HYPOXAEMIA AMONG CHILDREN WITH SEVERE OR VERY SEVERE PNEUMONIA AT KENYATTA NATIONAL HOSPITAL.

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

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DEDICATION

To my beloved wife Dorothy and daughter Joy who have been a great source of inspiration.
ACKNOWLEDGEMENTS

The success of this work is a result of inputs and help from various persons to whom I am very grateful.

To the Almighty God, the source and sustainer of life.

To my wife Dorothy for her unwavering support.

To my supervisors for their guidance and patience during the entire period from the inception of the proposal to the writing of the book.

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To members of the ‘Childhood Pneumonia Group’ for the team spirit during the entire period of data collection.

To Dr. Ambrose Agweyu and Mr. Moses Mwangi of KEMRI who helped with data analysis.
# TABLE OF CONTENTS

- DECLARATION .......................................................................................................................... 2
- DEDICATION ............................................................................................................................... 3
- ACKNOWLEDGEMENTS ......................................................................................................... 4
- TABLE OF CONTENTS ............................................................................................................. 5
- LIST OF ABBREVIATIONS AND SYMBOLS ..................................................................... 7
- LIST OF TABLES ......................................................................................................................... 8
- LIST OF FIGURES ...................................................................................................................... 9
- ABSTRACT .................................................................................................................................. 10

1.0 BACKGROUND AND LITERATURE REVIEW ................................................................. 12

2.0 STUDY JUSTIFICATION AND OBJECTIVES .................................................................. 25
  2.1 Problem Statement ..................................................................................................... 25
  2.2 Justification ................................................................................................................. 26
  2.3 Utility ........................................................................................................................... 27
  2.4 Study Objectives ........................................................................................................ 27

3.0 METHODOLOGY .............................................................................................................. 29
  3.1 Study Area .................................................................................................................. 29
  3.2 Study Population ........................................................................................................ 29
  3.3 Study Design ............................................................................................................... 29
  3.4 Sample Size Estimation ............................................................................................ 29
  3.5 Sampling Method ....................................................................................................... 30
3.6 Inclusion Criteria: ..................................................................................................... 30
3.7 Exclusion Criteria ..................................................................................................... 30
3.8 Case Definitions ......................................................................................................... 31
3.9 Equipment ................................................................................................................... 32
3.10 Study Procedures ....................................................................................................... 32
3.11 Data Analysis ............................................................................................................. 33
3.12 Ethical Considerations .............................................................................................. 34

4.0 RESULTS ....................................................................................................................... 37

5.0 DISCUSSION ................................................................................................................. 53

6.0 STUDY LIMITATIONS .............................................................................................. 58

7.0 CONCLUSIONS ............................................................................................................ 58

8.0 RECOMMENDATIONS .............................................................................................. 59

REFERENCES ............................................................................................................................ 60

APPENDICES ............................................................................................................................. 66

APPENDIX 1: QUESTIONNAIRE .................................................................................. 66

APPENDIX 2: PNEUMONIA MANAGEMENT PROTOCOL................................... 68

APPENDIX 3: INFORMATION AND CONSENT FORM............................................ 69

APPENDIX 4: BUDGET ................................................................................................... 75
**LIST OF ABBREVIATIONS AND SYMBOLS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALRI</td>
<td>Acute lower respiratory infections</td>
</tr>
<tr>
<td>SaO₂</td>
<td>Arterial haemoglobin oxygen saturation</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Arterial haemoglobin oxygen saturation by pulse oximetry</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Arterial blood oxygen tension</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>GoK</td>
<td>Government of Kenya</td>
</tr>
<tr>
<td>AVPU</td>
<td>Alert, Voice, Pain. Unconscious</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency virus</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>PCP</td>
<td>Pneumocystis jirovecii pneumonia</td>
</tr>
<tr>
<td>LIP</td>
<td>Lymphocytic interstitial pneumonia</td>
</tr>
<tr>
<td>KNH</td>
<td>Kenyatta National Hospital</td>
</tr>
<tr>
<td>PITC</td>
<td>Provider Initiated Testing and Counseling</td>
</tr>
<tr>
<td>PEU</td>
<td>Peadiatric Emergency Unit</td>
</tr>
<tr>
<td>DNA PCR</td>
<td>Deoxyribonucleic Acid Polymerase Chain Reaction</td>
</tr>
<tr>
<td>KEMRI</td>
<td>Kenya Medical Research Institute</td>
</tr>
<tr>
<td>SOPS</td>
<td>Standard operating procedures</td>
</tr>
</tbody>
</table>
LIST OF TABLES.

Table 1: Prevalence of Hypoxaemia Among Children With Severe or Very Severe Pneumonia................................................................. 21

Table 2: Age and Gender Distribution of Children Enrolled.......................... 39

Table 3: Distribution of Clinical Features at Admission.............................. 40

Table 4: Distribution of Pneumonia Severity in Study Population................. 41

Table 5: Sensitivity, Specificity and Predictive Values of GoK Criteria for Oxygen Therapy................................................................. 45

Table 6a: GoK Clinical Signs and their Ability to Predict Hypoxaemia............ 46

Table 6b: Other Clinical Signs and their Ability to Predict Hypoxaemia.......... 48

Table 7: Association Between HIV infection and Hypoxaemia..................... 48

Table 8: Multivariate Logistic Regression Showing Ability of Clinical Signs to Predict Hypoxaemia............................................................... 49

Table 9: Mortality Among Hypoxaemic and Non hypoxaemic Children........... 50

Table 10: Association Between HIV Infection and Mortality.......................... 52
LIST OF FIGURES

Figure 1: Flow Chart Showing Patient Screening and Enrolment ............... 38
Figure 2: Prevalence of Hypoxemia in Study Population ....................... 41
Figure 3: Prevalence of Hypoxaemia Stratified by Severity of Pneumonia ...... 42
Figure 4: Distribution of Oxygen Saturation Levels in Study Population .......... 43
Figure 5: Distribution of Oxygen Saturation Levels Stratified by Severity of Pneumonia .................. 44
Figure 6: Relationship between Hypoxaemia and Mortality (Oxygen saturation <90%) ....................... 51
Figure 7: Relationship between Hypoxaemia and Mortality (Oxygen saturation <85%) .................. 51
ABSTRACT

Background: Pneumonia is the leading cause of childhood morbidity and mortality in developing countries with hypoxaemia as the most common and fatal complication. Oxygen therapy is an important intervention for children with hypoxaemia. In many settings in Kenya, clinical signs are used to identify children who require oxygen. The Government of Kenya (GoK) has provided criteria for oxygen therapy. It states that oxygen should be administered to a child with any of these signs: cyanosis, inability to drink/breastfeed, impaired consciousness, grunting or head nodding. While there is data exploring the utility of clinical signs to identify hypoxaemic children, this GoK ‘decision rule’ has never been evaluated. There is paucity of information on some of the signs included in the GoK criteria and little local information on the prevalence of hypoxaemia among children with severe forms of pneumonia.

Objectives: To determine the prevalence of hypoxaemia and evaluate the sensitivity and specificity of the GoK criteria for oxygen therapy for children with severe or very severe pneumonia admitted at Kenyatta National Hospital, Nairobi, Kenya, to determine whether Human Immunodeficiency Virus (HIV) infection was a risk factor for hypoxaemia and to evaluate the association between hypoxaemia and short term in-patient mortality.

Methodology: This was a hospital based short longitudinal survey. We enrolled 343 children aged two to 59 months, assessed them for presence of clinical signs associated with hypoxaemia, measured their arterial oxygen saturation using a portable hand held
pulse oximeter and had them tested for HIV infection. We followed up the children for five days to determine mortality outcome.

**Results:** Prevalence of hypoxaemia was 50.7% in the study population. Stratified by severity, 39.7% and 59.4% of children with severe and very severe pneumonia respectively were hypoxaemic. Cyanosis and grunting were found to be independent predictors of hypoxaemia. The GoK criteria had a sensitivity of 65.5% and a specificity of 53.8% for detecting children who required oxygen therapy. Thirty one children (9.0%) were HIV infected. Oxygen saturation of <85% was associated with increased mortality (OR 3.3. 95% CI= 1.5 to 7.1, P=0.005).

**Conclusions:** Hypoxaemia is frequent, occurring in 50.7% of children hospitalized with severe or very severe pneumonia at Kenyatta National Hospital. The GoK criteria for oxygen therapy have a low sensitivity (65.5%) and specificity (53.8%) for predicting hypoxaemia. Severe hypoxaemia (SpO2 <85%) is associated with a 3.3 fold increased mortality.

**Recommendations:** The Government of Kenya should consider promoting the use of pulse oximetry in all public hospitals to detect hypoxaemia. A cost-benefit study on the use of pulse oximeters vis-à-vis continued use of clinical signs to determine which children require oxygen therapy should be carried out.
1.0 BACKGROUND AND LITERATURE REVIEW

Acute lower respiratory tract infections (ALRI), particularly pneumonia, are the leading causes of childhood morbidity and mortality in developing countries. ALRI cause more than 2 million child deaths worldwide each year, mostly from pneumonia. Ninety percent of these deaths occur in less-developed countries. It is estimated that 1.9 million children died from ALRI throughout the world in the year 2000 of which 70% occurred in Africa and Southeast Asia. Hypoxaemia is the most common and fatal complication of ALRI. Onyango et al in a study to determine short term mortality (death within 5 days of admission) among children with ALRI in Nairobi, Kenya found that hypoxaemic children were 4.3 times more likely to die than those without. Weber et al in a similar study in the Gambia found that the relative risk for death among hypoxaemic children with ALRI was 4.6 [95% Confidence Interval, 2.2 to 9.6]. (p=0.0007]). The case fatality rate was inversely related to the arterial haemoglobin oxygen saturation (SaO₂). Early detection of hypoxaemia and appropriate initiation of oxygen therapy is therefore an important intervention to improve outcome.

