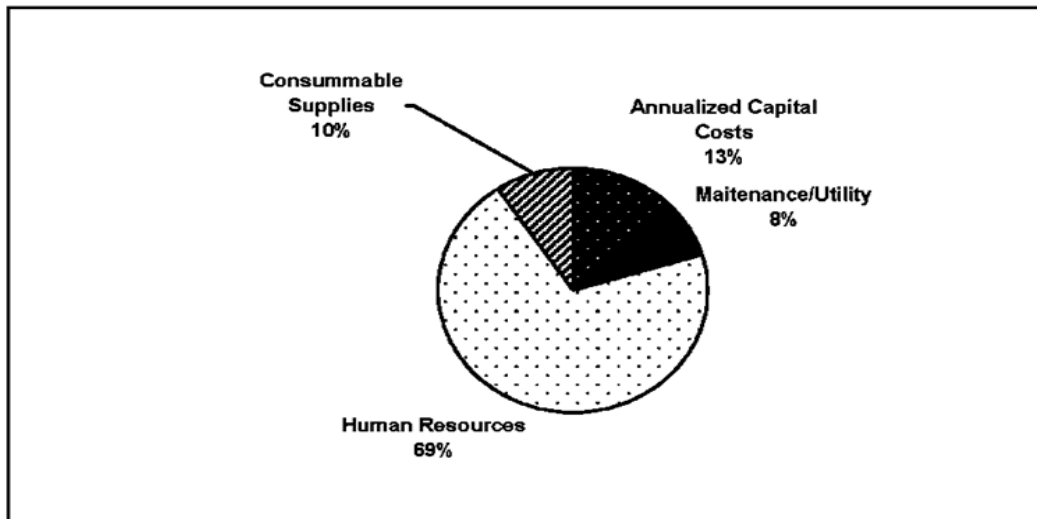
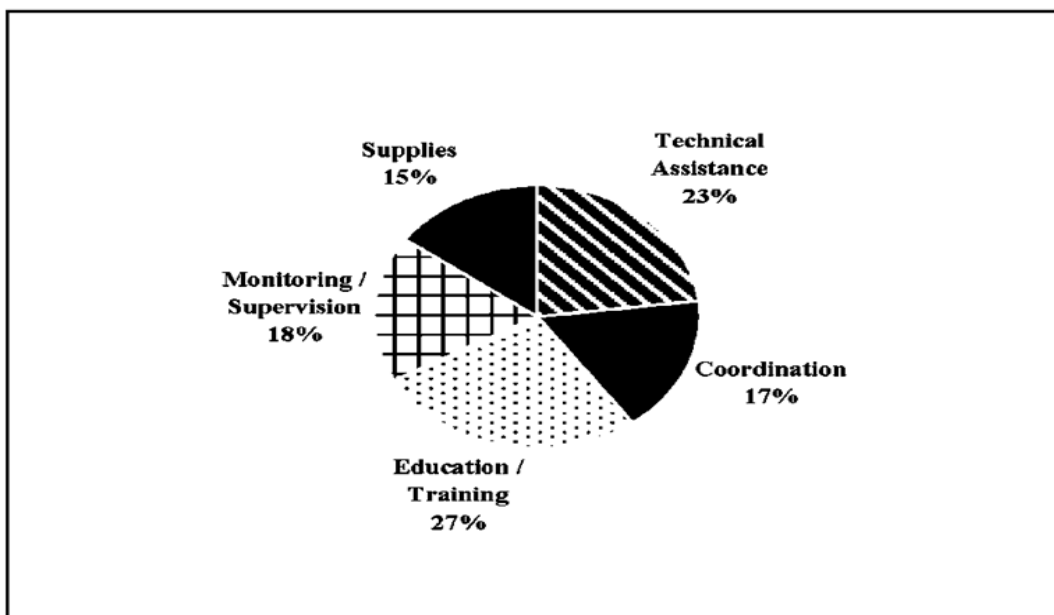


Figure 2. Breakdown of Gates funding expenditures



The fall-off of admissions in 2004 was due to poor central level supervision of programme during this period. The aggregate data does reflect the addition of new districts but when individual district admissions is analysed it demonstrates the following

**Table 1 Percentage increase in the number of pneumonia cases per district when compared to the first complete year of data collection.**

Districts	2001	2002	2003
Dedza	100	202.6	248.5
Mulanje	100	44.1	76.4
Nkhata Bay	100	-22.2	-33.2
Ntcheu	100	71.7	60.0
Thyolo	100	46.9	68.9
Balaka		100	25.2
Kasungu		100	23.2
Machinga		100	12.3
Rumphi		100	-7.0
Salima		100	144.0
Average increase		68.6	61.8
Max increase		202.6	248.5

The first complete year is used as the basis to ensure that other factors such as season or time of year do not confuse the calculation. The mean increase per annum varied between 61.8% and 68.6%.

#### 4 Case management training

The course focused on practical case management which was taught by using patients in clinics and hospitals. The philosophy used was one of knowledge transfer with the international course faculty progressively presenting less lectures and training sessions and the Malawi faculty taking on more and more responsibility for the course.

The implementation started in each district with the training of 10 staff members. These were divided into 2 groups and each group attends a 5-day course (40 hours) on Management of Childhood Lung Disease at District Hospital, using manuals and training materials developed by the Union in collaboration with local experts to teach the standard case management of major childhood lung disease, especially severe and very severe pneumonia. The courses were held at Lilongwe Central Hospital where the pediatric wards have a large number of children for the clinical practice sessions. The course agenda included clinical inter-active lectures, bedside clinical teaching, video clinical exercises, drills, clinical practice and exercises on the recording and reporting system. Although the course is entitled "child lung health", the curriculum includes the management of co-morbid conditions malaria, anaemia, measles, meningitis and severe malnutrition in relation to a child presenting with cough or difficult breathing, and also general pediatric issues such as triage of sick children, differential diagnosis of common problems, monitoring of sick children, discharge procedures and communication with parents.

During each course the participants were divided into three groups with an even distribution of members according to district, cadre and gender. These groups were formed for both clinical sessions and classroom group discussions.

The groups rotated through the three clinical areas i.e. inpatient, outpatient and health centre sessions. The clinical sessions were for 3 hours. The 2 groups in the hospital changed from inpatient to outpatient, and vice versa, halfway through sessions. The sessions provided adequate numbers of patients for the participants to assess, classify and identify correct treatment.

The MOH and DHO now provide funding within their SWAp budgets to continue with the annual training, as well as providing ongoing inservice training

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<sup>i</sup> Department of Planning, Ministry of Health. A joint programme of work for a health sector wide approach (SWAp) 2004-2010. Lilongwe Malawi: Republic of Malawi; March 2004.

<sup>ii</sup> Ministry of Health. Annual report for the work of the Malawi health sector for the period July 2007 to June 2008. Ministry of Health, Malawi. September 2008

## Chapter 5b

### Implementation of an oxygen concentrator system in district hospital throughout Malawi

Recent studies have found that effective implementation of these systems is more cost-effective than is usually perceived, and comparable in terms of cost to other already established major public health interventions for children. In order to assist with addressing these issues, health workers and administrators need information to help procure and maintain equipment, select the most robust and reliable products, and also to have data that makes a clear case for the investment in such systems. Effective implementation requires not just equipment but some training and a team approach that includes a range of expertise.

**Penny Enarson, Sophie La Vincente, Robert Gie, Ellubey Maganga & Codewell Chokani. Implementation of an oxygen concentrator system in district hospital paediatric wards throughout Malawi. Bulletin of the World Health Organization 2008;86:344–348.<sup>5</sup>**

This article describes the implementation of an oxygen system throughout Malawi based on oxygen concentrators to address the problem of hypoxaemia in children with severe pneumonia admitted to inpatient paediatric wards at District hospital level. The major finding from this process is that it is feasible to deliver oxygen countrywide at district hospital level in low-income countries through oxygen concentrators fitted with flow-splitters. Major challenge identified was the high staff-turnover rates among trained nurses and clinical officers, resulting in the need for regular ongoing training of new staff.

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<sup>5</sup> Reprinted with permission of the Bulletin of the World Health Organization.

# Implementation of an oxygen concentrator system in district hospital paediatric wards throughout Malawi

Penny Enarson,<sup>a</sup> Sophie La Vincente,<sup>b</sup> Robert Gie,<sup>c</sup> Ellubey Maganga<sup>d</sup> & Codewell Chokani<sup>e</sup>

**Problem** Hypoxaemia in children with severe or very severe pneumonia is a reliable predictor of mortality, yet oxygen was not available in most paediatric wards in Malawi.

**Approach** The Child Lung Health Programme in Malawi made oxygen available by supplying oxygen concentrators and essential supplies to 22 district and 3 regional hospitals' paediatric wards. Five key steps were taken to introduce concentrators: (1) develop a curriculum and training materials; (2) train staff on use and maintenance; (3) retrain electromedical departments on maintenance and repair; (4) conduct training once concentrators arrived in the country; and (5) distribute concentrators once staff had been trained.

**Local setting** The paediatric wards in 3 regional and 22 government district hospitals and 3 regional electromedical engineering departments in Malawi.

**Relevant changes** Main changes were: (1) provision of a source of oxygen in every paediatric ward in all district hospitals; (2) training of electrical engineering and health personnel in the use, maintenance and repair of oxygen concentrators; and (3) setting-up of high-dependency rooms or areas for severely ill children where oxygen is administered.

**Lessons learned** It is feasible to implement an oxygen system using concentrators throughout a low-income country. Oxygen delivery requires trained staff with necessary equipment and supplies. Regular maintenance and supervision are essential to ensure optimal utilization.

Bulletin of the World Health Organization 2008;86:344–348.

*Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.*

## Background

Hypoxaemia in children with severe or very severe pneumonia is a reliable predictor of mortality, increasing the risk of dying fivefold.<sup>1,2</sup> Hospitals throughout the developing world have very limited access to oxygen<sup>3</sup> and, when oxygen is available, the equipment required to deliver it is often lacking.<sup>4,5</sup> WHO has published technical guidelines for oxygen therapy in the management of childhood pneumonia in low-income countries, covering the indications for use, sources and equipment for the administration of oxygen.<sup>6</sup>

The Child Lung Health Programme (CLHP) is a collaborative project between the Government of Malawi, the International Union Against Tuberculosis and Lung Disease and the Bill and Melinda Gates Foundation. The CLHP has been incorporated into Malawi's existing health services and implemented by personnel carrying out

existing activities for control of acute respiratory infections within the integrated management of childhood illnesses. Policies and procedures, such as oxygen therapy, were coordinated with those in existing programmes.

Specific objectives of the CLHP were: (1) introduction of standard case management for the treatment of pneumonia at district hospital level; (2) improvement of health workers' practice through training and supervision; (3) direction of resources to children most at risk of dying; (4) uninterrupted supply and rational use of antibiotics and oxygen; and (5) generation and use of health services data to improve the quality of service.

In 2000, the International Union Against Tuberculosis and Lung Disease in collaboration with its partner, the Bill and Melinda Gates Foundation, technical experts, Ministry of Health and district health officers evaluated five district hospitals in Malawi to assess the burden

of disease of common childhood illnesses. The team observed the functioning of the paediatric ward, pharmacy, radiology and laboratory, reviewed the paediatric outpatient and inpatient registers for the previous 15 months and reviewed the case management of lung disease among hospitalized children. The main causes of morbidity and mortality in hospitalized children aged less than 5 years were malaria, pneumonia, diarrhoea and anaemia.

## Problem

During the situation analysis it was found that oxygen was not always available in four out of five district hospital paediatric wards visited. Health workers did not know when or how to administer oxygen to children. Oxygen cylinders were only provided to central hospitals and district hospital operating rooms, as they are expensive and difficult to deliver due to poor roads.

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doi:10.2471/BLT.07.048017

(Submitted: 26 September 2007 – Revised version received: 20 February 2008 – Accepted: 27 February 2008)

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Table 1. Cost of equipment and training

Item	Amount	Cost (US\$)
Concentrators all the same model – WHO approved	26 units	22 198
Flow-splitters	26 units	13 159
Spares for ongoing maintenance and repair including:	<ul style="list-style-type: none"> <li>• All filters</li> <li>• Tubing</li> <li>• Valve kits</li> <li>• Sieve beds</li> </ul>	8 594
Voltage surge prevention device	27 units	1 717
Nasal prongs and blanking-plugs	5 100 pieces	15 326
Training and materials	–	31 807
Shipping and handling	–	11 276
Cost of central level monitoring visits not included <sup>a</sup>	–	–
Cost of electrical engineering department not included <sup>b</sup>	–	–
<b>Total cost</b>	–	<b>104 077</b>

<sup>a</sup> Already included in Child Lung Health Programme (CLHP) budget.<sup>b</sup> Already included in the Ministry of Health budget.

Most of the concentrators that were available on the paediatric wards were more than 10 years old and did not meet WHO/United Nations Children's Fund (UNICEF) specifications.<sup>7</sup> Where newer WHO/UNICEF-recommended models were available, they did not have flow-splitters, which allow oxygen to be delivered simultaneously to up to four children. Electromedical engineers are responsible for service and repair of oxygen concentrators in all government hospitals but scheduled maintenance visits did not occur, mainly due to a lack of filters and spare parts resulting from financial constraints within the Ministry of Health. Where oxygen was available, nasal prongs and catheters were lacking. Electricity blackouts of 3 hours or more were frequent. In most hospitals the generator and back-up oxygen cylinders were available to operating theatres only.

## Approach

Following the situation analysis, the CLHP budget was revised to include oxygen concentrators, appropriate spares and supplies for oxygen delivery, and training of clinical staff and electromedical engineers, which had not been included originally. Therefore it was not possible to include extra funding required to repair and maintain those concentrators not purchased by the CLHP. Costs such as central level monitoring visits and travel allowances were already included within the existing budget. The Ministry of Health

already funded vehicle and travel costs and personnel for regular maintenance visits by electromedical engineers, but maintenance did not occur due to lack of the necessary filters and spare parts. The CLHP addressed this problem by funding these supplies (Table 1).

It was decided to supply oxygen concentrators in paediatric wards of all district hospitals, and to develop a package of information and tools to cover all stages from procurement, training, installation and maintenance of oxygen concentrators. This was achieved by undertaking the following steps.

1. Identify model/manufacture of concentrator suitable for Malawi.
2. Discuss with manufacturer's engineering department all the components necessary to introduce and maintain concentrators in Malawi.
3. Place order based on these recommendations.
4. Decide on mode of delivery – catheter versus nasal prongs. Calculate amount required and order. It was decided to use nasal prongs based on WHO recommendations<sup>6</sup> particularly as these provide the safest method and ease of use and care, which was important due to the high patient–nurse ratio.
5. Write guidelines for oxygen administration.
6. Develop training materials and curriculum.
7. Identify appropriate place to install concentrators in paediatric wards.

8. Install brackets to secure concentrator to wall so that it cannot be moved to the operating theatre or labour ward.
9. Identify and train staff at each hospital on concentrator use and maintenance.
10. Visit central and regional electromedical departments and discuss regular maintenance protocol and procedures.
11. Identify expert to conduct training once concentrators arrived in country.
12. Distribute concentrators to hospitals after training designated staff.
13. Lobby for paediatric wards to be included in hospital generator grid and provision of back-up oxygen cylinders.

## Training

Prior to the first installation of concentrators in 2002 by CLHP, training workshops were conducted by an electromedical engineer with expertise in maintaining and repairing oxygen concentrators and senior clinical and nursing personnel with expertise in concentrator use and oxygen administration. The first workshop included three electromedical engineers from the three central hospitals who assisted with subsequent training. One anaesthetist (clinical officer) and one senior state-registered nurse working in paediatrics were trained for each of the first five district hospitals implementing the CLHP. Training of general paediatric department staff in oxygen therapy was included in the annual clinical training course held before CLHP implementation in new districts.

The objectives of the workshop were to train electromedical engineers, anaesthetist officers and registered nurses in management and maintenance of concentrators and flow-splitters and in administering and monitoring oxygen therapy. The workshop consisted of technical and clinical presentations,<sup>8</sup> a WHO video on oxygen therapy,<sup>9</sup> theory and practical sessions on the use, maintenance and repair of the oxygen concentrator and flow-splitters, and hands-on training in the district hospitals (Box 1). Each district hospital received a brochure describing in brief the main points in concentrator use and maintenance,<sup>10</sup> a user instruction guide for the model of oxygen concentrators being supplied and a WHO

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manual on clinical use of oxygen.<sup>6</sup> Service manuals for specific oxygen concentrator maintenance were supplied to electromedical engineers.

**Relevant changes**

The paediatric ward in each district hospital established a separate “high-dependency” room or designated area for severely ill children where the oxygen concentrator was located. The staff were very innovative in setting up these rooms/areas, for example adding hooks for hanging intravenous fluids. Some district hospitals also set up four separate cots to reduce risk of nosocomial infection.

Posters on correct placement and use of nasal prongs and catheters, as well as procedures for administering oxygen, were mounted on the wall. Nasal prongs and filters were issued to each ward before the installation and regularly thereafter.

All district hospitals throughout Malawi now have an oxygen concentrator with flow-splitter on their paediatric ward with trained staff capable of administering oxygen to four children simultaneously.

**Monitoring**

The introduction of oxygen was only one element of the CLHP, which included the introduction of diagnostic guidelines and clinical staff trained in diagnosis and treatment based upon standard case management. Also included was a system of quality control, logistics to purchase and distribute standardized drugs to ensure uninterrupted supplies, and regular supervision and evaluation of the programme.

Quarterly maintenance visits were scheduled by the electromedical engineers. A logbook was issued with each concentrator to record specific routine preventive maintenance. This record was to be checked during quarterly monitoring visits by CLHP central level staff. Unfortunately many scheduled maintenance visits did not occur due to financial constraints within the electromedical engineering department.

**External oxygen review**

An external review of the sustainability of oxygen systems using concentrators was conducted in Malawi in June

**Box 1. Topics covered in the oxygen concentrator training workshop**

- Introduction and objectives
- Presentation on indications for oxygen therapy<sup>8</sup>
- Video on oxygen<sup>9</sup>
- Identifying common problems with oxygen supplies and administration in district hospitals (group discussions)
- Feedback and discussion from groups on current versus recommended practices and ways of improving them
- Introduction to oxygen concentrator – theory and practical (electromedical engineering department)
- How the concentrator works using a 4-way flow-splitter – practical demonstration (electromedical engineering department)
- Routine maintenance of the concentrator: what regional level electromedical engineering department does – practical demonstration (electromedical engineering department)
- Common faults and how to correct them at district hospital level
- Regular maintenance by clinical personnel in the hospital – theory and practical demonstration (such as changing filters)
- Organization of the ward – theory (senior nurse, paediatric ward, central hospital)
- Installing the concentrator in a designated area in paediatric ward – practical demonstration
- Discussion and recommendations

2007.<sup>11</sup> This review identified human resources as a major obstacle, with high staff-turnover rates among nurses and clinical officers, resulting in the need for regular ongoing training of new staff.

Concentrators had been used substantially less than expected, based on the annual number of very severe pneumonia admissions recorded for each hospital.<sup>11</sup> In addition to unwillingness among some parents for oxygen therapy, the difficulty in retaining well-trained personnel is likely to have contributed to this apparent underutilization of oxygen. Reliable records of the breakdown and repair of equipment were not available. All hospitals were found to have a functioning oxygen concentrator, thus a prolonged mechanical failure was unlikely to be the primary cause of underutilization.

