UNIVERSITY OF NAIROBI

Mortality among Children with Pneumonia at Seven Kenyan Hospitals

Principal Investigator: Dr. Ambrose Agweyu

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Department of Paediatrics and Child Health,

University of Nairobi, P.O. Box 30197 00100, Nairobi.

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DECLARATION

I declare that this dissertation is my own original work and has not been published elsewhere or presented for a degree in any other institution.

Dr. Ambrose Agweyu, MBChB, MSc

Senior House Officer, Department of Paediatrics and Child Health,

University of Nairobi, P.O. Box 30197 00100, Nairobi

……. ……

Signature Date

This dissertation had been submitted to the University of Nairobi with our full approval as University supervisors.

1. Professor Grace Irimu, MBChB, MMed, PhD

Associate Professor of Paediatrics, Department of Paediatrics and Child Health,

University of Nairobi, P.O. Box 30197 00100, Nairobi

……. ……

Signature Date

2. Professor Mike English, MD

Professor of International Child Health, University of Oxford and Senior Research Fellow,

KEMRI-Wellcome Trust Research Programme, P.O. Box 43640 00100, Nairobi

……. ……

Signature Date

3. Professor Elizabeth Maleche Obimbo, MMed, MPH, CPulm.

Professor of Paediatrics, Department of Paediatrics and Child Health,

University of Nairobi, P.O. Box 30197 00100, Nairobi

……. ……

Signature Date

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ABBREVIATIONS AND ACRONYMS

BOSTID	Board on Science and Technology for International Development
CFR	Case fatality rate
ERC	Ethical Review Committee
ETAT+	Emergency Triage Assessment and Treatment plus Admission Care
GAPP	Global Action Plan for the Prevention and Control of Pneumonia
GRADE	Grading of Recommendations Assessment Development and Evaluation
HAZ	Height for Age Z score
Hib	*Haemophilus influenzae* type B
HIV	Human Immunodeficiency Virus
KEMRI	Kenya Medical Research Institute
KNH	Kenyatta National Hospital
KPA	Kenya Paediatric Association
MoH	Ministry of Health
NTS	Non-Typhoidal Salmonella
PCV	Pneumococcal Conjugate Vaccine
PCR	Polymerase Chain Reaction
PERCH	Pneumonia Etiology Research for Child Health
RCT	Randomized Controlled Trial
RSV	Respiratory Syncitial Virus
UNICEF	United Nations International Children's Fund
WAZ	Weight for Age Z score
WHO	World Health Organization
WHZ	Weight for Height Z score

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1.0 ABSTRACT

Background: Studies conducted prior to the introduction of the pneumococcal and *Haemophilus influenzae* type B conjugate vaccines show that mortality related to childhood pneumonia may be higher among children from sub-Saharan Africa than in other regions. Current estimates of pneumonia case fatality in African children will provide useful evidence to support discussions on local adaptation of global guidelines.

Objectives: The primary objective of this study was to determine the case fatality rate among children admitted with pneumonia at Kenyan hospitals. Risk factors for mortality within this population were explored as a secondary objective.

Methods: A retrospective longitudinal survey of inpatient records of children hospitalized with pneumonia between September 2011 and August 2013 was conducted at seven public hospitals selected to represent the spectrum of common serious childhood illnesses in Kenya. Health workers at all sites were trained and provided with the national case management guidelines. Case records for children aged between 2 and 59 months were retrieved. Children diagnosed with severe malnutrition or meningitis and those with missing outcome data were excluded from the analysis. All eligible records for children hospitalized during the period of the study were sampled. Categorical data were tabulated and summarized as proportions while continuous variables were reported as means, with standard deviations or medians, with inter-quartile ranges (IQR) as appropriate. The primary outcome, cumulative inpatient mortality, was computed as a proportion with a corresponding 95% confidence interval (CI). Univariate associations of potential risk factors with mortality were explored using Chi-squared statistics. Findings from these univariate analyses were then used to fit a logistic regression model to determine independent risk factors for mortality.

Results: Of 5820 children aged 2 – 59 months admitted with pneumonia over the period of interest, 243 and 3478 with meningitis and severe malnutrition respectively and 115 with missing data on clinical outcome were excluded. 1984 eligible children were included in the analysis. The median age of the study participants was 14 months (IQR 7 to 24 months). Non-severe, severe and very severe pneumonia cases comprised 447 (23%), 956 (48%) and 481 (29%) of 1984 children respectively. The case fatality of all pneumonia cases was 77/1984 (3.9%). Mortality among non-severe, severe and very severe categories was 5/447 (1.1%), 22/956 (2.3%) and 50/581 (8.6%) respectively. In univariate analyses, younger age group (2-11 months), moderate and severe

malnutrition, mild to moderate and severe pallor, some and severe dehydration and admission at a Level V hospital were associated with increased mortality. Risk factors for mortality in multivariate analysis were: very severe pneumonia (versus non-severe pneumonia) (Odds ratio (OR) 6.0; P=0.04), both mild / moderate pallor and severe pallor (versus no pallor) (OR 6.1; P<0.01 and OR 16.4; P<0.01 respectively), both some and severe dehydration / shock (versus absence of dehydration) (OR 3.8 P=0.02 and OR 24.6; P<0.01 respectively), both moderate and severe malnutrition defined by weight for age Z score (OR 3.8; P=0.03 and OR 4.0; P=0.02 respectively) and hospitalization at Level V facilities (OR 3.3; P=0.01).

Conclusions: Case fatality for pneumonia was 3.9% and was substantially higher in the very severe category. Very severe pneumonia, pallor, dehydration, moderate and severe malnutrition, and hospitalization at Level V hospitals were associated with increased mortality in this population. Age and respiratory rate were not associated with mortality.

Recommendations: The findings of this study should be disseminated for use in policy meetings to update the current pneumonia guidelines. Prospective studies are required to determine the aetiology and optimize the management of pneumonia, particularly among children with very severe presentations, pallor and dehydration.

2.0 INTRODUCTION

Childhood pneumonia claims over one million lives annually and is a leading cause of morbidity worldwide (1). Over 90% of an estimated 120 million episodes of pneumonia per year occur in developing countries. The case fatality rate (CFR) from severe forms of pneumonia is highest in sub-Saharan Africa where 43% of global pneumonia-related deaths are estimated to occur (2).

In 2009, the World Health Organization (WHO) and the United Nations International Children's Fund (UNICEF) launched the Global Action Plan for the Prevention and Control of Pneumonia (GAPP) - a global campaign aimed at reducing pneumonia-related morbidity and mortality focusing on 15 countries with the highest burden. Kenya is among the 15 GAPP focus countries that account for approximately 75% of the global burden of pneumonia (3). Epidemiological modelling data from 2010 estimate the annual incidence of acute lower respiratory tract infections among Kenyan children at 0.25 episodes per child year, of which 11% progress to severe forms (2). Cross-sectional inpatient studies in Kenya estimate a prevalence ranging from 24% reported in a rural district hospital in coastal Kenya (4) to 30% in Kenyatta National Hospital (KNH) (5) confirming that pneumonia is indeed a leading cause of childhood illness in the country.

3.0 LITERATURE REVIEW

The past decade witnessed a considerable reduction in global child mortality. These gains are believed to be driven to a large extent by declining pneumonia-related mortality.

Case Fatality of Childhood Pneumonia

The risk of death among children with pneumonia varies widely across populations and by clinical severity. In a systematic review of 37 published hospital-based observational studies of children ranging from 0 – 59 months old with severe forms of pneumonia, reported case fatality was 0.4%

in industrialized countries, 2.1 % in southeast Asia and 3·9% in Africa (6). These data suggest that pneumonia-related mortality may be higher in sub-Saharan Africa than in other regions of the world including Asia, where the bulk of the data that informed the recent WHO pneumonia guideline updates (7). No published estimates of mortality among the non-severe category were found, likely due to the challenges of efficiently following up a large population of patients primarily managed in the community.

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Table 1: Case Fatality Rates for Severe Acute Lower Respiratory Infections in Children Younger than 5 Years by Region

Region	Aged 0 – 11 months		Aged 12 – 59 months		Aged 0 – 59 months	
	Studies	CFR (95% CI)	Studies	CFR (95% CI)	Studies	CFR (95% CI)
Africa	9	3·8% (2·4–5·9)	8	1·9% (1·2–3·2)	11	3·9% (2·7–5·5)
Americas	10	1·6% (1·1–2·4)	10	0·6% (0·2–1·3)	11	1·3% (0·8–1·9)
Europe	-	-	-	-	1	0·4% (0·3–0·5)
Southeast Asia	6	2·6% (1·4–4·7)	4	0·3% (0·1–0·9)	9	2·1% (1·1–4)
Western Pacific	1	2·4% (1·3–4·3)	-	-	3	2·3% (1·7–3·2)
Developing	25	2·4% (1·7–3·6)	21	0·8% (0·4–1·3)	32	2·3% (1·6–3·4)
Industrialized	1	0·8% (0·7–0·9)	1	0·3% (0·2–0·5)	3	0·6% (0·4–0·8)
Global	26	2·3% (1·5–3·4)	22	0·7% (0·4–1·2)	35	2·1% (1·4–3·1)

Adapted from Nair et al 2013(6)) CFR – Case Fatality Rate CI – Confidence interval

In Kenya, three observational studies (two conducted in a rural district hospital in Kilifi County (4, 8) and one in the national referral hospital in Nairobi (9)) report pneumonia CFR. For severe pneumonia, studies in rural settings report CFR of 3.5% (before introduction of the Hib vaccine) and 0.3% (after introduction of the Hib vaccine), while the CFR in the urban referral hospital was 1.2%. Among children with very severe pneumonia, CFR in rural hospitals is estimated at 11.5% and 18.9% before and after the introduction of the Hib vaccine respectively, and 10.5% in urban settings (after introduction of the Hib vaccine). All three studies were undertaken before the launch of the pneumococcal vaccine in 2010. The characteristics of the Kenyan studies and outcomes of the study participants are shown in Table 2.

Table 2: Pneumonia Case Fatality Rates in Kenyan Observational Studies

		Severe Pneumonia	**Very Severe Pneumonia**	**All pneumonia**
Author (year of publication)	**Location**	**Mortality (%)**	**Mortality (%)**	**Mortality (%)**
Berkley et al (2005)	Kilifi	52/1470 (3.5)	56/296 (18.9)	108/1766 (6.1)
Webb et al (2012)	Kilifi	1/353 (0.3)	15/131 (11.5)	16/484 (3.3)
Agweyu et al (2014)	Nairobi	2/169 (1.2)	21/201 (10.5)	23/370 (6.2)

CFR – Case Fatality Rate CI – Confidence Interval

Risk Factors for Mortality among Children with Pneumonia

If children in Africa do indeed represent a population at a high risk of death, it may be due to differences in sociodemographic or clinical characteristics associated with mortality. Sonengo et al studied risk factors for mortality in a large recently published systematic review of 77 studies conducted in low and middle income countries (10). Very severe pneumonia, age below two

months, *Pneumocystis carinii* infection, comorbidities including HIV infection and severe malnutrition, young maternal age, low maternal education, low socio-economic status, second-hand cigarette smoke exposure, and indoor air pollution were all independently associated with increased risk of mortality. Childhood immunisation and attendance of antenatal care were associated with decreased odds of death. The following section discusses some of these factors and others that may be responsible for the changing local pneumonia-related mortality postulated in this study.

Aetiology of Childhood Pneumonia and Introduction of Pneumococcal and Hib Vaccines

Studies examining the aetiology of pneumonia in developing countries date back to the mid-1980s (Table 3). The Board on Science and Technology in International Development (BOSTID) study group undertook a large longitudinal study across three continents (Africa, Asia and South America) from 1985 – 1989 (11). A total of 10 developing countries were represented including Kenya. In this project that enrolled a cohort of children aged 0 – 59 months, blood samples and aspirates from the nasopharynx were collected to study the aetiology of respiratory infections. Viruses were found to be more common than bacteria as causes of lower respiratory tract infections (14 – 64% versus 4.5 – 40%). However, the failure to obtain lung aspirate samples in this study may have reduced the ability to detect bacterial organisms. Consistent with other studies (12), Respiratory Syncitial Virus (RSV) was the most frequently isolated virus (11 – 37% of patients in whom samples were collected). The most common bacterial organisms were *Streptococcus pneumoniae* followed by *Haemophilus influenzae* at all sites except in Pakistan where *H. influenzae* was isolated more frequently.

The findings of the BOSTID studies are supported by other locally conducted studies. Using data collected from 1999 – 2001, Berkley et al studied data from over 11,000 paediatric admissions at

Kilifi District Hospital of whom 2803 (23.6%) were syndromically diagnosed with pneumonia (4). Slightly less than 5% of these children had positive bacterial blood cultures. The major organisms isolated were *S. pneumoniae* (37.5%), non-typhoidal Salmonella (NTS) (19.0%) and *Haemophilus influenzae* (15.3%). The known association between NTS and malaria (13, 14) may explain the high prevalence of NTS in this study where *Plasmodium falciparum* parasitaemia was detected in 45% of the children studied.

In a prospective study of 385 children hospitalized at KNH conducted in 2009 (9), bacterial blood cultures were reported for 338 children of whom 11 (3.3%) cultured pathogenic organisms (five *Streptococcus pneumoniae*, three *Salmonella typhimurium*, two *Escherichia coli* and one *Pseudomonas aeruginosa*). The microbiological findings from this study may have been influenced by the high frequency of prior treatment with antibiotics, which was reported in 64% of children enrolled.