Childhood pneumonia in developing countries, unlike in developed countries is caused more commonly by bacteria than viruses, the commonest aetiological agents being Streptococcus pneumoniae and Haemophilus influenzae. Bacterial pneumonia is associated with higher mortality rates than viral pneumonia. However, due to difficulties associated with diagnosing bacterial pneumonia in developing countries, the World Health Organization (WHO) has promoted the use of a clinical case-definition to
guide initiation of empiric antibiotic therapy. For children who have cough or difficult breathing, the WHO acute respiratory infection case management guidelines require only an assessment of the respiratory rate and the presence of visible and audible signs of respiratory distress. Very severe pneumonia is present when there is cough or difficult breathing plus any of the following danger signs: cyanosis, inability to drink/breastfeed, impaired level of consciousness, grunting or head nodding. Cough or difficult breathing with lower chest wall in-drawing and none of the above danger signs is categorized as severe pneumonia. Pneumonia is defined as the presence of cough and tachypnea (≥60 breaths per minute for infants up to 2 months of age, ≥50 breaths per minute for children 2 to 11 months and ≥40 breaths per minute for children 12 to 59 months) without any of the signs of severe pneumonia syndromes. The WHO acute respiratory infection algorithm has been shown to have a sensitivity and specificity of 80% for the diagnosis of pneumonia.

Defining Hypoxemia

Hypoxaemia refers to low oxygen level in blood. The best definition would be the level of blood oxygen associated with increased morbidity, risk of death or delayed recovery rather than a certain level of arterial haemoglobin oxygen saturation (SaO₂) below normal for the population. This is because SaO₂ varies with altitude. The arterial haemoglobin oxygen saturation by pulse oximetry (SpO₂) bears a relationship to arterial blood oxygen tension (PaO₂). At higher altitudes, the partial pressure of oxygen reduces and the normal range of SpO₂ progressively reduces. The mean SpO₂ at sea level is 97-99% with the
lower limit (two standard deviations below the mean) of 94%. Thus the normal range of SpO₂ is 94-100%. ¹⁰

The WHO defines hypoxaemia as any oxygen saturation <90% and does not take into account the variation in normal oxygen saturation with altitude¹¹. An SpO₂ of 90% corresponds to an arterial oxygen tension (PaO₂) of 60-70 mmHg. Below this, the haemoglobin oxygen dissociation curve falls steeply such that further decrease in arterial oxygen tension is associated with greater decrease in arterial oxygen saturation. An SpO₂ of <90% is therefore considered by most clinicians as an appropriate indication for administering oxygen. It has however been suggested that at higher altitudes, the threshold for initiating oxygen therapy may be lower ¹⁰.

A number of studies have been done with the aim of defining hypoxaemia based on altitude specific normal values. Haemoglobin oxygen saturation values 2-3 standard deviations (SD) below the population mean has been used by a number of investigators to define hypoxaemia. Duke et al measured SpO₂ of 151 well children aged between one to 60 months in Goroka Hospital in the highlands of Papua New Guinea at an altitude of 1600 metres. The mean SpO₂ was 95.7% (SD 2.7%).¹² Nairobi lies at an altitude of 1670 meters above sea level. Although no evaluation has been done among healthy children in Nairobi to establish normal values, it is likely to be comparable to that of children in Goroka as the two regions lie at almost the same altitude.
Subhi et al performed a systematic review of literature addressing normal values of oxygen saturation in children aged one week to 12 years. An SpO₂ of 90% corresponded to the 2.5th centile for a population of healthy children living at an altitude of approximately 2500 metres above sea level. This decreased to 85% at an altitude of about 3200 metres. He concluded that at altitudes greater than 2500 metres above sea level, an SpO₂ of <85% can be used to indicate the need for oxygen.1

Mechanism of Hypoxaemia

The principle mechanism of the hypoxia of acute respiratory infection is a mismatch between ventilation and perfusion. The infectious organism, whether viral or bacterial, causes areas of pneumonic consolidation, which become inappropriately under oxygenated relative to their hyper-perfusion. The mismatch is not redressed by vascular redistribution to the unaffected parts of the lung as most pneumonia in children is of a bronchopneumonic distribution rather than showing the lobar pattern seen in adults. Moreover, lung compliance decreases as consolidation develops, leading to increased work of breathing. Dehydration from fever, panting, and inability to drink leads to haemoconcentration, peripheral underperfusion and metabolic acidosis which worsen tissue hypoxia.14

Hypoxaemia also occurs in non-ALRI conditions. There are several reasons why children with non-ALRI illnesses have hypoxaemia. In meningitis, for example, upper airway obstruction may occur from retained secretions, increased or decreased upper airway tone and bradypnoea or apnoea which may occur because of the brain injury or from chest
wall rigidity during convulsions. In septicaemia, hypoxaemia may occur from intrapulmonary shunting of blood, pulmonary hypertension or pulmonary congestion.

Systemic oxygen transport is the product of cardiac output and systemic oxygen content. Cardiac failure of any aetiology resulting in reduced cardiac output leads to decreased oxygen transport and tissue hypoxia. Congenital heart defects in which there is mixing of oxygenated and deoxygenated blood through right to left shunts also cause hypoxaemia.

**Detecting Hypoxaemia.**

The most reliable method of detecting hypoxaemia is by arterial blood gas analysis or determination of the arterial haemoglobin oxygen saturation by a pulse oximeter. The principle of pulse oximetry is based on the red and infrared light absorption characteristics of oxygenated and deoxygenated haemoglobin. A transcutaneous sensor is used to measure the percentage of haemoglobin that is fully saturated with oxygen (Sp0₂). Pulse oximetry uses spectrophotometry and plethysmography. The pulse oximeter consists of a computerized unit and a sensor probe, which is attached to the patient’s finger, toe or earlobe. The sensor emits two different wavelengths of light, red (600-750 nanometer wavelength light band) and infrared (850-1000 nanometer wavelength light band). These lights are absorbed by hemoglobin and transmitted through tissues to a photo detector. Oxygenated haemoglobin absorbs more infrared light and allows more red light to pass through to the photo detector. Deoxygenated haemoglobin absorbs more red light and allows more infrared light to pass through to the photo detector. The amount of light transmitted is converted to a digital value. The ratio of absorbed red to infrared light indicates the degree of oxygenation.
The height of the plethysmographic (pulse) wave signifies the arterial pulsation. The signal between the pulse waves (baseline) is subtracted from the signal at the peak of the plethysmographic wave, the difference being due to inflowing arterial blood, so reflecting the saturation of arterial blood. A microprocessor compares the absorption of light at the peak (arterial pulse) and trough (baseline) at both red and infrared waveforms of light.  

The accuracy of SpO\textsubscript{2} measurements requires consideration of a number of factors that include hemoglobin level, arterial blood flow to the vascular bed, temperature of the digit or the area where the oximetry sensor is located and the amount of ambient light detected by the sensor\textsuperscript{15}.

**Predicting Hypoxaemia**

Despite a strong case for arterial blood gas analysis and use of pulse oximeters to reliably detect hypoxaemia, equipment to make these measurements are expensive, need constant maintenance and are not widely available in developing countries. As a result clinical signs continue to be used to identify severely ill children who require oxygen therapy. Many studies have been carried out to determine clinical signs that best predict hypoxaemia in children with ALRI. Some of these studies have been done in developing countries.

Usen et al studied possible clinical predictors of hypoxaemia among sixty nine children aged between two months and 5 years admitted to hospital in Gambia with ALRI and an SpO\textsubscript{2} < 90%. These children were compared with 67 children matched for age and
diagnosis from the same referral hospital with an SpO₂ of 90% or above (control group 1), and 44 children admitted to a secondary care hospital with ALRI (control group 2). Using multiple logistic regression analysis, drowsiness, cyanosis, head nodding, decreased air entry and nasal flaring were found to be independent predictors of hypoxaemia. Using a simple model of cyanosis or head nodding or not crying, the sensitivity to predict hypoxaemia was 59% and specificity 94%. Over half of the children with hypoxaemia could be identified with a combination of these three signs: extreme respiratory distress, cyanosis and severely compromised general status.10

Onyango et al followed 256 children aged seven days to 36 months with acute respiratory infection at Kenyatta National Hospital in Nairobi, Kenya to determine which clinical signs best predicted hypoxaemia. The most common diagnosis in the study population was pneumonia (53%) and bronchiolitis (33%). Fifty nine percent of the children admitted were hypoxaemic (SpO₂ <90%). For children aged 3-11 months, the best predictor of hypoxaemia with a sensitivity of 70% was a respiratory rate of ≥70 breaths per minute [Odds Ratio (OR ) 2.6; p=0.001]. For children aged 12 months and older, the sole best predictor was a respiratory rate of at least 60 breaths per minute with a sensitivity of 70% [OR 5.1; p=0.001].