While electricity failures were reported to be very frequent (daily in most hospitals), 10 out of 15 (67%) paediatric wards that were visited reported that a reliable generator provided the ward with a back-up power source.<sup>11</sup>

The review found that the difference in performance between the WHO-recommended model purchased by the CLHP and other models purchased by the Ministry of Health varied greatly.<sup>11</sup> This highlights the importance of uniformity of equipment and procurement that is appropriate for the environment. Additional details of this review are available from WHO.<sup>11</sup>

**Discussion**

The major finding from this process is that it is feasible to deliver oxygen countrywide at district hospital level in low-income countries through oxygen concentrators fitted with flow-splitters (Box 2). The success of such a system depends on: (1) all necessary equipment and supplies being available before installation of concentrators; (2) ongoing regular supply of equipment and supplies; (3) personnel being trained and in place before installation of concentrators; (4) regular maintenance and supervision of system and personnel; (5) use of logbooks to evaluate preventive maintenance; and (6) consideration of climate and environment in selection of equipment and maintenance schedule.

A designated area or room ensures those patients most likely to need oxygen have ready access to the concentrator(s). In Malawi, parents and guardians have been reluctant for their children to receive oxygen therapy, as they believe their child could die once oxygen is administered. Unfortunately, some children arrive at the hospital in a moribund condition and do not survive even when given appropriate care, including oxygen. Pulse oximeters may have assisted in showing parents the positive effects of oxygen therapy. Thus pulse oximetry should also be considered as an important tool to assess patient oxygen needs, instead of relying just on clinical signs.



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A challenge for the CLHP is to ensure that routine maintenance occurs and that systems are in place to ensure ongoing distribution of available spare parts. Improved communication between clinical, nursing, engineering and programme administration staff is likely to assist in meeting these challenges. Countries seeking to implement such a programme should ensure that, where high staff turnover is likely to be present, adequate support is available for ongoing training and regular supervision.

The last published data on field-testing and evaluation of oxygen concentrators was over a decade ago, reporting on a trial in Egypt.<sup>12</sup> There were no published data found on a similar trial that was conducted in Malawi. The concentrators used in both these trials are no longer produced<sup>13</sup> and no similar field experience to test sustainability

### Box 2. Summary of lessons learned

- It is feasible to deliver oxygen countrywide at district hospital level in low-income countries through oxygen concentrators fitted with flow-splitters.
- Multidisciplinary collaboration between clinical, nursing and engineering staff is required for the implementation and ongoing management of an oxygen concentrator system.
- Oxygen concentrators and equipment should be uniform and meet the WHO specifications and country climatic and environmental conditions.
- Regular supervision and training are required to ensure optimal utilization of oxygen concentrators.

of new models in developing countries has been reported in the literature since. It is hoped that the information on the introduction and sustainability, over a five-year period, of a newer model of concentrator that is in line with WHO specifications will encourage more countries to introduce a similar programme within paediatric wards for the management of pneumonia. ■

**Acknowledgements:** Sophie La Vincente is undertaking the Master of Applied Epidemiology Program at the National Centre for Epidemiology and Population Health, Australian National University. This programme is funded by the Australian Government's Department of Health and Ageing.

**Competing interests:** None declared.

## Résumé

### Mise en œuvre de concentrateurs d'oxygène dans des services pédiatriques hospitaliers de district à travers le Malawi

**Problématique** Chez l'enfant atteint d'une pneumonie très grave ou sévère, l'hypoxémie annonce de manière fiable une évolution mortelle. Pourtant, la plupart des services pédiatriques du Malawi ne disposaient pas d'oxygène.

**Démarche** Le Programme Santé pulmonaire de l'enfant au Malawi a mis l'oxygène à la disposition de 22 services pédiatriques hospitaliers de district et de 3 services pédiatriques d'hôpitaux régionaux, en leur fournissant des concentrateurs d'oxygène et les fournitures indispensables. L'introduction de ces concentrateurs s'est faite en cinq étapes clés : 1) mise au point d'un programme et de supports de formation ; 2) formation du personnel à l'utilisation et à la maintenance de ces appareils ; 3) recyclage des départements d'électronique médicale pour qu'ils puissent effectuer la maintenance et les réparations ; 4) dispensation d'une formation une fois les concentrateurs arrivés dans le pays ; et 5) distribution des concentrateurs une fois le personnel formé.

**Contexte local** Les services pédiatriques de 3 hôpitaux régionaux et de 22 hôpitaux publics de district et 3 départements régionaux de génie électronique médical du Malawi.

**Modifications pertinentes** Les principaux changements ci-après ont été apportés : 1) fourniture d'une source d'oxygène dans chaque service pédiatrique de l'ensemble des hôpitaux de district ; 2) formation du personnel sanitaire et spécialisé en électronique médicale à l'utilisation, à la maintenance et à la réparation des concentrateurs d'oxygène ; et 3) mise en place de salles ou de zones pour patients très dépendants où l'on administre de l'oxygène aux enfants gravement malades.

**Enseignements tirés** La mise en œuvre d'un système d'approvisionnement en oxygène utilisant des concentrateurs est faisable dans un pays à faible revenu. La délivrance de l'oxygène nécessite du personnel formé, ainsi des équipements et des fournitures. Une maintenance et une supervision régulières sont essentielles pour garantir une utilisation optimale.

## Resumen

### Implantación de un sistema de concentradores de oxígeno en salas de pediatría de hospitales de distrito en Malawi

**Problema** La aparición de hipoxemia en los niños con neumonía grave o muy grave es un factor predictivo fiable de la mortalidad. Pese a ello, la mayoría de las salas de pediatría de Malawi carecían de oxígeno.

**Enfoque** El Programa de Salud Pulmonar Infantil de Malawi suministró oxígeno facilitando concentradores y suministros esenciales a las salas de pediatría de 22 hospitales de distrito y 3 hospitales regionales. Se tomaron cinco medidas clave para introducir los concentradores: 1) desarrollo de un programa de estudios y de material didáctico; 2) formación del personal sobre su uso y mantenimiento; 3) actualización profesional de los

departamentos de electromedicina en materia de mantenimiento y reparación; 4) actividades de capacitación una vez llegados los concentradores al país; y 5) distribución de los concentradores tras haber formado al personal.

**Contexto local** Las salas de pediatría de 3 hospitales regionales y 22 hospitales de distrito públicos, y 3 departamentos regionales de ingeniería en electromedicina de Malawi.

**Cambios destacables** Los cambios principales fueron los siguientes: 1) instalación de una fuente de oxígeno en cada una de las salas de pediatría de todos los hospitales de distrito; 2) capacitación del personal de electroingeniería y salud en el uso,

## Special theme – Prevention and control of childhood pneumonia

### Implementation of an oxygen concentrator system in Malawi

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mantenimiento y reparación de los concentradores de oxígeno; y 3) acondicionamiento de habitaciones o zonas reservadas a grandes dependientes para los niños gravemente enfermos, incluida la instalación de sistemas de administración de oxígeno.

**Enseñanzas extraídas** Es posible implantar de forma generalizada un sistema de suministro de oxígeno a base de

concentradores en los países de ingresos bajos. La administración de oxígeno requiere personal especialmente preparado y dotado del equipo y suministros necesarios, y unas actividades regulares de mantenimiento y supervisión son fundamentales para que se haga un uso óptimo del material.

## ملخص

### تنفيذ نظام لتوفير وحدات تركيز الأكسجين في أجنحة الأطفال بمستشفيات المناطق في جميع أنحاء ملاوي

الحكومية بالمناطق، و3 أقسام هندسة طبية كهربائية في ملاوي. التغييرات ذات العلاقة: تمثّلت التغييرات الرئيسية في ما يلي: (1) توفير مصدر للأكسجين في كل جناح من أجنحة الأطفال بجميع مستشفيات المناطق؛ (2) تدريب العاملين في أقسام الهندسة الكهربائية، والعاملين الصحيين على استخدام، وصيانة وإصلاح وحدات تركيز الأكسجين؛ (3) إنشاء غرف أو مناطق تتميَّز بالكفاءة العالية، للأطفال الذين هم في حالة مرضية وخيمة، يعطون فيها الأكسجين.

**الدروس المستفادة:** يُعدُّ تنفيذ نظام لتوفير الأكسجين من خلال استخدام وحدات تركيز الأكسجين في أحد الأقطار المنخفضة الدخل، بكامل مناطقه، أمراً مجدياً. ويتطلَّب توفير الأكسجين وجود عاملين مدربين، مع توفر المعدات والإمدادات اللازمة، كما تُعدُّ الصيانة والإشراف الدوريان من الأمور اللازمة لضمان الاستخدام الأمثل لهذه الوحدات.

**المشكلة:** إنَّ نقص تأكسج الدم لدى الأطفال المصابين بالتهاب رئوي وخيم، أو وخيم جداً، هو أحد المنبئات الموثوقة بحدوث الوفيات. ورغم ذلك، لم يكن الأكسجين متوفراً في معظم أجنحة الأطفال في ملاوي.

**الأسلوب:** وقر برنامج الصحة الرئوية للأطفال في ملاوي الأكسجين عن طريق توفير وحدات تركيز الأكسجين، والإمدادات اللازمة لها، في أجنحة الأطفال في 22 من مستشفيات المناطق، و3 مستشفيات إقليمية. وقد أُخذت خمس خطوات أساسية من أجل إدخال هذه الوحدات، هي: (1) إعداد منهج دراسي ومواد تدريبية في هذا المجال؛ (2) تدريب العاملين على استخدام هذه الوحدات وصيانتها؛ (3) إعادة تدريب العاملين في أقسام الهندسة الطبية - الكهربائية على صيانة وإصلاح هذه الوحدات؛ (4) إجراء التدريب بمجرد وصول هذه الوحدات إلى القطر؛ (5) توزيع وحدات تركيز الأكسجين متى تلقى العاملون تدريبهم عليها.

**المرفق المحلي:** أجنحة الأطفال في 3 مستشفيات إقليمية، و22 من المستشفيات

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## Chapter 6

### **Reducing deaths from severe pneumonia in children in Malawi by improving delivery of pneumonia case management.**

The technical rationale supporting the CLHP was that the standard case management of children with pneumonia by trained staff with a regular supply of effective antibiotics should result in a significant decline of deaths in district hospitals. It was also foreseen that the impact would be detectable after some months of project implementation once the guidelines and procedures have been efficiently put into practice.

**Penny Enarson, Robert Gie, Charles Mwansambo, Ellubey Maganga, Carl Lombard, Donald Enarson, Stephen Graham. Reducing deaths from severe pneumonia in children in Malawi by improving delivery of pneumonia case management. PLoS ONE 9(7): e102955. doi:10.1371/journal.pone.0102955. Published July 22, 2014.**

A prospective nationwide public health intervention study to evaluate the impact on pneumonia specific CFR in infants and young children (0 to 59 months of age) following the implementation of a Child Lung Health Programme (CLHP) within paediatric inpatient wards in 24 of 25 district hospitals in Malawi. Following implementation, 47,228 children were admitted to hospital for severe/very severe pneumonia with an overall CFR of 9.8%. The majority (64%) of cases, 2-59 months, had severe pneumonia. In this group there was a significant effect of the intervention Odds Ratio (OR) 0.70 (95%CI: 0.50-0.98);  $p=0.036$ ), while in the same age group children treated for very severe pneumonia there was no interventional benefit (OR 0.97 (95%CI: 0.72-1.30);  $p=0.8$ ). No benefit was observed for neonates (OR 0.83 (95%CI: 0.56-1.22);  $p=0.335$ ). The results of this study were derived from the information system implemented to collect routine data which produced a very comprehensive and complete set of routine data collected over the duration of the study. Further research is required to establish the reasons for the lack of benefit for neonates, infants and children with very severe pneumonia.



# Reducing Deaths from Severe Pneumonia in Children in Malawi by Improving Delivery of Pneumonia Case Management

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## Abstract

**Objective:** To evaluate the pneumonia specific case fatality rate over time following the implementation of a Child Lung Health Programme (CLHP) within the existing government health services in Malawi to improve delivery of pneumonia case management.

**Methods:** A prospective, nationwide public health intervention was studied to evaluate the impact on pneumonia specific case fatality rate (CFR) in infants and young children (0 to 59 months of age) following the implementation of the CLHP. The implementation was step-wise from October 1<sup>st</sup> 2000 until 31<sup>st</sup> December 2005 within paediatric inpatient wards in 24 of 25 district hospitals in Malawi. Data analysis compared recorded outcomes in the first three months of the intervention (the control period) to the period after that, looking at trend over time and variation by calendar month, age group, severity of disease and region of the country. The analysis was repeated standardizing the follow-up period by using only the first 15 months after implementation at each district hospital.

**Findings:** Following implementation, 47,228 children were admitted to hospital for severe/very severe pneumonia with an overall CFR of 9.8%. In both analyses, the highest CFR was in the children 2 to 11 months, and those with very severe pneumonia. The majority (64%) of cases, 2–59 months, had severe pneumonia. In this group there was a significant effect of the intervention Odds Ratio (OR) 0.70 (95%CI: 0.50–0.98);  $p=0.036$ , while in the same age group children treated for very severe pneumonia there was no interventional benefit (OR 0.97 (95%CI: 0.72–1.30);  $p=0.8$ ). No benefit was observed for neonates (OR 0.83 (95%CI: 0.56–1.22);  $p=0.335$ ).

**Conclusions:** The nationwide implementation of the CLHP significantly reduced CFR in Malawian infants and children (2–59 months) treated for severe pneumonia. Reasons for the lack of benefit for neonates, infants and children with very severe pneumonia requires further research.

**Citation:** Enarson PM, Gie RP, Mwansambo CC, Maganga ER, Lombard CJ, et al. (2014) Reducing Deaths from Severe Pneumonia in Children in Malawi by Improving Delivery of Pneumonia Case Management. PLoS ONE 9(7): e102955. doi:10.1371/journal.pone.0102955

**Editor:** Rashida A. Ferrand, London School of Hygiene and Tropical Medicine, United Kingdom

**Received:** December 2, 2013; **Accepted:** June 26, 2014; **Published:** July 22, 2014

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**Funding:** The CLHP was primarily funded by the MoH of Malawi, who contributed 69% of the running costs comprising facilities and human resources that are part of the existing health system. The Bill and Melinda Gates Foundation funded the remaining 31% of the costs, 21% of which was investment and 79% operating costs. The Bill & Melinda Gates Foundation grant ID#: 413 <http://www.gatesfoundation.org/Pages/home.aspx>. The external funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing Interests:** The authors have declared that no competing interests exist.

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## Introduction

Pneumonia is the most frequent cause of death in children less than five years of age [1]. In sub-Saharan Africa, child pneumonia deaths account for an estimated 18% of under-five mortality of which three per cent occur in the neonatal period [1]. The incidence of pneumonia and the case-fatality rate are highest among infants and decline with increasing age [2].

In 1984, the World Health Organization (WHO) introduced standardized case-management (SCM) of pneumonia [3] that

became an important part of integrated child health programmes and WHO recommended approaches in clinical care [4]. Pneumonia-related deaths declined following the introduction of community-based SCM [5]. Hospitalized cases represent the more severe spectrum of disease and are more likely to die. The effectiveness of hospital-based SCM on pneumonia-related mortality has not been reported and there are no studies of the effectiveness of nation-wide, hospital-based programmes within existing health services.

The International Union Against Tuberculosis and Lung Disease (The Union) developed the Child Lung Health Programme (CLHP) for SCM of pneumonia in hospitalized children based on its model for tuberculosis services. The Union model for tuberculosis was adopted by the WHO in 1993 as the basis of its global strategy for control of tuberculosis (the DOTS strategy) [6] which the World Bank assessed as among the most cost-effective health interventions in low-income countries [7]. The model includes accurate accounting for services, materials, and training and permits management of supplies to ensure no disruption of essential therapies. The Ministry of Health (MoH), Government of Malawi, requested assistance from The Union to improve the management and outcome of pneumonia in Malawian children. The Union assisted the Ministry of Health to adapt and implement the CLHP within the country's existing health services to ensure sustainability. The model and its implementation have been previously described [8].

The aim of this study was to assess the benefits of this strategy by measuring the trend over time in the case fatality rate (CFR) in neonates, infants and young children (one week to 59 months of age) hospitalized with severe or very severe pneumonia.

## Methods

### Ethics Statement

The CLHP was routine patient management and data from it was routinely collected. The data used for the study was aggregated data from Monthly Recording Forms - no individual identification appeared on these reports. Permission to use the data was received from the Ministry of Health, Republic of Malawi. Approval to analyze the data was obtained from the Union's Ethical Advisory Group (EAG: 05/10) and the Human Research Ethics Committee (N10/09/285), Faculty of Medicine and Health Sciences, Stellenbosch University.

### Intervention Setting

The public health service delivery system in 2000 was district-based with 22 out of 24 districts having one government hospital with satellite health centres. The Government District Health Officer (DHO) was charged with the oversight of services in all government facilities, and co-ordination and supervision of all health providers and programmes in the district. There were three central hospitals (at Blantyre, Lilongwe and Zomba) which were tertiary referral hospitals, but which also acted as district hospitals for their 'host' District.

The DHO reported directly to the central level since the introduction of health sector reform measures removed regional level management in all but the tuberculosis and EPI Programmes. The district health team had a managerial and co-ordinating role, and provided technical support and supervision.

The Ministry of Health (MOH) was entirely financed by the government and external donors. The latter provided most of the development expenditure and financed a large percentage of the recurrent costs of preventive and promotive services [9]. Free medical care in government-run facilities was the policy throughout the country.

Many districts also had a private system, the Christian Health Association of Malawi (CHAM) Hospital within their boundaries. CHAM facilities were independent, owned and run by their respective churches. However, the MOH provided CHAM facilities with staff salaries and subsidised hospitalisation costs (0.75 Malawian Kwacha per day). These facilities were also allowed to operate cost recovery from patients who could afford it.

In 2000 Malawi was the 9<sup>th</sup> poorest country with a Gross National Product per capita of US\$ 170 leading to chronic underfunding of health care services - total public expenditure was 9.0% [9] and only increased to 9.3% by 2005 [10]. This resulted in an on-going chronic shortage of basic health services mainly due to shortage of trained personnel, lack of skills among health professionals to manage severe and very severe pneumonia and lack of essential drugs (especially antibiotics) and supplies (such as oxygen) throughout the country [11].

The main clinical staff was paramedical Clinical Officers and Medical Assistants, supported by State Registered Nurses, State Registered Enrolled Nurses and Midwives. There was an acute shortage of all health personnel with a 39.0% vacancy rate [11]. The MOH employee/ratio to population were as follows: Doctors 1:113,953, Registered Nurses 1:25,857 [11]. Each of the 22 district hospitals had on average a total of 32 health personnel to manage all services within the facility. The distribution was as follows: Medical doctor 1 or none, Clinical Officers 5, Medical Assistants 4 (only worked in the outpatient department), Registered Nurses 5 and Enrolled Nurses/Midwives 17 [11]. The attrition rate of health workers due to death from HIV/AIDS at this time was as high as 41% and also a major cause of absenteeism [12].

In Malawi the ratios of doctors and nurses to population remained lower than those of its neighbouring Sub-Saharan African countries. A comparison of information available from 2004 showed lower ratios for Malawi compared with Tanzania and Zambia [13]: for doctors, 1.1 compared with 3.0 and 6.9; for nurses, 25.5 compared with 36.6 and 113. The WHO Standard Doctor/Population Ratio is 10:100,000.

The intervention was carried out in the public health system in Malawi as described above. The CLHP was introduced into 24 of 25 district hospitals in Malawi. Two of these also functioned as a regional referral hospital located in a predominantly urban population while another urban-based regional referral hospital (Malawi's largest hospital based in Blantyre and also the College of Medicine's major teaching hospital) did not participate as it was better staffed and resourced. These were all non-fee paying services. Children with severe or very severe pneumonia may present at any health facility in a district but for inpatient care are referred to the dedicated paediatric wards at the district hospital according to national standards of care.

### Situational analysis

A situational analysis prior to the intervention in 2000, found that acute respiratory infection (ARI) was the second leading cause of morbidity in Malawian children below 5 years [14]. Pneumonia or lower respiratory tract infection was the most common diagnosis in hospitalized Malawian children accounting for one-quarter of paediatric admissions. Case-fatality rate for pneumonia prior to the intervention varied between 10% and 26% [15]. Problems identified included inadequate training, insufficient supplies of antibiotics, lack of adequate oxygen therapy, and lack of information to assist in planning services and procurement of essential items [15].