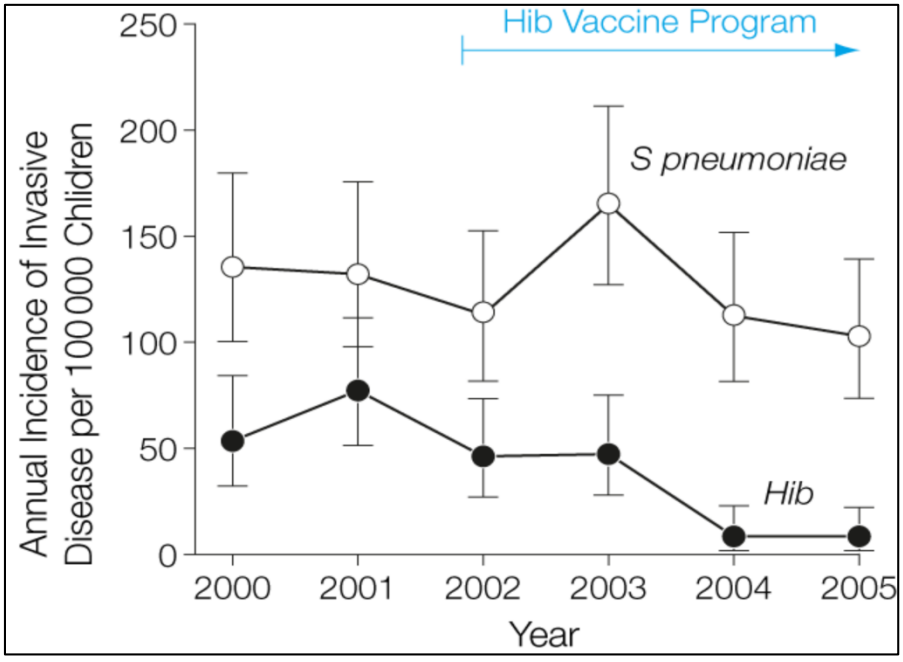
More recently, Hammitt et al conducted a case control study (15) as part the Pneumonia Etiology Research for Child Health (PERCH) project - a large multi-country study on the aetiology of pneumonia in children in the era after the introduction of the Hib and pneumococcal vaccines (16). A total of 810 children were recruited at Kilifi District Hospital. Among 257 case patients in whom cultures of blood and induced sputum, PCR of induced sputum, nasopharyngeal and oropharyngeal swabs were collected, bacteria were only identified in 24 (9%), viruses in 137 (53%), mixed viral and bacterial infection in 39 (15%), and no pathogen in 57 (22%); bacterial causes were more frequent than viral causes after considering the results of the case-control analysis. In line with previous work from the same site, the bacterial pathogens most frequently isolated in blood culture were *S. pneumoniae* (n = 30), non-typhoidal Salmonellae (n=6) and *H. influenzae* (n=4).

Table 3: Summary of Childhood Pneumonia Aetiological Studies

Author	Year of Publication	Setting	Hib Vaccine	PCV	N	Samples Collected	Organisms Isolated
Shann et al (17)	1986	13 studies conducted in 8 developing countries	No	No	1029	Lung aspirates	640 (62%) positive bacterial isolates 176 *H. influenzae* 186 *S. pneumoniae* 109 *S. aureus* 192 Other bacteria
BOSTID Study Group (11)	1990	10 Developing countries	No	No	4486	Blood cultures Nasopharyngeal aspirates	4.5 – 40% positive bacterial isolates* 14 – 64% positive viral isolates 11 – 37% RSV
Kariuki et al (18)	1987	Kenya	No	No	45	Lung aspirates	22 (49%) positive bacterial isolates 12 Coagulase negative *S. aureus* 4 *E. coli* 3 *K. pneumoniae*
Berkley et al (4)	2005	Kenya	No	No	2803	Blood cultures	189 (6.7%) positive bacterial isolates 71 *S. pneumoniae* 36 non-typhi Salmonellae 29 *H. influenzae* 16 *E. coli* 32 *Other bacteria*
Agweyu et al (9)	2014	Kenya	Yes	No	338	Blood cultures	11 (3.3%) positive bacterial isolates 5 *S. pneumonia* *3* non typhoidal Salmonella 2 *E. coli* 1 *P. aeruginosa*
Hammitt et al (15)	2012	Kenya	Yes	No	257	Blood cultures Oro /Nasopharyngeal aspirates Culture of induced sputum	24 (9%) positive bacterial isolates 39 (15%) mixed viral/ bacterial isolates 30 *S. pneumoniae* 6 non-typhi Salmonellae 4 *H. influenzae* 12 Other bacteria 137 (53%) positive viral isolates 176 (69%) positive viral isolates

* *S. pneumoniae* and *H. influenzae* most common bacteria isolated. Frequencies not reported

Epidemiologic data suggest that the introduction of the Hib vaccine has resulted in a notable decline in invasive disease due to Hib. Figure 1 illustrates the results of work by Cowgill et al from a bacterial culture-based surveillance programme at Kilifi District Hospital covering the period from 2000 – 2005 showing the frequency of isolation of Hib at Kilifi District Hospital (19).



.Source: Cowgill et al (2006)

Figure 1: Incidence of Invasive Hib Disease at Kilifi District Hospital Pre- and Post Hib Vaccine

This pattern is likely to be similar across the country where it is currently estimated that 86.4% of Kenyan children receive three doses of the pentavalent vaccine protective against Hib, Hepatitis B, Diphtheria, Pertussis and Tetanus (20). Following the introduction of the pneumococcal vaccine to the national childhood immunization schedule in January 2011, a similar trend in the incidence of invasive pneumococcal disease is expected.

Improved Case Management for Pneumonia

The need to develop an effective global strategy to tackle the enormous burden of childhood pneumonia in developing countries was first formally recognized in 1980 when a memorandum was drafted at a WHO meeting convened to outline a simple effective approach to management of children with acute lower respiratory tract infections in low level facilities (21). It was at this meeting that the algorithm used for the management of childhood pneumonia in Kenya (22) and several other developing countries was adopted.. Under these guidelines, children with a history of cough and difficulty in breathing are assigned to one of four levels of severity (very severe, severe, non-severe and no pneumonia) based on presenting clinical signs. It is these signs that then inform the choice of empirical antibiotic therapy (Table 4). Inpatient treatment is reserved for children with severe and very severe forms of pneumonia while children with non-severe pneumonia or "no pneumonia" are managed at home (23).

Table 4: Kenyan Ministry of Health Guidelines for Management of Children Aged 2 - 59 Months with Cough and/or Difficulty Breathing (22)*

Syndrome	Clinical Signs	Recommended Antibiotic Treatment
Very severe pneumonia	*Any one of: Cyanosis, Grunting, SPO_2<90%, Inability to drink, Altered consciousness*	Inpatient management Benzyl penicillin/ ampicillin and gentamicin (*plus* high dose co-trimoxazole for all HIV-exposed or infected)
Severe pneumonia	*Lower chest wall Indrawing AND without signs of very severe pneumonia*	Inpatient management Benzyl penicillin/ ampicillin monotherapy (if HIV-exposed or infected, treat as very severe pneumonia)
Non-severe pneumonia	*Fast breathing (RR≥50/min if age 2-11months; ≥40/min if age 12-59 months) AND without signs of severe or very severe pneumonia*	Outpatient management Co-trimoxazole (or amoxicillin if child has HIV and is receiving Co-trimoxazole prophylaxis)
No pneumonia	*Absence of any of the signs of very severe, severe or non-severe pneumonia*	Outpatient management. Antibiotics not indicated

* Applies to children without stridor, severe malnutrition or signs of meningitis

In a prospective survey conducted in 13 Kenyan district hospitals 2002 by English et al, the case management practices, including care for children with pneumonia were frequently found to be inconsistent with national or international guidelines (24). Subsequently, a cluster randomized trial was conducted to study the effectiveness of an intervention to improve paediatric care through training and dissemination of guidelines at eight Kenyan hospitals (25). This study demonstrated an overall improvement in care for children within intervention hospitals. Building on the experiences from this trial, training of health workers on case management of common childhood illnesses using a five day hospital based course named Emergency Triage Assessment and Treatment plus Admission Care (ETAT+) has been rolled out to dozens of facilities within the

country and in the East African region (26). Since 2007 over 3000 health workers and a similar number of medical students have been trained (Kenya Paediatric Association estimates). Although no formal studies have been conducted in Kenya to evaluate the impact of ETAT+ training on pneumonia mortality, empirical data from other settings have shown reductions in mortality of up to 50% following improved pneumonia case management (27).

Changing Patterns of Antibiotic Resistance

The current Kenyan guidelines recommend first line management for severe childhood pneumonia with benzyl penicillin monotherapy (Table 3) (23). Benzyl penicillin is an antibiotic derived from a fungus of the genus Penicillium. Benzyl penicillin (Penicillin G), the only natural penicillin, is highly active against sensitive strains of gram-positive cocci, but is also readily hydrolyzed by penicillinase. Widespread empirical use of penicillin has generated concerns over increasing resistance against these important antibiotics in the community. Unfortunately, local empirical evidence on antimicrobial resistance for common pneumonia causative pathogens is scarce. Unpublished data from positive bacterial blood cultures collected from children hospitalized at Kilifi district hospital from 2000 to 2008 suggest rising trends in resistance to cephalosporins and penicillins for *S. pneumoniae* isolates (Figure 2). Although penicillin-resistant pneumococci have

been frequently reported in paediatric populations, the clinical significance of *in vitro* resistance of *S. pneumoniae* in populations of children with pneumonia remains unclear (28).