Lozano et al studied children in Bogota (2640 m above sea level), Colombia to assess the usefulness of clinical signs in the diagnosis of hypoxaemia. Two hundred children aged 7 days to 36 months presenting to an urban emergency room with cough lasting less than seven days were studied. An SpO₂ <88% was used to define hypoxaemia. One hundred
and twenty five (63%) children had hypoxaemia. Rapid breathing as perceived by the child's mother, chest retractions, nasal flaring, and crepitations were associated with hypoxaemia.\textsuperscript{17}

Smyth et al conducted a prospective study in children with ALRI to determine which clinical signs identified children with hypoxaemia and at risk of death. Of 158 children studied, 55 were found to be hypoxaemic and 23 died. For children under 1 yr of age, a respiratory rate of >70 breaths per minute was the only significant predictor of hypoxaemia ($p<0.01$, sensitivity 63\%, specificity 89\%). In older children only the presence of crepitations/bronchial breathing was predictive of hypoxaemia ($p=0.018$, sensitivity 75\%, specificity 57\%).\textsuperscript{18}

Where pulse oximeters are not available, the WHO recommends the following clinical signs as indicators for oxygen therapy for children 2 months or older: presence of cyanosis, inability to drink, severe chest-wall in-drawing and a respiratory rate of over 70 breaths per minute.\textsuperscript{8}

The Government of Kenya (GoK) adapted its criteria for oxygen therapy from the WHO.\textsuperscript{8} This is outlined in the Ministry of Health Basic Paediatric Protocol\textsuperscript{10} and provides advice on which children should receive oxygen therapy. It states that oxygen should be administered to all children with any one or more of these danger signs that define very severe pneumonia: cyanosis, inability to drink/breastfeed, impaired consciousness, grunting or head nodding. For assessment of level of consciousness, the GoK has adapted
a simplified approach for determining the level of consciousness in children. It is a scale with four categories of levels of consciousness. A fully conscious child is classified as alert (A). Any child who is not alert is classified as able to respond to voice (V), to pain (P) or as unconscious (U). This categorization is commonly referred to as the AVPU coma scale. Any child who is categorized as not alert (AVPU<A) should receive oxygen.

**Prevalence of Hypoxemia in Childhood Pneumonia**

In the developing world each year there are an estimated 150 million episodes of pneumonia, 11 to 20 million of which require hospitalization. It is estimated that between 1.5 and 2.7 million children get hypoxaemia annually.

Most studies done to determine the prevalence of hypoxaemia have adopted the WHO recommended threshold of an SpO₂ of <90% to define hypoxaemia. Subhi R. et al performed a systematic review in the year 2008 of both published and unpublished studies that reported the prevalence of hypoxaemia in ALRI. Median prevalence of hypoxaemia among studies reviewed was 13% but prevalence in various studies varied widely ranging from 6.9% to 100% \(^{20}\). Selected studies reporting the prevalence of hypoxaemia in children with severe or very severe pneumonia are displayed in Table 1 below.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Setting</th>
<th>Altitude (metres above sea level)</th>
<th>Definition of hypoxemia SpO$_2$ (%)</th>
<th>WHO category of pneumonia severity</th>
<th>Proportion of children with hypoxemia</th>
<th>Percentage with hypoxemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu et al$^{11}$ (2006) Mexico, Bogota (Multicentre)</td>
<td>Tertiary hospitals</td>
<td>7 out of 9 sites at sea level</td>
<td>$&lt;90$ low alt $&lt;88$ high alt</td>
<td>Severe pneumonia</td>
<td>80/843</td>
<td>9.5%</td>
</tr>
<tr>
<td>Wandi et al$^{11}$ (2006) Papua New Guinea</td>
<td>Tertiary hospitals</td>
<td>1600</td>
<td>$&lt;90$</td>
<td>Severe and very severe pneumonia</td>
<td>315/578</td>
<td>54.2%</td>
</tr>
<tr>
<td>Ashraf et al$^{11}$ (2008) Bangladesh</td>
<td>Primary care</td>
<td>0</td>
<td>$&lt;90$</td>
<td>Severe and very severe pneumonia</td>
<td>143/251</td>
<td>57%</td>
</tr>
<tr>
<td>Bose et al$^{11}$ (2006) India</td>
<td>Tertiary hospital</td>
<td>0</td>
<td>$&lt;90$</td>
<td>Severe and very severe pneumonia</td>
<td>56/300</td>
<td>18.7%</td>
</tr>
<tr>
<td>Brooks et al$^{11}$ (2004) Bangladesh</td>
<td>Tertiary hospital</td>
<td>0</td>
<td>$&lt;90$</td>
<td>Severe and very severe pneumonia</td>
<td>37/270</td>
<td>13.7%</td>
</tr>
<tr>
<td>Gessner et al$^{11}$ (2003) Indonesia</td>
<td>Secondary hospital</td>
<td>0</td>
<td>$&lt;90$</td>
<td>Severe and very severe pneumonia</td>
<td>1616/4306</td>
<td>37.5%</td>
</tr>
<tr>
<td>Singhi et al$^{11}$ (2003) India</td>
<td>Tertiary hospital</td>
<td>0</td>
<td>$&lt;90$</td>
<td>Severe</td>
<td>86/331</td>
<td>26%</td>
</tr>
<tr>
<td>Mwaniki et al (Unpublished) Kenya</td>
<td>Secondary hospital</td>
<td>0</td>
<td>$&lt;90$</td>
<td>Severe</td>
<td>156/2267</td>
<td>6.9%</td>
</tr>
<tr>
<td>Nadim et al (Unpublished) Tanzania</td>
<td>Secondary hospital</td>
<td>0</td>
<td>$&lt;90$</td>
<td>Severe</td>
<td>21/259</td>
<td>8.1%</td>
</tr>
</tbody>
</table>
Studies reviewed showed wide variations in prevalence of hypoxaemia between geographical regions and at different altitudes. Most studies were done in Asia and only few studies reporting the prevalence of hypoxaemia in WHO-defined pneumonia from Africa were included in the review. Studies from Africa reported lower prevalence of hypoxaemia than similar studies from Asia even at similar altitudes and within comparable classifications of pneumonia severity. Majority of studies from Africa were conducted in secondary level hospitals as compared to the predominantly tertiary hospital setting of Asian studies. Tertiary hospitals serve as referral centres and may represent populations with more severe disease. High altitude has been found to be associated with a higher prevalence and severity of hypoxaemia than at sea level despite comparable clinical diagnostic criteria and an adjustment of the definition of hypoxaemia for a lower normal SpO$_2$ at altitude. There is however no evidence that geographical location is an independent determinant of hypoxaemia. Regional variations in pathogen aetiology, host epidemiology, prevalence and severity of co-morbidities and environmental factors have been identified as possible contributing factors to the regional differences in prevalence observed.

Pneumonia and Human Immunodeficiency Virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS) co-morbidity

Pneumonia is the leading cause of hospital admissions and the commonest cause of death in children infected with HIV. Sub-Saharan Africa is the most heavily affected region by HIV and AIDS in the world. An estimated 22 million people were living with HIV at the end of 2007 and approximately 1.9 million additional people were infected with HIV.
during that same year. Estimates for 2006 showed there were 2.5 million children infected globally with 2.25 million of these in Sub Saharan Africa. In Kenya, the prevalence of HIV and AIDS in 2007 was 7.4%, a rise from 5.9% in 2006 according to the report of Kenya Aids Indicator Survey of 2007. It is estimated that between 100,000 to 150,000 children are HIV infected in Kenya.

Most children infected with HIV present with recurrent bacterial pneumonia caused by Streptococcus pneumoniae and Haemophilus influenzae. Pneumocystis jirovecii pneumonia, previously known as Pneumocystis carinii pneumonia (PCP) has been identified as the most common opportunistic form of pneumonia among these children in Africa. The prevalence of PCP among HIV infected children hospitalized with pneumonia in Africa has varied from 10-49%.

Lymphocytic interstitial pneumonitis (LIP) is the most common chronic lower respiratory abnormality in HIV infected children occurring in approximately 25% of these children. Other causes of pneumonia in HIV infected children include cytomegalovirus, Mycobacterium tuberculosis and fungal infections.

Although the common presentation of the HIV infected child with pneumonia may be similar to that of the uninfected, the high prevalence of opportunistic infections contributes to increased morbidity and mortality. In addition to a strong association with PCP, HIV infection has been shown to be significantly and independently associated with fatal outcome. Data from a number of studies that investigated pneumonia mortality in
Zimbabwe showed that the risk of dying was three times higher in HIV infected children treated for pneumonia compared to HIV uninfected children.\textsuperscript{30}

A study by Bii et al showed HIV seropositivity of 60\% among children with severe pneumonia at Kenyatta National Hospital (KNH)\textsuperscript{37} Confirmatory Deoxiribonucleic Acid Polymerase Chain Reaction (DNA PCR) was not done for children 18 months and below. Maina et al found a prevalence of HIV infection of 18.9\% among children with WHO classified severe or very severe pneumonia admitted at KNH \textsuperscript{38} Confirmatory DNA PCR was done for children aged 18 months and below in this study.
2.0 STUDY JUSTIFICATION AND OBJECTIVES

2.1 Problem Statement

ALRI remain a major killer of children in developing countries with hypoxaemia as the most common and fatal complication. The Government of Kenya criteria as outlined in the Basic Paediatric Protocol provides guidance on which children should receive oxygen if only clinical evaluation is available. Signs indicating the need for oxygen therapy include any of the following signs: cyanosis, inability to drink/breastfeed, altered level of consciousness (AVPU<A), grunting or head nodding. All these signs indicate a classification of very severe pneumonia. The following observations have been made:

a. The sensitivity and specificity of this 'decision rule' has never been prospectively evaluated

b. Head nodding has only previously been evaluated as an indicator of hypoxaemia in two studies in The Gambia (Weber et al and Usen et al)\textsuperscript{6,16}

c. AVPU coma scale findings have never been evaluated as indicators of hypoxaemia

d. No previous studies of oxygen saturation have included all of these indicators

e. No previous studies have been of sufficient size to examine more extreme definitions of hypoxaemia such as saturations < 80%.

