CLINICAL FEATURES THAT PREDICT TREATMENT FAILURE AND DEATH IN CHILDREN PRESENTING AT KENYATTA NATIONAL HOSPITAL WITH SEVERE AND VERY SEVERE PNEUMONIA ON ADMISSION.

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DECLARATION

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

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DEDICATION

To my parents for showing me clear direction in life.

To my husband Jimmie and my son Jonathan for their support and for always being there for me.

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LIST OF ABBREVIATIONS

AVPU.................................Alert. Verbal response. response to pain. Unconscious

Bpm....................................Breaths per minute

GCS....................................Glasgow Coma Scale

GoK....................................Government of Kenya

Hib.....................................*Haemophilus influenzae* type b

HIV.....................................Human Immunodeficiency Virus

IU.......................................International units

IV.......................................Intravenous

KEMRI...............................Kenya Medical Research institute

Kg.......................................Kilogram

KNH....................................Kenyatta National Hospital

Mg.....................................Milli grams

NSP.....................................Non severe pneumonia

OR......................................Odds ratio

PEU....................................Paediatric Emergency Unit

Qid.....................................Four times a day

S.H.O..................................Senior House Officer

WHO..................................World Health Organization

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ABSTRACT

Background: Pneumonia kills more children than any other illness in the world and is a significant problem in communities with a high rate of under - five mortality placing a huge burden on families and health systems.[1] As of 2005, more than 150 million childhood pneumonia cases were estimated to occur every year in the developing areas of the world and acute respiratory infection is responsible for an estimated 1.9 million childhood deaths each year.[2]

Methods: Children between the ages 2 months to 59 months coming to the Pediatric Emergency Unit (PEU) at the KNH were screened for signs of pneumonia (cough and difficulty in breathing) and lower chest wall in drawing. The principal investigator, who worked with the other colleagues in the pneumonia study, was stationed at the PEU. Explanation of the purpose of the study and the procedures involved were given to the guardians/parents of the children and a written consent was sought from them. Of the children who presented with signs and symptoms of pneumonia, those with wheeze who responded to bronchodilators were excluded together with those ineligible for treatment. Emergency care such as oxygen and administration of fluids was instituted without delay arising from study procedure. Sociodemographic and clinical information was collected using a pretested questionnaire. At baseline, pulse oximetry and blood cultures were taken. The patients were followed up in the wards at 24 hours, 48 hours and 72hours whereupon the clinical signs and symptoms were checked for improvement or deterioration. Clinical failure was defined as persistence or worsening of signs and symptoms, clinician decision to change antibiotics or death at or before 48 hours.

Results: A total of four hundred and eighty seven children aged 2 to 59 months who presented to the pediatric emergency unit with cough and difficulty in breathing were assessed. A total of 385 children were admitted to the study. Of these, 171 (44.4%) had severe pneumonia while those with very severe pneumonia were 214 (55.6%). The proportion of children with treatment failure was 28.1%. Treatment failure rate was higher in those with very severe pneumonia at 39.7% compared to those with severe pneumonia 13.5%. One hundred and seventy one children with severe pneumonia 3(1.8%) died while 27(12.6%) with very severe pneumonia died. The clinical correlates of treatment failure in children with severe pneumonia included history of previous treatment which was associated with a 5 fold higher odds of failing treatment with a P=0.056. Grunting and level of consciousness less than A were associated with a 2.4 and 4.8 fold

increase in the odds of failing treatment respectively. The ability to drink and presence of wheeze were associated with a better outcome in treatment failure OR 0.5 (0.2-0.5), OR 0.4(0.2-0.8) respectively. Cough, wheeze and ability to drink were associated with better outcomes as regards to death OR 0.1 with a P value of 0.029; 0.4 with a P value of 0.048 and OR 0.1 with P value of 0.01 respectively.

Conclusions

The rate of treatment failure was 28.1% with 39.7% in the very severe pneumonia and 13.5% in the severe pneumonia group. Mortality was low within the severe pneumonia group therefore the correlates could not be assessed. Association of treatment failure in the severe pneumonia group included a borderline association with history of previous treatment. In general, wheeze and ability to drink were associated with better outcomes in treatment failure and death while grunting and reducing level of consciousness were associated with increased odds of failing treatment or dying in the very severe pneumonia group. Level of consciousness and ability to drink showed co-linearity, that is one varies with the other, they are not independent predictors of treatment failure and death.

Recommendations

Children with very severe pneumonia who present with grunting or reduced level of consciousness need to be prioritized because of the increased risk of treatment failure and death. Children with grunting, decreased level of consciousness and inability to drink should be prioritized within the wards for close monitoring and frequent clinical reviews and may require more supportive care in a higher dependency unit.

INTRODUCTION AND LITERATURE REVIEW

Pneumonia is an inflammatory disease of the parenchyma of the lungs due to infectious and non infectious causes. It affects all age groups but more commonly the young children and the elderly. It is associated with high mortality if untreated.

Pneumonia kills more children than any other illness in the world and is a significant problem in communities with a high rate of under five mortality placing a huge burden on families and health systems. [1]

As of 2005, more than 150 million childhood pneumonia cases were estimated to occur every year in the developing areas of the world and acute respiratory infection (ARI) being responsible for an estimated 1.9 million childhood deaths each year. [2]

The key strategies for the prevention of childhood pneumonia are first, prevention through vaccination[3] particularly the newer vaccines against *Haemophilus influenzae* type b and *Pneumococcus*; second, promotion of exclusive breast feeding during the first few months of life, and perhaps zinc supplementation,[1] together with improvement of living conditions particularly related to reduction in indoor air pollution.[5] None of these preventive measures is likely to completely prevent childhood pneumonia so there is still a need for treatment through case management now mainly through Integrated management of Childhood illnesses (IMCI) which provides treatment guidelines for children presenting for primary care. For children too ill for outpatient treatment, referral to hospital and inpatient treatment is recommended. Treatment with antibiotics in the community reduces mortality and morbidity from pneumonia.[6]

At hospital level pneumonia is a common cause of admission and death. Berkley et al[7] conducted an observational study involving a *priori definitions of a hierarchy of syndromic*

indications for antibiotics therapy derived from the WHO. IMCI and inpatients' guidelines and applied these rules to a prospectively collected dataset. Of 11.847 acute paediatric hospital admissions 2.803 met the definition of pneumonia syndrome warranting antibiotic treatment: 1.470(52%) had severe pneumonia. 296(11%) had very severe pneumonia and 1.037(37%) had mild pneumonia. Severe pneumonia was defined as presence of cough or difficulty in breathing plus respiratory distress (lower chest wall indrawing). Children who had signs of more severe illness together with cough and difficulty breathing. including one or more of prostration. cyanosis or hypoxia measured by oximetry. were considered to have very severe pneumonia. The prevalence of invasive bacterial infection with severe pneumonia syndrome was 7.1%. Streptococcus Pneumoniae (38%). Enterobacteriaceae (30%) and Hemophilus Influenzae (15%) were the common isolates. Case fatality was greater (P=0.001) in those with more severe disease. Out of 1037 children with mild pneumonia 15(1.5%) died compared with 52 out of 1470 (3.5%) and 56 out of 269 (19%) with severe and very severe pneumonia respectively.[7]

AETIOLOGY

Pneumonia is caused by a range of agents. Most cases of pneumonia are caused by microorganisms. but there are several non infectious causes. which include but are not limited to aspiration of food or regurgitant gastric acid. foreign bodies. hydrocarbons and lipoid substances.

A review of the aetiology of childhood community acquired pneumonia in both developed and developing countries by Nascimento- Carvalho[9] revealed that in North America and Europe (9 studies). the etiology of pneumonia was established in 62% of the studied children (range 43%-88%) using noninvasive specific methods for microbiologic diagnosis. The most often identified agents were Streptococcus pneumoniae (22%). respiratory syncytial virus (RSV) (20%). Haemophilus influenzae (7%). and Mycoplasma pneumoniae (15%). In Africa and South

America (8 studies), bacteria were recovered from 56% (range 32%-68%) of severely ill children with pneumonia studied by lung aspirate. The most often isolated bacteria were Streptococcus pneumoniae (33%) and Haemophilus influenzae (21%).[8]

The high prevalence of bacterial etiology of pneumonia is thought to be the cause of the higher mortality associated with acute respiratory infection in developing countries. Researchers using lung aspiration have isolated *Streptococcus pneumoniae* and *Haemophilus influenzae* (as well as others), in up to 74% of patients with pneumonia in developing countries. However, Pneumonia due to Haemophilus influenzae is on the decline due to the recently introduced and now widely practiced vaccination with Hib.[9]

CLINICAL FEATURES

There are many clinical signs associated with severity of respiratory distress and in Kenya grunting is used as an indicator of very severe pneumonia in infants (Government of Kenya guidelines).[10]

Maina[11] in a study at KNH on 251 children aged 2 – 59 months with severe pneumonia found that those presenting with grunting were 30%, with central cyanosis were 4%, with inability to breastfeed or drink were 25% and those with malnutrition were 29%. From the study, the majority of the children admitted with pneumonia had severe pneumonia at 70% and the short term case fatality of children admitted with pneumonia was 13.2%. HIV infection, inability to breastfeed or drink and central cyanosis were the best predictors of mortality in children admitted with pneumonia. However, this study did not examine treatment failure rates and was limited by being conducted on a convenience sample so there was no recruitment of children at weekends or nights who are often more seriously ill.

TREATMENT FAILURE

The mainstay of pneumonia therapy is early treatment with an antibiotic to which the organism is susceptible. WHO recommends penicillin for first line treatment of severe pneumonia and either chloramphenicol or penicillin plus gentamycin for treating very severe pneumonia. Both treatment options have good cover in the blood or lungs against sensitive strains of *Streptococcus pneumoniae*, the commonest cause of bacterial pneumonia [2]

A series of studies have been conducted during the past decade to assess treatment outcomes in children with WHO defined severe and very severe pneumonia treated using WHO recommended antibiotics. Table 1 below summarizes the most recent among these studies.