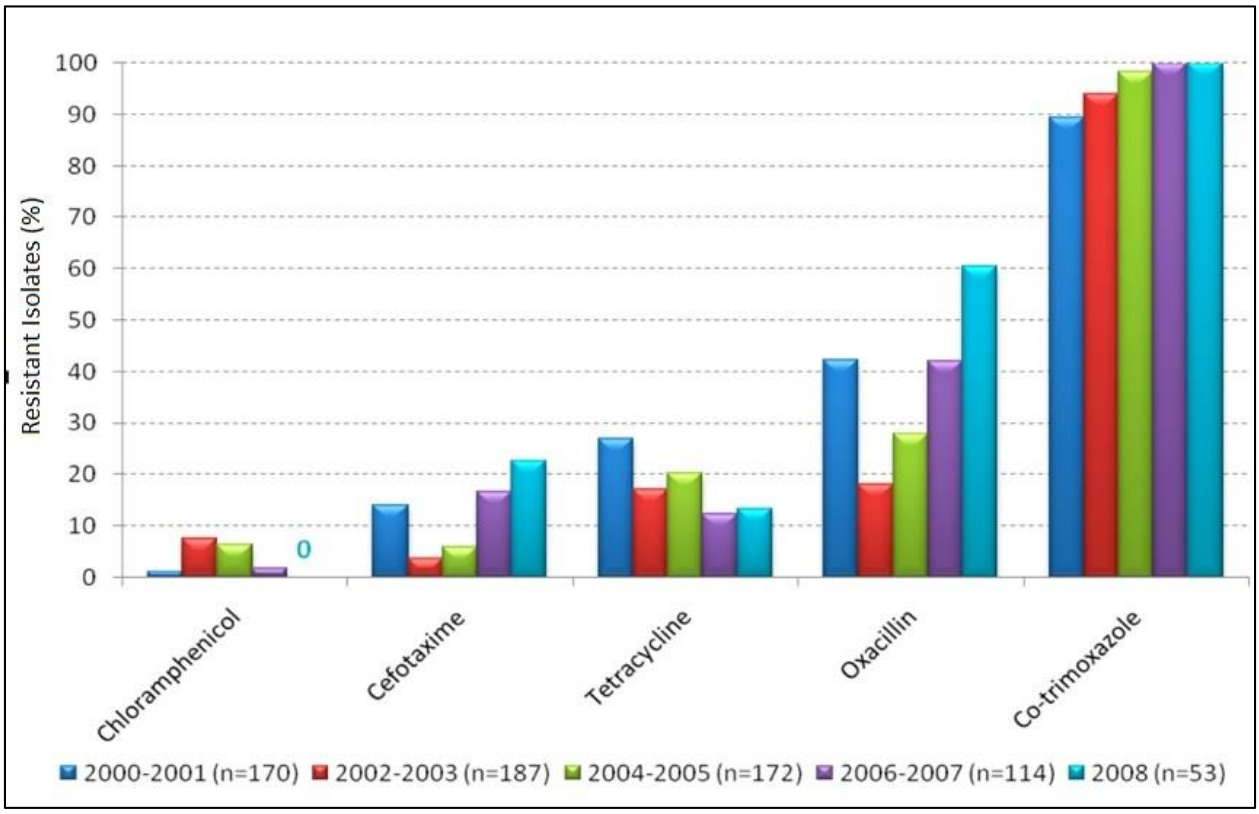


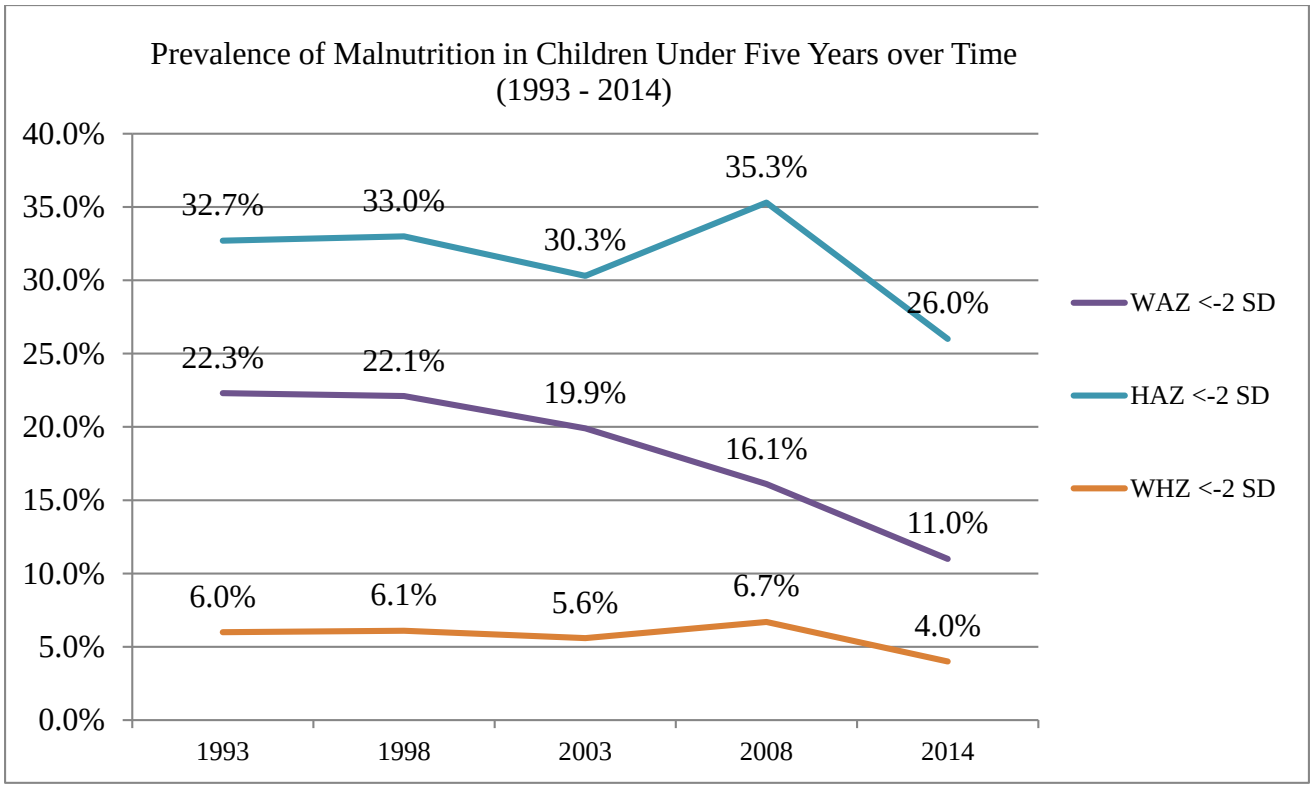
Figure 2: Resistance Profiles for *Streptococcus Pneumoniae* Isolates in Blood and Cerebrospinal Fluid Collected From Paediatric Admissions at Kilifi District Hospital (2000 - 2008)

Malnutrition and Pneumonia Mortality

Several studies have consistently demonstrated an association between malnutrition and mortality among children with pneumonia (10, 29-31). In a systematic review of 16 studies by Chisti et al children with pneumonia classified with moderate and severe forms of malnutrition were shown to have 2.9 to 121 times increased risk of death when compared to children of normal nutritional status (32). In eleven of the studies in the review which reported on aetiology (total of 215 positive

bacterial isolates studied), *Klebsiella pneumoniae* was the most frequently isolated pathogen (26%) followed by *Staphylococcus aureus* (25%), *Streptococcus pneumoniae* (18%) *Escherichia coli* (8%) and *Haemophilus influenzae* (8%). In the conclusion, the authors challenged the failure of the WHO guidelines to take account of the spectrum of pathogens responsible for pneumonia in malnourished children. The authors also acknowledged the limited data on other potential aetiological causes of pneumonia including Mycobacterium tuberculosis infection.

Data from the most recent Kenya Demographic Health Surveys (20) suggest a declining trend in prevalence of malnutrition among children under five years of age. The estimated prevalence of wasting (weight for height Z score less than -2 standard deviations (SD) below the median) and stunting (height for age Z score less than -2SD below the median) are at the lowest level since data on nutritional status began to be collected in the surveys. The proportion of children with a weight for age Z score less than -2SD below the median also appears to have reduced over the same period (Figure 3). The influence of these trends on pneumonia mortality in Kenyan children is currently not known.



WAZ – Weight for Age Z score HAZ – Height for Age Z score
WHZ – Weight for Height Z score SD – Standard Deviation
Source: Kenya Demographic and Health Surveys

Figure 3: Trends in Prevalence of Malnutrition among Children Under Five Years over Time.

HIV Infection and Pneumonia Mortality

HIV-infected children have a higher risk of acquiring pneumonia (33) and increased frequency of pneumonia-related death (31, 34, 35). In addition, the spectrum of organisms causing pneumonia differs between HIV-infected and immunocompetent children. *Mycobacterium tuberculosis* and *Pneumocystis jirovecii* are particularly important causes of pneumonia in HIV-infected children (34, 36). With increasing coverage of Prevention of Mother to Child Transmission (PMTCT) of HIV (90% of HIV infected mothers in the 2012) (37), the prevalence of HIV infection among children is expected to have declined. The most recent Kenya AIDS Indicator Survey reported a prevalence of HIV infection of 0.9% among children aged 18 months to 14 years (37). Notably

however, this estimate excludes the vulnerable age group of children under 18 months in whom mortality is highest (38). The prevalence of HIV infection among pneumonia inpatients in Kenyatta National Hospital in Nairobi has been shown to range from 10 – 60% (9, 39). A reduction in the prevalence of HIV infection in children is therefore expected to result in a decline in severe forms of pneumonia and associated mortality.

Recent Revisions in the Treatment Guidelines for Severe Pneumonia

In the most recent revision of the guidelines for treatment of childhood illnesses, the WHO adopted an evidence-driven approach to generate recommendations that were incorporated in the updated "Pocket Book for the Management of Sick Children" (7). In what is widely regarded to have been a major revision, the WHO guideline development panel made a strong recommendation based on moderate quality evidence that children fulfilling the clinical criteria for severe pneumonia (Panel 1) receive outpatient care with oral antibiotics (in contrast with previous guidelines recommending inpatient management with injectable antibiotics. This decision was based on evidence from three clinical trials conducted in predominantly Asian populations (40-42) and after considering additional factors including risks, benefits, acceptability and feasibility.

In a similar exercise conducted in Kenya in 2010 (prior to the WHO revision), a meeting of health professionals, academics and policy makers was convened to develop recommendations for the national paediatric clinical practice guidelines (43). The clinical question regarding appropriate antibiotics for severe pneumonia was presented along with systematic reviews that were very similar to those presented to the WHO team. However, upon presentation of the evidence to the guideline development panel, a substantial proportion of those present voted against a proposed amendment that would allow outpatient treatment of children with severe pneumonia. A major concern raised by those who were against the revision was the generalisability of the findings of

the three trials to children in sub-Saharan Africa who were felt to have a higher risk of mortality (44).

3.1 Study Justification and Utility

Evidence from local research conducted before the introduction of the pneumococcal conjugate and Hib vaccines indicates a significant risk of mortality in the Kenyan population of children with pneumonia. Since the introduction of the Hib and pneumococcal vaccines to the national paediatric immunization schedule in 2001 and 2011 respectively, the aetiology and outcome of childhood pneumonia is likely to have changed. Other factors that are believed to have influenced the clinical outcome of pneumonia include the changing prevalence of malnutrition and HIV infection, the rising trends of antibiotic resistance and improved case management. Following the recent change in global guidance from WHO for the case management pneumonia, it is likely that Kenya and other sub-Saharan African countries will review their national pneumonia guidelines. The decision on whether to revise the Kenyan national guidelines for the treatment of children with pneumonia in line with the revised WHO recommendations will need to be informed by data reflective of the local situation. Thus, a precise estimate of the risk of death from a representative sample of children, managed in routine clinical settings in the post-pneumococcal and Hib vaccine era is required. This study reports the case fatality among children with pneumonia admitted in Kenyan hospitals after the nationwide introduction of the pneumococcal conjugate vaccine. The valid and precise estimate of case fatality among Kenyan children with pneumonia reported will provide useful evidence to inform discussions on local adaptation of global guidelines.

4.0 RESEARCH QUESTION

What is the case fatality of pneumonia and risk factors for mortality among Kenyan children admitted to public hospitals in the post-pneumococcal and *Haemophilus influenzae* vaccine era?

4.1 PRIMARY OBJECTIVE

To determine the case fatality of pneumonia among children admitted to Kenyan public hospitals.

4.2 SECONDARY OBJECTIVE

To determine the risk factors for mortality among children admitted to Kenyan public hospitals and diagnosed with pneumonia; specifically sociodemographic characteristics, disease severity and comorbidities.

5.0 METHODOLOGY

5.1 STUDY DESIGN

A retrospective longitudinal survey was conducted.

5.2 STUDY AREA

Selection of the Study Sites

Paediatricians from public district (Level IV) and provincial (Level V) hospitals across the country were invited to participate in a clinical trial to compare antibiotic treatments for severe pneumonia in children (45). A meeting was convened in August 2010 for those who expressed interest. Study hospitals were selected to ensure adequate representation of the spectrum of common local childhood illnesses at sites with a large volume of potential cases. All the hospitals that were identified as sites for the clinical trial were also selected to participate in this observational study. In total, seven hospitals were selected (Figure 4). Mbagathi District Hospital is located in the Nairobi County at an altitude of 1700m above sea level (ASL). Three other sites (Embu, Chuka

and Kerugoya hospitals) are located in the Central region of Kenya at altitudes ranging from 1350m to 1700m ASL. Kisumu, New Nyanza and Bungoma hospitals are located in western Kenya around the Lake Victoria basin where malaria is endemic (altitude 1100m – 1300m ASL) (Figure 3). A summary of the characteristics of the study sites is shown in Table 5.

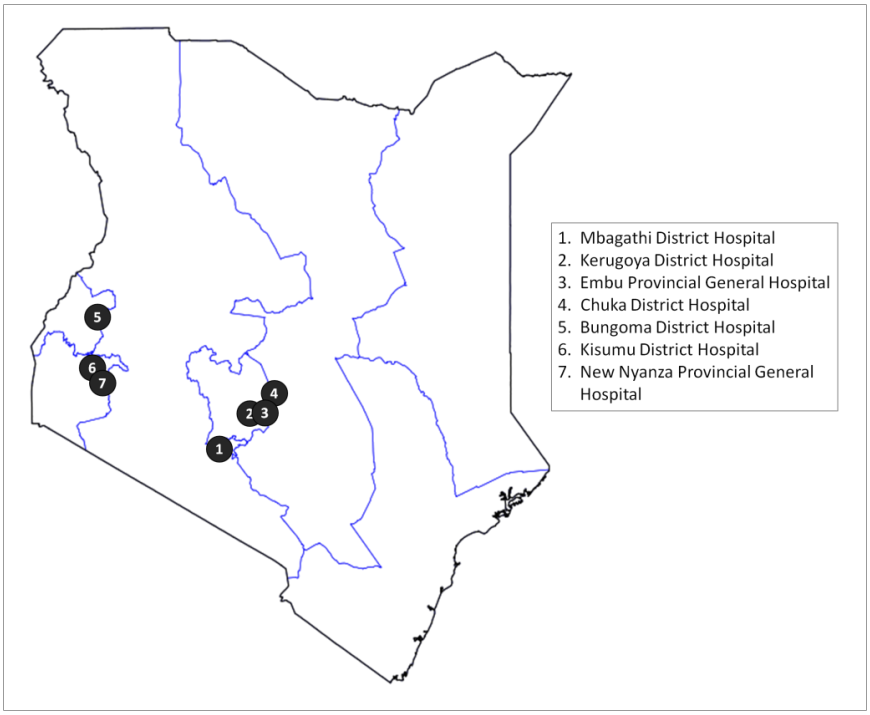


Figure 4: Study Hospitals

Table 5: Characteristics of Study Hospitals

Hospital	Annual Paediatric Admissions (2011)	Number of Paediatricians	Structured paediatric admission form used	Altitude (metres above sea level)
Mbagathi DH	4443	2	Yes	1700
Kerugoya DH	3280	1	Yes	1493
Embu PGH	2622	1	No	1350
Chuka DH	2000	1	No	1402
Bungoma DH	4418	1	No	1385
Kisumu DH	3370	1	No	1131
New Nyanza PGH	3649	3	No	1131

DH – District Hospital PGH – Provincial General Hospital

5.3 Study Population

Inpatient records for children aged 2 – 59 months with pneumonia at seven public hospitals (Table 5) across Kenya from September 2011 to August 2013 were screened for eligibility.

Eligibility Criteria

The following eligibility criteria were applied to determine the patients whose records were selected for the study.

5.3.1 Inclusion Criteria

i. Admitted at a study hospital
ii. Age 2 – 59 months
iii. Diagnosis of pneumonia documented by the admitting clinician – refer to case definitions in section 5.5.