### Background child health indicators

In the years just prior to the intervention, Malawi reported a high under-5 mortality of 189 per 1,000 live births for the period 1996-2000.<sup>8</sup> Known risk factors for frequency and severity of child pneumonia such as low birth weight (20% of live births), malnutrition (48% of children with moderate or severe stunting) and HIV infection (91,000 children living with HIV in 2006) were all highly prevalent in Malawi at the time of the intervention [16]. Immunization coverage over the intervention period was reported

as relatively high - >90% for BCG and DPT3, and >80% for measles (>80%) - and there were no outbreaks of measles reported. Haemophilus influenzae type b (Hib) conjugate vaccine was introduced in 2002 with high coverage (93%) reported for 2006 [16]. Pneumococcal conjugate vaccine (PCV) was not introduced until 2011 i.e. after the implementation of the CLHP was completed.

National antenatal HIV prevalence in 2001 was estimated to be 17.1% in people 15-24 years of age [17] of age with a prevalence of up to 30% in urban settings [18,19]. HIV prevalence among pregnant women at sentinel sites was 19.5%, 19.8% and 16.9% in 2001, 2003 and 2005. The rate of mother to child transmission in 2001 was 26.9% [20]. The estimated percentage of HIV+ pregnant women who received a full package of care to prevent mother-to-child transmission (MTCT) of HIV in 2004 was only 2.3%.

The majority of HIV-infected infants died before five years of age with pneumonia the most frequent cause of death [21]. The use of cotrimoxazole preventive therapy (CPT) for HIV-exposed infants and HIV-infected children, and the use of anti-retroviral therapy (ART) for HIV-infected children were not routinely available at the time of the intervention. Malawi received funding in 2004 from the Global Fund to Fight AIDS, Tuberculosis and Malaria to start to scale-up ART services but for children this was confined to the 3 government referral hospitals and 2 district hospitals supported by Doctors Without Borders [22].

### Intervention Design

The intervention was implemented in a stepped wedge design (non-randomized). Planning commenced on the 1<sup>st</sup> March 2000 and the first five district hospitals were included on the 1<sup>st</sup> October 2000. Five to eight additional district hospitals were included annually in a step-wise fashion until all hospitals had been included by July 2003. Data collection ended on the 31<sup>st</sup> December 2005. The sequence of hospital recruitment was chosen by the Ministry of Health according to service needs, logistical and financial reasons (Figure 1 and 2). The data recorded during the intervention were subsequently collected and analyzed for the present study from July 2011 to December 2012.

A pragmatic evaluation design was planned and was used to analyze the data, beginning with the introduction of a standardized information system that was introduced to ensure that the data generated by the health system were of good quality. Data on pneumonia admissions and outcomes were collected prospectively as part of routine care.

It was planned to use data that was collected during a pre-intervention period as the control group. The patient information forms were introduced into districts on an average of 4 months prior to implementation of the programme. Twelve districts were included and a total of 624 forms (an average 52 forms per district) were collected for analysis. A total of 373 children were admitted with a diagnosis of severe or very severe pneumonia but, of these, 123 records did not include either a diagnosis or known outcome. The remaining 250 forms contained insufficient data to ascertain if a correct diagnosis had been made.

No other reliable pre-intervention data were available. Therefore, for study purposes, it was only possible to use data collected in the first three months following implementation of the CLHP as the 'control' period. These data were of similar quality as that collected during the rest of the study.

### Intervention

The CLHP was based on the Union model [23] for delivering health services adapted to standard case management of the child

with cough and difficult breathing [24]. The introduction of the CLHP included a substantial programme of work which included establishing an information system, quality assurance mechanisms, training, regular supervision and assurance of provision of antibiotics and oxygen to address all the various problems identified in Table 1.

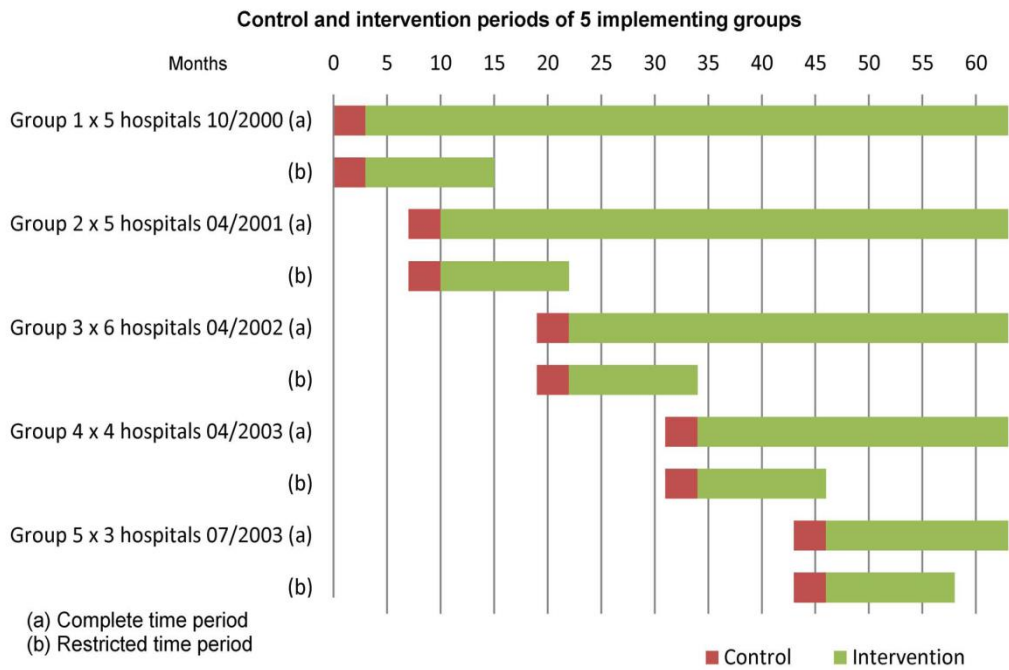
The essential elements of the CLHP were:

- Political commitment by the Government of Malawi to implement SCM strategies countrywide into the existing secondary health care system. This commitment implied:
  - a structure for delivering the services
  - no discrimination against patients in the delivery of services to promote access.
  - sufficient financial resources for control of lung disease and other childhood illnesses
- Diagnoses and treatment based upon SCM (Table 2) with a system of quality control.
- Training of all paediatric clinical staff in SCM
- Logistics to purchase standardized drugs and to distribute them to ensure uninterrupted supplies at the management level of the District Health Office
- Recording and reporting clinical outcomes of severe and very severe pneumonia
- Supervision and evaluation of the services

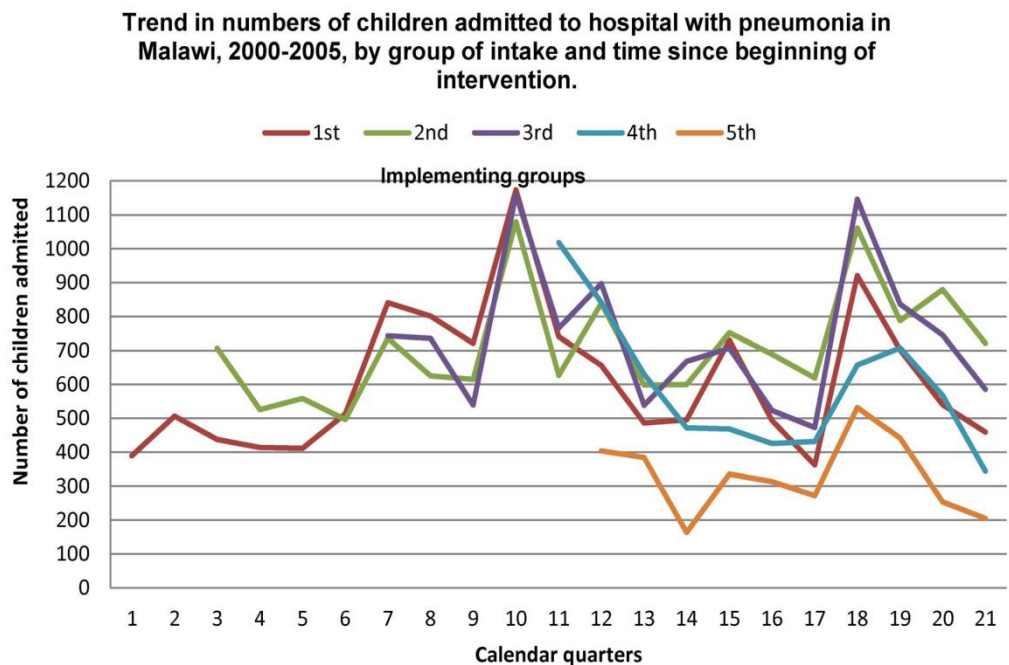
Health care workers from the 24 district hospitals that provide inpatient/outpatient care for children were selected for training by each hospital administration as each of the hospitals were recruited for implementation. All paediatric clinical staff was trained as on average this meant only 3-5 nurses and one to two clinical staff per hospital. Therefore it was decided to increase this number to at least 10 and over the intervention period, a total of 312 health care workers (representing approximately 30% of all health care workers in district hospitals) to ensure more staff had received training. This included Clinical Officers (41%), State Registered Nurses (20%), Enrolled Nurses (30%), Medical Assistants (8%), other (1%). As described above there was a chronic shortage of staff and a high attrition rate in those previously trained at the recruited hospitals which meant that the new staff for these hospitals was included in the next training course. To also address this issue ongoing in-service training was provided by senior nurses and clinicians on the paediatric ward using training materials produced by the CLHP.

The training in diagnosis and treatment of children with pneumonia according to WHO SCM guidelines [24,25] comprised an initial five day course during which theoretical and practical training occurred with a one day follow-up training one month later. Training objectives related to skills in standard case management, knowledge of child lung disease and management and planning. These included:

- General assessment of the child or young infant
- Directed history/examination, assessment and classification of a child with cough or difficult breathing
  - assess clinical signs (e.g., respiratory rate, chest indrawing, wheeze)
  - identify any danger signs indicating urgent care is needed
  - assess clinical signs to determine whether pneumonia is present and if so, its severity



**Figure 1. Control and intervention periods for 5 implementing groups for complete and restricted time periods.**  
doi:10.1371/journal.pone.0102955.g001



**Figure 2. Trend in numbers of children admitted to hospital with pneumonia in Malawi, 2000-2005, by group of intake and time since beginning of intervention.**  
doi:10.1371/journal.pone.0102955.g002

**Table 1.** Summary of the situational analysis carried out prior to the implementation of the child lung health programme (CLHP), intended interventions, output indicators and outputs achieved following the CLHP intervention.

<i>Situation Analysis findings</i>	<i>intervention activity</i>	<i>Output indicator</i>	<i>achieved through intervention</i>
No hospital was implementing standard case management guidelines	All children presenting with signs of pneumonia will be managed following the CLHP technical guidelines	Children diagnosed and treated correctly as per standard categories and treatment regimens	Technical guidelines adhered to in >90% of children presenting with respiratory symptoms
Less than 10% of health workers trained in SCM of pneumonia	Health care workers from all district hospitals trained in standard case management of pneumonia	Number of health workers trained in SCM	More than 300 health care workers trained (The target exceeded by 25%)
Frequent interruption of supply of antibiotics required for SCM regimens	A material management system introduced at all levels calculated on number of cases. Antibiotic reserve stock supplied	Regular uninterrupted supply of antibiotics at central, regional and district levels	No stock outs of antibiotics experienced at all levels.
No regular supply of oxygen available on paediatric wards	One designated oxygen concentrator be provided for each paediatric ward implementing CLHP	All infants <2 months admitted with severe/very severe pneumonia, all children 2–59 months admitted with very severe pneumonia or a RR $\geq$ 70 received oxygen therapy	All hospitals provided with an oxygen concentrator and personnel trained at central and district level in use and maintenance.
No regular reporting system in place	Each district hospital CLHP Coordinator to fill Monthly Reports on cases and treatment outcomes and submit to central level management unit	Monthly reports on Cases of Pneumonia and on Treatment Results	99.4% achievement as of December 2005 i.e. of 2274 reports expected 2260 were received
No regular standardized supervisory/support visits being carried out by Central Level Unit	Implementation of regular standardized supervisory/support visits to implementing hospitals by Central Level Unit	Regular standardized supervisory/support visits to implementing hospitals carried out by Central Level Unit	Standardized supervision tool developed and implemented. Monthly visits carried out for 6 months then quarterly
No evaluation of ARI control activities regularly carried out	A report on external evaluation/technical support visits to the CLHP sent to the MOH every 6 months	Evaluation reports	Eight external evaluation/technical support visits plus 1 independent external review visit to the CLHP carried out and a report on each visit sent to MOH.

doi:10.1371/journal.pone.0102955.t001

- identify other conditions and comorbidities (fever, anaemia, malnutrition, tuberculosis, malaria, asthma, HIV-related lung disease) that can be treated
- Identify differential diagnosis
- Prescribe appropriate treatment
- Supportive care
- Monitor child's progress
- Counselling and discharge planning
- Complete Recording Form

In addition the District Hospital Programme Coordinator was taught how to complete monthly reports and maintain adequate supply of drugs and supplies.

The training was followed by regular supervision visits to the hospitals six weeks after the training, with monthly visits for the first six months then regular three-monthly visits. On initiation of the CLHP the amount of antibiotics required for each district hospital was calculated, including one-month consumption needs plus one-month buffer stock. One year buffer stock was held at the central medical store. During supervision visits stock was checked to prevent stock-outs of antibiotics during the intervention.

Oxygen was available in a minority of district hospitals prior to the initiation of the CLHP. The CLHP acquired and installed oxygen concentrators in each district hospital paediatric ward [26].

### Patients and standard case-management

All children aged up to 59 months hospitalized with a clinical diagnosis of severe or very severe pneumonia were included. They were classified at the time of admission as severe or very severe pneumonia according to WHO recommendations. Neonates, less than two months of age, with severe and very severe pneumonia were combined in a single category. The CLHP was implemented within existing services, using treatment for pneumonia as recommended by the MoH protocols consistent with WHO guidelines [25]. Table 2 outlines the standard case management of children with pneumonia as recommended by the World Health Organization and used within the CLHP for training purposes and to guide patient care. These treatment protocols have since been updated in 2005 and 2013 [27].

### Data Collection

Demographic and clinical information was transcribed to the Hospital Inpatient Pneumonia Register, aggregated monthly and sent to a data management centre where they were entered into an EXCEL spread-sheet. The aggregated data included the following variables used in the analysis: Number of cases by age groups - <2 months, 2–11 months and 12–59 months; number of males and females; number of cases by severity - non-severe, severe and very severe and number of cases by outcome (died). There was no individual patient clinical data recorded on the monthly reports. Errors were followed up and corrected. At each supervision visit, a random sample of recording forms was checked for accuracy and



**Table 2.** WHO standard case management of pneumonia defined by age groups and severity of disease.

Standard Case Management		
Diagnosis	Presenting signs and symptoms	Recommended treatment regimens
<b>Child 2–59 months</b>		
	Respiratory rate:	
<b>Severe pneumonia</b>	≥50 aged 2–11 months	<b>Penicillin</b> 50 000 units/kg IM/IV Q6h for 3 days if improved then oral <b>amoxicillin</b> 25 mg/kg three times daily for total of 5 to 8 days
	≥40 aged 12–59 months	
	Lower chest wall in-drawing	
	Respiratory rate:	
	≥50 aged 2–11 months	<b>Chloramphenicol</b> 25 mg/kg IM/IV 8 hourly for 5 days if improved then three times daily for total of 10 days antibiotic treatment
	≥40 aged 12–59 months	
<b>Very severe pneumonia</b>	Lower chest wall in-drawing	
	Cyanosis	Oxygen therapy
	Unable to drink	
	Reduced level of consciousness	
	Severe respiratory distress	
<b>Infant &lt;2 months</b>		
	Respiratory rate: ≥60	<b>Gentamicin</b> 7.5 mg/kg once daily for 8 days
<b>Severe/Very severe pneumonia</b>	Severe lower chest wall in-drawing	<b>Penicillin</b> 50 000 units/kg Q6h IM/IV for three days if improved then oral <b>amoxicillin</b> 25 mg/kg three time daily for a total of 8 days antibiotic treatment
	Unable to breast-feed	
	Grunting	
	Apneic spells	Oxygen therapy
<b>Co-morbid conditions</b>		
<b>Pneumonia in severely malnourished child</b>	Signs and symptoms for severe/very severe pneumonia as above PLUS signs and symptoms for any of the following	<b>Cotrimoxazole</b> prophylaxis on admission if not acutely ill
	Marasmus	Treatment for severe or very severe pneumonia as above PLUS <b>Gentamicin</b> (7.5 mg/kg IM/IV) once daily for 7 days
	Kwashiorkor	
	<60 Weight for Height	If the child fails to improve within 48 hours, add <b>Chloramphenicol</b> (25 mg/kg IM/IV 8-hourly) for 5 days
	2–6-month-old child with central cyanosis	
	Hyper-expanded chest	<b>Continue first-line antibiotic</b> (such as <b>Chloramphenicol</b> ) as mixed infection with bacteria occurs
	Fast breathing	
<b>Known/suspected PcP</b>	Chest X-ray changes, but chest clear on auscultation	
	Enlarged liver, spleen, lymph nodes	<b>Oral Cotrimoxazole:</b> 120 mg three times daily if less than 5 kg; 240 mg three times daily if 5 kg or more for 21 days
	HIV test positive in mother or child	

doi:10.1371/journal.pone.0102955.t002

consistency. (See Text S1 for supplementary material for recording and reporting).

### Statistical Analysis

Statistical analysis was that used for a cluster-randomized trial with a stepped wedge design. Five groups of hospitals were included with different starting points. The hospitals within each group started simultaneously so providing contemporaneous data. Monthly reports formed the units of analysis. The first three months after implementation in each cohort, was taken as the

‘control’ period for purposes of comparison, and each of the months following that, the intervention period. The analysis used two approaches: 1) analysis using the entire follow-up of 63 months (unrestricted) and 2) analysis of first 15 months follow-up (restricted) at each district hospital. The latter was used to limit the influence of the underlying trend in improvement of outcome occurring over time.

The primary outcome was the proportion of children who died while in hospital (case fatality rate). In addition to an implementation indicator link to intervention month, other variables

included: 1) Year of the implementation; 2) Age group: <2 months, 2–11 months and 12–59 months; 3) Severity category at diagnosis: In children 2–59 months there were two categories severe and very severe which were recorded separately; 4) Region of the country: North, Central and South and 5) Season defined by month of year.

The time factor used in the analysis was month. Data within each facility were reported by this time period broken down by the covariates used in the analysis. It was then possible to recreate the individual records from the monthly report since the information reported the number of children who survived and died by unique covariate pattern. Hospitals were the clusters. All monthly records compiled at the districts were included in the analysis depending on the analysis restriction applied as outlined above.

Due to the pragmatic nature of the intervention and the stepwise implementation of the intervention it was decided to test the intervention effect in a fully adjusted model. Thus all covariates that were available from the monthly reports were included in the analysis. Interactions with the intervention were also considered. Calendar trend was extracted from the timing of the report as well as the region of the hospital.

A logistic regression model was used to estimate odds ratios and their standard errors for all the interactions of the covariates with the intervention. Of the interactions investigated only those with significant interaction between severity and intervention were retained. The clustering of children within districts was taken into account using a robust cluster variance approach. Taking only the basic design into account an overall crude intervention effect was estimated in a separate model with CLHP implementation as the only dependent variable.