TABLE 1: SUMMARY OF STUDIES THAT HAVE ASSESSED TREATMENT FAILURE IN PATIENTS WITH PNEUMONIA.

Reference	Age (no.) of children enrolled in the study	Setting and year of publication	Treatment given	Definition of treatment failure	Need to change antibiotics/no improvement	Death
NSP/Severe pneumonia Strauss et al[16]	2-59mo (876)	Outpatient and inpatient wards.Pakistan 1998	Oral trimethoprime-sulfamethoxazole or oral amoxicillin	One or more of: Sao$_2$ 87% or less for > 30 min when the child is calm. prolonged tachypnea(>2h).presence of any danger sign. no improvement after 48 hr therapy or deterioration in the opinion of a senior clinician	11(1.8%)	1
Severe pneumonia Addo – Yobo et al[17]	3-59 mo(1702)	Inpatient, International multiceter;2004	Parenteral penicillin or oral amoxicillin	Any of the following (up to or at the first 48hrs)danger signs, low sao$_2$,persisting indrawing, serious adverse drug reaction, received another antibiotic, newly diagnosed co morbidity, consent withdrawal, discharge against medical advice. death	310(18.2%)	7(0.4%)

TABLE 1 CONTINUED

Reference	Age (no.) of children enrolled in the study	Setting and year of publication	Treatment given	Definition of treatment failure	Need to change antibiotics/ no improvement	Death
Tabish Hazir et al[12]	3-59 mo (2037)	Outpatient and inpatient wards, multicenter Pakistan;2008	Parenteral ampicillin or oral amoxicillin	Any of the following: clinical deterioration, inability to take oral medication due to persistent vomiting; development of a co morbid condition requiring an antibiotic; persistence of fever>38 c with lower chest wall in drawing from day 3 to 6;hospitalization related to pneumonia; serious adverse event death	164(16.1%)	5(0.2%)
Prakash Jeena et al[14]	3 – 59 mo (523)	Outpatient and inpatient wards, multicenter Durban SA and Ndola, Zambia;2006	Parenteral penicillin or oral amoxicillin	Presence of danger signs(inability to drink, convulsions, and the patient being abnormally sleepy or difficult to wake) persistence of lower chest wall indrawing, saturated oxygen <80% on room air, serious adverse drug reaction, change in antibiotic therapy, newly diagnosed co morbid condition.death	57(12.3%)	2.2%

TABLE 1 CONTINUED

Reference	Age (no.) of children enrolled in the study	Setting and year of publication	Treatment given	Definition of treatment failure	Need to change antibiotics/ no improvem ent	Death
Very severe pneumonia (1116) Duke et al[13]	1-59 mo	Inpatient, Papua New Guinea:2002	Chlorampheni col or penicillin and gentamycin	Presence of 4 or more of the following(after 5 days of completed treatment): fever, tachypnea or apneas; moderate or severe chest indrawing; chest crepitations or bronchial breath sounds;sao$_2$ not improved from admission; worsening radiological changes on CXR or death or readmission within 1 month	119(10.7%)	7(0.6%)
Shann et al[9]	Age not stated	In patient, Papua New Guinea:1985	Chlorampheni col alone or chloramphenic ol with penicillin	Death or withdrawal for change of antibiotic	9(1.2%)	110(14.7%)

A study done by Duke et al[13] among children with severe pneumonia treated with chloramphenicol versus benzylpenicillin and gentamycin in Papua New Guinea found no significant difference in the probability of an adverse outcome in children in the two treatment groups. The study identified several early predictors of treatment failure including longer duration of cough more than 7 days (OR 2.88, 95% CI 2.0-3.9) and hemoglobin oxygen saturation of less than 70% (OR 2.1,95% CI 1.6-2.9). Treatment failure was considered if four of the following were present after 5 days of completed treatment: fever (axillary temperature>38⁰ c); tachypnea (respiratory rate>60 breaths/minute) or apneas, moderate or severe chest indrawing, chest crepitations or bronchial breath sounds, hemoglobin oxygen saturation not improved from the time of admission, or worsening radiological changes on chest radiograph.[13]

In a study done by Jeena et al [14] at a Durban Hospital in South Africa and Ndola in Zambia on children aged 3-59 months with severe pneumonia, treatment failure was defined as failure to improve on prescribed therapy by 48 hours or deterioration in respiratory status as evidenced by increasing respiratory rates and chest indrawing, increasing oxygen requirements and onset of danger signs during the 14 day study period. On the basis of findings during clinical assessment, after completing a period of therapy, about 10-20% of children were classified as treatment failures.

Hazir T. et al [15] in a randomized equivalency trial done at 7 study sites in Pakistan on children aged 2-59 months with severe pneumonia found that most treatment failures by day 6 were either due to development of danger signs or persistence of lower chest wall indrawing or fever. Several baseline characteristics such as infancy (3-5months) OR 3, significantly underweight for age (OR 2) and very fast breathing (OR 2) were predictive of treatment failure in the multivariate

model. Breast feeding at presentation was found to decrease the risk for pneumonia treatment failure by day 6 in children under the age of 24 months.

Straus et al [16] studied the effectiveness of co-trimoxazole compared with amoxycillin in non-severe and severe pneumonia therapy (WHO classification), and assessed the clinical impact of co-trimoxazole resistance among Pakistani children. The primary outcome was inpatient therapy failure defined as one or more of: oxygen saturation 87% or less, prolonged tachypnoea, presence of any danger sign; or no improvement after 48 hours or deterioration in the opinion of a senior clinician, or clinical evidence of pneumonia at outpatient follow up examination. The treatment failure rate was 20.5%.

In a randomized multicentre equivalency study done by Addo-Yobbo et al [17] in tertiary centres in eight developing countries (Africa, Asia and South America) on children aged 3 – 59 months with severe pneumonia, the baseline characteristic of the children that predicted treatment failure at 48 hours were age 3 – 11months (OR 3), antibiotics in the past 48 hours (OR 2), very fast breathing more than 70 breaths/minute in infants and more than 60 breaths/minute in children (OR 1.5) and hypoxemia (OR 2.5). The most common associated clinical feature with treatment failure at 48 hours was persisting lower chest wall indrawing at 16% in both groups of children who received either amoxicillin or parenteral penicillin.

OUTCOME OF PNEUMONIA

A great majority of patients with pneumonia recover fully. However mortality is common and influenced by various risk factors.

Shann et al [18] prospectively studied 748 children in Papua New Guinea who had severe pneumonia, as defined by the World Health Organization, with an aim of defining clinical signs

that can be used to identify children who have a high risk of dying from pneumonia. There was a very high mortality in children with a prolonged illness (sensitivity 72%; specificity 55%; P< 0.001), severe roentgenogram changes (sensitivity 67%; specificity 64%; P< 0.001), cyanosis (sensitivity 66%; specificity 56%; P<0.001), leukocytosis (sensitivity 36%; specificity 85%; P<0.001), hepatomegaly (sensitivity 53%; specificity 61%; P< 0.01), or inability to feed (sensitivity 32%; specificity 78%; P< 0.05), and there was a trend toward a higher mortality in children with grunting (sensitivity 47%; specificity 63%; P<0.06), or severe chest indrawing (sensitivity 41%; specificity 69%; P<0.06).

Spooner et al [19] examined the clinical signs and symptoms in 897 children less than 5 years of age presenting with pneumonia to Goroka Hospital in the highlands of Papua New Guinea between June 1982 and July 1985. The usefulness of the signs in predicting severity of disease was determined and risk factors for severe disease were identified. The strongest predictors of death were cyanosis [54 out of 61 children with cyanosis died (OR 17.41; P<0.001)] and poor feeding [38 out of 60 children died (OR 7.58; P<0.001)]; bronchial breathing (OR 3.35; P<0.001), grunting (OR 3.05; P<0.001), and nasal flaring (OR 2.52; P<0.01) also significantly increased the risk of dying. First-born children, children under 1 year of age, females, malnourished children, and children with symptoms for more than 7 days were at increased risk of severe disease and of dying. Fever alone did not increase the risk of dying unless it was present for more than 7 days. These clinical signs of severity and risk factors may be used to improve the efficiency of health education programmes, for both health workers and mothers, aimed at reducing childhood mortality from pneumonia.

Demers A. et al [20] did a study in Bangui, Central African Republic on risk factors for mortality among children hospitalized with acute respiratory infections and hypoxemia .The findings were

that oxygen saturations of less than 85% was a strong predictor of death in child with pneumonia(OR 15.92 p<0.0001). Other predictors of death in these children were chest indrawing (OR 22.99 p<0.0001), intercostal indrawing (OR 6.03 p<0.0001), lower chest wall indrawing (OR 10.29 p<0.0001), altered consciousness (stuporous / coma) (OR 12.55 p< 0.0001), nasal flaring (Or 5.91 p < 0.0001), grunting (OR 8.02 p<0.0001), and hepatomegally (OR 4.37 p<0.001). Independent predictors of death which were measurable at the time of admission in a study by Duke T. et al [13] were lower admission oxygen saturation if hemoglobin oxygen saturation was <70 % (OR 2.4; 1.4-4.2) and co existed with measles (OR 2.8; 1.5-5.4).