5.3.2 Exclusion Criteria

i. Missing outcome data (survival / death)
ii. Intercurrent diagnosis of meningitis
iii. Diagnosis of severe malnutrition documented by the admitting clinician

5.4 Case Definitions

Very severe pneumonia: The presence of clinical signs of very severe pneumonia (central cyanosis, grunting, head nodding, inability to drink, altered consciousness or oxygen saturation <90%) in a child with a history of cough and / or difficulty in breathing as defined in the Kenyan Ministry of Health Basic Paediatric Protocol (November 2013 edition) (46).

Severe pneumonia: Lower chest indrawing in the absence of clinical signs of very severe pneumonia in a child with a history of cough and / or difficulty in breathing as defined in the

Kenyan Ministry of Health Basic Paediatric Protocol (November 2013 edition) (46). Note that the 2013 revised WHO definition is not used in this report.

Non severe pneumonia: The absence of any clinical signs of very severe pneumonia and severe pneumonia in the presence of fast breathing in a child with a history of cough and / or difficulty in breathing as defined in the Kenyan Ministry of Health Basic Paediatric Protocol (November 2013 edition) (46).

5.5 Sample Size

Inpatient records for all children fulfilling the eligibility criteria admitted between 1st September 2011 and 31st August 2013 were included. Approximately 2000 eligible case records of children with pneumonia were expected.

Substituting the expected sample size in the formula for calculating sample sizes for estimating population proportions with specified absolute precision:

$$n = \frac{(Z^2 \times P(1-P))}{e^2}$$

Where:

n is the sample size (estimated 2000 case records of children with pneumonia classified according to the national guidelines – refer to case definitions in section 5.5)

Z is the value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P is expected true proportion of the outcome of interest (pneumonia-related mortality) (6% estimated in studies conducted in Kenyan children (4, 9))

e is expected precision,

the included records allowed for the estimation of the risk of mortality among Kenyan children hospitalized with pneumonia within a margin of +/- 1% and provided reasonably precise estimates of mortality within the severity classifications.

5.6 Sampling Method

Comprehensive sampling of all records was performed; thus all children fulfilling the eligibility criteria were included in the study.

5.7 Study Tools

The primary data collection tool was developed in REDCap, an electronic web-based database application (47). The structure of the database was based on the Ministry of Health's Paediatric Admission Record form (46) that captures data on patient biodata, clinical characteristics and admission diagnosis. Additional fields were included to capture data on daily inpatient care including treatment prescribed and information on discharge diagnosis and clinical outcome (survival or death). A printed copy of the tool used is attached to this proposal as Appendix 2.

The principal investigator piloted the study tool for three days using records of children admitted at Mbagathi District Hospital. Minor changes were then made to the original version after which it was deployed to mini-laptop computers for data entry.

Data entered on the REDCap database were saved locally on the mini-laptops by trained research assistants. This process was overseen by the principal investigator, who reviewed the data entered daily with the aid of a data cleaning script developed in STATA version 12.0 (Stata Corp, Texas, USA) and provided prompt feedback to the research assistants on identified errors and missing data.

5.8 STUDY PROCEDURES

The data proposed for use in this study were extracted from all eligible paediatric records at seven hospitals listed in section 5.2 above.

Training on Case Management Guidelines

The principal investigator conducted one-day training exercises on the Kenyan Ministry of Health childhood pneumonia guidelines for pneumonia for all paediatric staff in preparation for a multi-centre clinical trial comparing alternative antibiotic treatments for childhood pneumonia (45). Training was repeated at 3 – 6 monthly intervals. Copies of the national clinical practice guidelines were distributed to health workers in the paediatric departments of participating hospitals. Health care workers at six of seven of the hospitals also underwent a five-day course designed for the dissemination of the Ministry of Health paediatric guidelines for health facilities called Emergency Triage Assessment and Treatment Plus (ETAT+) (46) during the study period.

Selection, Training and Supervision of Research Assistants

Data were collected by research assistants recruited through a competitive process approved by the Hospital Management Teams at the participating sites. The minimum qualifications for potential data clerks was a Kenya Certificate of Secondary Education (KCSE) qualification with a mean grade of C minus, literacy in the Microsoft Office software suite, and availability for a minimum period of eight weeks. Preference was given to individuals with experience working in a hospital environment. Table 6 shows the profiles of the data clerks recruited for the initial data collection exercise.

Table 6: Profiles of Research Assistants Recruited for the Study*

Characteristic	Frequency (%) N=24
Age <25 years	19 (79)
Female	11 (46)
Highest academic qualification beyond Form four	7 (29)
Work experience in clinical environment	7 (29)
Prior research experience	2 (8)

* Number of research assistants at each hospital ranged from 2 to 4

Training of the research assistants took place over one week at each hospital. The trainees were introduced to the structure of hospital records, common medical abbreviations, use of the data collection tools and principles of data management. On the final two days of training, the assistants undertook practical sessions on data abstraction from a sample of hospital records. Data from these practice sessions were discarded.

Once the data collection exercise had commenced, follow up visits were conducted by the principal investigator every four to six weeks to provide additional supervisory support to the research assistants and the clinical staff in the paediatric departments including short training lectures and demonstrations on the clinical guidelines and study procedures when possible. Additional supervision was provided through regular telephone and email communication to the study sites.

Onsite supervision was overseen by the hospital paediatrician and a clinical officer whose roles included reporting attendance and monitoring progress of the clerks, facilitating cooperation from the hospital administration and the records department, addressing queries raised by the data clerks relating to the clinical records and ensuring security of the study equipment.

Selection and Retrieval of Patient Files

Sequential inpatient numbers of all paediatric admissions from the beginning of the study period (September 2011) were recorded from the master nursing registers in sets of 50 to 100. These were taken to records department where hospital information and records officers proceeded to retrieve the listed patient files. Upon retrieval, the research assistants proceeded with data entry for the available records. Once data entry for a set of records was complete, the files would be returned to the records departments with the next set of inpatient numbers for files to be retrieved. This exercise was repeated until data from all available files for the study period were extracted. At the end of the initial phase of data entry, a final physical search of the records departments at the study hospitals was undertaken in an effort to retrieve patient records which may have been incorrectly archived.

5.9 DATA MANAGEMENT

Data on pre-defined patient attributes extracted from retrieved inpatient records were analysed. Categorical data were tabulated and summarized as proportions while continuous variables were reported as means, with standard deviations or medians, with inter-quartile ranges as appropriate. The primary outcome, cumulative inpatient mortality, was computed as a proportion along with a 95% confidence interval.

Univariate associations of potential risk factors (independent variables) with mortality (dependent variable) were explored using Chi-squared test (categorical data) and Student's T-test (continuous variables). Findings from these univariate analyses were used to fit a logistic regression model to determine independent risk factors for mortality. Patient age and gender were included in the multivariate model as *a* priori covariates along with all other patient characteristics that were found to be associated with mortality in the univariate analysis with a p value less than 0.1. Additional

analyses were conducted to determine the crude incidence rates of mortality. Kaplan Meier survival curves for time to death in days following hospitalization were plotted comparing the three levels of pneumonia severity. Log rank tests were used to examine for equality across the survivor functions.

Independent Variables

Sociodemographic: Age, sex, hospital of admission

Clinical: fever, duration of illness, respiratory rate, nutritional status, pallor, hydration status, co-diagnosis of malaria, severity classification.

Dependent (Outcome) Variable

Inpatient death versus survival

5.10 Ethical Considerations

Data were extracted from patient records devoid of names and contact details that may identify individuals whose information was collected. The database is hosted on secure servers only accessible with appropriate authorization. Ethical approval for the primary study was obtained from the KEMRI National Ethical Review Committee and the Ministry of Health, centrally through the office of the Director of Medical Services and locally through the medical superintendents of the participating hospitals. Data entry was done following patient discharge from hospital or death, thus the exercise did not interfere with routine patient care, nor pose additional risk to potential study patients.

6.0 RESULTS

A total of 5820 inpatient records for children aged 2 – 59 months hospitalized with an admission diagnosis of pneumonia classified according to the Ministry of Health guidelines at the seven study hospitals between 1st September 2011 and 31st August 2013 were retrieved. Records for children with admission diagnoses of meningitis (n=243) and severe malnutrition (n=3478) were excluded from the analysis along with an additional 115 records that lacked outcome data. The analysis therefore included 1984 children aged 2 – 59 months with pneumonia. The largest number of cases came from Kerugoya District Hospital (DH) (29%), followed by Kisumu District Hospital (23%), Embu Provincial General Hospital (PGH) (15%), New Nyanza Provincial General Hospital (14%), Mbagathi District Hospital (11%), Bungoma District Hospital (7%) and Chuka District Hospital (1%). Figure 5 illustrates the flow of patient records included in the analysis and distribution across the seven study hospitals.

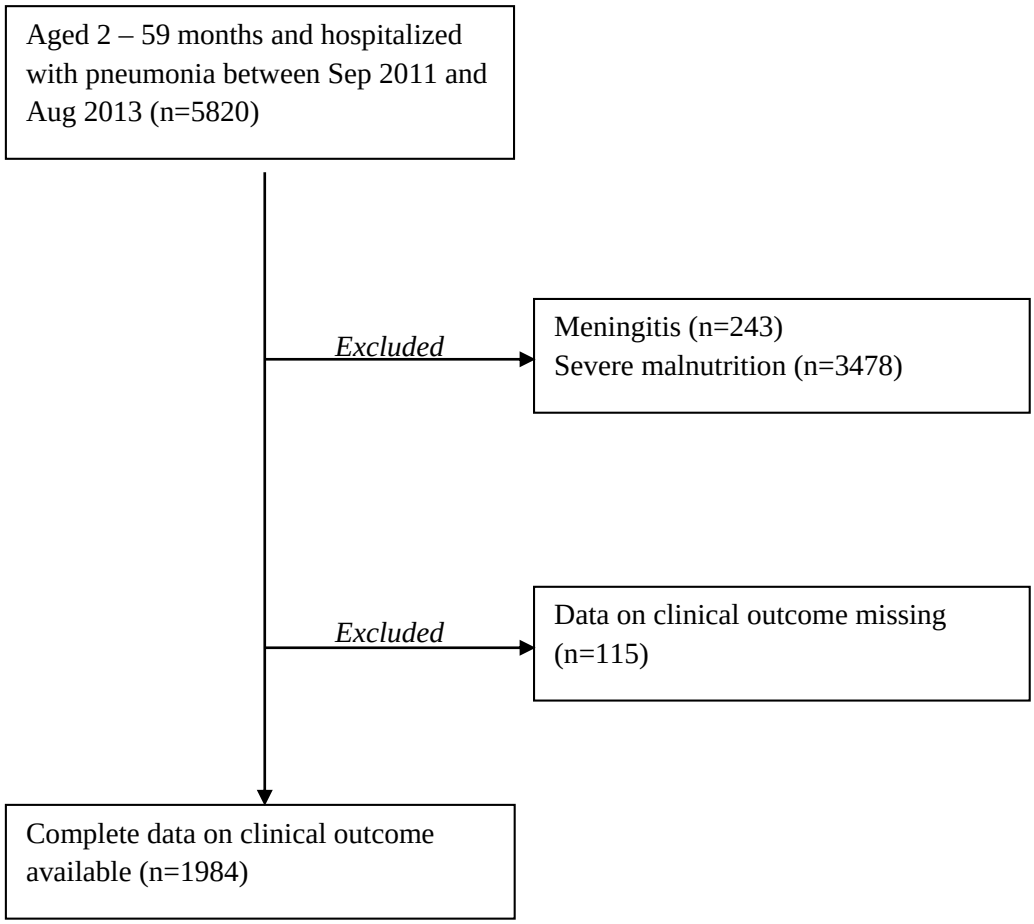


Figure 5: Flow of Patient Records Analysed

Sociodemographic Characteristics of the Study Participants

The median age of the population studied was 14 months (IQR 7 – 24). Children aged 2 – 11 months, 12 – 23 months and 24 – 59 months comprised 832 (41.2%), 529 (26.7%) and 623 (31.4%) respectively. A histogram of the age distribution of the study participants is shown in Figure 6.