In a recent systematic review of studies on prevalence of hypoxemia it was stated that the prevalence in Africa was lower than in Asia. In that review no studies from high
altitude in Africa were included either because they were of insufficient quality with
potential for serious bias or they included children with upper respiratory tract infections
making the reported prevalence hard to interpret. In the work of Onyango et al in 1993,
WHO criteria was not used to stratify the patients and thus no estimates of prevalence in
severe or very severe pneumonia was possible.

Children with severe forms of pneumonia with HIV co-morbidity are three times more
likely to die than HIV uninfected. Whether HIV infection is a risk factor for hypoxaemia
in this group of children has never been evaluated.

2.2 Justification

There is need for increased awareness of the burden of hypoxaemia and the need for
oxygen therapy as an important intervention for reducing child mortality. Since pulse
oximeters are not readily available and the decision to provide oxygen therapy in most
health facilities in Kenya is based on the GoK clinical criteria, there is need to
prospectively evaluate this ‘decision rule’.

At present, the evidence most likely to be cited internationally is that only 13% of
African children with severe or very severe pneumonia require oxygen therapy based on
the findings of the recent systematic review which stated that the prevalence in Africa
was lower than in Asia.\(^2\) Such data may seriously underestimate the need for oxygen in
KNH and in other high altitude areas of Africa if earlier work is indicative of true
prevalence. A large, comprehensive study is the best way to estimate true prevalence.
It is useful to know whether HIV infection is a risk factor for hypoxaemia. Through the PICT strategy, all sick children admitted at KNH are tested for HIV infection. Screening for HIV seropositivity is done using rapid antibody tests at the Paediatric Emergency Unit (PEU) which is the point of admission. Where a confirmatory test is required, this is done in the admission ward.

2.3 Utility
Evaluation of the GoK criteria for oxygen therapy will provide useful information that will enable judicious use of oxygen in our health facilities.

Data on the burden of hypoxaemia will help KNH to plan for adequate oxygen supply and develop efficient delivery systems.

If HIV infection is found to be a risk factor for hypoxaemia then it might be an additional criterion for provision of oxygen where only clinical evaluation is available. This is especially if it is found to be independently associated with hypoxaemia.

2.4 Study Objectives

Overall Objective
To determine the prevalence of hypoxaemia and evaluate the Government of Kenya criteria for oxygen therapy for children with WHO classified severe or very severe pneumonia.
Primary Objectives:

1. To determine the prevalence of hypoxaemia among children with WHO classified severe or very severe pneumonia.

2. To determine the sensitivity and specificity of the Government of Kenya criteria for oxygen therapy for children with severe or very severe pneumonia. Specific criteria of interest include cyanosis, inability to drink/breastfeed, altered level of consciousness (AVPU < A), grunting and head nodding.

Secondary Objectives

1. To determine whether HIV infection is a risk factor for hypoxaemia among children with severe or very severe pneumonia.

2. To evaluate the association between hypoxaemia and short term in-patient mortality among children with severe or very severe pneumonia.
3.0 METHODOLOGY

3.1 Study Area

The study was carried out at the PEU and the general paediatric wards in KNH which is the largest tertiary hospital in Kenya. It is located in Nairobi and receives patients from all parts of the country and also serves as a primary and secondary care hospital for acutely ill children from the city and its environs. All children admitted are tested for HIV according to the PITC policy unless a guardian opts not to have his/her child tested. There are trained staff who counsel and test patients either at the PEU or in the ward.

3.2 Study Population

All children aged between two to 59 months with cough/difficult breathing for a duration not exceeding 14 days were screened and recruited into the study.

3.3 Study Design

This was a short longitudinal survey.

3.4 Sample Size Estimation

The sample size was determined using the Fisher's formula for prevalence studies.

\[
N = \frac{Z^2 \cdot p \cdot (1-p)}{D^2}
\]

Where:

- \(N\) = minimum sample size
- \(Z\) = standard normal deviate for 95% confidence interval (= 1.96)
- \(p\) = estimated prevalence
- \(D\) = margin of error
p = estimated prevalence of hypoxaemia among children with severe or very severe pneumonia.

D = degree of precision (5%)

Estimated prevalence of 54.5%, based on a study by Wandi et al\textsuperscript{22} in Papua New Guinea (altitude 1600 metres above sea level) was used to calculate the required sample size giving a minimum of 381 children.

3.5 Sampling Method

Comprehensive sampling was used. The study was part of a larger study on pneumonia at KNH (Childhood Pneumonia Study), conducted by a group of eight Master of Medicine in Paediatrics students of the University of Nairobi. The principal investigator together with the other co-investigators of the ‘Childhood Pneumonia Study’ provided 24 hour coverage of the PEU for a period of four months between June and September 2009 and recruited all patients who met the inclusion criteria.

3.6 Inclusion Criteria:

All children aged two to 59 months with a diagnosis of severe or very severe pneumonia according to WHO classification were screened.

3.7 Exclusion Criteria

The following groups of children were excluded from the study: Children with chronic renal or cardiac disease or primary neurological abnormality such as cerebral palsy, children with wheeze who after bronchodilator therapy at the PEU were no longer
classified as having severe pneumonia, children with upper airway obstruction producing
stridor, children in shock due to severe dehydration and those arriving at the PEU already
on continuous oxygen therapy.

3.8 Case Definitions

**Very severe pneumonia:** Cough or difficult breathing plus one or more of the following
danger signs: cyanosis, inability to drink/breastfeed, altered level of consciousness
(AVPU<A), head nodding or grunting.

**Severe pneumonia:** cough or difficult breathing with chest-wall indrawing with or
without tachypnea (respiratory rate of ≥50 per minute for infants 2-11 months and ≥40
per minute for children 12-59 months).

**Hypoxaemia:** Oxygen saturation <90% by pulse oximetry.

**HIV infection:**

*Children >18 months:*

Two rapid HIV test kits (Determine and Bioline) were used to detect antibodies to HIV.
A child was considered infected if both tests were positive and negative if both were
negative. If one test was positive and one negative, a confirmatory HIV test using
Microparticle Enzyme Immunoassay (MEIA) technique was done at the University of
Nairobi laboratory at the Department of Paediatrics.

*Children < 18 months:*

Two rapid HIV tests using Determine and Bioline test kits were carried out. Where any of
the tests turned positive, Deoxyribonucleic Acid Polymerase Chain Reaction (DNA PCR)
test was performed at the University of Nairobi laboratory to confirm HIV infection.
Short term mortality: Death within five days of admission.

3.9 Equipment

A portable hand held battery powered pulse oximeter (Nellcor NPB-40 manufactured by Mallinckrodt Inc USA) with Nellcor sensors (Oxiband®, Model OXI-P/I) and sensor cables were used to measure arterial oxygen saturation. The sensors are reusable oxygen transducers with disposable non-sterile adhesive.

3.10 Study Procedures

Patient Enrolment

Patient recruitment was carried out at the PEU. The principal investigator together with a team of seven co-investigators of the ‘Childhood Pneumonia Study’ provided 24 hour coverage of the PEU each day for a period of four months and screened all children presenting with cough or difficult breathing. All children who met the inclusion criteria were enrolled into the study. All investigators had undertaken the five day Emergency Triage and Treatment plus Admission Care (ETAT+) course, a programme for dissemination of GoK guidelines. They had also undergone training on the use of the pulse oximeter as well as on all standard case definitions and procedures required for this study. The training was facilitated by trainers from the Kenya Medical Research Institute (KEMRI)/Wellcome Trust Research Programme.

Clinical Assessment

All children with history of cough and difficult breathing were assessed for presence of pneumonia and severity classification per the WHO management guidelines. For any
child who met the inclusion criteria, the investigator explained the nature of the study to the parent or guardian and sought written consent for their child to participate. Demographic data and clinical history was obtained and recorded in a pre-coded questionnaire. The investigator performed a thorough, focused physical examination and recorded the findings in the questionnaire (appendix 1).

**Determination of Oxygen Saturation**

A portable battery powered pulse oximeter (Nellcor NPB-40) with sensor probes of various sizes was used. The examiner explained to the parent or guardian briefly on pulse oximetry and its value. Ensuring the child was comfortably positioned and calm, the examiner selected an appropriately sized sensor probe for patient age and weight and attached the probe on the selected site (toe or finger) ensuring a good capillary refill at a point closest to the selected site. The probe was held in position until a steady reading was obtained with a good pulse wave and heart rate demonstrated. The value was recorded in the questionnaire.

**Patient Follow-up**

Patients were followed up in the general admission wards for 5 days and outcome (survival or death) during this period recorded.

3.11 **Data Analysis**

Data from the pre-coded questionnaire was entered into a computer database (Epidata Version 3.1) and verified. Categorical data was tabulated. Proportions were calculated
within 95% confidence interval and means, with standard deviations and standard errors, or medians, with inter-quartile ranges, derived as appropriate to provide descriptive summaries of the data.