As implementation began at varying times, the length of follow-up for different groups of hospitals varied, with those beginning the implementation having the longest follow-up. Therefore, the analysis was repeated (restricted analysis) using only the first 15 months follow-up at each district hospital in order to standardize the length of the intervention in the various hospitals (Figure 1). The restricted analysis became part of the model strategy to ensure contemporaneous time periods were not dominated by the intervention periods at the end of the intervention for those hospitals which started the implementation earliest. This approach was considered more objective as it limited the influence of the underlying trend in improvement of outcome that might have occurred over time in those hospitals with the longest implementation period.

## Results

Table 1 summarizes the results of the situation analysis undertaken prior to commencing implementation within the district hospitals and gives an outline of the elements of the intervention introduced by the CLHP, the output indicators used to monitor progress and the operational achievements during the course of the program. Adherence to guidelines improved from zero to over 90% among children presenting for care. Training of staff increased from less than ten per cent to over the target set for training all staff engaged in the care of small children. While interruption of essential supplies was frequent prior to the introduction of the program, it never occurred again after the program was introduced. All hospitals received the facility of oxygen supply during the implementation of the program. The poor case records and lack of routine reporting at the outset (preventing the use of any data on patient care prior to implementing the program) had been corrected with almost all

(99.4%) reports being submitted by the end of the intervention period.

A total of 48 285 children were recorded in the intervention of which 1057 (2.2%) cases were admitted for non-severe pneumonia and were excluded from further analysis resulting in 47 228 cases of severe and very severe pneumonia being analysed. Of the 2274 monthly report forms generated during this period, 2260 (99.4%) were received for analysis. Figure 1 indicates the routine data that were used for analysis within the intervention. It is clear that the follow-up periods varied according to the point of introduction of the program. The follow-up period was standardized within the restricted analysis by truncating the analysis at the same point of follow-up for each of the groups of hospitals.

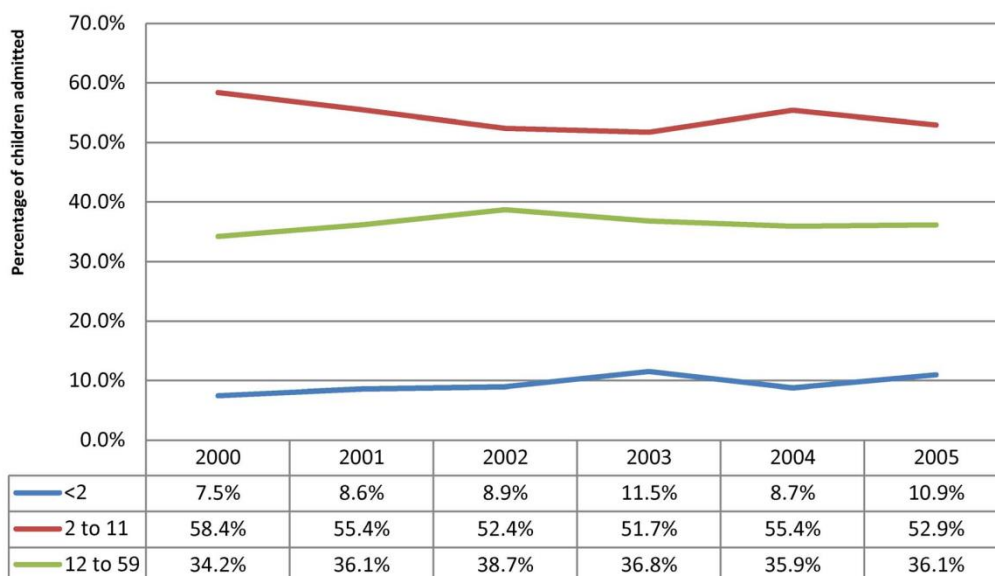
Hospitals reported a mean number of children treated for severe or very severe pneumonia of 1968 (range: 807 to 4458). Figure 2 indicates the trend in numbers of children with severe and very severe pneumonia admitted to hospital over the course of the intervention, by the hospital group of intake. The hospital intake per calendar quarter showed no significant change over the period of the intervention. The trend was similar for the proportion by age group (Figure 3) with no important change over the intervention period. There was some change in the distribution by severity grade among the children admitted to hospital (Figure 4), with a decline in the proportion of children aged two to 59 months with very severe pneumonia and a concomitant rise in the proportions classified as severe in this age group. The trend in proportions of young children (aged less than two months) showed no change over the period.

Table 3 shows the distribution of numbers of children admitted to hospital by calendar year, by age group and by classification of severity, for the entire period of follow-up and for the restricted period of follow-up. It also indicates the number and proportion of the children who died during the course of treatment. Overall, 4,605 children (9.8%) died compared with 1,600 (11.3%) when considering the more restricted period. Case fatality rate was highest for children with very severe pneumonia and was higher for younger as compared with older children. There was a steady decline in case fatality rate by calendar year overall and, to a lesser extent within the restricted period of follow-up. Deaths were equally likely to occur within the first 24 hours of hospitalization as compared with later in the course of treatment in the whole group (Table 4). The exception was the youngest age group in which a higher proportion of deaths occurred in the earlier time period. This was even more apparent for cases within the restricted period of follow-up.

Table 5 shows the results of statistical analysis of likelihood of death, overall and for the restricted period of follow-up. Deaths were not associated with the region of the country with results not significantly different for the north, central and southern regions. There was a significant variation by calendar month with fewer deaths occurring in the middle quarters of the year. Deaths were much more likely to occur in younger children.

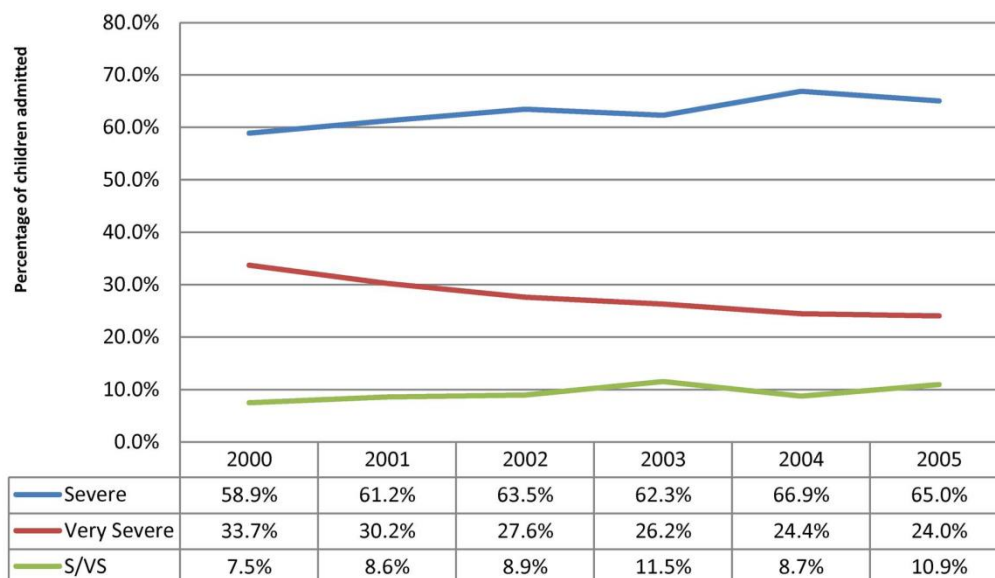
Multivariate analysis of the trend in deaths over the intervention period, adjusted for age, severity, calendar month and region, showed a significant decline over the calendar years of the intervention in the overall intervention group. In comparison, although there was a decline in the likelihood of death over the intervention period, the decline was not statistically significant in the group with the restricted period of follow-up. The significant reduction in likelihood of death overall was restricted to the group of older children with severe pneumonia; there was no difference at all among the older children with very severe pneumonia or for the group of younger children. These results remained significant in the analysis of the restricted period of follow-up.

**Trend , by age group, of children admitted to hospital with pneumonia in Malawi, 2000-2005.**



**Figure 3. Trend by age group of children admitted to hospital with pneumonia in Malawi, 2000–2005.**  
doi:10.1371/journal.pone.0102955.g003

**Trend , by severity category, of children admitted to hospital with pneumonia in Malawi, 2000-2005.**



**Figure 4. Trend by severity category of children admitted to hospital with pneumonia in Malawi, 2000–2005.**  
doi:10.1371/journal.pone.0102955.g004

**Table 3.** Numbers of children (0–59 months) treated for pneumonia by age, severity and case-fatality rate by year in district hospitals in Malawi, 2000–2005 for the restricted and unrestricted time periods.

Year	RESTRICTED n = 14 162			UNRESTRICTED n = 47 228		
	All	Died	CFR	All	Died	CFR
	Cases	No	%	Cases	No.	%
2000	389	73	18.8	389	73	18.8
2001	3558	473	13.3	3558	473	13.3
2002	3249	368	11.3	7364	771	10.5
2003	5216	560	10.7	12849	1225	9.5
2004	1750	126	7.2	9986	938	9.4
2005	-	-	-	13082	1125	8.6
<b>Total</b>	<b>14162</b>	<b>1600</b>	<b>11.3</b>	<b>47228</b>	<b>4605</b>	<b>9.8</b>
Age group (months)*	RESTRICTED n = 14 162			UNRESTRICTED n = 47 228		
	All	Died	CFR	All	Died	CFR
	Cases	No.	%	Cases	No.	%
<2	1386	156	11.3	4773	492	10.3
2–11	7640	1023	13.4	25153	2998	11.9
12–59	5136	421	8.2	17302	1115	6.4
Severity grade (aged 2–59 months)†	RESTRICTED n = 14 162			UNRESTRICTED n = 47 228		
	All	Died	CFR	All	Died	CFR
	Cases	No.	%	Cases	No.	%
severe	8727	509	5.8	30267	1445	4.8
very severe	4049	935	23.1	12188	2668	21.9

\* % of total number in age categories.

† infants &lt;2 months were not categorized or analyzed by separate degree of severity.

doi:10.1371/journal.pone.0102955.t003

In an effort to estimate an overall crude intervention effect, a logistic regression analyses without covariates taking only the basic design into account was estimated in a separate model with CLHP implementation as the only dependent variable. This showed that in the restricted analysis the overall effect of the CLHP did not significantly decrease CFR for children admitted to hospital for pneumonia (OR = 0.82; 95% CI 0.63–1.06;  $p = 0.14$ ). However in contrast to the unrestricted analysis showed there was a significant overall effect of the intervention in decreasing the CFR for all degrees of severity and age groups (OR = 0.79; 95% CI 0.64–0.99;  $p$ -value = 0.040).

## Discussion

The trend in case fatality rates in infants and young children (1 week to 59 months of age) hospitalized and treated for severe and very severe pneumonia was evaluated over the course of the implementation of a nationwide programme to deliver standardized case management for childhood pneumonia. We were able to demonstrate the significant decline in CFR overall was no longer significant when the period of follow-up was standardized in the restricted analysis, there remained a significant decrease in CFR in children, aged 2–59 months, treated for severe pneumonia. Similarly the CFR for neonates admitted for severe/very severe pneumonia remained unchanged. An important strength of this intervention was the nation-wide implementation of the program, the prevention of antibiotics stock outs and the comprehensive and complete set of data collected over the duration of the intervention.

The high overall CFR of around 10% is within the range of that reported from nine district hospitals in Kenya but higher than the overall CFR of 6% in the study [28]. The higher case-fatality rate associated with young age and very severe pneumonia is expected and consistent with other studies [3,29–31]. The lack of intervention effect in infants and children younger than 59 months suffering from very severe pneumonia is disappointing but the CFR is similar to other studies from the African region even when the studies have been conducted in central hospitals that have better resources than district hospitals [29,31].

The introduction of the CLHP included a substantial programme of work which included establishing an information system, quality assurance mechanisms, training, regular supervision and provision of antibiotics and oxygen to address all the various problems identified in Table 1 simultaneously. Interventions that may have contributed to improved outcomes were the continuous provision of antibiotics and oxygen. Due to the planning and supervision of CLHP no shortages of antibiotics at any stage were experienced. Oxygen concentrators were acquired and installed in all district hospitals during the course of the CLHP implementation, as previously described [26]. Few district hospitals had oxygen available at the beginning of the implementation. Oxygen therapy was delivered via nasal prongs and was indicated on the basis of clinical indicators as oximetry was not available. Clinical indicators are known to be inaccurate in detecting all cases of hypoxaemia and so the use of oximetry along with supplemental oxygen could potentially have further improved outcomes [32]. The outcome of the intervention might have been influenced by the attrition of health care workers trained in the

**Table 4.** Deaths before and after 24 hours of commencement of treatment by age and severity of pneumonia for the restricted and unrestricted pre and post intervention time periods.

UNRESTRICTED N = 47 228					
Characteristic	Deaths	Died<24	%	Died>24	%
<b>Age (months)</b>					
<2	492	298	60.6	194	39.4
2–11	2998	1378	46.0	1620	54.0
12–59	1115	559	50.1	556	49.9
Total	4605	2235	48.5	2370	51.5
<b>Severity grade</b>					
(2–59 months)*					
severe	1445	586	40.5	859	59.5
very severe	2668	1351	50.6	1317	49.4
<b>RESTRICTED N = 14 162</b>					
Characteristic	Deaths	Died<24	%	Died>24	%
<b>Age (months)</b>					
<2	156	103	66.0	53	34.0
2–11	1023	489	47.8	534	52.2
12–59	421	227	53.9	194	46.1
Total	1600	819	51.2	781	48.8
<b>Severity grade</b>					
(2–59 months)*					
severe	509	209	41.1	300	58.9
very severe	935	507	54.2	428	45.8

\*Infants <2 months were not categorized or analyzed by separate degree of severity.

doi:10.1371/journal.pone.0102955.t004

SCM of pneumonia. To minimize this effect an additional 30% more health care workers were trained.

It was not possible to determine the factors contributing to a poor outcome. There are a number of reasons that might explain a lack of benefit as seen in this analysis, especially for neonatal and very severe pneumonia in infants. First, neonates with pneumonia and infants with very severe pneumonia who are critically ill on presentation to the health services are high-risk groups for a poor outcome and often die within the first 24 hours after admission. The main impact of improved case management is likely to reduce deaths after 24 hours by clinical improvement in those that are not so critically ill at presentation, such as those with severe pneumonia.

In the HIV endemic setting, antibiotics and oxygen may not be effective against all causes of pneumonia. *Pneumocystis* pneumonia (PcP) which was common at the time of this intervention and usually fatal in Malawian infants presenting with very severe pneumonia would not have responded to first line antibiotics [30,31]. The impact of HIV is highlighted by studies carried out in urban hospitals in South Africa showing that HIV is associated with treatment failure and poor outcomes [29]. While health workers were trained to recognise and treat PcP and other HIV-related lung disease this almost certainly did not occur as almost all participants' HIV status was recorded as unknown. Although improved HIV/AIDS services in the country would be expected to also improve outcome of treatment of children with pneumonia, the improvement in such services has not been demonstrated and therefore could not have been sufficient to explain the effect we demonstrated. Similarly, the inclusion of the 13-valent PCV into

the Malawi EPI schedule since November 2011 is likely to further reduce the incidence and CFR of pneumonia in young children irrespective of HIV status [33,34].

The intervention did show a beneficial effect in infants and children with severe pneumonia but this may have been lessened by co-morbidities or clinical overlap with pathogens that would not be responsive to standard first-line therapy, such as *Mycobacterium tuberculosis*, malaria or non-typhoidal *Salmonella*. Malawi is endemic for tuberculosis (TB), and studies from the Africa region have shown that TB is common and sometimes fatal in infants and young children with acute severe pneumonia [29–31,35]. TB is likely to be under-recognised as a potential cause of acute severe pneumonia as health workers are trained to consider TB as a chronic disease associated with persistent rather than acute symptoms.

Severe malaria is common and seasonal in Malawi and can present with clinical features similar to pneumonia [36], especially severe malarial anaemia where fast breathing and chest in-drawing are common features [37]. Invasive salmonellosis is commonly associated with malarial anaemia, often presents with clinical features of pneumonia and is commonly fatal [38]. First-line antibiotics currently used for severe pneumonia in Malawi are not effective against sepsis due to non-typhoidal *Salmonella* [39]. It is notable that CFR was highest early in the rainy season and this is a peak time of year for severe malarial anaemia and invasive salmonellosis. Malnutrition is another important co-morbidity with a similar seasonal effect that could also increase the risk of poor outcome from pneumonia [40,41]. Childhood malnutrition is

**Table 5.** Odds ratios from logistic regression models for mortality on the covariates including intervention period for the restricted and unrestricted analyses.

Factor	Level	Restricted period				Unrestricted period				P value*
		Odds ratio	95 CI Lower	95 CI Upper	P value*	Odds ratio	95 CI Lower	95 CI Upper	P value*	
Year	2000	1			0.36	1			<0.001	
	2001	0.925	0.64	1.33		0.98	0.74	1.28		
	2002	0.798	0.48	1.32		0.79	0.54	1.15		
	2003	0.704	0.42	1.18		0.72	0.51	1.00		
	2004	0.533	0.24	1.18		0.75	0.52	1.06		
2005	N/A				0.69	0.5	0.95			
Month	January	1			<0.001	1			<0.001	
	February	0.78	0.60	1.02		0.72	0.60	0.88		
	March	0.53	0.35	0.80		0.61	0.49	0.76		
	April	0.75	0.55	1.02		0.77	0.63	0.93		
	May	0.69	0.51	0.94		0.72	0.57	0.92		
	June	0.65	0.50	0.85		0.81	0.68	0.96		
	July	0.72	0.56	0.92		0.77	0.63	0.95		
	August	0.52	0.32	1.14		0.74	0.60	0.91		
	September	0.69	0.51	0.93		0.81	0.68	0.97		
	October	0.85	0.66	1.10		0.95	0.76	1.17		
	November	0.92	0.68	1.26		1.00	0.81	1.22		
	December	0.86	0.64	1.15		0.99	0.83	1.20		
Region	South	1			0.63	1			0.87	
	Central	0.86	0.57	1.31		0.98	0.74	1.30		
	North	1.00	0.72	1.37		0.94	0.73	1.23		
Age	2-59 months	1			<0.001	1			<0.001	
	2-11 months	1.72	1.41	2.09		1.86	1.69	2.05		
Intervention by age and severity	2-59 months									
	Severe	1			0.0305	1			0.0052	
Very severe	pre	1				1				
	post	0.70	0.50	0.98		0.63	0.47	0.84	0.002	
<2 months**	pre	1				1				
	post	0.97	0.72	1.30		0.94	0.73	1.21	0.57	
	pre	1				1				
	post	0.83	0.56	1.22		0.80	0.57	1.14	0.20	

\* p-value for factor.  
 \*\* infants <2 months were not categorized or analyzed by separate degree of severity.  
 doi:10.1371/journal.pone.0102955.t005

very common in Malawi with high rates of stunting and wasting [42,43].

An important limitation is that the analysis is based on routinely collected aggregate data in the district hospitals after training had been undertaken. By using the first three months of data collected after training as the baseline for comparison due to the poor quality of available data prior to the intervention is likely to have underestimated the impact of the intervention. This underestimation is supported by the high CFR (10–26%) observed during the situational analysis prior to the implementation of the CLHP [15]. The trend of improved outcomes following the first three months of intervention is noteworthy as it suggests sustained improvements in care due to this CLHP approach, rather than a temporary improvement only following training as might have been expected.

In 2005, based on the programme's success the MoH included the CLHP (within inpatient services) in the Essential Health Package funded through the Sector Wide Approach. It would have been beneficial and informative to have undertaken a formal costing but this was not possible at the time. The CLHP has been sustained beyond the cycle of external funding due to the programme's success. The CLHP has now been maintained for 8 years since the end of external project funding and is currently being expanded to 16 nongovernment hospitals. All components of the programme were still functioning well.

Improvements in child survival are being noted in many settings but consistently child pneumonia-related mortality and neonatal mortality are two of the major challenges that need to be addressed in order to reach Millennium Development Goal targets and beyond [1]. This comprehensive prospective study of the

intervention to improve case-management in district hospitals in Malawi has highlighted the on-going challenges in these high mortality groups.