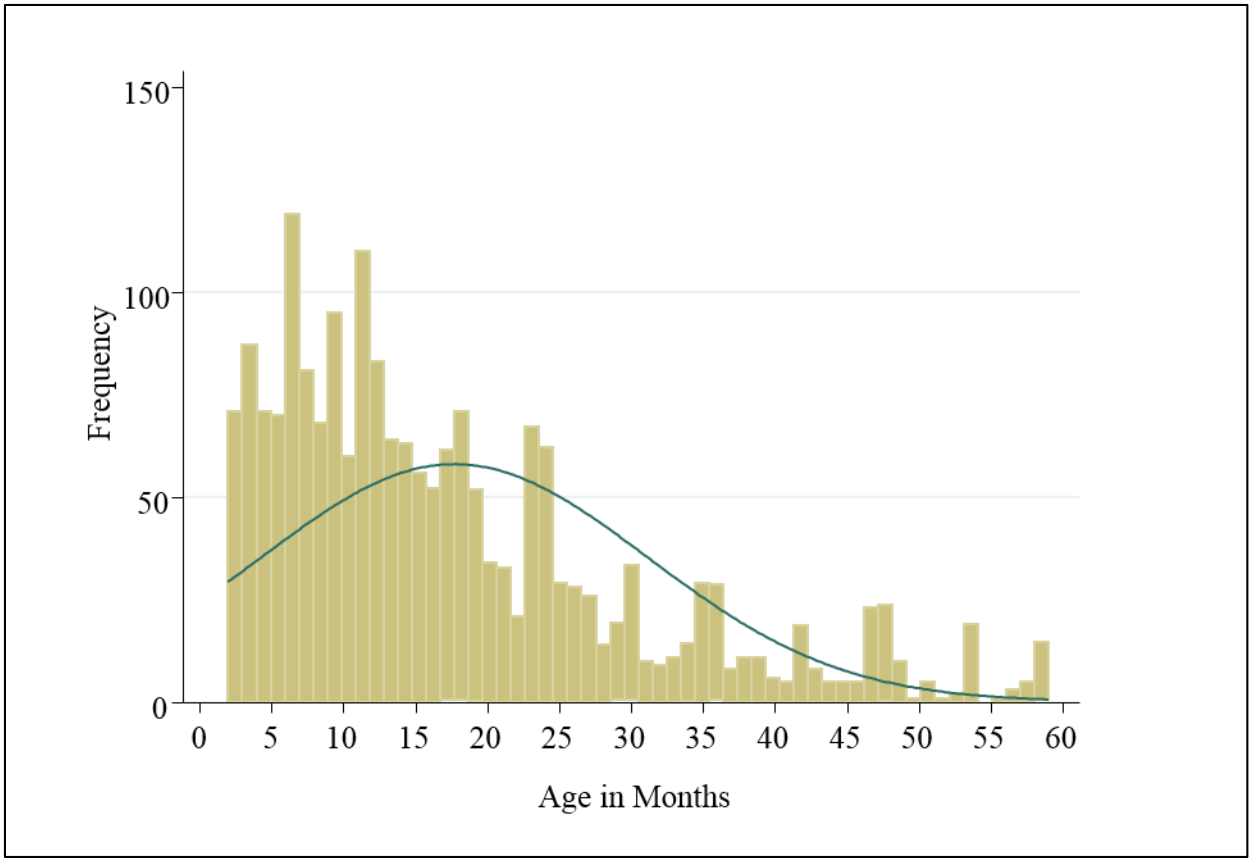


Figure 6: Age Distribution of Study Participants

Of 1955 children for whom gender was documented, 44% were girls. Children admitted at Level IV hospitals (Kerugoya, Kisumu, Mbagathi, Bungoma and Chuka District Hospitals) comprised 1405 (71%) of the total number studied. Another 579 children (29%) were admitted at the two Level V hospitals (New Nyanza and Embu Provincial General Hospitals) (see Table 6).

Table 7: Sociodemographic Characteristics of the Study Participants

Patient Characteristic	n (%)	N
Age group (months)		1984
2 – 11 months	832 (41.2)	
12 – 23 months	623 (31.4)	
24 – 59 months	529 (26.7)	
Gender		1955
Male	1087 (55.6)	
Female	868 (44.4)	
Study hospital		1984
Level IV		
Kerugoya District Hospital	571 (28.8)	
Kisumu District Hospital	460 (23.2)	
Mbagathi District Hospital	212 (10.7)	
Bungoma District Hospital	135 (6.8)	
Chuka District Hospital	27 (1.4)	
Level V		
Embu Provincial General Hospital	306 (15.4)	
New Nyanza Provincial General Hospital	273 (13.8)	

Clinical Characteristics of the Study Participants

Approximately half (48%) of the study participants were classified with severe pneumonia while 29% had very severe and 22% had non-severe pneumonia. (Figure 7).

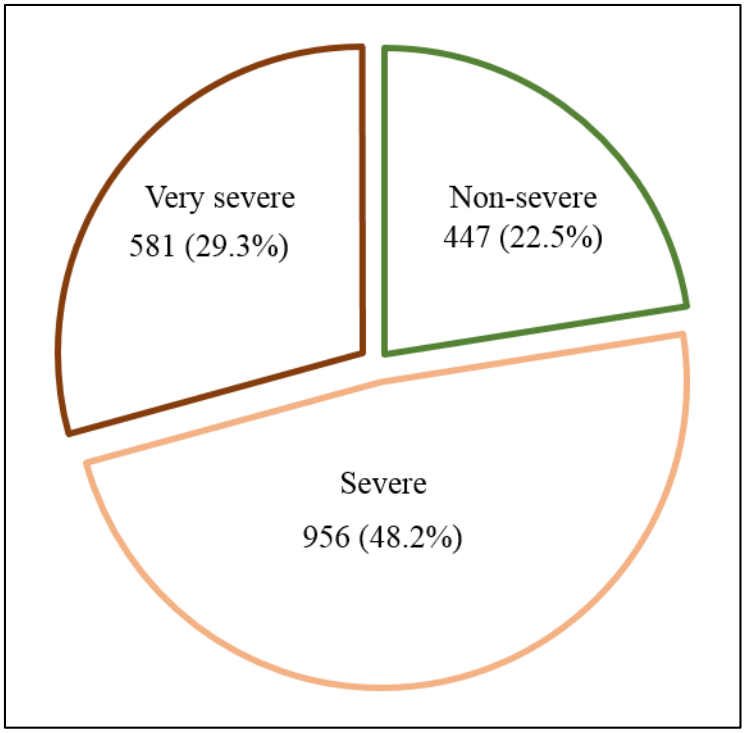
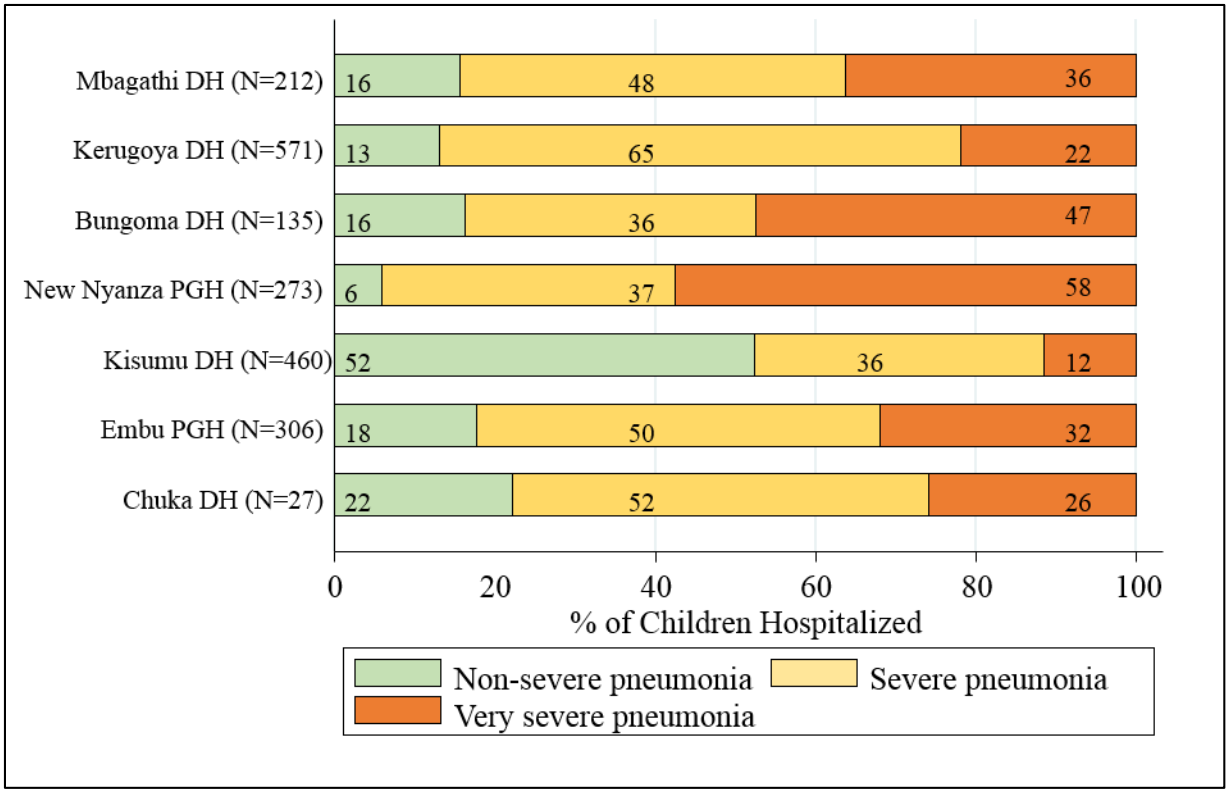


Figure 7: Distribution of Study Participants by Pneumonia Severity Category

A comparison of pneumonia severity by study hospital showed that children with very severe pneumonia comprised the majority of patients at New Nyanza PGH (58%). Interestingly, the majority of children admitted at Kisumu DH, located in the same city, presented with the non-severe category of pneumonia (52%). Other hospitals where very severe pneumonia was a frequent presentation were Mbagathi DH (36%), Bungoma DH (47%) and Embu PGH (32%) (Figure 8).



Numbers in the bars indicate proportions of pneumonia cases admitted

Figure 8: Pneumonia Severity by Study Hospital

A history of fever was reported in 89% of children for whom this symptom was documented. The median respiratory rate among children aged 2 – 11 months was 56 breaths per minute (IQR 48 – 66) and 49 breaths per minute (IQR 40 – 60) for children aged 12 – 59 months. Fast breathing defined by the age specific thresholds provided in the national guidelines (Table 3) was observed in 946/1272 (74.4%) of children studied. Although children for whom records showed an admission diagnosis of severe malnutrition were excluded from the analysis, we used recorded weight and age to compute weight for Age Z scores (WAZ) using WHO child growth standards (48). Each child was then categorized by severity as follows: normal nutritional status (WAZ >-1SD), mild malnutrition (WAZ <-1 to >-2 SD), moderate malnutrition (WAZ <-2 to >-3SD) and severe malnutrition (WAZ <-3SD). Data to compute WAZ scores were available for 1727 children

of whom 996 (58%) had normal nutrition 358 (20%) had mild malnutrition, 233 (14%) had moderate malnutrition and 140 (8%) had severe malnutrition. Clinically defined pallor was recorded in 10.6% of children (7.1% mild / moderate pallor and 3.5% severe pallor), while 239/1984 (12%) of the children studied were reported to have dehydration. The predominant form of dehydration recorded was some dehydration (9%), followed by severe dehydration (3%) and shock (0.1%).

HIV status was only ascertained for 169 (8.5%) of the study participants. HIV antibody negative children comprised 108 (5.4%) of the participants. Forty children (2%) aged below 18 months and 21 (1.1%) aged 18 – 59 months were HIV antibody positive. The HIV status of the majority of the study participants - 1815 (91.5%) was unknown. Further analyses for correlates of mortality for this variable was therefore not pursued.

Malaria was diagnosed in 469 (23%) participants of whom 391 (20%) and 78 (4%) were classified as having non-severe and severe forms respectively (Table 8).

Table 8: Clinical Characteristics of the Study Participants

Patient characteristic	Frequency (%) or median (IQR)	N
Pneumonia severity		1984
Non-severe pneumonia	447 (22.5)	
Severe pneumonia	956 (48.2)	
Very severe pneumonia	581 (29.3)	
History of fever		1755
Present	1564 (89.1)	
Absent	191 (10.9)	
Respiratory rate (breaths / minute)		1272
2 – 11 months	56 (48, 66)	574
12 – 59 months	49 (40, 60)	698
Nutritional status		1727
WAZ >-1SD	996 (57.7)	
WAZ <-1 to >-2 SD (mild malnutrition)	358 (20.7)	
WAZ <-2 to >-3SD (moderate malnutrition)	233 (13.5)	
WAZ <-3SD (severe malnutrition)	140 (8.1)	
Pallor		1639
Absent	1466 (89.4)	
Mild / moderate	116 (7.1)	
Severe	57 (3.5)	
Dehydration		1984
Absent / no dehydration	1745 (88.0)	
Some dehydration	185 (9.3)	
Severe dehydration	53 (2.7)	
Shock	1 (0.1)	
HIV infection		1984
HIV antibody negative	108 (5.4)	
HIV-antibody positive < 18 months	40 (2.0)	
HIV-antibody positive 18 – 59 months	21 (1.1)	
Unknown HIV status	1815 (91.5)	
Malaria		1984
Absent	1515 (76.4)	
Non-severe	391 (19.7)	
Severe	78 (3.9)	
Duration of hospital stay		1905
Less than 5 days	1314 (69.0)	
5 to 14 days	490 (25.7)	
More than 14 days	101 (5.3)	

The proportion of children admitted with malaria varied widely across hospitals with less than 10% of patients in Mbagathi and Kerugoya District Hospitals having the diagnosis at admission compared with up to two thirds of children admitted at Bungoma and Kisumu Hospitals (Figure 9) where severe forms were also most frequently observed (19 % and 7% of all admitted patients respectively).