Results were presented in descriptive form using frequency tables, pie charts, graphs and cross tabulation. Association between clinical features being evaluated and the presence of hypoxemia were independently tested using Chi-square statistics or Fisher’s Exact testing where numbers were small. The same applied in determining the relationship between hypoxaemia and mortality. Multivariate analysis was performed using binary logistic regression. Occurrence of hypoxaemia was modeled using clinical features and mortality outcome. Determination of whether HIV infection was an independent risk factor for hypoxaemia was also explored in the multivariate analysis.

Analysis was conducted using Statistical Package for Social Sciences (SPSS) version 11.5.

3.12 Ethical Considerations

The study was designed to comply with international ethical guidelines and those of KNH and was carried out after approval by the Department of Paediatrics and Child Health, University of Nairobi and KNH Scientific and Ethics Committee.
Risks and Benefits to Subjects

Risks

No experimental investigations or products were employed in this study. Measuring blood oxygen saturation using a pulse oximeter is entirely non-invasive and carries no risk. The risks of serious adverse consequences of blood taking in this study were very low. Blood taking for the purpose of the study was co-ordinated with that required for routine hospital care to avoid additional discomfort attributable to the study.

Benefits

Patients were carefully evaluated in a standardized way which enabled standardized therapeutic decisions. Patients also benefited from early identification of hypoxaemia by pulse oximetry which is not routine at KNH PEU enabling early initiation of oxygen therapy. Children found to be HIV exposed or infected were referred to the KNH Comprehensive Care Clinic (CCC) or linked to any other CCC for further management and follow up.

Confidentiality

Confidentiality of patient information and HIV results was maintained. On admission every child was allocated a unique identifying number which was used as the linking identifier for clinical and laboratory databases. This database was only accessible to investigators. Access to study data after the completion of the study for reasons not specified in this application was not permitted without a further application to the KNH Scientific and Ethics Committee.
**Information Sharing**

Clinically important findings and laboratory results were made readily available to the medical team managing the children. The purpose and nature of this study was explained to KNH staff at ward-based meetings and within the Department of Paediatrics, University of Nairobi by the investigators prior to the study's start. The study findings were presented to both the University and KNH staff and will be shared more widely with the Ministry of Health and other parties.

**Informed Consent**

Consent was obtained in writing and after adequate explanation (see appended consent form) for enrolment in this study. A participant was free to withdraw from the study at any stage without penalty.
4.0 RESULTS

4.1 Patient Enrolment

We screened a total of 487 children presenting at the PEU with cough or difficulty breathing between June and September 2009. Twenty eight children did not meet the inclusion criteria. Seventy four children with wheeze had good response to bronchodilator therapy and were therefore excluded. The rest of the children (385) were assessed and admitted to the general paediatric wards. Forty two children however failed to have oxygen saturation determined by pulse oximetry and were therefore excluded. We followed up 343 children in the wards for five days to determine mortality outcome.

Testing for HIV infection was done for 301 children either at the PEU or in the admission ward. Thirty one children aged 18 months and below with a positive HIV antibody test had DNA PCR test.

Figure 1 is a flow chart showing patient screening and enrolment.
487 Children 2–59 months of age with cough or difficulty in breathing + lower chest wall indrawing or danger sign

28 Children with chronic cardiopulmonary conditions, meningitis, cerebral palsy → Exit

Bronchodilator → Discharged

74 Wheeze responsive to bronchodilator

96 Wheeze non-responsive to bronchodilator reclassified

385 Children with severe forms of pneumonia admitted

343 Children followed up to day 5 or death/discharge

42 children missed Pulse oximetry → Excluded

301 had HIV rapid test

31 <18 mo, PCR done

Figure 1: Flow Chart Showing Patient Screening and Enrolment
4.2 Demographic Characteristics

The median age was 8.9 months (IQR: 5.1-15.7). Males were 165 (48.1%) and females were 178 (51.9%). Table 2 shows age and gender distribution of the study population.

Table 2: Age and Gender Distribution of Children Enrolled.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=343</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group in months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-5 months</td>
<td>104</td>
<td>30.3</td>
</tr>
<tr>
<td>6-11 months</td>
<td>115</td>
<td>33.5</td>
</tr>
<tr>
<td>12-23 months</td>
<td>68</td>
<td>19.8</td>
</tr>
<tr>
<td>24-35 months</td>
<td>27</td>
<td>7.9</td>
</tr>
<tr>
<td>36-47 months</td>
<td>13</td>
<td>3.8</td>
</tr>
<tr>
<td>48-59 months</td>
<td>7</td>
<td>2.0</td>
</tr>
<tr>
<td>Non response</td>
<td>9</td>
<td>2.6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>165</td>
<td>48.1</td>
</tr>
<tr>
<td>Female</td>
<td>178</td>
<td>51.9</td>
</tr>
</tbody>
</table>

A larger proportion of children (63.8%) were aged less than 12 months, 19.8% were aged between 12 to 23 months, 7.9% (27) between 24 to 35 months, 3.8% (13) between 36 to 47 months while 2.0% (7) were aged 48 to 59 months. There was missing data on date of birth for a small proportion of the children (2.6%).

4.3 Clinical Characteristics of Study Population

The distribution of clinical features observed on the day of admission is listed in Table 3. The vast majority of children, 339 (98.8%) had lower chest wall in-drawing, 192 (89.7%) of children aged 2-11 months and 110 (95.7%) of those aged 12-59 months had tachypnea. One hundred and twenty two children (35.6%) had inability to drink, 106 (31.1%) had head nodding, 89 (25.9%) had grunting, 44 (12.8%) had altered consciousness (AVPU<A) on the AVPU coma scale while 25 (7.3%) had central
cyanosis. Of the 301 children tested for HIV infection, thirty one (9.0%) were infected.

Of the HIV infected children, 17 (54.8%) had stage 3 disease whereas 14 (45.2%) had stage 4 disease.

Table 3: Distribution of Clinical Features at Admission

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Number with symptom/sign (%)</th>
<th>Total number of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to drink</td>
<td>122 (35.6)</td>
<td>343</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>25 (7.3)</td>
<td>342</td>
</tr>
<tr>
<td>AVPU&lt;A</td>
<td>44 (12.8)</td>
<td>343</td>
</tr>
<tr>
<td>Grunting</td>
<td>89 (25.9)</td>
<td>343</td>
</tr>
<tr>
<td>Head nodding</td>
<td>106 (31.1)</td>
<td>341</td>
</tr>
<tr>
<td>Tachypnea:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-11 months ≥50/min</td>
<td>192 (89.7)</td>
<td>214</td>
</tr>
<tr>
<td>12-59 months ≥40/min</td>
<td>110 (95.7)</td>
<td>115</td>
</tr>
<tr>
<td>Lower chest wall in-drawing</td>
<td>339 (98.8)</td>
<td>343</td>
</tr>
</tbody>
</table>

4.4 Prevalence of Hypoxaemia

Among the 343 children enrolled, 174 were hypoxaemic which represents 50.7% (95% CI: 45.4 - 56.0) of the children (Figure 2). One hundred and fifty one children (44%) had severe pneumonia (95% CI: 38.7 - 49.5) whereas 192 (56%) had very severe pneumonia (95% CI: 50.5 - 61.3) (Table 4). Stratified by severity, prevalence of hypoxaemia was 39.7% (95% CI: 31.9 - 47.6) among children with severe pneumonia and 59.4% (95% CI: 52.4 - 66.3) among those with very severe pneumonia (Figure 3).
Figure 2: Prevalence of Hypoxemia in Study Population

Table 4: Distribution of Pneumonia Severity in Study Population

<table>
<thead>
<tr>
<th>WHO category</th>
<th>Number</th>
<th>95% CI for Pneumonia Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe pneumonia</td>
<td>151</td>
<td>39.7 (38.7 - 49.5)</td>
</tr>
<tr>
<td>Very severe pneumonia</td>
<td>192</td>
<td>59.4 (50.5 - 61.3)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>343</td>
<td></td>
</tr>
</tbody>
</table>
Median oxygen saturation was 89.0% (IQR: 84%-94%) for the whole population. Stratified by categories, median saturation was 91% (IQR: 88%-96%) among children with severe pneumonia and 88% (IQR 79%-92%) among those with very severe pneumonia. Figure 4 shows the distribution of oxygen saturation levels for the whole population while Figure 5 shows the same in the two categories of pneumonia severity. The spread of arterial oxygen saturation was much wider with greater variability among
children with very severe pneumonia (minimum 48%, maximum 100%) compared to those with severe pneumonia (minimum 68%, maximum 100%) reflecting the greater number of hypoxaemic children in this category. The number of children with oxygen saturation of 100% was however comparable in both groups of children.