Pepin et al [21] conducted a study to measure the performance of the current WHO algorithm in identifying children at higher risk of death. Children aged 2-59 months who presented with cough and/or difficult breathing and were admitted into the paediatric hospital of Bangui (Central African Republic) were investigated. Among children with a 'severe pneumonia', those who also fulfilled the 'very severe disease' definition had a higher risk of death (31/132, 23.5%) than those who did not (12/106, 11.3%, P = 0.02). Among children with severe pneumonia, fulfilling the very severe disease definition was associated with death among those with saturation less than 95% [OR 3.02; 95%CI 1.18-7.90, p=0.02]. However, this 'very severe disease' definition did not predict death when used in children who did not have severe pneumonia. The factors that were significantly associated with death included: moderate/severe alteration (general status) OR 10.3, (95% CI 3.9-31.9); oxygen saturations of 90-94%: OR 2.8(1.1-7.3); acute malnutrition OR 2.6 (1.0-6.6); grunting OR 5.2(2.5-10.9); moderate/severe indrawing OR 3.5(1.6-8.0); hepatomegaly OR 4.5(1.9-10.7). To identify variables that would better predict death, combinations of symptoms and signs were examined among the subgroup of children with indrawing. Nine combinations had both a sensitivity and specificity of over 60%.

'Grunting and/or nasal flaring' had a sensitivity of 72% and a specificity of 66% in predicting death, and might be easier to use by primary health care personnel than other combinations. In health facilities where intravenous antibiotics, and/or oxygen are available, entry into a 'very severe pneumonia' category would be based on 'grunting and/or nasal flaring' among children with indrawing. In this study population, the mortality rates in the categories based on these definitions were 0.8% (1 out of 127) in children with no pneumonia, 0.9% (1 out of 116) in children with pneumonia, 7.7% (12 out of 156) in children with severe pneumonia and 31.1% (33 out of 106) in children with very severe pneumonia.[21]

In a Kenyan study[22], hypoxemia among children admitted at KNH predicted early mortality. Children admitted with hypoxemia were 4.3 times more likely to die within 5 days than children without hypoxemia. Hypoxemia on admission thus predicted short term hospital mortality with 90% sensitivity.

JUSTIFICATION /UTILITY OF THE STUDY

Pneumonia is a leading cause of morbidity and mortality in children worldwide. Appropriate management depends on accurate diagnosis and assessment of disease severity. For the majority of children in the developing countries the assessment is based on clinical signs and symptoms alone. At present such clinical definitions only identify the severity of illness and indicate the standard antibiotic therapy appropriate for this severity. However, it is possible that on admission children who are likely to fail such first line treatment can be identified. If this proves to be true then alternative treatment strategies should be tested in this high risk group to determine if they improve outcome.

Observations made at KNH during our mortality meetings (unpublished data) and Mutai, Mmed thesis, UON, unpublished[23] are that of the deaths that occur within 5 days in children admitted, 41% occur within 24hours and 25% occur in the first 48 hours especially during the nights. Therefore a study like this was useful in identifying the signs and symptoms that were associated with poor outcome (treatment failure and death) and also identified those at risk among the overwhelming numbers of children who are admitted.

Studies done to ascertain which signs and symptoms are likely predictors of treatment failure and death in children presenting with severe and very severe pneumonia in Kenya even if the WHO management protocol is followed have never been done, providing the main rationale for this research. Therefore, at present we do not know how effective current antibiotic strategies are.

Reduction of pneumonia mortality could be achieved by early identification of likely treatment failures and/or change of antibiotics. This study identified the early predictors of treatment failure and death and therefore will allow the health workers to put in appropriate interventions.

OBJECTIVES

STUDY QUESTION.

What admission symptoms and signs predict first line antibiotic treatment failure and death within 48 hours of admission in children with severe and very severe pneumonia at Kenyatta National Hospital?

PRIMARY OBJECTIVES:

This study was undertaken:

I.   To define the clinical correlates of first line antibiotic treatment failure in children admitted with **severe pneumonia**

II.   To define the clinical correlates of first line antibiotic treatment failure in children admitted with **very severe pneumonia**.

SECONDARY OBJECTIVES:

I.   To define the clinical predictors of death in children admitted with **severe pneumonia**

II.   To define the clinical predictors of death in children admitted with **very severe pneumonia**

NULL HYPOTHESIS:

There is no association between admission signs and symptoms with treatment failure and death in children 2-59 months presenting to the PEU of KNH with severe and very severe pneumonia.

STUDY METHODOLOGY

STUDY DESIGN.

This was a prospective descriptive study.

STUDY SITE.

The study was carried out at the Kenyatta National Hospital Paediatric Emergency Unit and the pediatric wards. KNH is a national referral hospital with a bed capacity of about 1860 of which 355 are general pediatric beds. KNH also manages non referred patients from Nairobi city and its environs.

STUDY POPULATION.

PATIENTS.

The study population comprised of children aged between 2 months to 59 months with signs of severe and very severe pneumonia at the Paediatric Emergency Unit and the pediatric wards at the Kenyatta National Hospital (KNH).

STUDY DURATION/ PERIOD.

The children were enrolled over a period of 4 months duration of data collection from June 2009 to September 2009.

EXCLUSION CRITERIA

I.   Children with known cardiac disease or renal disease that was considered the primary cause of their respiratory distress (for example through causing congestive cardiac failure).

II.   Presence of known childhood malignancies and the child is on follow up care.

III. Children ineligible for treatment with first line therapies:

- Referral with previous inpatient treatment.

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- Known pulmonary tuberculosis.

- Allergy to primary WHO recommended drugs for pneumonia treatment.

IV. Severe malnutrition diagnosed as clinically obvious marasmus, kwashiorkor or marasmic-kwashiorkor (these children are ineligible for standard pneumonia antibiotic regimens).

SAMPLING METHOD:

Comprehensive consecutive sampling was done for 7 days a week over 24 hours. The children who presented with pneumonia were identified at the Paediatric Emergency Unit and those who met the inclusion criteria were sampled.

SAMPLE SIZE ESTIMATION

The average number of children admitted with pneumonia within 3 months in 2008 was 730 children. The number of children presenting with pneumonia in a three months period was therefore estimated to be approximately 730. Of these 730, it was assumed that up to 25% with wheeze would be excluded if they responded to immediate bronchodilator therapy. Therefore about 543 children with respiratory distress clinically attributable to pneumonia were likely to be included in the study. Within this group, based on the proportions from an earlier study, it was expected that children with severe pneumonia would comprise 70% of the sample (n = 380) and those with very severe pneumonia 30% (n = 163).

In a previous study done at KNH by Maina B[11] for MMed dissertation 2006 (unpublished), clinical features of the children being admitted with pneumonia to KNH included grunting with a prevalence of 30%. Other features and their prevalence were oxygen saturations of <90% at a

prevalence of 50%. inability to feed at a prevalence of 25%. and age> 11 months at a prevalence of 40%. Taking 30% as a representative prevalence for risk factors I computed the odds ratios that would be detectable (at power 90% and at 5% significance) for illustrative sample sizes representing the whole study group and the two specified sub-groups. severe pneumonia and very severe pneumonia. The formula chosen was able to calculate simple proportions based on an estimated odds ratio.

Using the above values the following formula was used.[24]

$$\frac{\{U\sqrt{[\pi_0(1-\pi_0)+\pi_1(1-\pi_1)]}+V\sqrt{[2\bar{\pi}(1-\bar{\pi})]}\}^2}{(\pi_1-\pi_0)^2}$$

$$\text{where } \bar{\pi} = \frac{\pi_0+\pi_1}{2}$$

Where:

OR estimated odds ratio is 3

U One sided percentage of the normal distribution corresponding to 100%- power e.g if power = 90%. U= 1.28

π_0 proportions exposed to risk factor in group without favourable outcome= 0.30 (30%) .

π_1 Proportion of cases exposed in the poor outcome group = 0.5625(0.30 as π_0) calculated from:

$\pi_1 = \dfrac{\pi_0\ \text{OR}}{1+\pi_0\ \text{OR-1}}$

V Percentage point of normal distribution corresponding to the two sided significance level if significance level = 5% V= 1.96

Common proportion:

$$\bar{\pi} = \frac{\pi_0 + \pi_1}{2}$$

$$=0.43125$$

Using the values computed and the formula above the total number of patients required to demonstrate an odds ratio of 3 is, N= 122

Thus an observed odds ratio of 3 or greater in any sample size more than 122 (The size of the smaller sub-group) will be unlikely to be due to chance assuming a risk factor prevalence of 30%.

Using the same formula we computed that for analyses based on the total group size (n = 543) an observed odds ratio of more than 2.0 associated with any risk factor (still assuming a risk factor prevalence of 30%) would be unlikely to be due to chance. This study is therefore adequately powered for exploratory analyses of risk factors of modest prevalence, able to detect odds ratios of more than3 in any sample size of more than 122 and odds ratios of more than 2 in the total sample size (n=543).

PROCEDURES.

Children between the ages of 2 months to 59 months coming to the Paediatric Emergency Unit at the KNH were screened for signs of pneumonia (cough and difficulty in breathing) and lower chest wall in drawing. The Principal Investigator or trained assistants who were stationed at the PEU then explained the purpose of the study and the procedures involved to the guardians of the children and a written consent was sought. Of the children presenting with signs and symptoms of pneumonia, those with wheeze who responded to bronchodilators were excluded together with

those ineligible for treatment. Emergency care such as oxygen and administration of fluids were instituted as required and were not delayed by any study procedure. The questionnaire was then filled.

Investigation procedures

Clinically appropriate investigations were requested in accordance with Government of Kenya protocols.

a. Oxygen saturation

On enrolment, the child's transcutaneous haemoglobin oxygen saturation was assessed using portable pocket Nonin pulse oximeter by placement of the probe on a toe or a finger with the patient breathing at room air. This was also done routinely during study period for all patients before oxygen supplementation. Hypoxaemia was defined as oxygen saturation less than 90% as recorded by pulse oximetry.

b. HIV Counseling and testing

Most children were tested for the presence of antibodies to HIV. This is in line with the GOK Provider initiated Diagnostic counseling and testing. Pretest counseling to the parents was done prior to collection of blood. The parallel testing methods with rapid kits of Bioline and Determine which detect antibodies to HIV-1 and HIV-2 in human whole blood were used to assess HIV serostatus. Using this method, patients were considered to be HIV seropositive if both tests were positive or were considered negative when both tests were negative. However if the two kits showed discordant results then blood was taken for confirmatory test using Enzyme Linked Immunorsorbent Assay (ELISA) from Dade Behring Inc. For children below 18 months, if rapid test was positive, a confirmatory HIV DNA antigen Polymerase Chain Reaction (PCR) test was done.