## Supporting Information

**Text S1 Supplementary material for recording and reporting.**  
(DOCX)

## Acknowledgments

We wish to thank the Malawi MoH for its request to The Union to assist with the implementation of the CLH Programme and its continued support throughout the scale-up process and beyond the funding cycle. Partial funding was provided by the Bill and Melinda Gates Foundation. We wish to express our appreciation to all members of the training teams for donating their time so readily. We particularly wish to thank the Community Health Science Unit ARI/CLHP Management Team who were involved in running, monitoring and evaluating the ongoing programme; the District Health Officers for their continued support and the CLHP Coordinators whose work made it all possible.

## Author Contributions

Conceived and designed the experiments: PME RPG DAE. Performed the experiments: PME RPG CCM ERM SMG DAE. Analyzed the data: PME CJL RPG DAE. Contributed reagents/materials/analysis tools: PME RPG ERM CJL DAE. Wrote the paper: PME RPG CCM ERM SMG DAE CJL.

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**Text S1 Supplementary materials for recording and reporting**

District Hospital

**PNEUMONIA INPATIENT RECORDING FORM**

District Registration No: \_\_\_\_\_

Name: \_\_\_\_\_  
 Address: \_\_\_\_\_

Chest Xray Yes  No   
 If yes date taken and results: \_\_\_\_\_

Age (months): \_\_\_\_\_ Sex (M/F): \_\_\_\_\_  
 Number of days of signs/symptoms: More than 21 days  Less than 21 days   
 Antibiotic treatment prior to coming to hospital: Yes  No  Self referral  Referred by Health Centre   
 Date of hospital admission: \_\_\_\_\_

Previous pneumonia in the last 12 months Yes  No   
 Previous hospital admissions for pneumonia in last 12 months Yes  No

Weight Kg \_\_\_\_\_ Temperature \_\_\_\_\_ °C Respiratory rate x 1 minute \_\_\_\_\_

Clinical features	Classification	Treatment						
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
<b>CHILD 2 MONTHS TO 5 YEARS</b> Chest in-drawing Yes <input type="checkbox"/> No <input type="checkbox"/> Severe respiratory distress Yes <input type="checkbox"/> No <input type="checkbox"/> Central cyanosis Yes <input type="checkbox"/> No <input type="checkbox"/> Sleepy/difficult to wake Yes <input type="checkbox"/> No <input type="checkbox"/> Convulsions Yes <input type="checkbox"/> No <input type="checkbox"/> Not able to breastfeed Yes <input type="checkbox"/> No <input type="checkbox"/> Not able to drink Yes <input type="checkbox"/> No <input type="checkbox"/> Stridor in calm child Yes <input type="checkbox"/> No <input type="checkbox"/> Wheeze Yes <input type="checkbox"/> No <input type="checkbox"/>	Very severe pneumonia <input type="checkbox"/> Severe pneumonia <input type="checkbox"/> Pneumonia <input type="checkbox"/> PCP <input type="checkbox"/> Other (specify) <input type="checkbox"/>	Antibiotic Benzylpenicillin Amoxycillin Chloramphenicol Cotrimoxazole Other antibiotic (specify) Other treatment						
<b>YOUNG INFANT &lt;2 MONTHS</b> Chest in-drawing Yes <input type="checkbox"/> No <input type="checkbox"/> Sleepy/difficult to wake Yes <input type="checkbox"/> No <input type="checkbox"/> Not feeding well Yes <input type="checkbox"/> No <input type="checkbox"/> Wheeze Yes <input type="checkbox"/> No <input type="checkbox"/> Grunting intermittent Yes <input type="checkbox"/> No <input type="checkbox"/> Grunting continuous Yes <input type="checkbox"/> No <input type="checkbox"/> Stridor (calm child) Yes <input type="checkbox"/> No <input type="checkbox"/> Apnoeic spells Yes <input type="checkbox"/> No <input type="checkbox"/> Convulsions Yes <input type="checkbox"/> No <input type="checkbox"/>	Very severe pneumonia/disease <input type="checkbox"/> Severe pneumonia <input type="checkbox"/> PCP <input type="checkbox"/> Other (specify) <input type="checkbox"/>	Antibiotics Gentamicin Benzylpenicillin Amoxycillin Other antibiotic (specify) Other treatment						
HIV status Positive <input type="checkbox"/> Negative <input type="checkbox"/> Blood film (malaria) Positive <input type="checkbox"/> Negative <input type="checkbox"/>	Measles at this visit or in past 2 months Yes <input type="checkbox"/> No <input type="checkbox"/> Severe malnutrition * (see below) Yes <input type="checkbox"/> No <input type="checkbox"/>							

• Severe malnutrition is visible severe wasting or oedema in both feet **please turn over**

### Hospitalisation

Duration of hospitalisation in either \_\_\_\_\_ Hours \_\_\_\_\_ Days  
 Admission diagnosis \_\_\_\_\_ Discharge diagnosis \_\_\_\_\_

#### Discharge and Follow-up

Course of antibiotics to be completed at home	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Child returned for follow-up visit	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Mother informed to return with child once antibiotics completed	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Course of antibiotic completed**	Yes <input type="checkbox"/>	No <input type="checkbox"/>
	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Child fully recovered**	Yes <input type="checkbox"/>	No <input type="checkbox"/>

#### Treatment Results

Treatment completed(1)	<input type="checkbox"/>	Failure at 48 hrs (2)	<input type="checkbox"/>	Failure at Day 5	<input type="checkbox"/>
Left against advise(3)	<input type="checkbox"/>	Transferred (4)	<input type="checkbox"/>	Outcome unknown (5)	<input type="checkbox"/>
Died within 24 hours of admission	<input type="checkbox"/>	Died after 24 hours of admission	<input type="checkbox"/>	<b>(See below for definitions)</b>	

**Additional Remarks:**

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#### Rationale for Information/Recording System

When the decision is reached that the child has pneumonia and requires hospitalisation then the “*Pneumonia Inpatient Recording Form*” must be completed in addition to other forms that may be used, such as critical care pathways. The use of this form is a prerequisite of the Project providing the drugs for treatment of such cases. The form is initiated when the patient is started on treatment and is completed on discharge. The form is provided to assist the health worker in providing good quality care for the patient. All information is transferred to the *Pneumonia Inpatient Register*.

- \* If NO then tick Outcome Unknown (5) in Treatment Results section
- \*\* If YES then child can be registered as Treatment Completed(1) in Treatment Results section
- 1. Course of antibiotics completed and child fully recovered
- 2. Treatment failure means: Worsening of fast breathing, or Worsening of chest in-drawing, or Development/persistence of abnormal sleepiness or difficulty in awakening, or development/persistence of inability to drink or poor breastfeeding.
- 3. Child removed from the hospital against medical advise before treatment is completed
- 4. Child is referred for treatment to another health facility and the result of treatment is unknown; where the result is known, that result should be recorded in place of the result "transferred
- 5. When mother does not return with child for follow-up visit once course of antibiotic(s) is finished



Associated Conditions	Diagnosis Confirmed by Xray Y/N	HIV Status			Admitted		Antibiotics for Pneumonia				Addition treatment	Treatment Results									
		P	N	U	Y	N	Benzylpenicillin	Chloramphenicol	Gentamicin	Anoxy-cillin		Other(s) (Specify)	Treatment Completed (2)	Failure 48 hrs (3)	Failure 5 days (3)	Left against advice (4)	Transferred (5)	Died before 24 hrs	Died after 24 hrs		
Respiratory																					

- 1 If "No" due to admission refused indicate with "R"
- 2 Course of antibiotics completed and child fully recovered
- 3 Treatment failure means: Worsening of chest in-drawing, or Development/persistence of abnormal sleepiness or difficulty in awakening, or Development/persistence of inability to drink or poor breastfeeding.
- 4 Child removed from the hospital against medical advice before treatment is completed
- 5 Child is referred for treatment to another health facility and the result of treatment is unknown; where the result is known, that result should be recorded in place of the result "transferred"

CHILD LUNG HEALTH PROJECT

**MONTHLY REPORT OF PNEUMONIA TREATMENT RESULTS**

(REGISTERED IN THE HOSPITAL IN THE PREVIOUS MONTH)

Name of District _____	Hospital Coordinator _____
Name of Hospital _____	Signature _____
Patients registered in _____ Month/year _____	Date _____

Type of case	Antibiotic given	Total no: of pneumonia patients registered in above month	Completed Treatment	Left against advise	Transferred	Outcome unknown	Treatment Failures			Died		
							48 hrs	5 days	Before 24 hrs	After 24 hrs		
<b>Young infants:</b> (1 through 8 weeks) Severe pneumonia And Very severe Pneumonia/disease	Benzylpenicillin/Gentamicin/ Amoxicillin											
	Other(s) (specify):											
<b>Children:</b> (2 through 59 months) Pneumonia	Cotrimoxazole	2 to 11	2 to 11	2 to 11	2 to 11	2 to 11	2 to 11	2 to 11	2 to 11	2 to 11	2 to 11	2 to 11
	Other(s) (specify):											
Severe pneumonia	Benzylpenicillin/ Amoxicillin											
	Other(s) (specify):											
Very severe pneumonia	Chloramphenicol											
	Other(s) (specify):											

please turn over for definitions to use when completing the form

CHILD LUNG HEALTH PROJECT

**MONTHLY REPORT OF PNEUMONIA TREATMENT RESULTS**

(REGISTERED IN THE HOSPITAL IN THE PREVIOUS MONTH)

Name of District _____ Name of Hospital _____ Patients registered in _____ Month/year _____	Hospital Coordinator _____ Signature _____ Date _____
---------------------------------------------------------------------------------------------------	-------------------------------------------------------------

Type of case	Antibiotic given	Total no. of pneumonia patients registered in above month	Completed Treatment		Left against advise	Transferred	Outcome unknown	Treatment Failures			Died	
			2 to 11	12 to 59				48 hrs	5 days	Before 24 hrs	After 24 hrs	
<b>Young infants:</b> (1 through 8 weeks) Severe pneumonia  And Very severe Pneumonia/disease	Benzylpenicillin/Gentamicin/ Amoxicillin											
	Other(s) (specify):											
<b>Children:</b> (2 through 59 months)  Pneumonia  Severe pneumonia	Cotrimoxazole											
	Other(s) (specify):											
	Benzylpenicillin/ Amoxicillin											
Very severe pneumonia	Other(s) (specify):											
	Chloramphenicol											
	Other(s) (specify):											

please turn over for definitions to use when completing the form

## Definitions to use when completing the form:

### Severity of pneumonia

YOUNG INFANT (1 to 8 weeks):

Severe pneumonia and very severe pneumonia/disease

a patient with cough or difficult breathing who presents with fast breathing and/or chest indrawing and with any one or more of the following:  
not feeding well, convulsions, abnormally sleepy or difficult to wake, stridor in a calm child, wheezing, raised temperature ( $>38^{\circ}$ ) or low temperature ( $<35.5^{\circ}$ ), central cyanosis, grunting or apnoeic episodes.

CHILD (2-59 months old):

Pneumonia  
Severe pneumonia  
Very severe pneumonia

a patient presenting with cough or difficult breathing with fast breathing  
a patient presenting with cough or difficult breathing with fast breathing and/or chest indrawing  
a patient with severe pneumonia who has central cyanosis and/or is unable to drink

### Treatment results

Treatment completed

Course of antibiotics completed i.e. all prescribed injections/tablets/capsules have been given and the young infant/child is fully recovered i.e. respiratory rate, temperature and drinking/eating/feeding pattern, for the particular child, have returned to normal.

Treatment failure

Failure of initial antibiotic treatment/antibiotic was changed because of: Worsening of fast breathing, or Worsening of chest indrawing, or Development/persistence of abnormal sleepiness or difficulty in awakening, or development/persistence of inability to drink or poor breastfeeding. It should be recorded if this was at 48 hours or 5 days.

Left against advise

Child removed from the hospital against medical advice before treatment is completed

Transferred

Child is referred for treatment to another health facility and the result of treatment is unknown; where the result is known, that result should be recorded in place of the result "transferred".

Outcome unknown

When mother does not return with child for follow-up visit once course of antibiotic(s) is finished

Died

When a child dies during treatment it should be recorded whether the child died during or after the first 24 hours following admission

## Chapter 7

### **Potentially modifiable factors associated with death of infants and children with severe pneumonia routinely managed in district hospitals in Malawi.**

The previous study based on the aggregate data did show a significant reduction of CFR in children two to fifty-nine months of age with severe pneumonia but not for the same age group with very severe pneumonia or for infants less than two months of age. To investigate the reasons for this poor outcome we undertook further research of a subset of this cohort to determine the individual factors including demographics of the study population, recognised co-morbidities and clinical management that were associated with inpatient death.

**Penelope M Enarson, Robert P Gie, Charles C Mwansambo, Alfred Chalira, Norman Lufesi, Ellubey R Maganga, Donald A Enarson, Neil A Cameron, Stephen M Graham. Potentially modifiable factors associated with death of infants and children with severe pneumonia routinely managed in district hospitals in Malawi.**

**Submitted for publication 26/09/2014.**

The subset included all children aged 0-59 months admitted with severe and very severe pneumonia to the paediatric wards in the first sixteen district hospitals throughout Malawi between 1<sup>st</sup> October 2000 and 30<sup>th</sup> June 2003. We compared individual factors between those that survived (n = 14 076) and those that died (n = 1 633) with an overall CFR of 10.4%. Very severe pneumonia was associated with a significantly higher CFR than those classified as severe pneumonia. The lack of intervention effect in infants and children younger than 59 months suffering from very severe pneumonia is similar to other studies from the African region even when the studies have been conducted in central hospitals that have better resources than district hospitals.

We were surprised to discover the extent of misclassification in this group of patients as we had previously concluded that standard case management was an important approach to reduce case fatality in this setting. We were unable to judge the extent of misclassification in our previous study (Chapter 6) because we reported only aggregate data from routine reports. It was only when we analysed individual data in this part of the study that we were able to determine the extent of the misclassification, hence justifying the importance of analysing individual data in addition to reporting the results from analysis of aggregate data.



**Potentially modifiable factors associated with death of infants and children with severe pneumonia routinely managed in district hospitals in Malawi.**

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Running title: Factors associated with outcome in children with severe pneumonia

Keywords: pneumonia, child, case management, mortality, modifiable factors

## Abstract

**Objective:** To investigate recognised co-morbidities and clinical management associated with inpatient pneumonia mortality.

**Methods:** Prospective cohort study, of patient records, carried out in Malawi between 1<sup>st</sup> October 2000 and 30<sup>th</sup> June 2003. The study included all children aged 0-59 months admitted to the paediatric wards in sixteen district hospitals throughout Malawi with severe and very severe pneumonia. We compared individual factors between those that survived (n = 14 076) and those that died (n = 1 633)

**Results:** From logistic regression analysis, predictors of death in hospital, adjusted for age, sex and severity grade included incorrect antibiotic administered (OR = 2.27, 95% CI 1.91-2.70), comorbid conditions of meningitis (OR = 2.96, 95% CI 1.89-4.64), malnutrition (OR = 2.83, 95% CI 2.36-3.40) and severe anaemia (OR = 1.61, 95% CI 1.29-2.01). Receiving oxygen (OR = 2.12, 95% CI 1.86-2.41) and intravenous therapy (OR = 3.71, 95% CI 2.69-5.11) were associated with death while blood transfusion was no longer significant (OR = 1.05, 95% CI 0.75-1.46) when the model included severe anaemia.

**Conclusions:** This study identified a number of challenges to improve outcome for Malawian infants and children hospitalised with pneumonia. These included improved assessment of co-morbidities and more rigorous application of standard case management.

## Introduction

Pneumonia is consistently estimated to be the single major cause of death in infants and young children (1-59 months of age) and almost all these deaths occur in low-income countries. [1-3] It is estimated that approximately 50% of all deaths due to pneumonia in children occur in sub-Saharan Africa. [4] However, there are a number of acknowledged limitations to attributing a death to a single disease entity. [5-7] First, in infants and young children with severe pneumonia, co-morbidities such as malnutrition or HIV infection are common and increase the risk of death. [8,9] Second, there is clinical overlap with diseases such as severe anaemia, malaria or septicaemia that may result in death being wrongly attributed to pneumonia. [10,11] Finally, it is also recognised that bacterial pneumonia can occur as a co-infection or secondary complication in children with other infections such as measles, severe malaria or tuberculosis. [12-14] Nonetheless, health workers in high mortality settings are required to manage sick children according to standard case-management protocols on the basis of clinical findings with very limited diagnostic support.

We recently reported outcomes from a prospective implementation programme that included 47,228 Malawian children admitted to district hospitals in Malawi for severe and very severe pneumonia over a five year period. [15,16] We have further analysed data from a subset of this cohort to determine the individual factors including demographics of the study population, recognised co-morbidities and clinical management that were associated with inpatient death.

## Methods

### *Study participants*

We reviewed the sequential records of all infants and young children (< 5 years) that were admitted to one of 16 district hospitals in Malawi between 1<sup>st</sup> October 2000 and 30<sup>th</sup> June 2003 as part of the Malawi Child Lung Health Programme (CLHP). The Malawi CLHP included a prospective evaluation of the implementation of standard case-management for 47,228 children admitted with severe or very severe pneumonia to one of the 24 district hospitals in Malawi over a 5-year period (2000-2005).

The implementation, methodology, evaluation and main outcomes of the Malawi CLHP have been described in detail in previous publications. [15,16] Briefly, all neonates, infants and young children between 0 and 59 months of age hospitalised with a clinical diagnosis of severe or very severe pneumonia, according to WHO definitions at the time, were included. The implementation followed training of staff to follow the recommended WHO pneumonia standard case management approach (Box 1) and it was ensured that supplies of treatment for child pneumonia (i.e. recommended antibiotics and oxygen therapy) were available.

### *Study procedures*

All children included in the Malawi CLHP were allocated a “Pneumonia Inpatient Recording Form” which prospectively collected relevant data including demographic data, clinical data including weight, classification of severity of pneumonia, detailed data of management, and outcome data. In addition to training on the WHO standardised case-management approach to child pneumonia, staff were also trained on the diagnosis and management (according to national guidelines) of other related causes of common childhood illness such as malaria, anaemia or malnutrition.

The diagnosis and investigation of co-morbidities depended on clinical suspicion and usually clinical diagnosis. In addition, a thick blood film was examined for *Plasmodium falciparum* malaria diagnosis, or a haematocrit or haemoglobin were determined for diagnosis of anaemia. Chest radiography was not carried out on admission routinely but was only used in those cases not responding to first-line antibiotics. No diagnostic tools were available or used to determine aetiological pathogen(s) causing pneumonia such as bacteria, viruses or fungi such as *Pneumocystis jirovecii*. Testing for HIV infection was rarely undertaken at the time of this study.

Weight was plotted for age on the Road to health card, and severe malnutrition was diagnosed if there was severe wasting or nutritional oedema. Severe malaria was diagnosed clinically in children with altered consciousness and/or convulsions

### *Data management*

Data from the Inpatient Recording Forms were double entered into an ACCESS® database, and then transferred to EXCEL® for cleaning. The following variables were selected for analysis: age, sex, classification of severity of pneumonia, any recorded comorbid conditions (included malaria, malnutrition, severe anaemia, meningitis and sepsis), origin of referral (self or transfer from a primary health care centre), antibiotic use prior to admission, and treatment given. See Table 1 for frequency of variables. Pneumonia classification and antibiotic therapy were determined as correct or incorrect according to standardised case-management using clinical data available by the study investigators at the time of review.

### *Statistical Analysis*

Data were analysed using SPSS, version 7.5 for Windows and web-based OpenEpi (version 2.3). Because of the large sample size an effect size was arbitrary set at  $<0.67$  and  $>1.5$  to determine the importance of the odds ratio (OR). A univariate analysis was run to find the distribution and mortality rates for the different variables using chi-square test. A probability level of  $<0.05$  was considered significant and was used for inference.