Figure 4: Distribution of Oxygen Saturation Levels in Study Population
4.5 Sensitivity and Specificity of GoK Criteria for Oxygen Therapy

We compared the number of children diagnosed as 'hypoxaemic' using clinical signs outlined in the GoK criteria with that obtained by pulse oximetry. In the GoK guidelines, oxygen therapy is indicated in the presence of any of the signs of very severe pneumonia which are: cyanosis, altered level of consciousness (not alert on AVPU coma scale), inability to drink/breastfeed, grunting or head nodding (Table 5).
Table 5: Sensitivity, Specificity and Predictive Values of GoK Criteria for Oxygen Therapy

<table>
<thead>
<tr>
<th>Oxygen Saturation by Pulse Oximetry</th>
<th>Hypoxaemic n (%)</th>
<th>Non hypoxaemic n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GoK Criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Therapy Indicated (^1)</td>
<td>114 (59.4)</td>
<td>78 (40.6)</td>
<td>192</td>
</tr>
<tr>
<td>Oxygen Therapy Not Indicated (^2)</td>
<td>60 (39.7)</td>
<td>91 (60.3)</td>
<td>151</td>
</tr>
<tr>
<td>Total</td>
<td>174 (50.7)</td>
<td>169 (49.3)</td>
<td>343</td>
</tr>
</tbody>
</table>

\(^1\) Presence of Cyanosis or Altered level of consciousness or Inability to drink/breastfeed or Grunting or Head nodding (very severe pneumonia).

\(^2\) Absence of any of the above signs (severe pneumonia).

Sensitivity = \((114/174) \times 100 = 65.5%\)

Specificity = \((91/169) \times 100 = 53.8%\)

Positive Predictive Value = \((114/192) \times 100 = 59.4%\)

Negative Predictive Value = \((91/151) \times 100 = 60.3%\)

4.6 Clinical Signs and their Ability to Predict Hypoxaemia.

An analysis of each of the signs that define very severe pneumonia as outlined in the GoK guidelines and its ability to predict hypoxaemia was done at both univariate and multivariate levels. The signs analysed included: cyanosis, altered level of consciousness (less than alert on AVPU coma scale), inability to drink/breastfeed, grunting or head nodding. The result on univariate analysis is shown in Table 6a.
Table 6a: GoK Clinical Signs of Very Severe Pneumonia and their ability to Predict Hypoxaemia

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Hypoxaemic n (%)</th>
<th>Non-hypoxaemic n (%)</th>
<th>Odds Ratio (95% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanosis(^1)</td>
<td>22 (88.0)</td>
<td>3 (12.0)</td>
<td>8.0 (2.3 - 27.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Grunting(^1)</td>
<td>56 (62.9)</td>
<td>33 (37.1)</td>
<td>2.0 (1.2 - 3.2)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Head nodding(^1)</td>
<td>71 (67.0)</td>
<td>35 (33.0)</td>
<td>2.7 (1.7 - 4.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Reduced consciousness(^2)</td>
<td>24 (54.5)</td>
<td>20 (45.5)</td>
<td>1.2 (0.6 - 2.3)</td>
<td>0.630</td>
</tr>
<tr>
<td>Inability to drink/breastfeed(^1)</td>
<td>68 (55.7)</td>
<td>54 (44.3)</td>
<td>1.4 (0.9 - 2.2)</td>
<td>0.177</td>
</tr>
</tbody>
</table>

\(^1\)Reference category used was ‘No’
\(^2\)Reference category used was ‘Alert’ versus less than alert on AVPU coma scale

*Significant at 0.05 level.

There was significant association between occurrence of hypoxaemia and cyanosis (OR: 8.0; 95% C.I: 2.3 - 27.1; P<0.001). Hypoxaemia was present in 88.0% of children with cyanosis compared to 47.9% among children without this sign. A child with cyanosis had an odds of 8.0 for hypoxaemia compared to one without this sign.

Grunting was also significantly associated with hypoxaemia (OR: 2.0; 95% C.I: 1.2 – 3.2; P=0.010). Hypoxaemia occurred in 62.9% of children with this sign compared to 46.5% among those without. A child with grunting had an odds of 2.0 for hypoxaemia compared to one without.
Similarly, there was a significant association between occurrence of hypoxaemia and head nodding (OR: 2.7; 95% C.I: 1.7 – 4.4; P<0.001). A child with this sign had an odds of 2.7 for hypoxaemia than one without.

Altered level of consciousness and inability to drink/breastfeed were not significantly associated with hypoxaemia. Hypoxaemia was present in 54.5% of children with altered level of consciousness and in 50.2% of children who were alert (OR: 1.2; 95% C.I: 0.6 – 2.3; P=0.630). Hypoxaemia occurred in 55.7% of children who were unable to drink/breastfeed and in 48.0% of those who were able (OR:1.4; 95% C.I: 0.9 – 2.2; P=0.177). A child who was unable to drink/breastfeed had an odds of 1.4 for hypoxaemia although this did not achieve statistical significance.

We undertook to evaluate two clinical features not included in the GoK criteria (high respiratory rate and lower chest-wall indrawing) to determine their ability to predict hypoxaemia. We progressively raised the cut off for respiratory rate (RR) to determine whether there would be a significant association with hypoxaemia. None of the factors was significantly associated with hypoxaemia. The result of the univariate analysis is shown in Table 6b.
Table 6b: Other Clinical factors and their Ability to Predict Hypoxaemia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypoxaemic n(%)</th>
<th>Non-hypoxaemic n(%)</th>
<th>OR (95% C. I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Respiratory rate(^1)</td>
<td>91(55.5)</td>
<td>73(44.5)</td>
<td>1.4 (0.9-2.2)</td>
<td>0.098</td>
</tr>
<tr>
<td>High Respiratory rate(^2)</td>
<td>68(56.2)</td>
<td>53(43.8)</td>
<td>1.4 (0.9-2.2)</td>
<td>0.143</td>
</tr>
<tr>
<td>High Respiratory rate(^3)</td>
<td>46(57.5)</td>
<td>34(42.5)</td>
<td>1.4 (0.9-2.3)</td>
<td>0.175</td>
</tr>
<tr>
<td>Lower chest wall in drawing</td>
<td>166(49.0)</td>
<td>173(51.0)</td>
<td>3.1(0.3-30.4)</td>
<td>0.366</td>
</tr>
</tbody>
</table>

\(^1\) RR >60 for children 12-59 months; RR >70 for children 2-11 months.
\(^2\) RR >65 for children 12-59 months; RR >75 for children 2-11 months.
\(^3\) RR >70 for children 12-59 months; RR >80 for children 2-11 months.

4.7 HIV infection as a Risk Factor for Hypoxaemia

We sought to determine whether HIV co-infection among children with severe forms of pneumonia was a significant risk factor for hypoxaemia. The prevalence of hypoxaemia was 54.8% among HIV infected children and 47.9% among uninfected children. HIV infection was not significantly associated with hypoxaemia (OR 1.4, 95% CI= 0.6 to 2.9, P=0.42) (Table 7).

Table 7: Association Between HIV infection and Hypoxaemia

<table>
<thead>
<tr>
<th>HIV infection</th>
<th>Hypoxaemic n (%)</th>
<th>Non-hypoxaemic n (%)</th>
<th>Odds Ratio (95% C. I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV uninfected</td>
<td>128 (47.6)</td>
<td>141 (52.4)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HIV infected</td>
<td>17 (54.8)</td>
<td>14 (45.2)</td>
<td>1.4 (0.6 - 2.9)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
4.8 Multivariate Analysis

We conducted a multivariate analysis to determine whether any of significant univariate factors were independently associated with hypoxaemia. After adjusted analysis, we found that only two factors (cyanosis and head nodding) remained independently associated with hypoxaemia. Grunting which was significantly associated with hypoxaemia at univariate analysis was no longer associated with hypoxaemia in adjustment analysis. The result of the multivariate analysis is as shown in Table 8.

Table 8: Multivariate Logistic Regression Showing Ability of Clinical Signs to Predict Hypoxaemia

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>Adjusted OR (95.0% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanosis(^{1})</td>
<td>6.3 (1.8 – 22.0)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Grunting(^{1})</td>
<td>1.3 (0.8 – 2.3)</td>
<td>0.298</td>
</tr>
<tr>
<td>Head nodding(^{1})</td>
<td>2.3 (1.4 – 3.9)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

\(^{1}\) Reference category used was 'No'

*Significant at 0.05 level.

4.9 Mortality Outcome in the Study Population

A total of twenty eight children (8.2%) died during the study period. There were sixteen deaths (9.2%) among hypoxaemic children and twelve (7.1%) among the non hypoxaemic (SpO\(_{2}\) <90%). We then examined mortality with severe hypoxaemia (SpO\(_{2}\) <85%). There was a significant difference in mortality between children with SpO\(_{2}\) <85%
compared to those with higher oxygen saturation. These children had a 3.3 fold increased mortality compared to those with oxygen saturations ≥ 85% (OR: 3.3; 95% CI:1.5 - 7.1; P=0.005). Mortality was 15.9% among children with SpO2 <85% compared to 5.5% among those with SpO2 ≥ 85%. *(Table 9, Figure 6 and Figure 7).*

**Table 9: Mortality Among Hypoxaemic and Non hypoxaemic Children**

<table>
<thead>
<tr>
<th></th>
<th>Dead (%)</th>
<th>Alive (%)</th>
<th>OR (95% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90%</td>
<td>Yes</td>
<td>16 (9.2)</td>
<td>158 (90.8)</td>
<td>1.3 (0.61 - 2.9)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>12 (7.1)</td>
<td>157 (92.9)</td>
<td>1.3 (0.61 - 2.9)</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;85%</td>
<td>Yes</td>
<td>14 (15.9)</td>
<td>74 (84.1)</td>
<td>3.3 (1.5 - 7.1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>14 (5.5)</td>
<td>241 (94.5)</td>
<td>3.3 (1.5 - 7.1)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>28 (8.2)</td>
<td>315 (91.8)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 6: Relationship Between Hypoxaemia and Mortality \((\text{SpO}_2 < 90\%)\).