Upon obtaining results of HIV status, parents of the children were informed following post test counseling. The child's primary clinician was also informed of the result to assist in further patient management.

Treatment procedures

All children enrolled in the study were seen by one of the pneumonia study paediatric SHOs at PEU. Any child requiring emergency care in PEU received treatment as a first priority with study data being collected only after stabilization of the child and if it was deemed possible.

Children were treated according to standard Government of Kenya guidelines for severe or very severe pneumonia after ensuring there were no known allergies or contra-indications to recommended antibiotics. For severe pneumonia benzyl penicillin was given parenterally at 50,000units/kg per dose 6 hourly. For very severe pneumonia combination of benzyl penicillin at 50,000units/kg/dose 6 hourly and gentamicin at 7.5mg/kg daily was given. Children who were HIV antibody positive and classified as either severe or very severe pneumonia were treated with antibiotics appropriate for very severe pneumonia and with high dose oral cotrimoxazole at 8mg/kg/dose trimethoprim and 40mg/kg/dose sulphamethoxazole three times a day for 3 weeks; as empiric treatment for Pneumocystis jirovecii pneumonia according to WHO guidelines. For those who were aged less than 18 months, positive antibody tests were followed by definitive testing as per current KNH protocols (see HIV SOP Appendix III).

Supportive care with oxygen, fluids and / or feeds was provided on admission according to GoK basic paediatrics protocols. All patients' care was guided by a clinical care pathway (see appendix) but with definitive decisions made by the ward-based consultant-led team responsible for the patient. Thus, decisions determining treatment failure, choice of second line antibiotics if

required and initiation of anti-tuberculous treatment if required was at the discretion of the responsible consultants.

The children were then reviewed at 24 hours and at 48 hours. Careful evaluation to detect clinical signs and symptoms that had not changed and noting any new ones were made. Improvement of clinical signs and symptoms was considered treatment success while deterioration of the clinical signs and symptoms or new danger signs was considered a treatment failure. The assessment was done independent of the routine care and as need arose; reviews were by the primary clinicians managing the patients. Treatment and other managements were administered by the consultant-led ward team in accordance to GOK basic Paediatrics protocols.

CLINICAL CORRELATES INCLUDED:

I.   Age.

Ii.   Sex.

III. Oxygen saturation.

IV.   Very rapid respiratory rate (≥60 bpm).

V.   Auscultatory findings of crackles. bronchial breathing or pleural rub.

VI.   Inability to drink/feed.

VII. Grunting.

VIII. Flaring of alae nasi.

IX.   Wheezing.

X.   Lower chest wall indrawing.

XI.   Temperature > 38° C.

XII. Level of consciousness.

OUTCOME MEASURES

I.   Treatment failure.

II.   Death.

DATA MANAGEMENT

- The data was collected on a pre-coded questionnaire and immediately entered into a database using EPI data. To ensure data quality range. validity checks were employed at the time of data entry.

- Categorical data was tabulated and numeric data was examined to assess the distribution (normal / non-normal) prior to analysis.

- Data was stored in password protected computers with access restricted to the Principal Investigators.
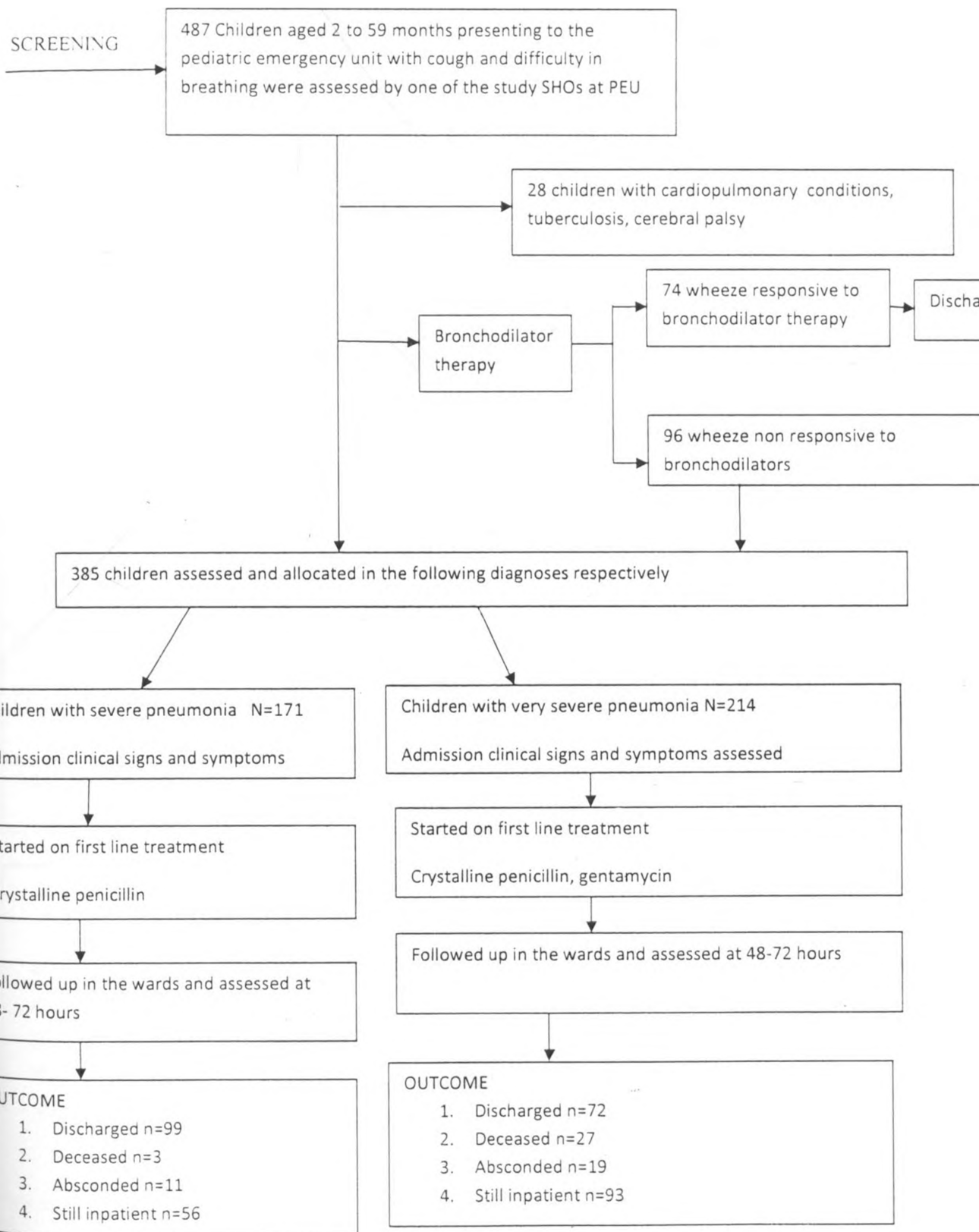
- Analysis was conducted using Epi Info version 3.46

- Associations were explored in 2 x 2 or 2 by n tables and Odds ratios were used to estimate risks of treatment failure and death

- Chi square or Fisher's exact tests were used to test for associations in categorical variables.

- Student's T test and Wilcoxon Rank Sum test were used to compare means and medians respectively.

- Logistic regression was performed to identify independent predictors of treatment failure and death.

- All statistical tests were interpreted at 5% significance (95% confidence interval).

ETHICAL CONSIDERATION

I. Only the children whose parents gave informed written consent participated in the study.

II. Children requiring emergency or immediate care received it and the study procedures did not interfere with this process.

III. Permission to carry out the study was sought from the KNH Research and Ethical committee.

IV. Data collected on individuals was kept confidential and no personal identifiers were used in any reports arising from this work.

V. No patient incurred any extra cost in the study.

VI. Information useful to the improved care of the patient was given to the primary doctor/clinician.

VII.   The care of the patient on the wards remained the responsibility of the appropriate consultant and registrar team and decisions on optimal care were made by this team and not the research team.

VIII.   Resulting feedback to be made available to the KNH as recommendations for appropriate action.

PATIENT FLOW CHART

SCREENING → 487 Children aged 2 to 59 months presenting to the pediatric emergency unit with cough and difficulty in breathing were assessed by one of the study SHOs at PEU

28 children with cardiopulmonary conditions, tuberculosis, cerebral palsy

Bronchodilator therapy

74 wheeze responsive to bronchodilator therapy → Discha...