Both univariate and logistical regression analysis were performed to determine the association between variables by estimating the odds ratio (OR) and 95% Confidence Intervals (CI) were calculated. Logistical regression was run to measure the independent effects of the significant variables on outcome - the proportion of the children who died while in hospital or case-fatality rate (CFR) was the primary outcome indicator measured. The Odds Ratio (OR) and 95% Confidence Intervals (CI) were calculated to estimate the risk adjusting for potential confounders.

### *Ethical considerations*

The CLHP was routine patient management and data from it was routinely collected. Patient identifiers such as names, geographic location by sub-district, patient registration number and specific date (except month and year) of admission were not included in database. Permission to use the data was received from the Ministry of Health, Republic of Malawi. Approval to analyze the data was obtained from the Union's Ethical Advisory Group (EAG: 05/10) and the Human Research Ethics Committee (N10/09/285), Faculty of Medicine and Health Sciences, Stellenbosch University.

### **Results**

A total of 17,585 of infants and young children were admitted with pneumonia in the 16 district hospitals and 17,480 (99.4%) records were available for analysis. From these, 1771 were excluded for reasons shown in the study flow chart in Figure 1; 15,709 children were included in the final analysis. The age distribution of this group is shown in Figure 2. There were 1633 deaths in this cohort with an overall CFR of 10.4%. Very severe pneumonia was associated with a significantly higher CFR than those classified as severe pneumonia (Figure 3).

Table 1 lists management characteristics of the study group and compares CFR according to these variables by calculating odds ratios. The majority (76.8%) of admissions were self-referred and children who were self-referred were less likely to receive an antibiotic prior to admission as compared to those referred from a primary health care centre (17.0% compared to 55.0%:  $p < 0.001$ ). Self-referral was associated with a significantly lower CFR than referral from a primary health centre but prior use of antibiotic was not.

A total of 5183 (33.0%) were misclassified according to severity grade. Incorrect classification on admission varied across age groups and severity grades. For very severe pneumonia, the numbers and proportions misclassified were: 118 (12.6%) for < 2 months, 1509 (61.6%) for 2-11 months, and 135 (8.3%) for 12-59 months, and for severe pneumonia, 500 (69.0%), 2268 (39.8%) and 653 (15.3%) respectively.

Table 2 shows that 5493 (35.1%) children received an incorrect antibiotic with the majority occurring in those incorrectly classified (4559, 88.6%) whereas if children were correctly classified the number receiving the wrong antibiotic was less (934, 8.9%). Giving an incorrect antibiotic when the correct classification was made was most frequent in those with very severe pneumonia who were 2 to 11 months of age (102, 10.9%) and those 12 to 59 months of age (269, 18.1%). Figure 4 illustrates that for all categories of age group and severity grade, those who were given an incorrect antibiotic were more likely to die.

Table 3 shows logistic regression analysis of predictors of death in hospital, adjusted for age, sex and severity grade. Type of referral, and receiving an antibiotic prior to admission were not associated with death. Incorrect classification of severity grade was significantly associated with death (OR = 1.22, 95% CI 1.09-1.37). The addition of receiving an incorrect antibiotic into the model demonstrated a significant association with death (OR = 2.27, 95% CI 1.91-2.70). In this model, the previously demonstrated increased risk of death with incorrect classification of severity grade was no longer demonstrated.

Comorbid conditions were present on admission in 6 541 (61.2%) of severe pneumonia cases and in 2 806 (56.5%) of very severe pneumonia cases. Malaria was the most frequent comorbid condition being diagnosed in 8 013 (51.0%) of cases. Table 1 shows the results of analysis of CFR associated with comorbid conditions. A diagnosis of meningitis, malnutrition or severe anaemia was associated with death, and these all remained significant associations following logistic regression analysis adjusted for age, sex, severity grade and additional treatment (Table 3). CFR for those with a clinical diagnosis of sepsis was higher than for those without but this was not a statistically significant difference. The CFR for those with malaria was similar to that in those without malaria.

Table 1 shows additional treatment modalities. The most frequent were receiving antimalarials 6 288 (40.0%) or oxygen therapy 1 954 (12.4%). Those who were treated with antimalarials had a lower CFR than those that did not, while those receiving other additional treatments, including intravenous fluids, oxygen therapy and blood transfusion had a significantly higher CFR. On logistic regression analysis, oxygen or intravenous therapy remained significantly associated with a higher CFR while anti-malarial therapy was associated with a significantly lower CFR.

There were 621 children diagnosed with severe anaemia of whom 399 (64.3%) received a blood transfusion and experienced a 13.0% CFR. Those 222 (35.7%) not receiving a blood transfusion had a much higher CFR 27.5% (OR 2.52, 95% CI 1.67-3.83). Receiving a blood transfusion was

no longer a significant predictor of death when the model included severe anaemia (Table 4). Malaria comorbidity became statistically significant (OR = 1.18, 95% CI 1.03-1.36) when anti-malarials were included in the model (Table 5).

## Discussion

We found a high mortality in a large cohort of 15,709 Malawian infants and children with severe pneumonia managed in 16 district hospitals. The CFR is similar to that previously reported for an even larger cohort of which this group reported here represent a sub-set. [16] The majority of cases presented to the hospital directly. Initial classification of severity and therefore use of first-line antibiotic therapy were incorrect in one-third of cases overall and higher than this in those with very severe pneumonia. The commonest co-morbidity was malaria which was diagnosed in half of the cases. Features associated with an increased pneumonia-related mortality were the severity of pneumonia, the presence of co-morbidities such as malnutrition, severe anaemia or meningitis, and the incorrect classification and therefore treatment of child pneumonia cases. While none of these associations is unexpected, the unique characteristic of the study is that these features have been analysed following prospective and complete clinical data collection from children managed under routine conditions at a district hospital level in a high mortality setting.

While data from a routine setting is a strength of the study, there are a number of important limitations that must be acknowledged. A major limitation of our study was that HIV prevalence data were not available for this cohort. While health workers were trained to recognise and treat *Pneumocystis jirovecii* pneumonia (PcP) and other HIV-related lung disease, this almost certainly did not occur as almost all participants' HIV status was recorded as unknown. The lack of testing reflected both a lack of policy of routine testing in children with severe pneumonia, and a lack of willingness by health workers to undertake testing due to stigma compounded by a lack of access to anti-retroviral therapy at the time of the study. However, the potential importance of HIV as a common co-morbidity in Malawian infants and children with severe pneumonia that had an impact on aetiology and outcome is recognised from studies reported from urban-based tertiary hospitals in Malawi and the region. [9] PcP is a common and often fatal cause of severe or very severe pneumonia in HIV-infected Malawian infants, especially between 2 and 6 months of age, and is likely to have contributed to the age-related mortality that was noted (Figure 3). [17,18]

The other major limitation is that the diagnosis of other co-morbidities in this study was usually clinical without laboratory confirmation such as for malaria, sepsis or severe anaemia. Therefore, it cannot be determined whether these conditions were under-diagnosed or over-diagnosed, especially as there is clinical overlap with severe pneumonia. [19] Further, while recognised as co-morbidities that can influence outcome, the evidence of association for this study is weakened by

the lack of laboratory confirmation. Similarly, malnutrition is a major recognised co-morbidity that increases pneumonia incidence and mortality, [5,7,8] but objective measure of nutritional status such as weight-for-age has not been determined for this cohort.

It is interesting to note that those that received antibiotics prior to admission had worse outcomes. However, while this may appear to be a surprising finding, there is evidence to suggest that this may have reflected severity of disease and health-seeking behaviour rather than the use of antibiotic before referral *per se*. Those that attended and received an antibiotic at a primary care facility prior to admission to the district hospital had more severe disease, and severity of disease is strongly associated with outcome. We were also not able to determine other related issues of access to care or distance from facilities, or other socio-economic or behavioural factors that also determine use of care facilities and duration of symptoms before presentation.

Previous studies have noted major deficiencies with quality of care at the district hospital setting in many resource-limited settings. [20-22] Quality of care along with ready availability of effective therapy such as antibiotics and oxygen have an impact on outcome. [23] Efforts were made to minimise the impact of these important potential confounders on outcomes in this study population. This study was undertaken following training of health workers on standardised case management as well as ensuring provision of an uninterrupted supply of antibiotics and oxygen therapy. However, despite a one-week training course, large numbers of children were still incorrectly classified. One issue that could not be addressed was the low staff numbers and the high turnover in all settings. [14]

It was noted that the provision of oxygen therapy, intravenous fluids or blood transfusion were all independently associated with a significantly higher CFR. The use of these therapies are all likely indicators of the severity of pneumonia and the presence of co-morbidities. Severity of hypoxaemia in children with pneumonia is associated with an increased risk of death. [24] There is clear evidence that oxygen therapy improves outcome in children with severe pneumonia, and that the routine use of oximetry improves effectiveness of oxygen therapy as it is more sensitive and specific for identifying hypoxaemic children than clinical indicators. [25] It is likely that in our study, the most hypoxaemic children were selected for oxygen therapy as pulse oximetry was not routinely available in this study and clinical indicators were relied upon. This is supported by the observation that mortality was higher in those that received oxygen, which reflects severity rather than impact of oxygen. The poor outcome in those receiving oxygen also suggests that PcP was not uncommon in this cohort. [23]



This study has identified several co-morbidities such as malnutrition and severe anaemia for which prevention is called for to improve the health of these vulnerable children. It also identified a number of potentially modifiable aspects of care where adjustments to the implementation of SCM are indicated. These include enhancing correct classification of the severity of the disease, the use of correct antibiotics according to standard case management, more extensive availability and use of oxygen together with oximetry to guide its use, universal testing for HIV and more routine use of simple laboratory tests to detect malaria and anaemia. To improve the outcome of these children with pneumonia, structural improvements are needed to address these needs. In addition, more comprehensive training to deal with co-morbid conditions might improve the quality of care. Further research is needed to investigate the process of transfer to hospital through the primary services and to demonstrate how laboratory services could be more efficiently used.

In conclusion, pneumonia-related mortality is common in Malawian infants and children cared for in the routine care hospital setting. Reducing mortality might be achieved through improved assessment, more rigorous application of standard case management and more accurate identification and effective management of co-morbidities.

### **Acknowledgments**

We wish to thank the Malawi MoH for its continued support throughout the scale-up process and beyond the funding cycle of the CLHP. Partial funding was provided by the Bill and Melinda Gates Foundation. We particularly wish to thank the District Health Officers for their continued support and the CLHP Coordinators and nursing staff whose work made it all possible.

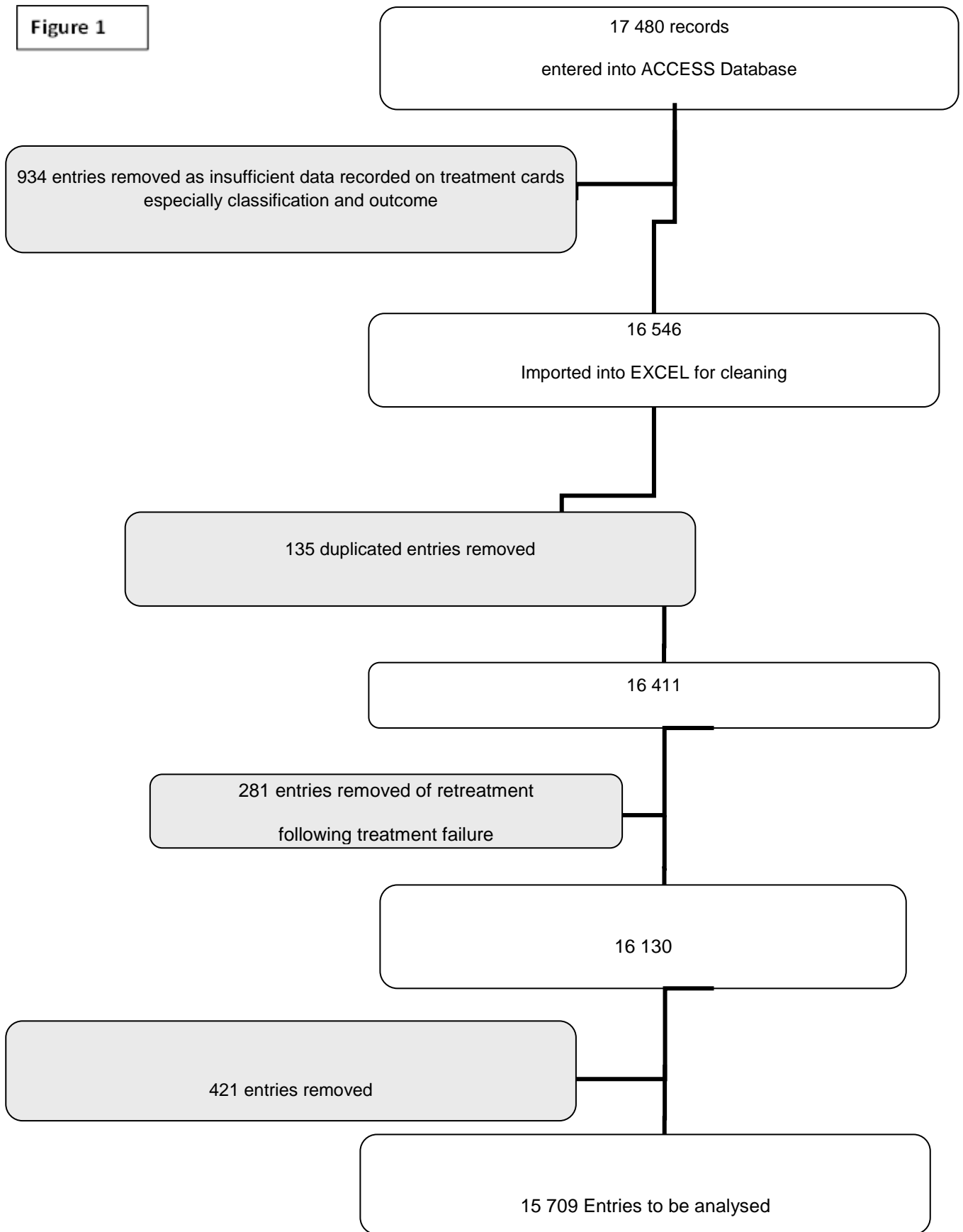
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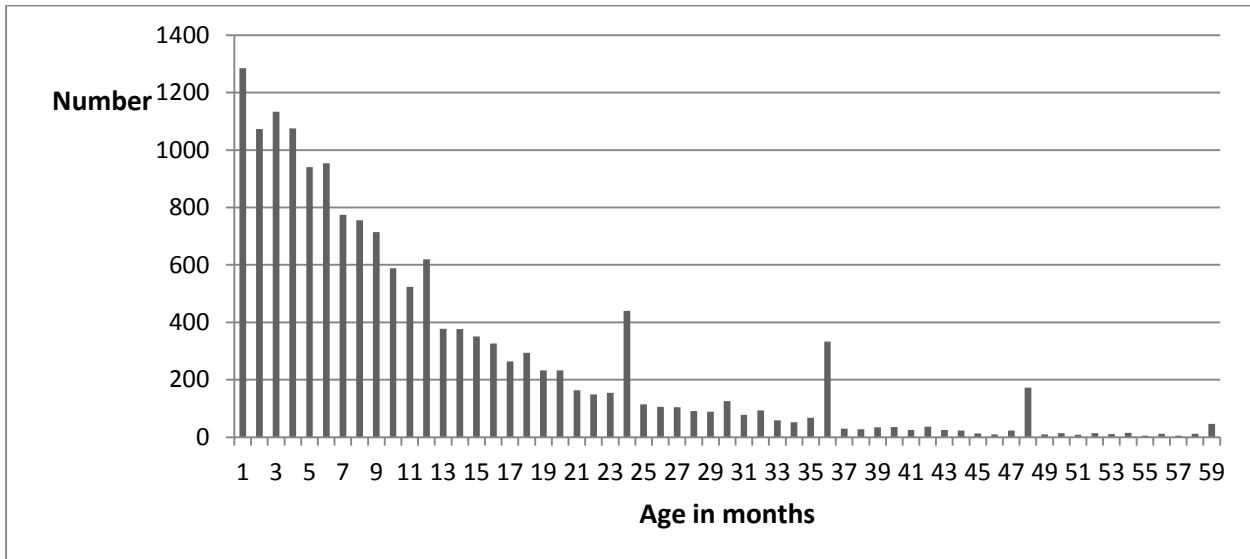
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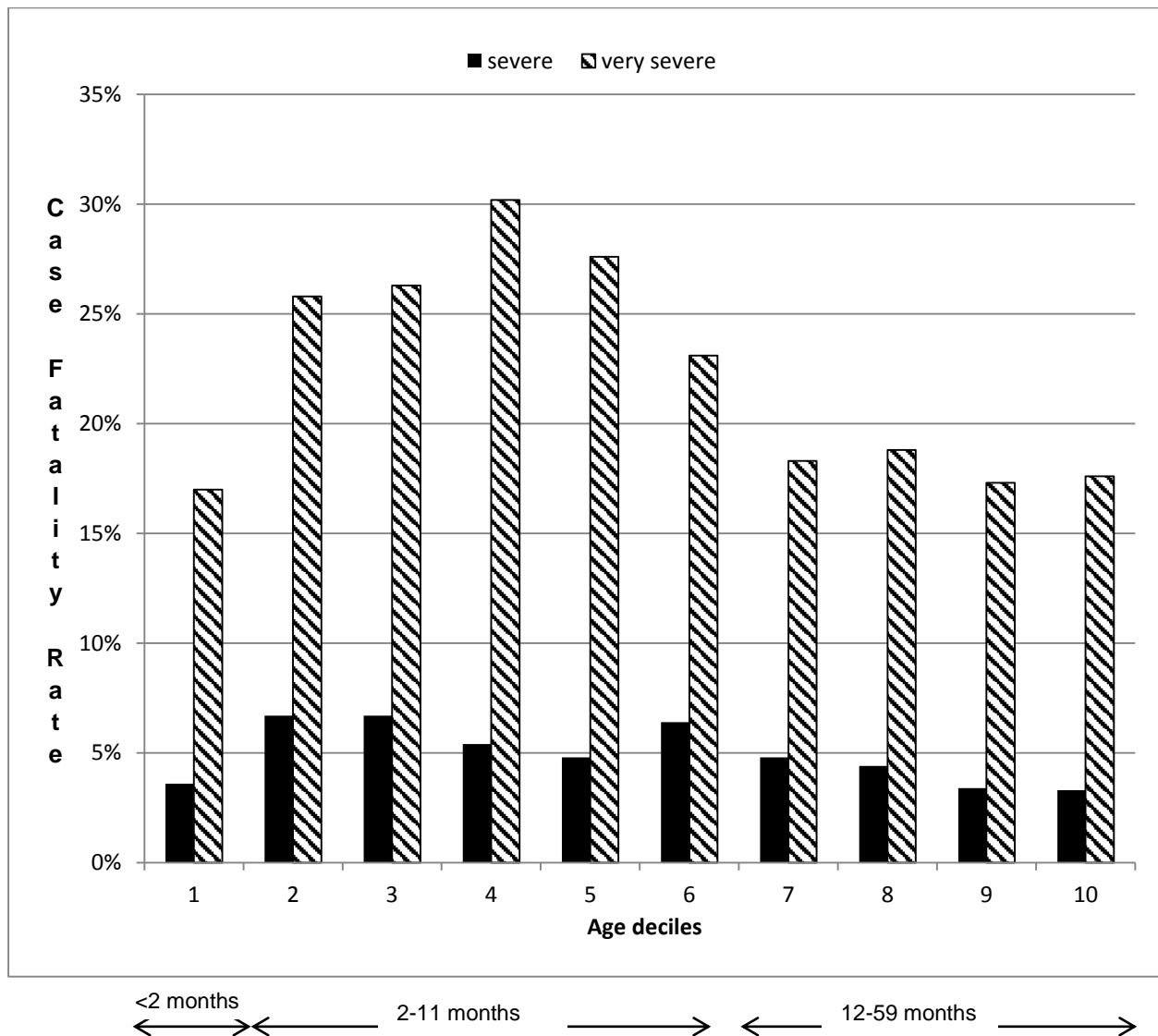
**Figure 1**