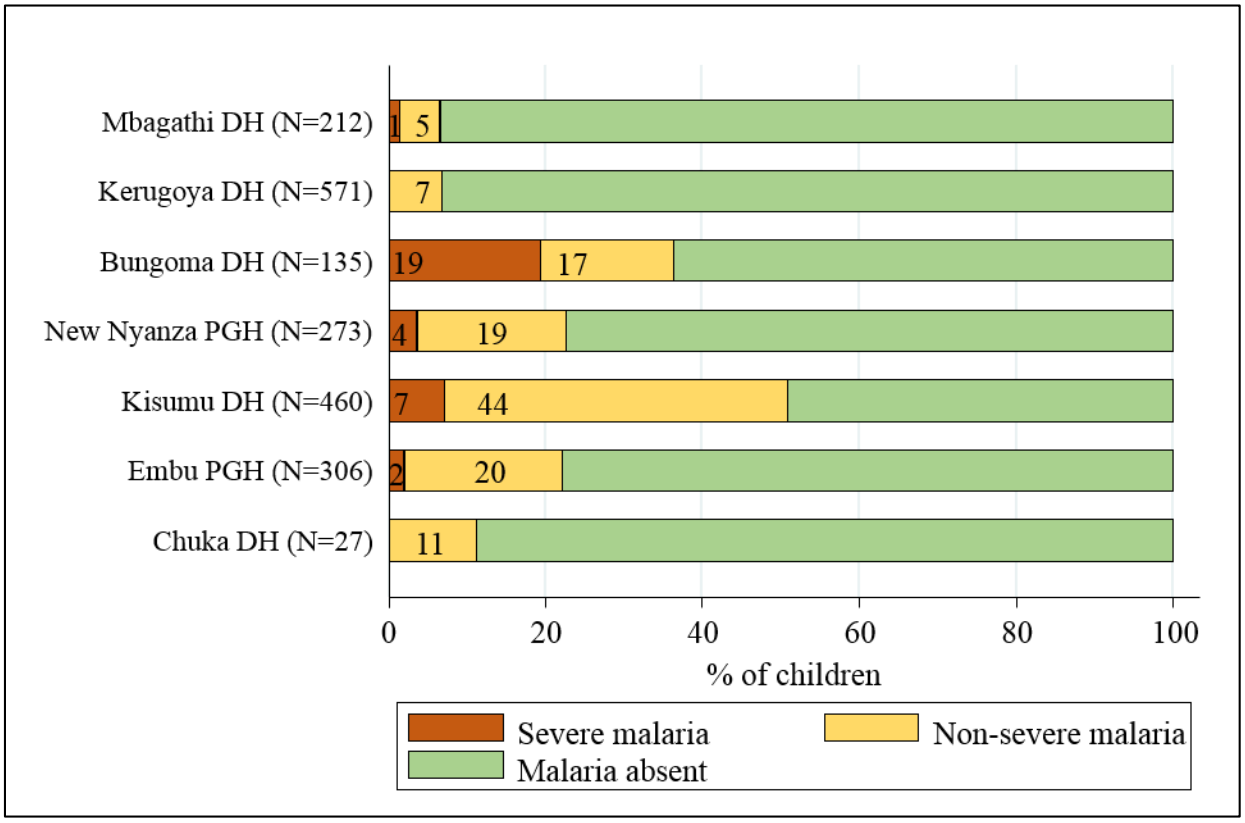


Figure 9: Proportion of Patients with Malaria Co-diagnosis by Study Hospital

Mortality among Children Hospitalized with Pneumonia

Over the period of the study, 77/1984 deaths were observed yielding a CFR of 3.9% (95% CI 3.1 to 4.8). Mortality was 1.1% (5/447) and 2.3% (22/956) in the non-severe and severe categories respectively. In contrast, the proportion of deaths among those with very severe pneumonia was 8.6% (50/581) (Table 9).

Table 9: Case Fatality Rates among Study Participants

Disease severity	Deaths / Number of patients	Mortality % (95% CI)
Non-severe	5/447	1.1 (0.4, 2.6)
Severe	22/956	2.3 (1.5, 3.5)
Very severe	50/581	8.6 (6.5, 11.2)
All pneumonia	77/1984	3.9 (3.1, 4.8)

The case fatality rates observed across the three levels of severity and overall are illustrated in Figure 10.

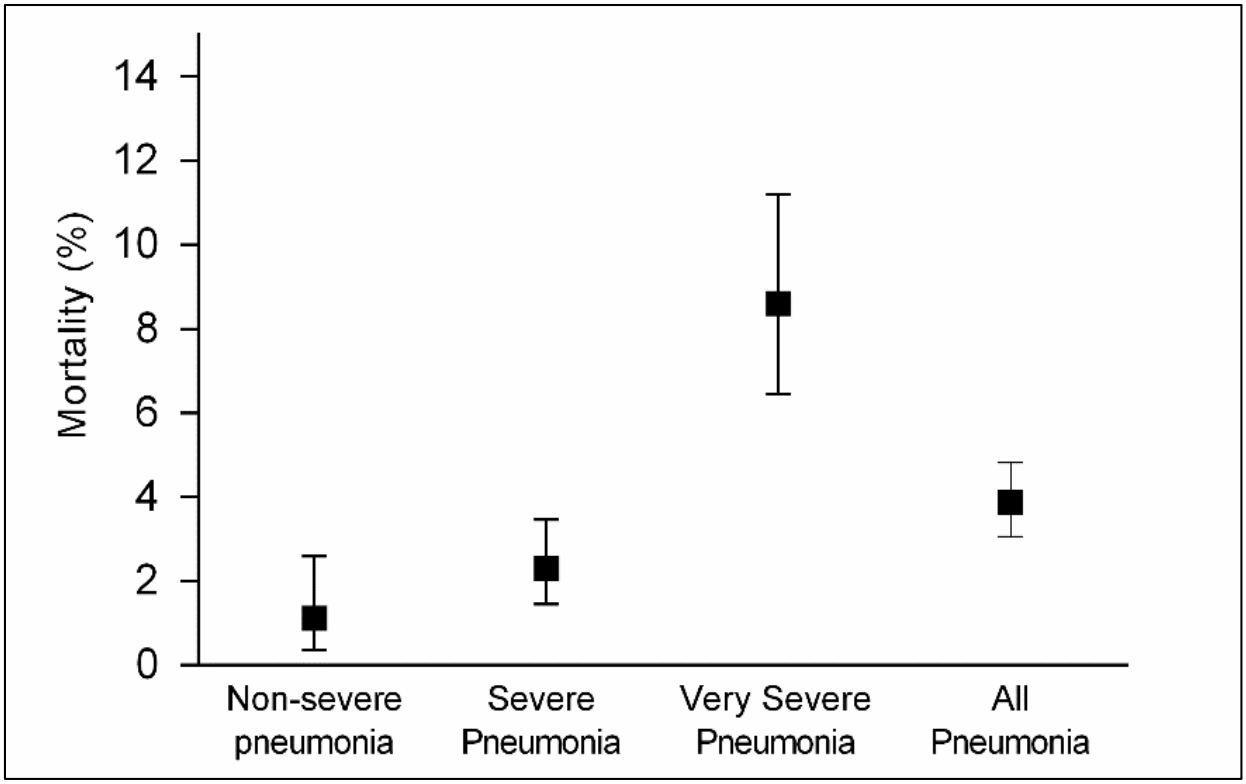


Figure 10: Distribution of Case Fatality Rates by Severity Category

Length of Hospital Stay

Over two thirds of the study participants (69%) were hospitalized for less than five days. A further 490 (26%) were discharged or died from 5 to 14 days after admission, while a smaller proportion 101 (5%) were inpatients for more than 14 days. The overall median length of stay was 3 days (IQR 2 to 5 days) and varied by outcome. Children who survived experienced a significantly longer duration of hospitalization (3 days; IQR 2 to 5 days) than those who died (1 day; IQR 0 to 3 days) (Mann Whitney *U* test P value <0.01) (Figure 11)

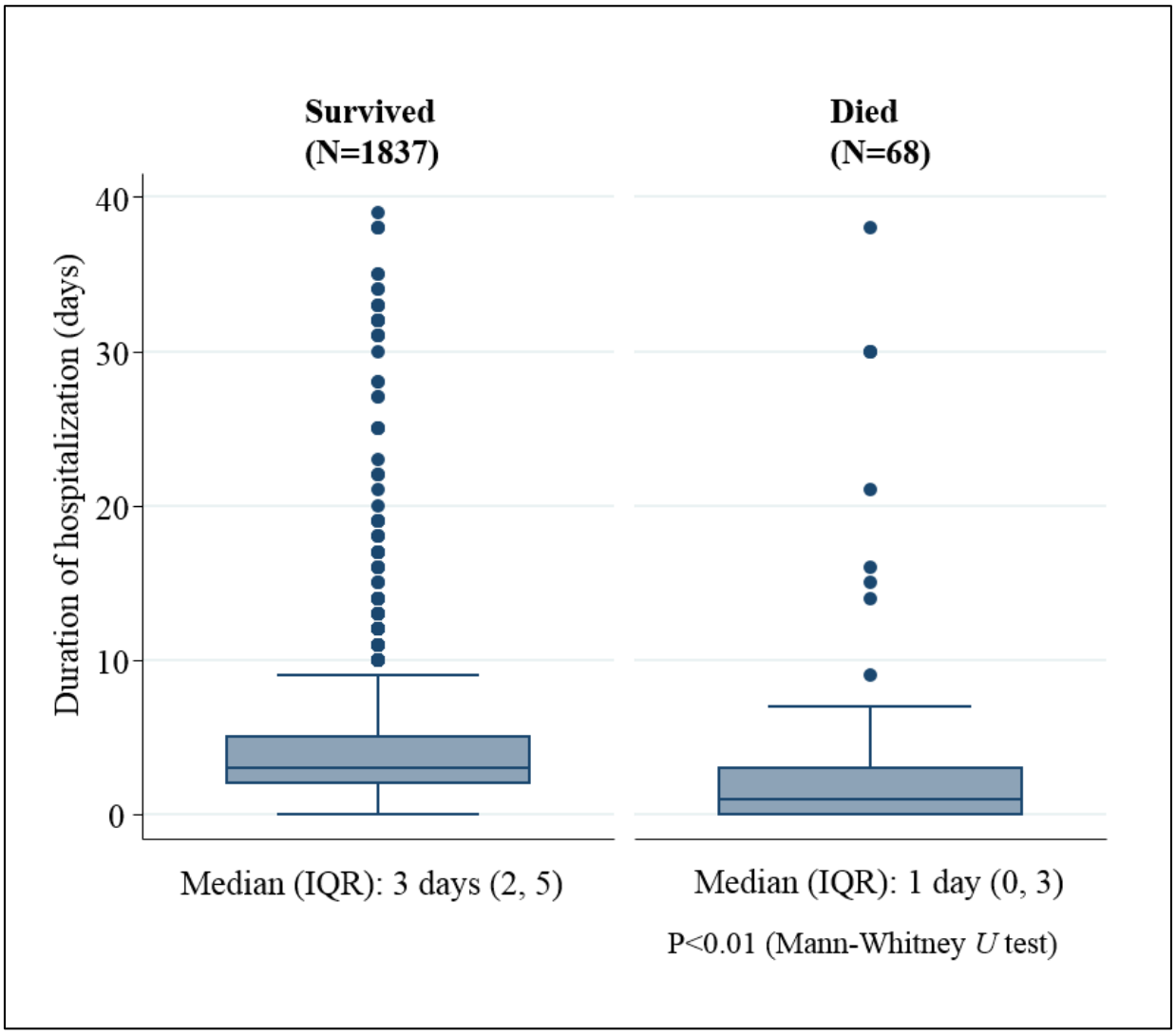


Figure 11: Median Duration of Hospital Stay in Days by Clinical Outcome

Incidence of Mortality among Children Hospitalized with Pneumonia

The incidence of mortality among all children with pneumonia was 7.1 deaths per 1000 person-days. The rate varied by severity category with children classified with non-severe, severe and very severe pneumonia experiencing mortality rates of 2.9, 4.4 and 13.0 deaths per 1000 person-days respectively (Log-rank test P<0.01) (Figure 12).