96 wheeze non responsive to bronchodilators

385 children assessed and allocated in the following diagnoses respectively

Children with severe pneumonia N=171

Admission clinical signs and symptoms

Children with very severe pneumonia N=214

Admission clinical signs and symptoms assessed

Started on first line treatment

Crystalline penicillin

Started on first line treatment

Crystalline penicillin, gentamycin

Followed up in the wards and assessed at 48- 72 hours

Followed up in the wards and assessed at 48-72 hours

OUTCOME
1. Discharged n=99
2. Deceased n=3
3. Absconded n=11
4. Still inpatient n=56

OUTCOME
1. Discharged n=72
2. Deceased n=27
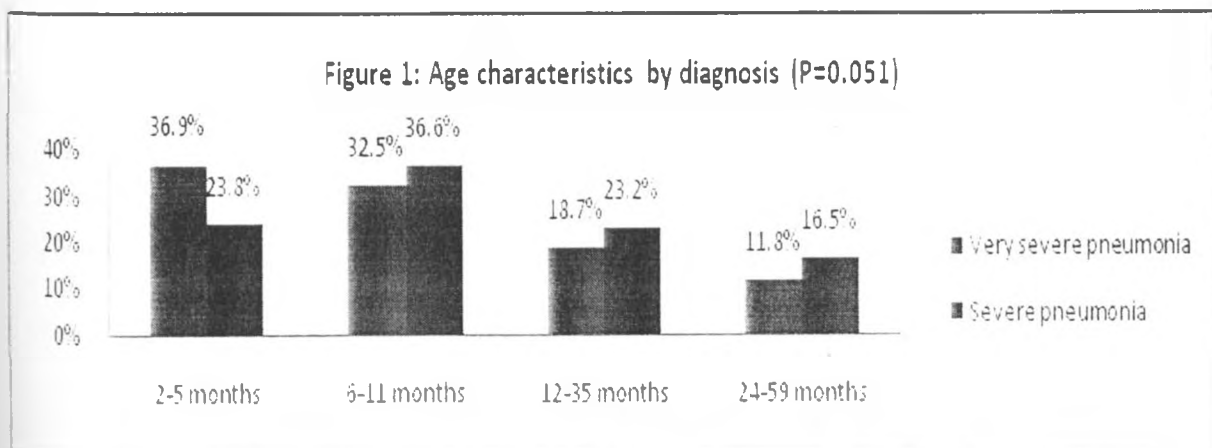3. Absconded n=19
4. Still inpatient n=93

RESULTS.

A total of four hundred and eighty seven children aged 2 to 59 months who presented to the pediatric emergency unit with cough and difficulty in breathing were assessed. Twenty eight (28) children were excluded according to the exclusion criteria. Seventy four (74) children who had a wheeze that responded to therapy were also excluded making a total of 102 that were excluded. Therefore, a total of 385 children were admitted to the study. Of these 171 (44.4%) had severe pneumonia while those with very severe pneumonia were 214 (55.6%). Below is a summary of the biodata of the patients who participated in the study.

TABLE 2: THE BASELINE CHARACTERISTICS OF PATIENTS WHO SATISFIED THE W.H.O CRITERIA FOR SEVERE PNEUMONIA/ VERY SEVERE PNEUMONIA (N=385)

Characteristics	Very severe pneumonia (n=214; 55.6%)	Severe pneumonia (n=171; 44.4%)
Gender Male Female	96 (44.9) 118 (55.1)	85 (49.7) 86 (50.3)
	Median	**IQR**
Age (months)n=385	8.75	5.1 – 15.7

Figure 1: Age characteristics by diagnosis (P=0.051)

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In the group of children with very severe pneumonia. 44.9% were male and 55.1% were female. In the group with severe pneumonia. 49.7% were male and 50.3% were female. There was no significant difference in the distribution of the sexes in the two groups. The median age for the study population was 8 months.

A higher proportion (36.9%) of the study participants were between 2 to 5 months in the very severe pneumonia group as compared to 23.8% in the severe pneumonia group. The difference in age distribution was of borderline significance (P=0.051).

The severity of pneumonia decreased with increase in age and this could be due to immature immunity in the younger children and hence they tend to get more severe disease and the severity reduces as their immunity matures. These children could also have presented with more invasive disease. The severe disease in the younger group could also have been due to the respiratory mechanics in terms of the narrow airway in the younger children and therefore the inflammatory process in pneumonia gives them a severe form of illness because of the anatomically narrow airways.

TABLE 3: CLINICAL CHARACTERISTICS OF THE PATIENTS ADMITTED WITH SEVERE AND VERY SEVERE PNEUMONIA

Characteristics	Very severe pneumonia (n=214)	Severe pneumonia (n=171)
History of cough:		
Yes	206 (97.2)	164 (97.6)
No	6 (2.8)	4 (2.4)
Difficulty in breathing:		
Yes	206 (97.6)	160 (95.2)
No	5 (2.4)	8 (4.8)
Fever:		
Yes	180 (87.0)	140 (83.8)
No	27 (13.0)	27 (16.2)
Nights of fever:		
Median (IQR)	3.0 (2.0-6.0)	3.0 (2.0-6.0)
Nights of illness:		
Median (IQR)	3.0(2.0-6.0)	5.0(3.0-7.0)
Previous admission:		
Yes	33 (20.5)	21 (19.3)
No	128 (79.5)	88 (80.7)
Previous wheeze:		
Yes	31 (19.9)	27 (25.7)
No	125 (80.1)	78 (74.3)
Recent admission:		
Yes	7 (4.0)	4 (3.0)
No	170 (96.0)	129 (97.0)
Cyanosis on admission:		
Yes	20 (9.7)	2 (1.2)
No	186 (90.3)	163 (98.8)

Children who presented with a history of cough were 97.2%, fever 87% and difficulty in breathing 97.6% in the very severe pneumonia group while those in the severe pneumonia group who presented with cough were 97.6%, fever 83.8% and difficulty in breathing 95.2%.

The median nights of illness (defined as the nights of illness before seeking treatment at Kenyatta National Hospital) in those with very severe pneumonia was 3 nights (IQR. 2-6) as compared to those with severe pneumonia which was 5 nights (IQR. 3-7). This could be explained by the severity of illness in those with very severe disease who were likely to seek medical attention earlier than those in the severe group or that pathogens causing very severe pneumonia result in more rapidly progressive disease prompting earlier care seeking while finally the younger children may be brought earlier to hospital.

Fifty six percent of the patients did not have a history of previous admission while 77% of the patients did not have a recent admission.

TABLE 4: SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE CAREGIVER

Characteristics	Very severe pneumonia (n=214)	Severe pneumonia (n=171)
Parent		
No	5 (2.4)	4 (2.3)
Yes	207 (97.6)	167 (97.7)
Gender		
Male	5 (2.4)	4 (2.3)
Female	207 (97.6)	167 (97.7)
Age group		
<25yrs	69 (41.6)	57 (43.5)
>/=25yrs	97 (58.4)	74 (56.5)
Marital status		
Married	169 (81.6)	146 (88.0)
Single	21 (10.1)	15 (9.0)
Widowed	5 (2.4)	3 (1.8)
Separated	12 (5.8)	2 (1.2)
Education		
None	6 (2.9)	6 (3.6)
Primary	106 (51.2)	79 (47.3)
Secondary	78 (37.7)	63 (37.7)
Tertiary	17 (8.2)	19 (11.4)
Parity		
1 child	75 (35.4)	50 (29.6)
More than 1 child	137 (64.6)	119 (70.4)
Mother alive		
Yes	210 (99.1)	170 (99.4)
No	2 (0.9)	1 (0.6)
Father alive		
Yes	202 (97.1)	163 (97.6)
No	6 (2.9)	4 (2.4)
Relationship to parent		
Mother	205 (97.2)	163 (95.3)
Father	1 (0.5)	4 (2.3)
Grandparent	2 (0.9)	2 (1.2)
Other	3 (1.4)	2 (1.2)
Delay in care		
<3 days	128 (60.7)	96 (58.2)
>=3 days	83 (39.3)	69 (41.8)

Most (97%) of the children were accompanied by their parent. Almost all the children admitted were under the care of the mother 374(97%). Fifty seven percent of the caretakers were more

than 25 years of age. More than half (66%) of the caretakers were married and 96% of the caretakers had primary education and above. About 60% of the caretakers sought treatment at KNH within 3 days.

TABLE 5a: ADMISSION CLINICAL EXAMINATION CHARACTERISTICS OF THE PATIENTS

Characteristics	Very severe pneumonia (n=214)	Severe pneumonia (n=171)
Respiratory rate Mean (SD)	68.4 (14.1)	63.5 (12.6)
Temperature Mean (SD)	38.0 (1.3)	38.0 (1.1)
Oxygen saturations Mean (SD)	85.2 (9.9)	90.7 (6.0)
Lower chest wall indrawing		
Yes	209 (98.6)	168 (98.2)
No	3 (1.4)	3 (1.8)
Wheeze		
Yes	51 (24.1)	41 (24.0)
No	161 (75.9)	130 (76.0)

TABLE 5b: CHARACTERISTICS SPECIFIC TO VERY SEVERE PNEUMONIA

Characteristics	Very severe pneumonia (n=214)
Grunting	
Yes	96 (45.3%)
No	116 (54.7%)
Head nodding	
Yes	114 (54.3%)
No	96 (45.7%)
AVPU	
A	166 (78.3%)
V	30 (14.2%)
P	10 (4.7%)
U	6 (2.8%)

The mean respiratory rate of the patients on the day of admission was higher in the children with very severe pneumonia at 68.4 compared to that of the patients with 63.5 of those with severe

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pneumonia. The mean respiratory rate is higher in those with very severe pneumonia as compared to those with severe pneumonia as a compensatory mechanism of coping with the very severe illness.

The mean temperature was 38°C. Most of the children, 98%, had lower chest wall indrawing. Grunting, head nodding and reduced level of consciousness were specific to very severe pneumonia.

For treatment failure definitions - see appendix 1.