Figure 7: Relationship Between Severe Hypoxaemia and Mortality \((\text{SpO}_2 < 85\%)\).
4.10 Association Between HIV Infection Status and Mortality

Mortality was found to be higher among HIV infected compared to uninfected children. Five (16.1%) of the HIV infected and 15 (5.6%) of uninfected children died indicating a significant association between HIV co-infection and mortality (OR: 3.1; 95% CI: 1.1 - 9.3; P=0.048) (Table 10).

Table 10: Association Between HIV Infection and Mortality.

<table>
<thead>
<tr>
<th>HIV status</th>
<th>Mortality Outcome</th>
<th>Odds Ratio (95% C. I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dead n (%)</td>
<td>Alive n (%)</td>
<td></td>
</tr>
<tr>
<td>HIV infected</td>
<td>5 (16.1)</td>
<td>26 (83.9)</td>
<td>3.1 (1.1 - 9.3)</td>
</tr>
<tr>
<td>HIV uninfected</td>
<td>15 (5.6)</td>
<td>254 (94.4)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20 (6.6)</td>
<td>281 (93.4)</td>
<td></td>
</tr>
</tbody>
</table>
5.0 DISCUSSION

In our study, there was an equal distribution between males (48.1%) and females (51.9%). Majority of the children (63.8%) were less than one year of age indicating that infants are the most vulnerable to severe forms of pneumonia.

The study indicates that hypoxaemia is a frequent occurrence among children with severe or very severe pneumonia. Prevalence of 50.7% in KNH, Nairobi (altitude 1630m) is comparable to that of a study by Wandi et al in Papua New Guinea (altitude 1600m) of 54.2% in this group of patients.

Prevalence in our study was however higher than reported by many other studies. Fu et al\(^\text{21}\) reported a prevalence of 9.5% in a multicentred study which included Mexico and Bogota among other sites. Seven of these sites were at sea level and a threshold of <90% was used to determine hypoxaemia. Two sites were at high altitude and threshold for hypoxaemia was <88%. Brooks et al\(^\text{26}\) reported a prevalence of 13.7% in Bangladesh (altitude 0 m) and Bose et al\(^\text{23}\) a prevalence of 18.7% in India (altitude 0 m).

Stratified by severity, prevalence of hypoxaemia was 39.7% and 59.4% among children with severe and very severe pneumonia respectively. This is much lower than that reported by Basnet et al\(^\text{25}\) in Nepal (1300m altitude) in which prevalence was 80% and 100% among children with severe and very severe pneumonia respectively. In that study, a total of 250 children categorized as having cough/cold, pneumonia, severe pneumonia
or very severe pneumonia were recruited and assessed. Only 45 children had severe or very severe pneumonia. Twenty five children had severe pneumonia and twenty had very severe pneumonia. With such a small number, it is likely that there was selection for very sick children. Compared to a study by Singhi et al\textsuperscript{28} in India (altitude 0 m), prevalence of hypoxaemia in our study was higher among children with severe pneumonia (39.7\% compared to 26\%) but lower (59.4\% compared to 73.8\%) among children with very severe pneumonia.

A large number of the above studies were conducted at low altitude (seven out of nine sites in Fu et al\textsuperscript{21}, Brooks et al\textsuperscript{26}, Bose et al\textsuperscript{25}, Singhi et al\textsuperscript{26}). Low altitude has been associated with lower prevalence of hypoxaemia. In a systematic review by Subhi et al\textsuperscript{20} of both published and unpublished studies reporting the prevalence of hypoxaemia in ALRI, median prevalence of hypoxaemia among studies reviewed was 13\% but prevalence in various studies varied widely ranging from 6.9\% to 100\%. There were however, wide variations between different regions even at similar altitudes and cut-off values for hypoxaemia which means there could be other factors in our set up contributing to the high prevalence of hypoxaemia. Factors that have been thought to contribute to the wide variations in prevalence include: regional variations in pathogen aetiology, host epidemiology, prevalence and severity of co-morbidities and environmental factors.\textsuperscript{20} We did not explore the effect of co-morbidities in our study.
Hypoxaemia as a complication of pneumonia has been widely studied. Most studies on hypoxaemia in developing countries have mainly been on the ability of clinical signs to predict hypoxaemia.

Most of the signs seen in pneumonia have been found to be associated with hypoxaemia by different studies. Drowsiness, cyanosis, decreased air entry, head nodding, nasal flaring, grunting, chest retractions, and a respiratory rate of >70 breaths per minute for children three to 11 months or >60 breaths per minute for those 12 months or older have all been reported to be predictors of hypoxaemia. No single sign has however been found to predict hypoxaemia with both high sensitivity and specificity. Despite this, clinical signs including some on which there is limited data (head nodding and AVPU coma scale) have been included in the GoK guidelines as indicators for oxygen therapy.

Our evaluation of the GoK criteria for oxygen therapy (presence of any of these signs: cyanosis, inability to drink/breastfeed altered level of consciousness (AVPU<A), grunting or head nodding) found this `decision rule` to have both low sensitivity (65.5%) and specificity (53.8%). This means using this criteria about one third (34.5%) of children with hypoxaemia would miss oxygen therapy with increased risk of mortality and almost half of the children (46.7%) who do not require oxygen would be given oxygen leading to wastage. Administering oxygen to children who do not require it may not be a problem in centres such as KNH where oxygen is harvested from the atmosphere by use of oxygen concentrators and so may be relatively cheaper but is a challenge for
small hospitals which depend on oxygen supplied in cylinders. This is expensive and sometimes hospitals run out of oxygen posing increased risk of mortality for those who require it. The government funds public health facilities in Kenya. It is regrettable that a lot of money is spent on purchase of oxygen much of which ends up being used by children who do not require it. Even at KNH where concentrators are used and therefore relatively cheaper compared to use of oxygen cylinders, the increased demand for oxygen is an additional cost to the hospital. Oxygen is an expensive and precious resource that should be used judiciously.

We evaluated the five clinical signs recommended by the GoK as indicators of oxygen therapy. We found cyanosis, grunting and head nodding to be associated with hypoxaemia at univariate level but at multivariate analysis only cyanosis (OR: 9.1; 95% CI:1.99 - 44.0, P=0.06) and grunting (OR: 2.1; 95% CI:1.2 - 3.6. P=0.013) were independently associated with hypoxaemia.

Altered level of consciousness (AVPU<A) may be associated with other complications such as hypoglycemia which may occur in severely ill children. It is possible that some of the children had altered consciousness due to hypoglycemia. We did not collect data on hypoglycaemia and therefore cannot verify its effect on our findings. Similarly, other complications of severe illness other than hypoxaemia may result in inability to drink/breastfeed.
Our study, unlike other previous studies did not show a significant association between hypoxaemia (arterial oxygen saturation <90%) and mortality but did show a significant association when the cut off was reduced to <85% (OR: 3.3; 95% CI: 1.5 - 7.1, P=0.005).

In the study by Onyango et al\textsuperscript{5} hypoxaemic children were 4.3 times more likely to die than non-hypoxaemic children. Weber et al\textsuperscript{6} in a similar study in the Gambia found that the relative risk for death among hypoxaemic children with ALRI was 4.6 and the case fatality rate was inversely related to the arterial haemoglobin oxygen saturation. All children with hypoxaemia received oxygen and management for pneumonia according to the standard protocols. We believe other factors such as treatment failure and co-morbidities may have contributed significantly to mortality in our cohort of patients.

Thirty one children (9.0%) were HIV infected. Although our results suggested a possible association between HIV infection and hypoxaemia, the number of HIV infected children in this study was small so we were not powered to make this conclusion. HIV co-infected children had an odds of 3.1 for mortality than uninfected children. This compares with Zimbabwean studies which showed the risk of mortality among children treated for pneumonia was three times higher in those with HIV co-infection.\textsuperscript{30} Although not the main focus of this study, our finding validates the recommendation by the GoK to treat HIV co-infected children more aggressively. HIV infected children with either severe or very severe pneumonia are treated with both crystalline penicillin and gentamycin as first line therapy whereas for the uninfected, gentamycin is given to only those with a classification of very severe pneumonia.
6.0 STUDY LIMITATIONS

1. We had limited time over which we had to complete the study as dictated by the Postgraduate academic calendar. A longer duration of data collection would have yielded a larger sample size that would allow greater precision in reporting of estimates for proportions or odds ratios. In addition, a longer study period would reduce the possible influence of seasonal variation on reported estimates and hence improve generalisability.

2. Kenyatta National Hospital, being a tertiary facility receives patients referred from lower-level hospitals. Our study population may have comprised of “sicker” patients than those attending other hospitals in Kenya thus limiting the applicability of our results on prevalence of hypoxaemia to these other health facilities.

7.0 CONCLUSIONS

1. Prevalence of hypoxaemia was high, occurring in 50.7% of children hospitalized with severe forms of pneumonia. Prevalence was highest (59.4%) among children hospitalized with very severe pneumonia.

2. The Government of Kenya criteria for oxygen administration (presence of any of these signs: cyanosis, inability to drink/breastfeed, altered level of consciousness (AVPU<A), grunting or head nodding) have a low sensitivity (65.5%) and specificity (53.8%) for predicting hypoxaemia among children with severe forms of pneumonia.
3. Severe hypoxaemia (SpO₂ < 85%) is associated with a 3.3 fold increased mortality among children hospitalised with severe forms of pneumonia.