**Figure 2.** Age distribution of consecutive children (0-59 months) treated for pneumonia in district hospitals in Malawi, 2000-2003

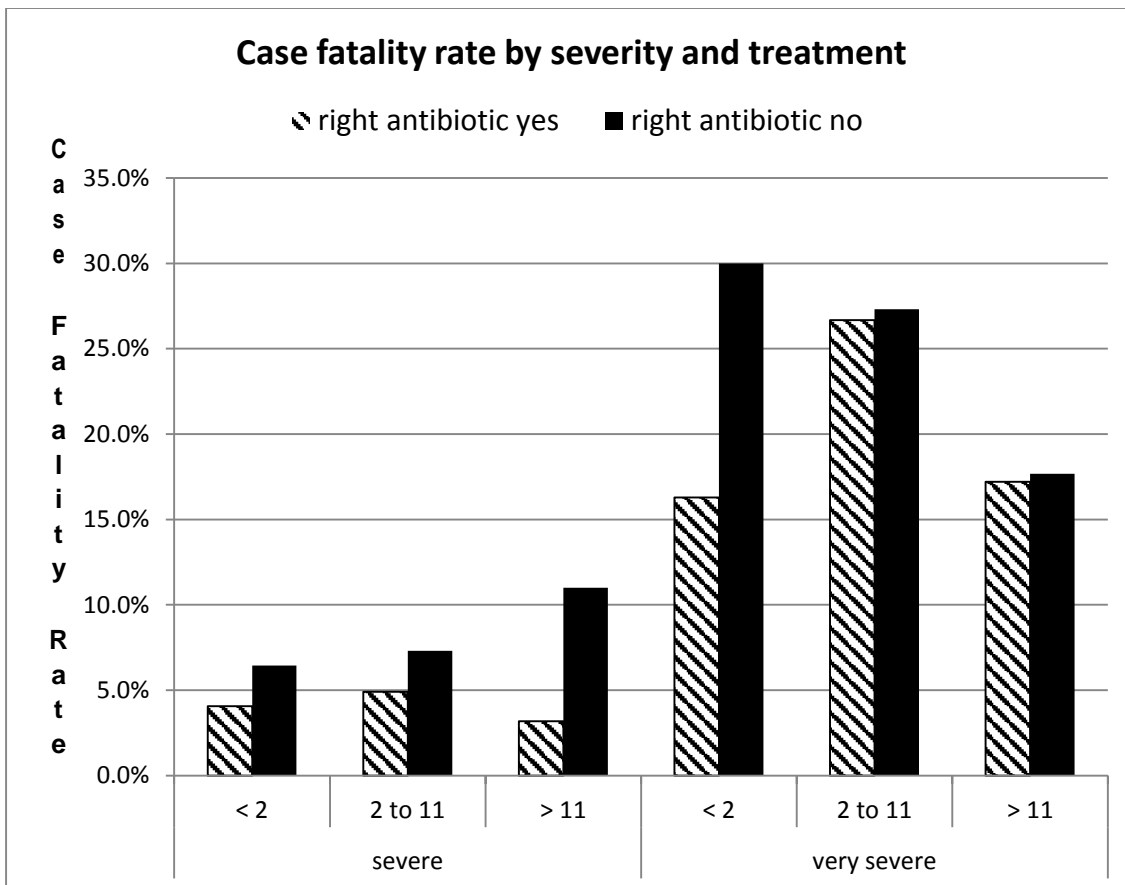


**Figure 3.** Case fatality rate of consecutive children (0-59 months) treated for pneumonia in district hospitals in Malawi, 2000-2003 by severity grade.



For ease of comparison the children were sorted by age and then divided into ten equal groups (deciles). Consequently each of the ten deciles contains an equal number of children.

**Figure 4.** Case fatality rate of consecutive children (0-59 months) treated for pneumonia in district hospitals in Malawi, 2000-2003 by age, severity grade and antibiotic regimen.



**Table 1.** Distribution and CFR of consecutive children (0-59 months) treated for pneumonia in district hospitals in Malawi, 2000-2003 from univariate analysis.

Variable	Category	Number of cases	% of total	CFR%	Crude Odds ratio	95% confidence interval	
						lower	upper
	All children	15,709		10.4			
<b>Management</b>							
<b>Type of referral</b>	Self	12062	76.8	9.5			
	HC	2441	15.5	13.8	0.65	0.57	0.74*
	Unknown	1206	7.7				
<b>Antibiotic prior to admission</b>	No	12288	87.2	10.1	0.88	0.78	0.99
	Yes	3421	21.8	11.4			
<b>Correct Classification as per SCM</b>	No	5183	33.0	12.3	1.35	1.21	1.49
	Yes	10526	67.0	9.4			
<b>Correct Antibiotic as per SCM</b>	No	5493	35.0	14.1			
	Yes	10137	64.5	8.4	1.79	1.62	1.99
	Unknown	79	0.5				
<b>Comorbidity</b>							
<b>Malaria</b>	Yes	8,013	51.0	9.6	0.84	0.76	0.93
	No	7,696	49.0	11.2			
<b>Malnutrition</b>	Yes	826	5.3	23.2	2.83	2.38	3.35
	No	14,883	94.7	9.7			
<b>Severe anaemia</b>	Yes	621	4.0	18.2	1.99	1.61	2.45
	No	15,088	96.0	10.1			
<b>Sepsis</b>	Yes	99	0.6	16.2	1.67	0.97	2.86
	No	15,610	99.4	10.4			
<b>Meningitis</b>	Yes	93	0.6	35.5	4.82	3.14	7.39
	No	15,616	99.4	10.2			
<b>Additional treatment</b>							
<b>Oxygen</b>	Yes	1954	12.4	28.5			
	No	13754	87.6	7.8	4.68	4.17	5.26
	Unknown	1	0.0				
<b>IV fluids</b>	Yes	191	1.2	41.4	6.43	4.73	8.49
	No	15518	98.8	10.0			
<b>Antimalarials</b>	Yes	6288	40.0	8.6			
	No	9420	60.0	11.6	0.71	0.62	0.79
	Unknown	1	0.0				
<b>Blood transfusion</b>	Yes	494	3.1	16.8	1.78	1.39	2.27
	No	15215	96.9	10.2			

CFR: case-fatality rate; SCM: standard case-management



Table 2. Association between classification and antibiotic use in consecutive children (0-59 months) treated for pneumonia in district hospitals in Malawi, 2000-2003

severity	age group	classification	all	Incorrect antibiotic	
				No.	%
severe	<2	correct	223	7	3.1%
		incorrect	496	24	4.8%
	2 to 11	correct	3422	229	6.7%
		incorrect	2261	2261	100.0%
	>11	correct	3603	318	8.8%
		incorrect	644	644	100.0%
very severe	<2	correct	813	9	1.1%
		incorrect	118	1	0.8%
	2 to 11	correct	938	102	10.9%
		incorrect	1502	1502	100.0%
	>11	correct	1483	269	18.1%
		incorrect	127	127	100.0%
All cases		correct	10482	934	8.9%
		incorrect	5148	4559	88.6%
Total			15630	5493	35.1%

**Table 3.** Odds ratios from logistic regression models for mortality on management and comorbidity covariates adjusted for age, sex and severity grade of consecutive children (0-59 months) treated for pneumonia in district hospitals in Malawi, 2000-2003.

Model	Variable	Odds Ratio	95% Confidence Limit	
			Lower	Upper
1	Age	0.99	0.98	0.99
	Sex	1.12	1.00	1.25
	Severity Grade	5.26	4.69	5.91
	Type of referral	0.70	0.60	0.80
	Prior Antibiotic	1.02	0.89	1.17
2	Age	0.99	0.98	0.99
	Sex	1.10	0.98	1.23
	Severity Grade	5.20	4.66	5.81
	Incorrect Classification	1.22	1.09	1.37
3	Age	0.98	0.98	0.99
	Sex	1.10	0.99	1.23
	Severity Grade	5.03	4.50	5.62
	Incorrect Classification	0.63	0.52	0.75
	Incorrect Antibiotic	2.27	1.91	2.70
4	Age	0.99	0.98	0.99
	Sex	1.10	0.99	1.22
	Severity Grade	5.19	4.65	5.80
	Malaria	0.95	0.85	1.06
5	Age	0.98	0.98	0.99
	Sex	1.10	0.98	1.22
	Severity Grade	5.11	4.57	5.71
	Malnutrition	2.83	2.36	3.40
6	Age	0.99	0.98	0.99
	Sex	1.10	0.99	1.22
	Severity Grade	5.13	4.60	5.74
	Severe Anaemia	1.61	1.29	2.01
7	Age	0.99	0.98	0.99
	Sex	1.10	0.99	1.22
	Severity Grade	5.21	4.66	5.82
	Sepsis	0.92	0.53	1.61
8	Age	0.99	0.98	0.99
	Sex	1.09	0.98	1.22
	Severity Grade	5.14	4.60	5.74
	Meningitis	2.96	1.89	4.64

**Table 4.** Odds ratios from logistic regression models for mortality on comorbidity and additional treatment covariates adjusted for age, sex and severity grade of consecutive children (0-59 months) treated for pneumonia in district hospitals in Malawi, 2000-2003.

Model	Variable	Odds Ratio	95% Confidence Limit	
			Lower	Upper
1	Age	0.99	0.98	0.99
	Sex	1.10	0.99	1.22
	Severity Grade	3.83	3.39	4.32
	O2	2.12	1.86	2.41
	IV	3.71	2.69	5.11
	Antimalarials	0.77	0.68	0.86
	Blood transfusion	1.47	1.13	1.91
2	Age	0.99	0.98	0.99
	Sex	1.10	0.99	1.22
	Severity Grade	3.81	3.37	4.31
	Malaria	1.21	1.05	1.39
	O2	2.15	1.88	2.45
	IV	3.68	2.67	5.07
	Antimalarials	0.67	0.58	0.78
Blood transfusion	1.46	1.12	1.90	
3	Age	0.98	0.98	0.99
	Sex	1.10	0.98	1.22
	Severity Grade	3.74	3.31	4.23
	Malnutrition	2.85	2.37	3.43
	O2	2.16	1.89	2.46
	IV	3.53	2.56	4.87
	Antimalarials	0.76	0.68	0.86
Blood transfusion	1.46	1.12	1.90	
4	Age	0.99	0.98	0.99
	Sex	1.10	0.99	1.22
	Severity Grade	3.79	3.36	4.29
	Severe Anaemia	1.63	1.21	2.18
	O2	2.12	1.86	2.42
	IV	3.73	2.71	5.14
	Antimalarials	0.75	0.67	0.84
Blood transfusion	1.05	0.75	1.46	
5	Age	0.99	0.98	0.99
	Sex	1.10	0.99	1.22
	Severity Grade	3.83	3.39	4.33
	Sepsis	0.89	0.51	1.56
	O2	2.12	1.86	2.41
	IV	3.71	2.69	5.11
	Antimalarials	0.76	0.68	0.86
Blood transfusion	1.47	1.13	1.91	
6	Age	0.99	0.98	0.99
	Sex	1.10	0.98	1.22
	Severity Grade	3.78	3.34	4.27
	Meningitis	2.92	1.83	4.65
	O2	2.12	1.86	2.42
	IV	3.64	2.64	5.02
	Antimalarials	0.76	0.67	0.85
Blood transfusion	1.46	1.12	1.90	

**Table 5.** Odds ratios from logistic regression models for mortality on malaria and additional treatment covariates with and without anti-malarials adjusted for age, sex and severity grade of consecutive children (0-59 months) treated for pneumonia in district hospitals in Malawi, 2000-2003.

<b>Model</b>	<b>Variable</b>	<b>Odds Ratio</b>	<b>95% Confidence Limit</b>	
			<b>Lower</b>	<b>Upper</b>
<b>With anti-malarials</b>				
1	Age	0.98	0.98	0.99
	Sex	1.10	0.98	1.22
	Classification	3.67	3.24	4.14
	Malaria	1.18	1.03	1.36
	Malnutrition	2.82	2.34	3.39
	Severe anemia	1.49	1.11	2.01
	Sepsis	0.82	0.47	1.45
	Meningitis	2.89	1.81	4.59
	Oxygen therapy	2.19	1.92	2.51
	Intravenous fluids	3.44	2.48	4.76
	Antimalarials	0.67	0.58	0.78
	Blood transfusion	1.10	0.78	1.54
<b>Without anti-malarials</b>				
2	Age	0.98	0.98	0.99
	Sex	1.10	0.98	1.22
	Classification	3.72	3.29	4.20
	Malaria	0.93	0.83	1.04
	Malnutrition	2.82	2.35	3.40
	Severe anemia	1.44	1.07	1.94
	Sepsis	0.83	0.47	1.47
	Meningitis	2.89	1.82	4.60
	Oxygen therapy	2.16	1.89	2.47
	Intravenous fluids	3.33	2.41	4.60
	Blood transfusion	1.04	0.74	1.45

**Box 1.** WHO standard case management of pneumonia defined by age groups and severity of disease

<b>Standard Case Management</b>		
<b>Diagnosis</b>	<b>Presenting signs and symptoms</b>	<b>Recommended treatment regimens</b>
<b>Child 2-59 months</b>		
<b>Severe pneumonia</b>	Respiratory rate (bpm): ≥ 50 aged 2 – 11 months ≥ 40 aged 12 – 59 months Lower chest wall indrawing	<b>Penicillin</b> 50 000 units/kg 6 hourly for 3 days if improved then oral <b>amoxicillin</b> 25 mg/kg three times daily for total of 5 to 8 days
<b>Very severe pneumonia</b>	Respiratory rate (bpm): ≥ 50 aged 2 – 11 months ≥ 40 aged 12 – 59 months Lower chest wall in-drawing Cyanosis Unable to drink Reduced level of consciousness Grunting (infants)	<b>Chloramphenicol</b> 25 mg/kg 8 hourly for 5 days if improved then three times daily for total of 10 days antibiotic treatment
<b>Infant &lt;2 months</b>		
<b>Severe/Very severe pneumonia</b>	Respiratory rate: ≥ 60 breaths per minute	<b>Gentamicin</b> 7.5 mg/kg once daily for 8 days <b>Penicillin</b> 50 000units/kg 6 hourly for three days if improved then oral <b>amoxicillin</b> 25 mg/kg three times daily for a total of 8 days antibiotic treatment
<b>Co-morbid conditions/pneumonia treatment</b>		
<b>Pneumonia in severely malnourished child</b>	Signs and symptoms for severe/very severe pneumonia as above. PLUS signs and symptoms for any of the following: <ul style="list-style-type: none"> <li>• Marasmus</li> <li>• Kwashiorkor</li> <li>• &lt;60% Weight for Height</li> </ul>	<b>Cotrimoxazole</b> prophylaxis on admission if not acutely ill Treatment for severe or very severe pneumonia as above PLUS <b>Gentamicin</b> (7.5 mg/kg IM/IV) once daily for 7 days >If the child fails to improve within 48 hours, add <b>Chloramphenicol</b> (25 mg/kg IM/IV 8-hourly) for 5 days.
<b>Known/suspected PcP</b>	2–6-month-old child with central cyanosis Hyper-expanded chest Fast breathing Chest X-ray changes, but chest clear on auscultation Enlarged liver, spleen, lymph nodes HIV test positive in mother or child	<b>Continue first-line antibiotic</b> (such as <b>Chloramphenicol</b> ) as mixed infection with bacteria occurs <b>Oral Cotrimoxazole:</b> 120mg three times daily if less than 5 kg; 240 mg three times daily if 5 kg or more for 21 days

## Chapter 8

### Discussion

The aim of this dissertation was to address the problem of death from pneumonia in children less than five years of age in Malawi. The hypothesis was that improving inpatient care in all district hospitals throughout Malawi would be associated with a decrease in the in-hospital CFR.

Standard case management of pneumonia is a relatively inexpensive intervention that is effective and with universal coverage, 65% of pneumonia deaths can be prevented. The challenge was to bring this strategy to scale and, in doing so, it was possible to evaluate the use, impact and sustainability in a low-income country, such as Malawi, where the health services were unable to deliver this intervention to a sufficient number of children at a high enough level of quality that would result in a significant impact.

The research of this dissertation is an operational based research model which analyses the delivery of the public health intervention (the CLHP), determines limitations in order to provide a basis to address these limitations. The research process included reviewing existing knowledge and evaluating practice in implementation in a specific setting – Malawi a low-income/resource and high HIV/malaria- endemic country in sub-Saharan Africa.

The findings and discussion could be relevant to other low-income/resource and high HIV/malaria-endemic country in sub-Saharan Africa where approximately 50% of all deaths due to pneumonia in children occur.[1-3] Children in developing countries being treated for pneumonia frequently have one or more comorbid conditions which increases their risk of dying.[4-6] This study assessed the risk factors, including comorbid conditions, that predicted a fatal outcome for pneumonia in children admitted to first level referral hospital. Besides examining the clinical factors involved in SCM we also examined factors related to the quality of curative care at first level referral hospitals for children with common, serious diseases that were referred by primary-level IMCI.[7,8]

While standard case management of pneumonia has been shown to be an effective strategy in reducing pneumonia-related deaths in children <5 years of age, a major challenge is how to deliver the strategy to sufficient children that would result in a significant impact on the pneumonia mortality rate. A situation analysis of the quality of inpatient care of children with severe, very severe pneumonia in district hospitals prior to the implementation of the CLHP identified the following (1) inadequate health-worker skills/inadequate training; (2) inadequate supplies of

antibiotics and equipment to administer oxygen therapy; (3) lack of routine supervision and quality assurance mechanisms; (4) deficient use of strategic information in hospitals to assist in planning services and procurement of essential items and to evaluate quality of care.

There was a need to distinguish between the known effective intervention strategy - SCM for pneumonia – and the “delivery strategy” to bring it to the child at risk.[9] This was achieved country-wide through the CLHP, based on a public health service delivery framework (the delivery strategy), for the surveillance, diagnosis and management of respiratory diseases and major comorbidities in children admitted to in-patient paediatric wards in district hospitals.

The CLHP aimed to improve case management of childhood pneumonia in hospital and address specific resource barriers. The activities implemented were: 1) Diagnostic and treatment guidelines; 2) Training of clinical staff in the standardized approach to the interventions against the targeted diseases; 3) Logistics to purchase and distribute standard drugs thus ensuring uninterrupted supplies at the management level of the District Health Office; 4) Recording and reporting system providing data on outcomes of the interventions, to enhance reproducibility and sustainability; 5) Internal routine supervision and evaluation of the programme by external experts/consultants and 6) Mechanisms to assess quality of practice.

We demonstrated that it was feasible to implement both the CLHP and the oxygen concentrator system country-wide in Malawi within first-level referral hospitals. Sustainability beyond the cycle of external funding the programmes was ensured by their inclusion in the Essential Health Package funded through the Sector Wide Approach. The CLHP has now been maintained for 8 years since the end of external project funding and is currently being expanded to 16 non-government hospitals. All components of the programme are still functioning well.[10]

The major strengths of the CLHP were that it was tailored to the address the specific needs of the country identified in the situation analysis, was implemented countrywide, and was incorporated within country's existing structure for organisation of health services and was implemented by the personnel already working within these services. Such personnel already carried out existing activities for control of acute respiratory infections and the programme for the integrated management of childhood illnesses. Other important strengths were the prevention of antibiotic stock outs and the comprehensive and complete set of data collected over the duration of the intervention which enabled us to conduct a comprehensive prospective study to evaluate the pneumonia specific case fatality rate over time following the implementation. Our cohort consisted of hospitalized cases representing the more severe spectrum of disease that are more likely to die.