FIGURE 2: PROPORTIONS OF CHILDREN WITH TREATMENT FAILURE
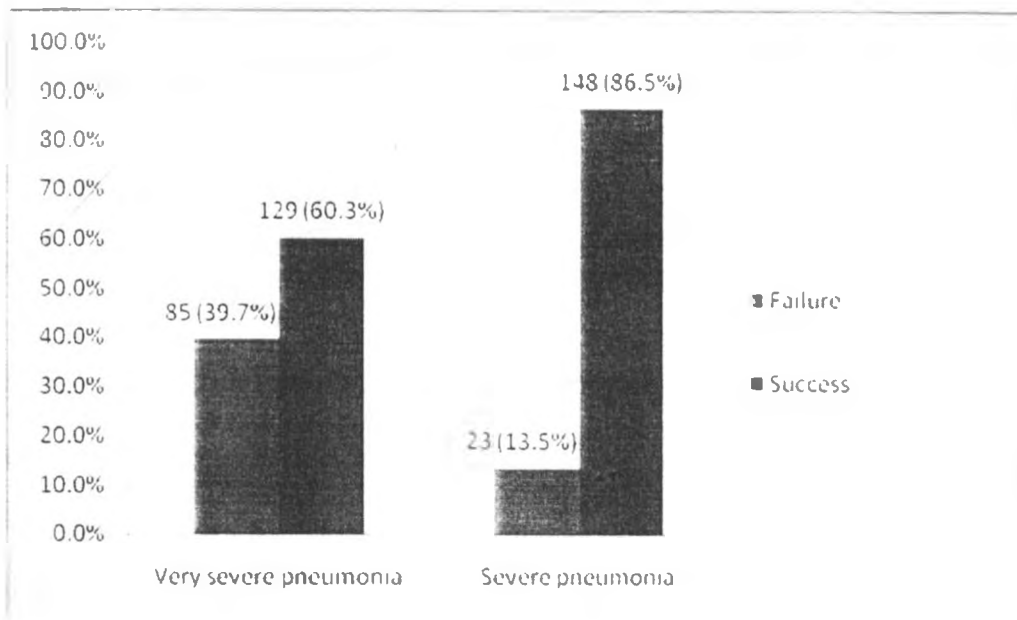
The Chi square test for associations was used. Of the 385 children with severe or very severe pneumonia, the proportion of children who failed treatment was 28.1%. Treatment failure rate was higher in those with very severe pneumonia at 39.7% (85/214) compared to those with severe pneumonia 13.5 % (23/171) and the difference was statistically significant with a P value

of less than 0.001. Very severe pneumonia increased the odds of failing treatment by 4.2(OR 2.5-7.1) as compared to severe pneumonia.

FIGURE 3: PROPORTIONS OF CHILDREN WHO DIED
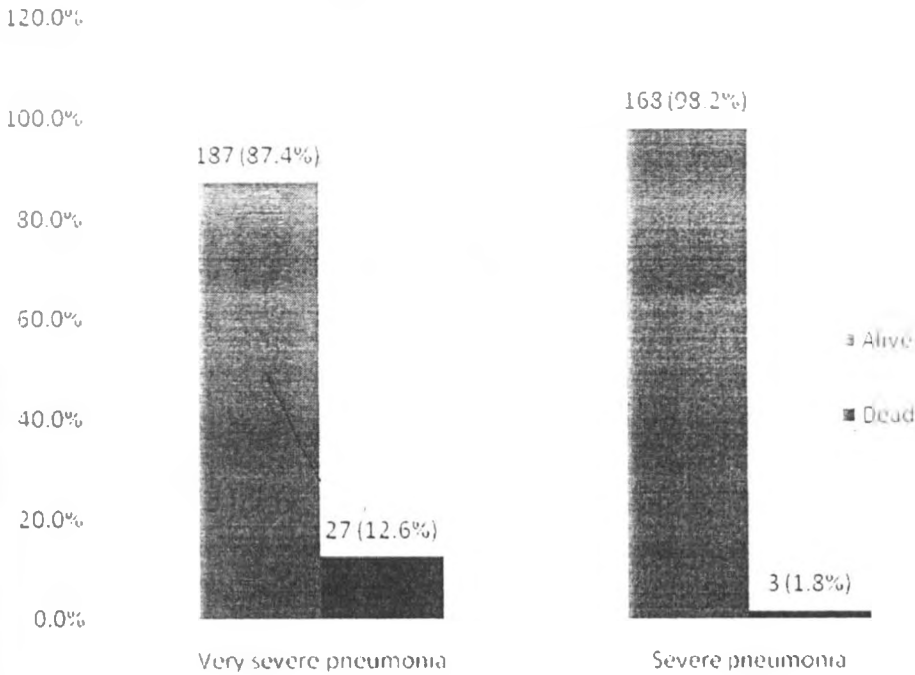
On examining the outcome of children within the study population defined as death within 48 hours, the proportion of children who died was 7.8%. Of the 171 children with severe pneumonia 3/171(1.8%) died while 27/214 (12.6%) with very severe pneumonia died within 48 hours. The difference was statistically significant with a P value of less than 0.001. Very severe pneumonia increased the odds of dying by 8.1(2.4-27.1). The confidence interval is wide and therefore might require a study with a larger sample size to confirm the results. The higher mortality rate in those with very severe disease reflects the severity of the illness and supports the idea that this WHO classification identifies children in the highest risk groups

TABLE 6: A UNIVARIATE ANALYSIS OF CLINICAL CORRELATES OF TREATMENT FAILURE IN CHILDREN WITH SEVERE PNEUMONIA

CLINICAL VARIABLE	TREATMENT		OR(95%CI)	P VALUE (X^2/Fisher's Exact Test)
	FAILURE	SUCCESS		
Cough				
Yes	23 (100.0%)	141 (97.2%)	Undefined	0.552
No	0 (0.0%)	4 (2.8%)		
Cyanosis				
Yes	1 (4.5%)	1 (0.7%)	6.8 (0.4-11.3*)	0.250
No	21 (95.5%)	142 (99.3%)		
Wheeze				
Yes	8 (34.8%)	36 (24.3%)	1.7 (0.7-4.2)	0.286
No	15 (65.2%)	112 (75.7%)		
Crepitations				
Yes	18 (78.3%)	123 (83.1%)	0.7 (0.2-2.2)	0.376
No	5 (21.7%)	25 (16.9%)		
Care givers education level				
None	1 (4.5%)	5 (3.4%)	Reference	
Primary	14 (63.6%)	65 (44.8%)	1.1 (0.1-9.9)	0.948
Secondary	6 (27.3%)	57 (39.3%)	0.5 (0.1-5.3)	0.585
Tertiary	1 (4.5%)	18 (12.4%)	0.3 (0.0-5.3)	0.278
Delay in care				
Less than 3 days	12 (52.2%)	84 (59.2%)	0.8 (0.3-1.8)	0.529
More or equal to3 days	11 (47.8%)	58 (40.8%)		
History of previous treatment	17 (94.4%)	89 (75.4%)	5.5 (0.7-43.5*)	0.056
Yes	1 (5.6%)	29 (24.6%)		
No				
HIV status				
positive	0 (0.0%)	13 (9.5%)	Undefined	0.145
negative	21 (100.0%)	124 (90.5%)		

*These variables on analysis have 95% confidence intervals that are wide. Because of the power

of the study, the study was unable to confirm these variables as correlates of treatment failure in

children with severe pneumonia. A study with a larger sample size could be able to confirm the association. This could also be due to the low prevalence of the variables.

In a univariate analysis of clinical correlates of treatment failure in children with severe pneumonia (Table 6), history of previous treatment was associated with a 5 fold higher odds of failing treatment with a P value of 0.056 (borderline significance). The univariate analysis of the clinical correlates of death in children with severe pneumonia was not possible due to the small number of deaths (n = 3 in this group) and therefore no inferences were made.

TABLE 7: A UNIVARIATE ANALYSIS OF CLINICAL CORRELATES OF TREATMENT FAILURE IN CHILDREN WITH VERY SEVERE PNEUMONIA

CLINICAL VARIABLE	TREATMENT		OR(95%CI)	P VALUE (X^2- TEST)
	FAILURE	SUCCESS		
Cough :Yes	81 (95.3%)	125 (98.4%)	0.3 (0.1-1.8)	0.177
No	4 (4.7%)	2 (1.6%)		
Cyanosis:Yes	10 (12.2%)	10 (8.1%)	1.6 (0.6-4.0)	0.327
No	72 (87.8%)	114 (91.9%)		
Wheeze: Yes	12 (14.1%)	39 (30.2%)	0.4 (0.2-0.8)	0.007
No	73 (85.9%)	90 (69.8%)		
Grunting:Yes	49 (58.3%)	47 (36.7%)	2.4 (1.4-4.2)	0.002
No	35 (41.7%)	81 (63.3%)		
Head nodding:Yes	45 (54.2%)	69 (54.3%)	1.0 (0.6-1.7)	0.987
No	38 (45.8%)	58 (45.7%)		
Nasal flaring:Yes	80 (95.2%)	117 (92.1%)	1.7 (0.5-5.6)	0.374
No	4 (4.8%)	10 (7.9%)		
Level of Consciousness				
Less than Alert	27 (32.1%)	19 (14.8%)	2.7(1.4-5.3)	0.003
Alert	57 (67.9%)	109 (85.2%)		
Crepitations:Yes	71 (84.5 %)	104 (81.3%)	1.3 (0.6-2.6)	0.539
No	13 (15.5 %)	24 (18.8%)		
Care givers educn level				
None				
Primary	2 (2.4%)	4 (3.2%)	reference	
Secondary	40 (48.8%)	66 (52.8%)	1.2 (0.2-6.9)	0.829
Tertiary	34 (41.5%)	44 (35.2%)	1.5 (0.3-8.9)	0.627
	6 (7.3%)	11 (8.8%)	1.1 (0.2-7.8)	0.931
Delay in care				
Less than 3 days	49 (57.6%)	79 (62.7%)	0.8 (0.5-1.4)	0.461
More than or equal to3 days	36 (42.4%)	47 (37.3%)		
History of previous treatment				
Yes	52 (81.3%)	87 (80.9%)	0.9 (0.4-2.0)	0.865
No	12 (18.8%)	21 (19.1%)		
Ability to drink				
Yes	21 (25.0%)	54 (42.2%)	0.5 (0.2-0.8)	0.010
No	63 (75.0%)	74 (57.8%)		

*This variable on analysis has a 95% confidence interval that is wide. Because of the power of

the study, the study was unable to confirm the variable as a correlate of treatment failure in

children with severe pneumonia. A study with a larger sample size could be able to confirm the association.