8.0 RECOMMENDATIONS

Based on findings in this study, we recommend the following:

1. That the government of Kenya promotes the use of pulse oximeters for detection of hypoxaemia in all public hospitals.

2. That the Government consider carrying out a cost-benefit study on the use of pulse oximeters vis-a-vis continued use of clinical signs to determine which children require oxygen therapy.
REFERENCES


APPENDICES

APPENDIX 1: QUESTIONNAIRE

Questionnaire Serial Number

Data collectors serial number (Please circle one).
1......2......3......4......5......6......7......8......

Patient Data

1. Name ........................................................... Hospital No...............................................
2. Gender Male.......0......Female........1.....
3. Date of Birth ............/......../................ Missing ............0..........................
4. Age at admission (months)...........................................................
   For children above 1 year, state Years........... Months.............
5. Informant (Relationship to child)...................................................

Symptoms

I = Present 0 = Absent

6. Cough ........................................................... Duration (in days)
   ...... ......................................................

7. Difficult breathing ...........................................................
   ...... ......................................................

8. Inability to feed or breastfeed ...........................................................
   ...... ......................................................

9. Abnormally sleepy ...........................................................
   ...... ......................................................

Physical Examination

Circle the appropriate response

1. Level of consciousness (AVPU) A.......V.......P.......U......
2. Inability to feed/ breastfeed Y / N............

3. Oxygen saturation by pulse oximeter
Reading 1 ...........%  
Reading 2 ...........%  
Average of reading 1 and 2 ............%  
4. Respiratory rate (state) ........ breaths per minute 

*State whether present or absent*

5. Flaring of alae nasi Y/N  
6. Grunting Y/N  
7. Head nodding Y/N  
8. Cyanosis Y/N  
9. Chest wall in drawing Y/N  
10. Crepitations Y/N  
11. Rhonchi Y/N 

**Investigations**  
*Tick as appropriate*

1. HIV rapid antibody test .............................................  
   Negative....... Positive....... Indeterminate.......  

2. If child is <18 months and rapid test is positive, state DNA PCR result:  
   Negative....... Positive....... Not done.......  

**Outcome on day 5 of admission**  
*Tick as appropriate*  
Alive (in the ward) ...........  
Discharged or absconded ...........  
Dead .............
Pneumonia management for children aged 2 months to 5 years (for a child without stridor, severe malnutrition or signs of meningitis) – in accordance with GOK guidelines.

<table>
<thead>
<tr>
<th>VERY SEVERE PNEUMONIA</th>
<th>Cough / Difficulty Breathing plus one or more of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Cyanosis or Oxy Sat’n &lt; 90%</td>
</tr>
<tr>
<td></td>
<td>• Inability to drink / breast feed</td>
</tr>
<tr>
<td></td>
<td>• AVPU &lt; A (or GCS &lt; 14)</td>
</tr>
<tr>
<td></td>
<td>• Grunting or head nodding</td>
</tr>
<tr>
<td>If criteria for very severe pneumonia NOT met – SEVERE PNEUMONIA</td>
<td></td>
</tr>
</tbody>
</table>

| Treatment | Penicillin @ 50,000iu/kg/dose qds. plus Gentamicin @ 7.5mg/kg od Plus oxygen and fluids / feeds as required |

HIV Positive

Give Pen & Gent to ALL children with severe or very severe pneumonia and give oral co-trimoxazole @ 8mg/kg/dose trimethoprim and 40mg/kg/dose sulphamethoxazole tds for 3 weeks.

APPENDIX 3: INFORMATION AND CONSENT FORM

CHILDHOOD PNEUMONIA STUDY

PART A: PARENT/GUARDIAN INFORMATION SHEET

The following information is to enable understand what this study entails so that you provide informed consent for your child to participate in this study. Please read the information carefully before signing the consent form. [Part B]

What is this study about and why am I doing the study?
The study is on pneumonia. Severe pneumonia is one of the most common reasons why children get admitted to hospital and it can be very serious, even causing some children to die. I am trying to understand one of the main complications of this disease referred to as hypoxaemia. Hypoxaemia is low level of oxygen in the blood and is a serious complication of in severe pneumonia. This information will help us understand the magnitude of the problem of hypoxaemia and may help us provide better treatment for it in the future.

Who is the study being done by?
I am Dr. Mugane S. Kihika. I am currently undertaking postgraduate training in Paediatrics and Child Health at the University of Nairobi. The training is based here at the Kenyatta National Hospital. I am the principal investigator in this study. I will also be doing the study together with other doctors from the University of Nairobi, the Kenyatta National Hospital and researchers at the Kenya Medical Research Institute (KEMRI).
**Why are we requesting to include your child?**

The study is on severe forms of pneumonia. Your child has features suggesting he/she has pneumonia severe enough to indicate that admission is necessary. We are doing a study on such severe pneumonia and would like to explain this to you and ask your permission to include your son / daughter (name ____________________________).

We are asking if we can study all children with these forms of severe pneumonia coming to Kenyatta National Hospital – so your child is one of many we are asking about as pneumonia is a common, serious disease.

**What will the study involve for my child if I agree?**

If you are happy for your child to be involved we would like to ask you questions about the child’s illness, examine them carefully and record the information about your child’s illness.

For this study, we will measure the level of oxygen in the blood using this device (show oximeter) that is entirely painless and takes only 1-2 minutes. Testing for HIV is now a routine test on admission to this hospital – it is recommended for all inpatients and should be done for all children whether or not they are in the study. I will explain this in more detail separately and ask if you agree to the test on your child. You are free to refuse the HIV test after this explanation. There may be other blood tests you may need. These are not part of any study but we will try and do all the tests needed at the same time to avoid any extra needles.
After examining your child and doing the necessary tests and giving the recommended treatment, your child will be admitted to the general paediatric ward. We will not be in charge of the treatment all the time, your ward doctors will be in charge but we will come and check on your child's progress from time to time and also by looking at your child’s hospital records at the time they are discharged.

Are there any risks to my child participating?

Pulse oximetry is a completely painless procedure and takes only 1-2 minutes.
For the HIV test, we will require only about 3 to 4 drops of blood. Taking blood from the tip of the index or middle finger causes a small amount of temporary pain, but the amount taken is too small to affect your child’s health and we will take the blood test for the study at the same time with any other routine blood tests that may be needed.
There may be some slight inconvenience to you because of the time taken to answer the questions and get the tests but this should not cause any harm.

Are there any benefits to my child participating?

Your child will receive no major benefit. The tests being done as part of the research may sometimes help us provide better treatment to your child. There will be no extra cost to you. The research may help us provide better treatment to children in the future.

What happens if I refuse to participate?

All participation in research is voluntary. You are free to decide if you want your child to take part. If you do agree you can change your mind at any time and withdraw your child
from the research. This will not affect your child’s care now or in the future. If you do not agree for your child to be included that will cause no problem.

**Who will have access to information about me/my child in this research?**

Information that is important to providing the right medical care for your child will be shared with the doctors looking after your child but all of the staff at KNH will ensure your medical records are kept confidentially. All the research records are stored securely without the name of you or your child and only people who are closely concerned with the research will be able to view information.

**Who has allowed this research to take place?**

A committee from KNH has looked carefully at this work and has agreed that the research is important, that it will be conducted properly and that participants’ safety and rights have been respected.

**What if I have any questions?**

Please feel free to ask any questions about the study. If there is any part of this form that you do not understand, be sure to ask questions about it. You can contact me or those who are responsible for the care of your child and this research. For any question or clarification please contact me,

Dr. Mugane S.K.

Department of Paediatrics and Child Health

University of Nairobi,
PART B: CONSENT FORM

I, being a guardian of .................................................. (name of child), Hospital Number....................................., have understood the information in Part A above on what the research entails. I have also had a chance to ask questions which have been answered satisfactorily. I understand that I can withdraw from the research at any stage and it will not affect me/my child in any way.

☐ I agree to allow my child to take part in this research and for the collection of clinical data.

Parent/guardian’s signature: ___________________________ Date: __________

Parent/guardian’s name: _______________________________ Time: __________
I certify that I have followed all the study specific procedures in the SOP for obtaining informed consent.

Designee/investigator’s signature: ___________________________ Date: ___________________________

Designee/investigator’s name: ______________________________ Time: ________________________

Only necessary if the parent/guardian cannot read:

I* attest that the information concerning this research was accurately explained to and apparently understood by the parent/guardian and that informed consent was freely given by the parent/guardian.

Witness’ signature: ___________________________ Date: ___________________________

Witness’ name: ___________________________ Time: ________________________

*A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.

Thumbprint of the parent as named above if they cannot write:

__________________________ Investigator’s statement
## APPENDIX 4: BUDGET

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Equipment: Pulse oximeter</td>
<td>70,000</td>
</tr>
<tr>
<td>2. Supplies: Rechargeable batteries</td>
<td>5,000</td>
</tr>
<tr>
<td>3. Stationery, printing, data entry and other office costs</td>
<td>10,000</td>
</tr>
<tr>
<td>4. Personnel, salaries and other disbursements</td>
<td>NIL</td>
</tr>
<tr>
<td>5. Contingency (15%)</td>
<td>12,750</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>97,750</strong></td>
</tr>
</tbody>
</table>

### Justification of the budget

The budget covers the cost of purchase of a pulse oximeter, probes, batteries and simple office costs. The eight principal investigators will undertake this study as part of their Masters of Medicine in Paediatrics programme and are therefore not entitled to salaries or any other disbursements.