This was the first nation-wide, hospital-based programme study to investigate the effectiveness of hospital-based SCM on pneumonia-related mortality.

The trend in case fatality rates in infants and young children (0 to 59 months of age) hospitalized and treated for severe and very severe pneumonia was evaluated over the course of the implementation (63 months) of the CLHP. Over the study period, 47,228 children were admitted to hospital for severe/very severe pneumonia with an overall CFR of 9.8% which, although high, is within range of those reported from neighbouring countries.[11-13] The higher case-fatality rate associated with young age and very severe pneumonia is expected and consistent with other studies.[14-17]

The findings from this study showed that the majority (64%) of cases, 2-59 months, had severe pneumonia. In this group there was a significant effect of the intervention (Odds Ratio (OR) 0.70 (95%CI: 0.50-0.98);  $p=0.036$ ), while in the same age group children treated for very severe pneumonia there was no interventional benefit (OR 0.97 (95%CI: 0.72-1.30);  $p=0.8$ ). No benefit was observed for neonates (OR 0.83 (95%CI: 0.56-1.22);  $p=0.335$ ). While data routinely collected in the district hospitals after training is a strength an important limitation of this study must be acknowledged in that it is based on the analysis of aggregate data and therefore it was not possible to determine the factors contributing to the lack of benefit as there was no individual patient clinical data recorded on the monthly reports.

Another limitation was that the poor quality of patient records and lack of routine reporting prior to implementing the program prevented the use of any data on patient care. Consequently we used the first three months of data collected after training as the baseline for comparison which is likely to have underestimated the impact of the intervention. This underestimation is supported by the high CFR (10-26%) observed during the situational analysis prior to the implementation of the CLHP. The trend of improved outcomes following the first three months of intervention is noteworthy as it suggests sustained improvements in care due to this CLHP approach, rather than a temporary improvement only following training as might have been expected.

To investigate the reasons for the poor outcome in infants less than two months of age and those with very severe pneumonia reported in the previous study further research of a subset of this cohort was carried out to determine the individual factors including demographics of the study population, recognised co-morbidities and clinical management that were associated with inpatient death. The subset included all children aged 0-59 months admitted with severe and very severe pneumonia to the paediatric wards in the first sixteen district hospitals throughout Malawi between



1<sup>st</sup> October 2000 and 30<sup>th</sup> June 2003. We compared individual factors between those that survived (n = 14 076) and those that died (n = 1 633).

The CFR of 10.4% for this subset is similar to that reported for the larger cohort. The age and severity grade distribution is also similar to the larger study with the majority (63.5%) of children in the 2-59 month age category with severe pneumonia. Also very severe pneumonia was associated with a significantly higher CFR than those classified as severe pneumonia.

The lack of intervention effect in infants and children 2 to 59 months suffering from very severe pneumonia is disappointing but the CFR is similar to other studies from the African region even when the studies have been conducted in central hospitals that have better resources than district hospitals.[12,13,18] There are a number of reasons that might explain this.

In an HIV/TB-endemic setting, such as Malawi, children with severe pneumonia are commonly co-infected with HIV and these HIV-infected children have a much higher CFR than children with pneumonia who are HIV-uninfected.[19] The highest risk group are infants. HIV-infected infants are more likely to have disease due to a wider range of pathogens and mixed infection including *Pneumocystis jiroveci*, *Cytomegalovirus*, *Mycobacterium tuberculosis*, Gram-negative bacteria and co-infections.[20] The impact of HIV has been reported in studies carried out in hospitals in southern Africa which showed that HIV is associated with treatment failure and an increase in pneumonia-related fatality.[12,18-20]

A study carried out by Graham et al. in 2005 assessed the impact of HIV Infection on the aetiology and outcome of severe pneumonia in Malawian children admitted to a large urban teaching hospital.[13] Their findings were consistent with other studies in the region. HIV prevalence was 51%. Of the confirmed bacterial pneumonia the most common bacterial isolates were *Streptococcus pneumoniae* and *Salmonella typhimurium*. PcP was confirmed in 16 patients who were younger, had more severe and persistent hypoxia with a poorer outcome (CFR 75%) compared to those with confirmed bacterial pneumonia (CFR 5%). The overall CFR was 10% - the majority of deaths occurred in infants of 2 to 6 months of age and 57% of deaths were associated with PcP.[13] The overall CFR was consistent with our findings despite the high nurse-to-patient ratio and clinical monitors available at the tertiary level hospital, the use of antibiotics appropriate to local antimicrobial susceptibility and the use of high-dose oral cotrimoxazole if PcP was suspected on admission.

The prevalence of HIV among pregnant women at sentinel sites throughout Malawi was very high during the study period (19.5%, 19.8% and 16.9% in 2001, 2003 and 2005). The rate of mother to

child transmission in 2001 was 26.9%.[21] In 2004 the estimated percentage of HIV+ pregnant women who received a full package of care to prevent mother-to-child transmission (MTCT) of HIV was only 2.3%.[21]

The introduction of preventive strategies to reduce maternal and perinatal HIV infection, routine testing and the introduction of early HAART to HIV+ pregnant women, not dependent on C4 count, has been shown to reduce the risk of new HIV infections in babies.[22] The introduction of cotrimoxazole preventive therapy (CPT) to all HIV-exposed children and early introduction of HAART have been shown to be effective in reducing the incidence of PcP, hospitalization and pneumonia-related deaths.[19,23-26] Violaro et al. in a randomized controlled study of infants assigned to either deferred or early antiretroviral therapy showed a dramatic decrease (76%) in all-cause early infant mortality for severe childhood pneumonia and a reduction of HIV progression by 75% in the early therapy group.[27]

A major limitation of the study was that HIV prevalence data were not available for the patients treated in the district hospitals. While health workers were trained to recognise and treat *Pneumocystis jirovecii* pneumonia (PcP) and other HIV-related lung disease, this almost certainly did not occur as almost all participants' HIV status was recorded as unknown. The lack of testing of children to ascertain their HIV status was due to resource constraints within the MOH, and a lack of willingness by health workers to undertake testing due to stigma compounded by a lack of access to anti-retroviral therapy at the time of the study.

Malawi, besides being a HIV high burden country, also has a high burden of TB. A study carried out in Malawi of the case-load of the National TB Programme (NTP) in 1998 found 2,739 (11.9%) children 0-14 years of age with the majority 1,615 (7%) in the <5 years age group and had poor treatment outcomes.[28] Graham et al. in their study of 327 children admitted with severe and very severe pneumonia found 10 (3.1%) cases of TB, based on clinical assessment alone, 3 of which were already on TB treatment, and a further 35 (10.7%) children had a known household contact, 20 of which were sputum smear-positive TB.[13] A number of studies from surrounding countries found that *Mycobacterium tuberculosis* was the underlying cause for pneumonia admissions in a high percentage of children. In neighbouring Zambia Chintu *et al.* reported that *Mycobacterium tuberculosis* was the third most common autopsy finding (18.8%) in children dying from pneumonia irrespective of their HIV status.[29] Prospective clinical studies of South African children hospitalized with severe pneumonia confirmed TB as the cause in 7-8% of admissions.[30] McNally in a more recent study of South African children admitted with severe/very severe pneumonia (WHO-defined) found that 15% had culture-proven TB.[12]

Weismuller et al. in a study of the diagnosis of TB in children in Malawi found that diagnostic practices remained inadequate.[31] They found that in the majority of children with PTB that the diagnosis was based on a chest X-ray alone with other investigations, e.g. skin-testing, rarely performed due to the fact that only four hospitals had access to tuberculin skin test reagents. Due to lack of testing of children to confirm their TB status at the district level due to resource constraints within the MOH meant that the diagnosis of TB was not comprehensive in this group of patients.

In this situation health workers need to be aware that if a child presents with persistent fever and signs of pneumonia and does not respond to antibiotics, they should evaluate the child for tuberculosis. The evaluation would include enquiring about recent close contact with a TB case and a chest X-ray as a minimum. This would be a challenge as chest X-rays and their interpretation are not widely available and few if any other diagnostic investigations are widely used outside sputum smear microscopy. The diagnosis of TB can be suspected in the majority of children using careful clinical assessment. It is however difficult to confirm a diagnosis of childhood TB.

It is recommended that at first referral level hospitals the staff should be trained to diagnose and initiate empirical treatment of uncomplicated tuberculosis in children. They should be able to recognise the symptoms and signs of probable tuberculosis, perform tuberculin skin tests and have access to a chest X-ray. All hospitalized children diagnosed with tuberculosis and commenced on TB treatment should be referred to the National Tuberculosis Programme and on discharge to continue treatment at the appropriate health centre. It is also recommended that all children suspected of having TB should be tested for HIV.[32]

The WHO antibiotic recommendations were made prior to the HIV era and have since been shown to be not as effective in HIV positive children with pneumonia. [12,18-20] In high HIV/TB prevalent areas the management of pneumonia needs to be based on region/county specific knowledge of the wider spectrum of pathogens and antimicrobial resistance leading to a high failure rate.[20]

It is recommended that bacterial aetiology and resistance studies be undertaken to inform high HIV-prevalent countries of the changes required in tailoring antibiotic use in standard case management (SCM) regimens. It is also recommended following the introduction of the H. influenzae type b and pneumococcal conjugate vaccine as they are likely to affect causes of bacterial pneumonia.[33]

Hypoxia is common in children with respiratory disease and is associated with significant morbidity and mortality, especially in young infants, those with very severe (hypoxic) pneumonia and PcP. There is clear evidence that oxygen therapy improves outcome in children with severe pneumonia, and that the routine use of oximetry improves identifying children requiring oxygen therapy as it is more sensitive and specific for identifying hypoxaemic children than clinical indicators.[34,35] As pulse oximetry was not routinely available during the study period the most hypoxaemic children were selected on clinical criteria for oxygen therapy. This is supported by the observation that mortality was higher in those that received oxygen, which likely reflects severity of disease rather than impact of oxygen. This also meant that we could not calculate the direct impact oxygen had on the CFR. The poor outcome in those receiving oxygen also suggests that PcP was not uncommon in this cohort.[14]

Despite the fact that the CLHP had provided oxygen concentrators to all district hospital paediatric wards we found that oxygen had been used substantially less than expected, based on the annual number of very severe pneumonia admissions recorded for each hospital. One reason for this was the high attrition rate of staff that had been trained in the use and maintenance of the concentrators. Another reason was that parents and guardians were reluctant for their children to receive oxygen therapy, as they believed their child could die once oxygen is administered. Pulse oximeters may have assisted in actually showing parents the positive effects of oxygen therapy.

A positive outcome of providing oxygen concentrators in the paediatric wards, capable of supplying oxygen to four children simultaneously, was that it resulted in the staff setting up a separate “high dependency” room or area within the pediatric ward where oxygen could be administered to a number severely ill children.

This study found that comorbid conditions associated with an increased pneumonia-related mortality were malnutrition, severe anaemia and meningitis. While none of these associations is unexpected, the unique characteristic of the study is that these factors have been analysed following prospective and complete clinical data collection from children managed under routine conditions at a district hospital level in a high mortality setting. A major limitation of the study is that the diagnosis of co-morbidities was usually clinical without laboratory confirmation for malaria, sepsis or severe anaemia. Therefore, it cannot be determined whether these conditions were under-diagnosed or over-diagnosed, especially as there is clinical overlap with severe pneumonia. Also while recognised as co-morbidities that can influence outcome, the evidence of association for this study is weakened by the lack of laboratory confirmation and objective measure of nutritional status such as weight-for-age.

Additional treatments, including oxygen, intravenous fluids or blood transfusion were all independently associated with a significantly higher CFR and are likely indicators of the severity of pneumonia and the presence of co-morbidities. The poor outcome in those receiving oxygen also suggests that PcP was not uncommon in this cohort.

Children that attended and received an antibiotic at a primary care facility prior to admission to the district hospital probably had more severe disease, and severity of disease was strongly associated with a poorer outcome. We were not able to determine related issues of access to care such as distance from facilities, socio-economic or behavioural factors that determined use of care facilities or the duration of symptoms before presentation.

Studies on quality of inpatient care of children with pneumonia have identified deficiencies, the main ones being poor case management including inadequate triage and assessment, over or under diagnosis of severe illness, and lack of implementation of appropriate guidelines for managing severe illness.[36] Other identified problems were over, under or inappropriate treatment with antibiotics, fluids and oxygen and lack of ongoing assessment/monitoring of the severely ill child.[8,37] Problems identified within health systems included lack of appropriately trained health workers at all levels, insufficient level of staffing, poor supervision of staff, lack of quality assurance monitoring and insufficient supplies, drugs and equipment.[7] The CLHP and oxygen system were development and implementation throughout Malawi to address these deficiencies as described in chapter 5a and 5b.

This study was undertaken following training of health workers on standardised case management as well as ensuring provision of an uninterrupted supply of antibiotics and oxygen therapy. However, despite a one-week training course on SCM of pneumonia, follow-up and ongoing in-service training, routine supervision and the introduction of mechanisms for quality assurance a large number of children were still incorrectly classified and therefore incorrectly treated. Incorrect treatment was associated with an increased pneumonia-related mortality.

The major challenge faced in the implementation of both of these programmes has been the chronic ongoing shortage of all categories of health care workers required to deliver quality health care and to maintain medical equipment. The attrition rate of trained workers has been high because of recruitment to the private sector, transfer of trained staff to other government hospitals, and deaths from HIV/AIDS. Malawi experienced a six-fold increase in mortality of health workers from AIDS-related diseases between 1985 and 1997.[38] To address this challenge extra training courses, regular in-service and on-the-job training needed to be introduced for all categories of health-care workers. The MOH also increased the intake to nurses' training institutes and restarted

the Medical Assistant training programme. In 2007 Malawi health service vacancy levels remained static at 46% due to the continued high attrition rate and deaths which alone represented 50% of all trained staff losses.[39]

This study has identified a number of reasons for poor pneumonia-related outcomes in young infants and children with very severe pneumonia. First were several co-morbidities such as malaria, malnutrition, severe anaemia and HIV infection for which preventive measures to address these need to be introduced. It also identified a number of potentially modifiable aspects of care where adjustments to the implementation of SCM are indicated.

To improve the outcome of these children with pneumonia, organizational improvements are needed to address these needs.

#### **It is recommended that:**

1. Pulse oximetry should be introduced as it is an important tool to assess patient oxygen needs, instead of relying just on clinical signs.
2. Pre-service training be introduced in institutions at all levels of health care workers to include correct classification of the severity of the disease and the use of correct antibiotics according to SCM of pneumonia. In addition, a more comprehensive training to deal with co-morbid conditions which might improve the quality of care.
3. Regular supportive supervision of clinical and nursing staff, to monitor quality of care, be given high priority.
4. First referral level hospitals staff should be trained to diagnose and initiate empirical treatment of uncomplicated tuberculosis in children.
5. All children suspected of having TB should be tested for HIV
6. Antibiotic regimens used in SCM of pneumonia be tailored to country specific pathogens and resistance patterns..
7. Universal testing for HIV, especially in pregnant women, be introduced
8. The implementation of strategies that prevent HIV and Pneumocystis pneumonia be scaled-up
9. More routine use of simple laboratory tests to detect malaria and anaemia

#### **Future research**

1. Research to evaluate the effect of the high dependency area on the quality of care and outcomes of children with very severe pneumonia.
2. Research to determine related issues of access to care such as distance from facilities, socio-economic or behavioural factors that determined use of care facilities and the duration of symptoms before presentation.

3. Research to investigate the process of transfer to hospital through the primary services
4. Research to demonstrate how laboratory services could be more efficiently used to assist with diagnosis of pneumonia and co-morbidities.
5. Aetiology studies to provide country specific pathogens and resistance patterns to inform antibiotic use.
6. Research into the management of human resources in relation to staffing levels, length of rotation through paediatric ward and utilization of staff trained in the SCM of childhood illnesses and the effect on outcomes.
7. Cost assessment study

In conclusion, pneumonia-related mortality is common in Malawian infants and children cared for in the routine care hospital setting. It was possible to implement and sustain the CLHP in all district hospitals throughout the country. Implementation of the CLHP was associated with a declining death rate among children aged two to fifty nine months with severe pneumonia. Further reduction of mortality might be achieved through improved assessment, more rigorous application of standard case management and more accurate identification and effective management of co-morbidities.

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## Acknowledgements

Prof. Robert Gie thank you for your critical assessment and never failing encouragement, for your enthusiasm for the project and for all the time you spent with me in discussion and for sharing your knowledge and wisdom and for providing invaluable guidance throughout this long process.

Prof. Stephen Graham thank you for your willingness to share your clinical experience for management of childhood pneumonia and comorbid disease in Malawi, especially your experience within the Government health services and the challenges that arise within a low-income/resource setting, it was was invaluable.

Dr. Neil Cameron thank you for your support and assistance throughout the process.

Dr. Carl Lombard from the Medical Research Council (MRC) of South Africa for his invaluable assistance with the statistical analysis.

A special thank you to my husband, Don Enarson, for your keen interest from the very beginning when we gave shape to the main ideas and for providing valuable epidemiological insight and ensuring that we stayed on the straight and narrow.

I wish to thank the Malawi MoH for its request to The Union to assist with the implementation of the CLH Programme and its continued support throughout the scale-up process and beyond the funding cycle.

I wish to express my appreciation to all members of the training teams, especially Dr Peter Kazembe and Dr Charles Mwansambo for donating their time so readily and for their unending support to and their advocacy of the CLHP.

I particularly wish to thank the Community Health Science Unit ARI/Child Lung Health Programme Management Team, Mrs Ellubey Maganga, Mr Norman Lufesi and Alfred Chalira, who were responsible in running, monitoring and evaluating the ongoing programme.

I want to specifically acknowledge all of the District Health Officers for their continued support and the CLHP Coordinators, the clinical and nursing staff whose work made it all possible.

## Funding

The CLHP was primarily funded by the MoH of Malawi, who contributed 69% of the running costs comprising facilities and human resources that are part of the existing health system. One point nine million dollars from the Bill and Melinda Gates Foundation funded the remaining 31% of the costs, 21% of which was investment and 79% operating costs.

The Bill & Melinda Gates Foundation grant ID#: 413  
<http://www.gatesfoundation.org/Pages/home.aspx>).

## List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
AMC	Advance Market Commitment
ARI	Acute Respiratory Infection
ART	Antiretroviral therapy
CAP	Community acquired pneumonia
CCM	Community case management
CFR	Case Fatality Rate
CI	Confidence Interval
CLHP	Child Lung Health Programme
CMV	Cytomegalovirus
CPT	Cotrimoxazole preventive therapy
EHP	Essential Health Package
ETS	Environmental tobacco smoke
GAVI	Global Alliance for Vaccines and Immunisation
Hib	Haemophilus influenzae type b
HIV	Human Immunodeficiency Virus
HR	Human resources
HSSP	Health Sector Strategic Plan
IAP	Indoor air pollution
IM	Intramuscular
IMCI	Integrated Management of Childhood Illness
IMR	Infant Mortality Rate
IPD	Invasive pneumococcal disease
IUATLD/UNION	International Union against Tuberculosis and Lung Diseases
IV	Intravenous
LRTI	Lower respiratory tract infection
MDG5	Millennium development goal five
MOH	Ministry of Health
OR	Odds Ratio
PcP	Pneumocystis carinii pneumonia
PCV	Pneumococcal conjugate vaccine
PERCH	Pneumonia Etiology Research for Child Health
PMTCT	Prevention of Mother to Child Transmission
RCT	Randomised clinical trial
RR	Risk ratio
SCM	Standard Case Management
SD	Standard deviation
SPSS	Statistical Package for Social Science
SWAp	Sector Wide Approach
TB	Tuberculosis
UNAID	Joint United Nations Programme on HIV/Acquired Immune Deficiency Syndrome
UNICEF	United Nations International Children's Emergency Fund
UR	Uncertainty range
USA	United States of America
WHO	World Health Organization