In the univariate analysis of clinical correlates of treatment failure in children with very severe pneumonia. having wheeze was associated with a decreased odds of failing treatment OR 0.4 (0.2-0.8) with a P value of 0.007. Grunting was associated with 2.4 fold increase in the odds of failing treatment compared with those without grunting.

Those having a level of consciousness assessed by the AVPU tool at V (verbal), P (pain) or U (unconsciousness) were associated with 2.7 fold increase in the odds of failing treatment and this was statistically significant with a P value of 0.003. The ability to drink was associated with a decreased odds of failing treatment OR 0.5 (0.2-0.5) with P value of 0.01.

No association was seen between treatment failure and cough. cyanosis. head nodding, nasal flaring and crepitations. There was also no significant association with history of previous antibiotic treatment and delay in seeking care.

TABLE 8: A UNIVARIATE ANALYSIS OF CLINICAL CORRELATES OF DEATH IN CHILDREN WITH VERY SEVERE PNEUMONIA

| CLINICAL VARIABLE | OUTCOME | | OR (95%CI) | P VALUE |
	DIED	ALIVE		(X^2- TEST)
Cough:Yes	24 (88.9%)	182 (98.4%)	0.1 (0.0-0.7)	0.029
No	3 (11.1%)	3 (1.6%)		
Cyanosis:Yes	4 (15.4%)	16 (8.9%)	1.9 (0.6-6.1)	0.233
No	22 (84.6%)	164 (91.1%)		
Wheeze:Yes	3 (11.1%)	48 (25.7%)	0.4 (0.1-1.3)	0.097
No	24 (88.9%)	139 (74.3%)		
Grunting:Yes	17 (63.0%)	79 (42.7%)	2.3 (1.0-5.3)	0.053
No	10 (37.0%)	106 (57.3%)		
Head nodding:Yes	15 (57.7%)	99 (53.8%)	1.2 (0.5-2.7)	0.710
No	11 (42.3%)	85 (46.2%)		
Nasal flaring				
Yes	25 (92.6%)	172 (93.5%)	0.9 (0.2-4.1)	0.558
No	2 (7.4 %)	12 (6.5%)		
Level of Consciousness				
Less than Alert	13 (48.1%)	33 (17.8%)	4.8(1.8-9.9)	<0.001
Alert	14 (51.9%)	152 (82.2%)		
Crepitations				
Yes	21 (77.8%)	154 (83.2%)	0.7 (0.3-1.9)	0.322
No	6 (22.2%)	31 (16.8%)		
Care givers education				
Primary*	0 (0.0%)	6 (3.3%)	Reference	
Secondary	12 (46.2%)	94 (51.9%)	1.5 (0.6-3.6)	0.343
Tertiary	12 (46.2%)	66 (36.5%)	1.1 (0.2-5.5)	0.897
Delay in care				
Less than 3 days	12 (46.2%)	100 (55.2%)	0.9 (0.4-2.1)	0.873
More than or equal to 3 days	14 (53.8%)	81 (44.8%)		
History of previous treatment				
Yes	16 (59.3%)	112 (60.9%)	0.9 (0.3-2.9)	0.898
No	11 (40.7%)	72 (39.1%)		
Hiv status				
positive	18 (81.8%)	121 (80.7%)	2.9 (0.9-9.0)	0.069
negative	4 (18.2%)	29 (19.3%)		
Ability to drink				
Yes	5 (26.3%)	18 (11.0%)	0.1 (0.0-0.5)	0.001
No	14 (73.7%)	146 (89.0%)		

* This includes those who did not have any education plus those who had a primary education.

This was analyzed together because there were no parents without education.

Cough was associated with decreased odds of death OR 0.1 with a P value of 0.029 while those who had wheeze were also less likely to die (odds ratio 0.4, P value of 0.048). Probably this may have been because cough led to early recognition of disease, with associated early hospital visit and also it's more likely that if you cannot cough you are unconscious.

Reduced level of consciousness was associated with increased risk of death compared with being alert. Consciousness level less than alert was associated with a 4.8 fold increase in the odds of dying and this was statistically significant with a P value of less than 0.001. Being able to drink was found to be associated with a better outcome with death OR 0.1 with P value of 0.01. For both severe and very severe groups there was no significant difference in the times taken to seek care. The biologically related variables that were significant in the univariate analysis were then analyzed further in the multivariate analysis.

Treatment failure was analyzed separately in the two groups, severe and very severe pneumonia because some variables are only present in the very severe pneumonia group and thus gives zero in the model which gives an infinite odds ratio. The treatment failure definitions were also different in the two groups hence they were analyzed differently.

TABLE 9a: MULTIVARIATE ANALYSIS OF THE PREDICTORS OF TREATMENT FAILURE AMONG CHILDREN WITH VERY SEVERE PNEUMONIA.

Variable	OR (95% CI)	P value
Grunting	2.4 (1.3-4.2)	0.004
Ability to drink	0.6 (0.3-1.1)	0.089
Level of Consciousness		
Less than Alert	2.0(1.0-4.2)	0.056

TABLE 9b: LEVEL OF CONSCIOUSNESS DROPPED

Variable	OR (95% CI)	P value
Grunting	2.4 (1.4-4.3)	0.002
Ability to drink	0.4 (0.2-0.8)	0.011

TABLE 9c: ABILITY TO DRINK DROPPED

Variable	OR (95% CI)	P value
Grunting	2.3 (1.3-4.1)	0.004
Level of consciousness less than A	2.6 (1.3-5.1)	0.007

In the multivariate analysis, the predictor of treatment failure among children diagnosed with very severe pneumonia (including those who died) was grunting OR 2.4 with a P value of 0.005. Reduced level of consciousness less than alert was associated with 2.0 increased odds of failing treatment.

Level of consciousness and ability to drink showed co-linearity (as when one varies the other varies) and this limits the ability to identify associations between them and treatment failure when they are both included in models. As ability to drink and level of consciousness are in many ways likely to reflect similar pathophysiological disturbance either one could be used as an indicator or predictor of treatment failure. However, grunting predicts treatment failure.

TABLE 10: MULTIVARIATE ANALYSIS OF THE PREDICTORS OF DEATH AMONG CHILDREN WITH VERY SEVERE PNEUMONIA.

Variable	OR (95% CI)	P value
Cough	0.1 (0.0-0.8)	0.032
Grunting	2.2 (0.9-5.4)	0.076
Ability to drink	0.2 (0.0-0.8)	0.026
Level of consciousness		
Less than Alert	2.5(1.0-6.2)	0.049

In the multivariate analysis of the predictors of death in children with very severe pneumonia, being able to drink was predictive of reduced odds of death OR 0.2 with a P value of 0.027.Cough decreased the odds of dying OR 0.1 with a P value of 0.032.

As for treatment failure, reduced level of consciousness was associated with higher odds of death OR 2.5 with a significant P value of 0.049.

DISCUSSION

The aim of this study was to define the clinical correlates of treatment failure and death in children 2 to 59 months with WHO classified severe and very severe pneumonia. It evaluated the clinical signs and symptoms as predictors of treatment failure and death in children admitted at Kenyatta National Hospital so that those at the highest risk were identified.

Three hundred and eighty five children were reviewed whose characteristics were shown in table 1. Out of the 385 children, 44.4% had severe pneumonia and 55.6% had very severe pneumonia. It was also noted that the severity of the pneumonia decreased as the age increased. The younger infants tended to have more severe disease and this could have been due to their immature immune systems and probably the younger age which prompted the caregivers to seek medical care from a tertiary facility.

Most of the previous studies were done in developing countries like Papua New Guinea, Bangui in Central Africa and Pakistan. These countries have similar socio-economic situations as Kenya. Most of the studies were also done in children less than 5 years. Kenya being a developing country, and KNH a tertiary center, the results from our study are comparable to those in the previous studies.

The variable found to be the clinical correlate of treatment failure in severe pneumonia was a borderline association with history of previous treatment. Kenyatta National Hospital (KNH) is a tertiary hospital therefore most of the children that were admitted to the study had some exposure to treatment with oral antibiotics prior to admission in KNH and this would have contributed to the treatment failure though it was not statistically significant. The clinical correlates of death in

children with severe pneumonia was not analyzed because of the low mortality in this group; n=3 (1.8%).

The clinical correlates of treatment failure in very severe pneumonia included: wheeze, grunting, reducing level of consciousness and ability to drink. Wheeze and ability to drink were associated with a better outcome. The children who presented with wheeze also received nebulisation with bronchodilators and this could have contributed to their overall improvement. Also, it's more likely that wheeze was not related to the bacterial infection and it was the severe bacterial infections that caused death. Ability to drink was associated with a better outcome because pathophysiologically, those who were able to drink were also alert and hence the better outcome. Grunting and reduced level of consciousness were associated with increased odds of failing treatment. The children who had grunting and reduced level of consciousness less than alert had very severe disease which contributed to failure of treatment.

The clinical correlates of death in children with very severe pneumonia included cough and ability to drink which were associated with a better outcome. Cough was associated with a better outcome and this could be explained by cough being a protective mechanism of clearing and protecting the airway and children who could cough were less likely to be unconscious. Reduced level of consciousness was associated with increased odds of dying as it was a sign of very severe disease.

The association between ability to drink with treatment failure and death was confounded by level of consciousness and vice versa. These two variables showed colinearity that is ability to drink varies with reduced level of consciousness when analyzed together. As ability to drink and

level of consciousness are in many ways likely to reflect similar pathophysiological disturbance either one could be used as an indicator or predictor of treatment failure.

In univariate analysis grunting correlated with death in children with very severe pneumonia as expected from a factor so close to the ultimate outcome in the causal pathway of death from severe or very severe pneumonia. Grunting was associated with high odds for death as in Papua New Guinea study.[14] However, in the multivariate model the association between grunting and death was not statistically significant.