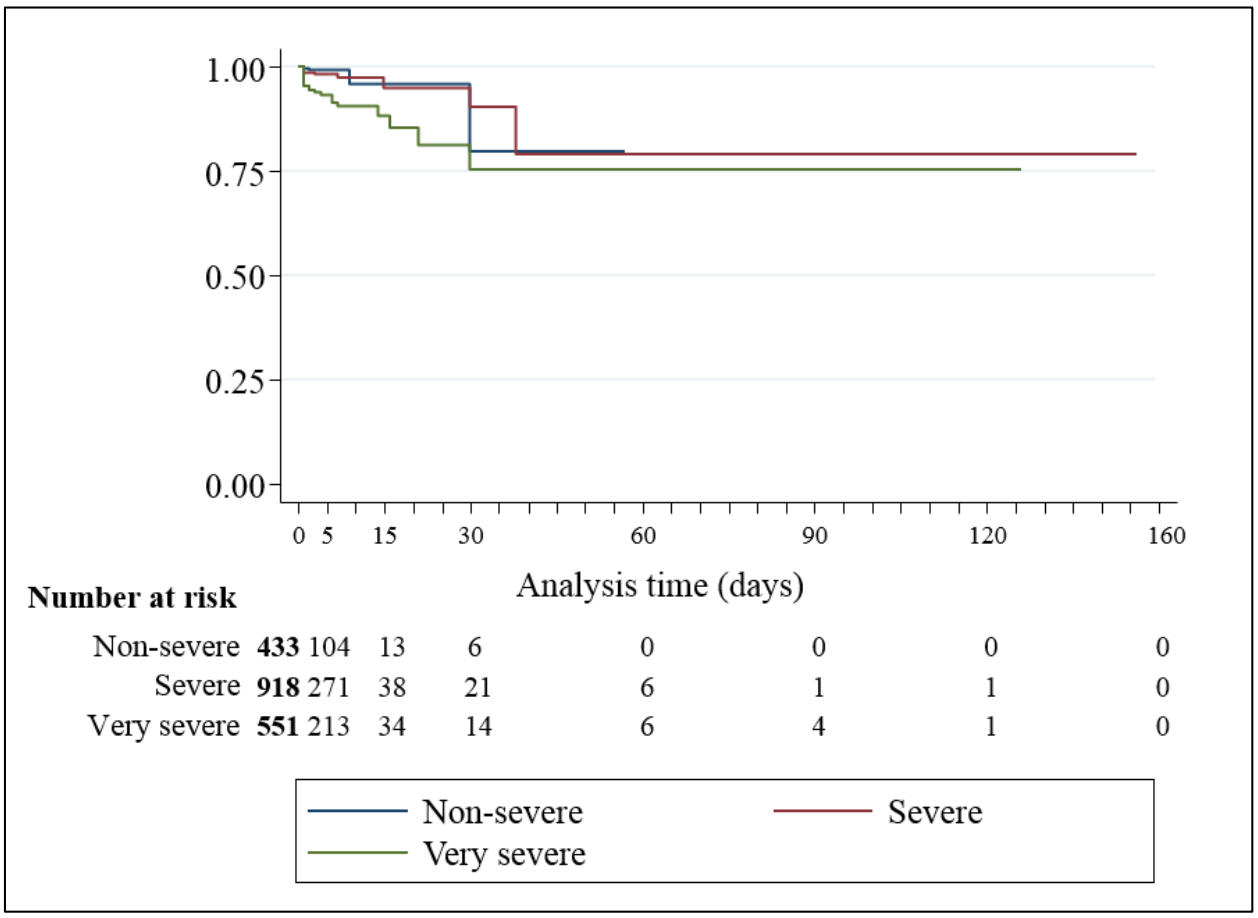


Figure 12: Kaplan-Meier Survival Curves for Mortality by Pneumonia Severity Classification

The incidence rate ratios for mortality were similar between children with severe versus non-severe pneumonia (IRR 1.5; 95% CI 0.5 to 5.5) and significantly higher among children with very severe versus non-severe pneumonia (IRR 4.4; 95% CI 1.7 to 14.2) (Table 10)

Table 10: Incidence Rates for Mortality by Pneumonia Severity Category

Severity category	Incidence Rate per 1000 person-days (95% CI)	Incidence Rate Ratio (95% CI)	P value
Non-severe pneumonia	2.9 (1.2, 7.1)	1.0	
Severe pneumonia	4.4 (2.8, 6.8)	1.5 (0.5, 5.1)	0.44
Very severe pneumonia	13.0 (9.6, 17.5)	4.4 (1.7, 14.2)	<0.01

CI – Confidence interval

Univariate Associations for Mortality among Children Hospitalized with Pneumonia

Risk factors for mortality were initially examined in univariate analyses. Mortality was highest among children aged below 12 months (5.8%) when compared with those aged 12 – 59 months (2.5). While no statistical difference was detected between mortality among children with non-severe pneumonia versus those with severe pneumonia (OR 2.1; 95% CI 0.8 to 5.5), the diagnosis of very severe pneumonia was associated with an eight-fold increased odds of mortality compared to the non-severe category (OR 8.3 95% CI 3.2 to 21.3). Mortality increased with increasing severity of dehydration. Among children with no dehydration, mortality was 3.0% while children with some dehydration and severe dehydration suffered mortality rates of 8.7% and 14.8% respectively (Score test for linear trend P value <0.01). Similarly, mortality appeared to increase with increasing severity of pallor. Among children with no pallor, mild / moderate pallor and severe pallor, mortality was 2.1%, 11.2% and 21.1% respectively (Score test for linear trend P value <0.01). Mortality was highest among children with severe malnutrition (10.3%) compared to those with moderate malnutrition (5.2%) or mild malnutrition / normal nutritional status (2.1%). Score test for linear trend P<0.01). No association with mortality was found for fever (OR 1.1; 95% CI 0.5 to 2.7), gender (male versus female OR 1.1; 95% CI 0.7 to 1.7), tachypnoea defined by age specific cut offs (OR 1.6 95% CI 0.8 to 3.4) nor for an admission diagnosis of malaria (non-

severe malaria versus no malaria OR 0.7, 95% CI 0.3 to 5.4; severe malaria versus no malaria OR 0.9, 95% CI 0.5 to 9.7) (Table 11).

Table 11: Univariate Associations for Mortality in Children Hospitalized with Pneumonia

Patient characteristic	Number of Deaths/N	(% Mortality)	Odds Ratio (95% CI)	P value χ^2 test	P value score test for trend
Age 2 – 11 months	48/832	(5.8)	1.0		
Age 12 – 59 months	29/1152	(2.5)	0.4 (0.4, 0.9)	<0.01	
Female gender	33/868	(3.8)	1.0		
Male gender	44/1087	(4.1)	1.1 (0.7, 1.7)	0.78	
History of fever: No	6/191	(3.1)	1.0		
History of fever: Yes	56/1564	(3.6)	1.1 (0.5, 2.7)	0.76	
Non-severe pneumonia	5/447	(1.1)	1.0		<0.01
Severe pneumonia	22/956	(2.3)	2.1 (0.8, 5.5)	0.13	
Very severe pneumonia	50/581	(8.6)	8.3 (3.2, 21.3)	<0.01	
Respiratory rate normal	9/326	(2.8)	1.0		
Respiratory rate increased*	42/946	(4.4)	1.6 (0.8, 3.4)	0.18	
Malaria: No	63/1515	(4.1)	1.0		0.35
Malaria: Non-severe	11/391	(2.8)	0.7 (0.3, 5.4)	0.22	
Malaria: Severe	3/78	(3.9)	0.9 (0.5, 9.7)	0.89	
Pallor absent	31/1466	(2.1)	1.0		<0.01
Pallor mild / moderate	13/116	(11.2)	5,8 (2.9, 11.6)	<0.01	
Pallor severe	12/57	(21.1)	12.3 (5.8, 26.1)	<0.01	
Dehydration absent	53/1745	(3.0)	1.0		<0.01
Some dehydration	16/185	(8.7)	3.0 (1.7, 5.4)	<0.01	
Severe dehydration / shock	8/54	(14.8)	5.6 (2.5, 12.4)	<0.01	
Malnutrition (WAZ): Normal / mild	27/1300	(2.1)	1.0		<0.01
Malnutrition (WAZ): Moderate	12/233	(5.2)	2.6 (1.3, 5.1)	<0.01	
Malnutrition (WAZ): Severe	20/194	(10.3)	5.4 (3.0, 9.9)	<0.01	

* Increased respiratory rate defined by age- specific thresholds in the Kenyan and WHO guidelines
WAZ – Weight for Age Z score. Malnutrition classification based on Kenyan and WHO guidelines

A comparison across the seven sites revealed mortality rates ranging from 0.7% at Kerugoya DH to 8.1% at New Nyanza PGH. A total of 31 (2.2%) deaths were observed at the four Level IV hospitals compared with 46 (7.9%) at the two Level V facilities, indicating higher mortality in Level V compared to Level IV hospitals (OR 3.8; 95% CI 2.4 – 6.1) (Table 12).

Table 12: Univariate Associations for Mortality by Study Site

Study site	Number of Deaths/N	(% Mortality)	Odds Ratio (95% CI)	P value χ^2 test
Level IV	**31/1405**	**(2.2)**	**1.0**	
Kerugoya District Hospital	4/571	(0.7)		
Kisumu District Hospital	10/460	(2.2)		
Mbagathi District Hospital	7/212	(3.3)		
Bungoma District Hospital	7/135	(5.2)		
Chuka District Hospital	2/27	(7.4)		
Level V	**46/579**	**(7.9)**	**3.8 (2.4, 6.1)**	**<0.01**
Embu Provincial General Hospital	24/306	(7.8)		
New Nyanza Provincial General Hospital	22/273	(8.1)		

Multivariate Associations for Mortality among Children Hospitalized with Pneumonia

A multivariate model including 1423 observations was fitted to determine independent risk factors for mortality in the study population.

Very severe pneumonia was associated with a six-fold increased odds of mortality compared to non-severe pneumonia (adjusted odds ratio (aOR) 6.0; 95% CI 1.1 to 33.0). In comparison, mortality was similar among children with severe and non-severe pneumonia (aOR 1.4; 95% CI 0.2 to 8.0).

Pallor was shown to be associated with mortality. The presence of mild / moderate forms was associated with a six-fold increased odds of death (aOR 6.1; 95% CI 2. to 17.8) while an even greater association found for severe forms (aOR 16.4; 95% CI 4.6 to 58.1).

Mortality increased proportionate to severity of dehydration (aOR 3.8; 95% CI 1.2 to 11.8 and OR 24.6; 95% CI 6.2 to 97.3 for some and severe dehydration / shock respectively). Similarly, mortality increased with severity of malnutrition (moderate malnutrition aOR 3.8, 95% CI 1.1 to 12.5; severe malnutrition aOR 4.0, 95% CI 1.3 to 12.2).

Admission at the Level V hospitals (Embu and New Nyanza PGH) was also shown to be associated with increased odds of mortality in comparison with the Level IV district hospitals (OR 3.3; 95% CI 1.3 to 8.5) (Table 13).

Table 13: Multivariate Associations for Mortality (N=1423)

Patient characteristic	Odds Ratio (95% CI)	P value
Age 2 – 11 months	1.0	
Age 12 – 59 months	0.91 (0.4, 1.9)	0.79
Female gender	1.0	
Male gender	2.0 (0.8, 5.0)	0.15
Non-severe pneumonia	1.0	
Severe pneumonia	1.4 (0.2, 8.0)	0.72
Very severe pneumonia	6.0 (1.1, 33.0)	0.04
Pallor absent	1.0	
Mild / moderate pallor	6.1 (2.1, 17.8)	<0.01
Severe pallor	16.4 (4.6, 58.1)	<0.01
Dehydration absent	1.0	
Some dehydration	3.8 (1.2, 11.8)	0.02
Severe dehydration / shock	24.6 (6.2, 97.3)	<0.01
Malnutrition (WAZ): Normal / mild	1.0	
Malnutrition (WAZ): Moderate	3.8 (1.1, 12.5)	0.03
Malnutrition (WAZ): Severe	4.0 (1.3, 12.2)	0.02
Hospital category: Level IV	1.0	
Hospital category: Level V	3.3 (1.3, 8.5)	0.01

Discharge Diagnoses

Among all children with pneumonia diagnosed upon hospital admission, 233 (11.7%) were documented to have diagnoses other than pneumonia. The major discharge diagnoses documented in this group of children were meningitis (119 cases), malaria (47 cases), and diarrhoea / acute gastroenteritis (43 cases). Anaemia, malnutrition, asthma and tuberculosis were reported less frequently in 12, 11, 10 and 9 cases respectively. Of those admitted with pneumonia but discharged with other diagnoses, 17/233 (7.3%) died. The largest number of deaths (47.1%) had a diagnosis of meningitis. (Table 14).

Table 14: Discharge Diagnoses for Patients without Diagnoses of Pneumonia upon Discharge

Discharge Diagnosis	Number survived (%)*	Number died (%)*	Total (%)*
Malaria	47 (21.8)	0 (0.0)	47 (20.2)
Acute gastroenteritis / Diarrhoea	42 (19.4)	1 (5.9)	43 (18.5)
Malnutrition	11 (5.1)	0 (0.0)	11 (4.7)
Anaemia	10 (4.6)	2 (11.7)	12 (5.2)
Meningitis	111 (51.4)	8 (47.1)	119 (51.1)
Asthma	10 (4.6)	0 (0.0)	10 (4.3)
Tuberculosis	9 (4.2)	0 (0.0)	9 (3.9)
All with discharge diagnoses other than pneumonia	216	17	233

* Total exceeds 100% as some patients had multiple discharge diagnoses

7.0 DISCUSSION

This study sought to estimate the case fatality of pneumonia among children admitted for care at seven Kenyan hospitals and their risk factors for mortality. Previous local research addressing this question have been limited to individual sites and were conducted prior to the introduction of either one or both of the vaccines targeting the leading bacterial causes of pneumonia. The overall risk of mortality among children hospitalized with pneumonia was 3.9% in our setting. This estimate matches the findings of a recently published meta-analysis of 11 African studies where the pooled mortality for children with severe acute lower respiratory infections aged 0 – 59 months was also reported as 3.9% (6). It must however be noted that we excluded children below 2 months old among whom mortality would be expected to be higher. A similar figure was reported in an observational study of over 500 children admitted at a district hospital along the Kenyan coast

after the introduction of the Hib vaccine but before the pneumococcal vaccine where the overall mortality was estimated at 3.3% (8).

A comparison across the severity strata revealed a six-fold higher odds of death among children with very severe pneumonia compared with those in the non-severe category. This contrasted with the case fatality in the severe category which, although double in magnitude (1.1% versus 2.3%), was statistically no different from the non-severe group in both univariate and multivariate analyses. The revised WHO pneumonia classification considers the former "non-severe" and "severe" pneumonia categories as a single group now referred to as "pneumonia" while what was very severe pneumonia has since been renamed severe pneumonia. There has been reluctance to adopt this new classification, particularly in sub-Saharan Africa, where there are concerns that children with pneumonia manifesting with lower chest wall indrawing represents a population with a high risk of death (44, 49). The findings of our research offer some insight into the comparative risks of mortality across the three categories of pneumonia severity in an African setting. The implications of treatment of children with indrawing in outpatient settings cannot however, be directly addressed with these data.

The median duration of hospitalization of three days indicates the acute nature of illness among the children studied. Length of hospitalization was significantly shorter within the group of children who died versus those who survived (1 day versus 3 days). This finding supports efforts towards improving emergency care within hospitals through enhancing capacity to offer intensive care services at tertiary facilities and provision of basic care at all levels through interventions such as ETAT+ (26) - a five day course that specifically focuses on equipping health workers with skills to attend to children with severe illnesses during the first 48 hours of presentation to a health facility.

Pneumonia was not documented as a diagnosis at the time of discharge for 12% of the study participants. More than half of these children were diagnosed with meningitis and 7.3% died (of whom more than half had meningitis). Pneumonia and meningitis share aetiological pathogens – particularly *Streptococcus pneumonia* which is the major bacterial cause of the two conditions (50). It is possible that meningitis may have developed as a complication of pneumonia or may have been undetected at the time of admission. This finding indicates the importance of comprehensive evaluation of severely ill children at initial presentation and intensive monitoring to assess for both improvement and deterioration.

In univariate analyses, lower age group was noted to be associated with mortality. Surprisingly, despite evidence from multiple previous studies describing increased mortality among young children (10, 34), the adjusted model showed no association in this analysis. The association between HIV infection and mortality among children with pneumonia has previously been described (10, 34, 51). Unfortunately the low number of participants for whom HIV status could be ascertained limited the ability to examine the effect of this factor on mortality. The presence of pallor (both mild to moderate and severe forms) was strongly associated with mortality in both univariate and multivariate analyses. Pallor is commonly used as a clinical marker for anaemia with diagnostic sensitivity and specificity above 80% for children with packed cell volumes below 15% (52, 53). While there is no common direct association between pallor and pneumonia, local data identify malaria as the leading cause of severe anaemia among hospitalised children (54). Respiratory distress resulting from metabolic acidosis in this population is a complication of severe malaria and dehydration that has been associated with high mortality (55, 56). It is possible that the diagnosis of pneumonia based on signs of respiratory distress among children with severe pallor and similarly, those with dehydration, was in fact attributable to metabolic acidosis. Of note

however, was the lack of association between malaria diagnosed at admission and mortality. The challenge of diagnosing pneumonia among children with metabolic acidosis resulting from acute diarrhoea was studied by Saha *et al*, who reported a specificity of the WHO guidelines for diagnosis of pneumonia of only 6.9% at enrolment that increased to 65.5% after initial rehydration (57). It was not possible to confirm the underlying causes of respiratory distress in this study population, since blood gas analysis was not available at any of the study sites and chest radiography was not performed routinely.

Although children with documented admission diagnoses of severe malnutrition were excluded from this study, WAZ scores computed using data on weight and age revealed that 140 (8.1%) of the study population were severely malnourished – without the apparent awareness of the admitting clinician. Furthermore, 233 (13.5%) were moderately malnourished. Both moderately and severely malnourished children experienced increased mortality with odds of death directly associated with increasing severity of malnutrition. The odds of death were found to increase with increasing severity. This is finding is supported by literature from previous studies summarized in a systematic review of 16 studies conducted in developing countries (32). It further challenges the appropriateness of the Kenyan and WHO guidelines that currently fail to recognize children with moderate forms of malnutrition as a population with a high risk of death (23, 58).

Very severe pneumonia was also independently associated with increased mortality compared with the non-severe category. Despite the change in terminology in the revised WHO guidelines (currently referred to as severe pneumonia), the management of this population of children remains unchanged, requiring aggressive management with broad spectrum parenteral antibiotics and inpatient supportive care. Studies focusing on addressing the high mortality in this group are required including clinical trials to compare alternative treatment regimens.

The odds of death among children admitted at Level V hospitals was three times greater than in Level IV hospitals. Level V hospitals serve as regional referral facilities in contrast to the other five district hospitals. The difference observed may therefore be attributed to the population of patients admitted at large referral hospitals, who tend to be more severely ill and present with clinical complications.

Strengths

The large sample size drawn from multiple hospitals spread across the country resulted in precise estimates that were representative of the population of children hospitalised with severe pneumonia in many parts of the country. The collection of data covering two years further enhanced the representativeness through eliminating seasonal bias – an important consideration in studies on acute respiratory infections in children (59). Rigorous training and close supervision of the research assistants, in addition to the training provided to the clinical staff at the hospitals and dissemination of clinical guidelines improved the quality of the data collected.

Limitations

The limitations of this study are largely related to its retrospective design. The analyses presented relied on data from routine hospital records archived in records departments. A limitation of this approach was the potential for selection bias arising from misplaced patient records that could not therefore be included in the analysis. Important variables such as oxygen saturation were not adequately documented and could therefore not be included in the analysis. It was also not possible to confirm the extent to which treatments prescribed such as antibiotics, oxygen, blood transfusion and fluids were received. This consideration is particularly relevant in situations where hospitals experience shortages of staff and various essential treatments. Finally, all seven study sites were internship training centres with paediatric departments headed by at least one paediatrician. The

clinical staff also underwent ETAT+ training which is likely to have impacted on the quality of care provided. The findings of this study may therefore not be representative of lower level health facilities with limited staff and resources.

8.0 CONCLUSIONS

1. In this retrospective longitudinal survey of children aged 2 – 59 months admitted with pneumonia at seven Kenyan hospitals, the overall case fatality for pneumonia was 3.9%with relatively low mortality observed among children with non-severe and severe pneumonia (1.1% and 2.3% respectively), and significantly higher mortality among children with very severe pneumonia (8.6%)..
2. Very severe pneumonia, the presence of any pallor, any dehydration, moderate and severe malnutrition and hospitalization at the higher level referral hospitals were independently associated with increased mortality in these children.

9.0 RECOMMENDATIONS

Our findings provide useful evidence to inform local and regional guidelines and policy on childhood pneumonia, at a time when African countries are considering the recent WHO revisions on childhood pneumonia.

Young children presenting with pneumonia and the risk factors identified in our study (very severe presentation, pallor, dehydration and malnutrition) may require more aggressive management as they suffer an increased risk of death.

Routine data from public hospitals can be utilised to address a policy-relevant clinical questions on childhood pneumonia and possibly other common childhood illnesses. However, improved

documentation by clinicians is required to enhance the quality of data and ensure validity of the results obtained.

10.0 APPENDICES

Study Tool

Hospital ID. _____ Clerk ID. _____

Q'nnaire No. _____ Pt's initials _____

Patient record ☐ PAR ☐ Free text

Date of Adm. (dd/mm/yy) ___ __/___ ___ /___ ___

Weight	_____kg			Age	_____ yr		_____ months	
Sex	M	F		Temperature	_____ °C			
BCG	Y	N	U	OPV/DPT 1	Y	N	U	
OPV/DPT 2	Y	N	U	OPV/DPT 3	Y	N	U	
PCV 1	Y	N	U	PCV 2	Y	N	U	
PCV 3	Y	N	U	Measles	Y	N	U	

History				**Examination**					
Length of illness	_____d		U	Airway	☐ Clear	☐ Stridor			
Cough	Y	N	U	Breathing					
Cough >3wk	Y	N	U	Resp. rate	_____ bpm	U			
Difficulty breathing	Y	N	U	Cyanosis	Y	N	U		
Diarrhoea	Y	N	U	Indrawing	Y	N	U		
Diarrhoea >14d	Y	N	U	Grunting	Y	N	U		
Diarrhoea bloody	Y	N	U	Acidotic breathing	Y	N	U		
Convulsions	Y	N	U	Wheeze	Y	N	U		
Partial/ focal fits	Y	N	U	Crackles	Y	N	U		
Vomiting	Y	N	U	Circulation					
Vomiting everything	Y	N	U	Pulse	☐ weak	☐ norm	U	____bpm	
Difficulty feeding	Y	N	U	Cap refill	☐ <2s	☐ 2-3s	☐ >3s	E	
				Pallor / Anaemia	0	+	+++	E	

General / nutrition				Dehydration					
Height / length	_____ cm		U	Sunken eyes	Y	N	U		
MUAC	_____ cm		U	Skin pinch	☐ 0s	☐ 1s	☐ ≥2s	E	
Severe wasting	Y	N	U	Disability					
Oedema of kwash	Y	N	U	AVPU	A	V	P	U	E
Jaundice	Y	N	U	Cannot drink / breastfeed	Y	N	U		
Lethargy / reduced playfulness	Y	N	U	Bulging fontanelle	Y	N	U		
Fever >1wk	Y	N	U	Stiff neck	Y	N	U		

Admitting clinician's details

Clinician's initials _____

Clinician's designation ☐ MO Intern ☐ MO ☐ CO Intern ☐ RCO ☐ Paed'cian E

Hospital ID. _____ Clerk ID. _____

Q'nnaire No. _____ Pt's initials _____

Admission Diagnoses

A. In this section, please record the diagnoses of the first admitting clinician ONLY

Pneumonia severity	☐ Pneumonia	☐ Sev' pneum	☐ Very sev' pneum	☐ Other class'n	
Co-diagnoses					
Asthma	☐ Y	☐ N	☐ U		
	☐ Mild asthma	☐ Sev' asthma	☐ Very sev' asthma	☐ Other class'n	
Malaria	☐ Y	☐ N	☐ U		
	☐ Non-sev malaria	☐ Sev' malaria	☐ Other class'n		
Dehydration	☐ Y	☐ N	☐ U		
	☐ No dehyd'n	☐ Some dehyd'n	☐ Sev' dehyd'n	☐ Shock	☐ Other
HIV	☐ Y	☐ N	☐ U		
Malnutrition	☐ Y	☐ N	☐ U		
	☐ Mild malnut'n	☐ Mod malnut'n	☐ Sev' malnut'n	☐ Other class'n	
Meningitis	☐ Y	☐ N	☐ U		
Anaemia	☐ Y	☐ N	☐ U		
	☐ Mild/mod'	☐ Sev' anaemia			
Other 1	_____				
Other 2	_____				
Clinician 1 initials	_____				
Clinician 1 designation	☐ MO Intern	☐ MO	☐ CO Intern	☐ RCO	☐ Paed'cian ☐ U

B. Was this child seen again on admission by a clinician other than clinician 1? ☐ Y ☐ N

If No, skip this section

Clinician 2 initials	_____				
Clinician 2 designation	☐ MO Inter n	☐ MO	☐ CO Intern	☐ RCO	☐ Paed'cian ☐ U
Did clinician 2 change the diagnosis in any way?	☐ Y	☐ N If Yes, record below			
Pneumonia severity	☐ Pneumonia	☐ Sev' pneum	☐ Very sev' pneum	☐ Other class'n	
Asthma	☐ Mild asthma	☐ Sev' asthma	☐ Very sev' asthma	☐ Other class'n	
Malaria	☐ Y	☐ N	☐ U		
Dehydration	☐ No dehyd'n	☐ Some dehyd'n	☐ Sev' dehyd'n	☐ Shock	☐ Other
HIV	☐ Y	☐ N	☐ U		
Malnutrition	☐ Mild malnut'n	☐ Mod malnut'n	☐ Sev' malnut'n	☐ Other class'n	
Meningitis	☐ Y	☐ N	☐ U		
Anaemia	☐ Mild/mod'	☐ Severe			
Other	_____				

Hospital ID. _____ Clerk ID. _____

Q'nnaire No. _____ Pt's initials _____

Treatment record (**IMMEDIATELY BEFORE DISCHARGE / FINAL OUTCOME**)

For each drug prescribed, indicate the route of administration, dose and frequency. If not recorded, enter [U]

Treatment	Prescribed?	Route		Dose (specify units)		Frequency (x hourly)	
Penicillin	Y N	_____	U	_____	U	_____	U
Gentamicin	Y N	_____	U	_____	U	_____	U
Chloramphenicol	Y N	_____	U	_____	U	_____	U
Amoxicillin	Y N	_____	U	_____	U	_____	U
Ceftriaxone	Y N	_____	U	_____	U	_____	U
Co-trimoxazole	Y N	_____	U	_____	U	_____	U
Metronidazole	Y N	_____	U	_____	U	_____	U
Oxygen	Y N	_____	U	_____	U	_____	U
Bronchodilators	Y N	_____	U	_____	U	_____	U
Prednisone	Y N	_____	U	_____	U	_____	U
Antimalarials	Y N	_____	U	_____	U	_____	U
Fluids	Y N	_____	U	_____	U	_____	U
Zinc	Y N	_____	U	_____	U	_____	U
Blood	Y N	_____	U	_____	U	_____	U
Heamatinics	Y N	_____	U	_____	U	_____	U
Antipyretics	Y N	_____	U	_____	U	_____	U
Diazepam	Y N	_____	U	_____	U	_____	U
Phenobarbitone	Y N	_____	U	_____	U	_____	U
Vitamin A	Y N	_____	U	_____	U	_____	U
10% Dextrose	Y N	_____	U	_____	U	_____	U
Feeds	Y N	_____	U	_____	U	_____	U
Other 1 _____		_____	U	_____	U	_____	U
Other 2 _____		_____	U	_____	U	_____	U
Other 3 _____		_____	U	_____	U	_____	U

Outcome Information

Outcome: ☐ Alive ☐ Dead ☐ Referred ☐ Absconded ☐ Unknown

Date of Outcome (dd/mm/yy) _____/_____/_____

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