Education level, marital status, parity and delay in seeking care, which are potential proxies for the mother's competence in dealing with disease, were not significantly associated with treatment failure and death in children presenting with severe and very severe pneumonia. This suggests that host determinants are more important with regard to mortality from severe or very severe pneumonia than the mothers' response to the disease or that the population coming to KNH is different as education generally is associated with poor outcomes.

Unlike the study done in Kilifi Kenya previously by Berkerly et al on children aged 1 month to 50 months which reported the children with severe pneumonia were 52%, very severe pneumonia were 11% and 37% had mild pneumonia, this study showed that admission of children with very severe pneumonia was higher than those with severe pneumonia, 55.6% and 44.4% respectively. This is the inverse of what was found in the Kilifi study. This difference could be that the majority of the children in the study were younger and therefore had more severe disease due to the immature immune systems or may represent the difference between a tertiary hospital and a district hospital. Kenyatta being a tertiary hospital, had a large population of children possibly treated earlier elsewhere before seeking care at the hospital.

The treatment failure rate was 39.7% in the very severe pneumonia group and 13.5% in the severe pneumonia group. Treatment failure rates were higher in those with very severe pneumonia because these children as expected had advanced disease process with associated pathophysiological derangement which required more support and probably had been treated in another facility with the standard first line antibiotics to which they may not have responded well.

The rate of treatment failure overall was 28.1% and this was noted to be higher than what was found by Strauss et al[17] which showed a treatment failure rate of 20.3%. This could be explained by the fact that majority of the children having more severe disease and the younger age of the children in our study population. The population of children in the study by Strauss had non severe and severe pneumonia while our population had severe and very severe pneumonia. Most of the studies done previously compared different treatment regimes in treatment of severe and very severe pneumonia and reported treatment failure rates but did not correlate the treatment failure with the clinical signs and symptoms therefore the findings of this study under treatment failure could not be compared with other studies.

The mortality rate in our study was 12.6% in the very severe pneumonia group and 1.8% in the severe pneumonia group. The children with very severe pneumonia had lower levels of oxygen saturation, were grunting and had a tendency to reduced level of consciousness therefore were at a higher risk of dying. This could also have been for the same reason of advanced pathophysiological changes at presentation for the very severe pneumonia.

The overall mortality rate in the study was found to be 7.8%, being lower than the 12.4% found by Demers et al[21] in a study at Bangui, Central Africa. This study found grunting and reducing

level of consciousness to be associated with death. Increased odds of mortality in children who had grunting, altered level of consciousness and refusal to take fluids was also reported in Bangui central Africa. These findings are similar.

Shann et al [8] found inability to drink was associated with mortality (sensitivity 47%; specificity 63%; P<0.05) and there was a trend towards a higher mortality in children with grunting (sensitivity 47%; specificity 63%; P = less than 0.06).

Spooner et al [20] found the strongest predictors of death to be inability to feed OR 7.58; P <0.001, grunting OR 3.05; P = less than 0.001

This study was conducted seven days a week with twenty four hour coverage of the Pediatric Emergency Unit and therefore was able to capture all of the children presenting with severe and very severe pneumonia within the study period. This was important in capturing the very severely ill children who tend to present at night after visiting other health facilities and over the weekends.

The study was not able to control for factors responsible for poor clinician compliance with WHO and national guidelines. Some clinicians changed treatment before 48 hours based on their clinical decisions. There was a high rate of pretreatment of the children before presenting to KNH which might have contributed to treatment failure in these children.

The study was based in a referral hospital, we therefore cannot directly infer what would happen at the primary health care level, but it seems likely that the findings would allow the selection for referral of the children at a higher risk of treatment failure and death.

Conclusions:

1. The proportion of children who failed treatment in the population was 28.1%.

2. History of previous exposure to antibiotics was associated with treatment failure in the severe pneumonia group.

3. Mortality was low within the severe pneumonia group therefore the correlates could not be assessed (1.8%).

4. Wheeze and ability to drink were associated with a better outcome OR 0.4 and 0.5 respectively when correlated to treatment failure in the severe pneumonia group.

5. Cough and ability to drink were associated with a better outcome OR 0.1 and 0.1 respectively when correlated with death in the very severe pneumonia group.

6. Grunting and reduced level of consciousness increased the odds by OR 2.4 and 2.7 respectively of failing treatment and OR 2.3 and 4.8 respectively of death in the very severe pneumonia group.

7. Level of consciousness and ability to drink showed co-linearity, that is one varies with the other.

Recommendations:

1. Very severe pneumonia cases need to be prioritized in care because of the increased risk of treatment failure and death.

2. Children with grunting, decreased level of consciousness and inability to drink should be prioritized within the wards for close monitoring, frequent clinical reviews and may require care in a higher dependency unit.

3. Further studies are needed to assess the effectiveness of beginning treatment with second line antibiotics in those children presenting with the clinical features associated with treatment failure and death.

STUDY LIMITATIONS:

1. The study was not able to control for factors responsible for non compliance to clinical guidelines by health workers. It did not control for the attitudes of staff towards WHO case management of pneumonia and other factors that may influence change of treatment regimes. However, about 80% of the Paediatrics residents, clinical officers did undergo ETAT+ training in the previous 24 months. During this course they had lectures and didactic teachings on WHO case management of pneumonia.

2. There was contamination of the 1st and 2nd line treatments because of previous documented or undocumented antibiotics use by the . patients. The investigators specifically enquired of any previous use of antibiotics within previous 7 days.

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APPENDIX I

CLINICAL DEFINITIONS

SEVERE PNEUMONIA (W.H.O)

Cough and difficulty in breathing plus:

Lower chest wall indrawing

VERY SEVERE PNEUMONIA (WHO)

Cough plus difficulty in breathing plus at least one of the following:

Cyanosis or oxygen saturation <90%

Inability to drink/breastfeed

AVPU<A (or GCS<14)

Grunting or head nodding in a child < 12 months

FIRST LINE TREATMENT WHO for:

Severe pneumonia: Penicillin at 50,000 iu/kg/dose qds

Very severe pneumonia: Penicillin at 50,000 iu/kg/dose qds, plus

Gentamycin at7.5mg/kg o.d

HIV positive: Given penicillin and gentamycin to ALL children with severe and very severe pneumonia and give oral co-trimoxazole at 8mg/kg/dose trimethoprim and 40mg/kg/dose sulphamethoxazole tds for 3 weeks

DANGER SIGNS

Inability to drink. abnormal sleepiness, convulsions, central cyanosis

TREATMENT FAILURE

INITIAL DIAGNOSIS IS SEVERE PNEUMONIA THEN;

Development of signs associated with very severe pneumonia (cyanosis, inability to drink. altered level of consciousness-AVPU <A, convulsions, oxygen saturation or arterial blood gas indicating need for oxygen) **at any point within 48 hours**

Assessment at 48 hours that demonstrates that **none** of the following clinical features have improved: Indrawing, measured temperature. respiratory rate (should show a reduction in RR of > 5bpm).improvement in **only one** clinical feature suggests that the treatment is working and should be continued.

INITIAL DIAGNOSIS IS VERY SEVERE PNEUMONIA THEN;

Observed deteriorating level of consciousness (reduction in AVPU or modified GCS score) or development of respiratory failure resulting in ICU transfer at **any time point within 48 hours**

Assessment at 48 – 72 hours that demonstrates that **none** of the following clinical features have improved: severity of in drawing, measured temperature, respiratory rate (should show a reduction in RR of > 5 bpm), requirement for supplemental oxygen, ability to feed. Improvement

in **only one** clinical feature suggests that the treatment is working and should be continued until reassessment at day 5

TREATMENT SUCCESS

Considered when patient receives and completes first line treatment only for 3 to 10 days, improves and is discharged

Appendix II. Information and Consent Form

(This consent form is for use by the pneumonia childhood study group)

Childhood Pneumonia Study

Information and consent form

Your child's illness

Your child has features suggesting they have 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* _____).

Who is the study being done by?

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

Why are we doing the study and what is this study about?

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. We are trying to understand what are some of the causes of this illness, what makes it hard to treat some children with this illness and

get information that may help us provide better treatment for this illness in the future.

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.

If there is wheeze – we will also try to treat your child with a medicine now that may help the breathing, it is possible if this medicine works that your child may not need admission and your child could go home with medicines and that would be the end of the study for your child.

If your child needs admitting - we would also like to measure the level of oxygen in the blood using this device (*show oximeter*) that is entirely painless and takes only 1-2 minutes. Then we would like to take a blood test that is commonly done in children with serious illness and that sometimes helps us find the cause of the pneumonia. There may be other blood tests your child needs to help us give the correct treatment, 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. 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.

☐ *If there is very severe pneumonia or (eligible) severe pneumonia and admission from 08.00-16.00 Monday-Friday* – Because your child has the severe form of pneumonia we would also like to do a chest X-ray to see the type of lung problem. You will not be charged for this test.

☐ *If the child is HIV positive on rapid antigen testing* – We are doing additional tests on some children with severe pneumonia who are at high risk of a serious lung disease called PCP. This involves taking a specimen of mucus from the nose using a soft plastic tube and sucking (demonstrate NPA device). This sometimes helps us find this very serious cause of pneumonia and helps us learn how common it is here. You will not be charged for this test.

After examining your child, doing the necessary tests and giving the recommended treatment we

would also like to follow-up your child in the ward to check their progress and see how well the treatment is working. No new treatments are being tried on your child – they will get the treatment that all other children admitted with this problem should get. 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?

Taking blood from the arm 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 as any other routine blood tests that are 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. You will not be charged for tests that are part of the research. 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 should 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 this 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 also contact those who are responsible for the care of your child and this research:

Dr Caroline Kosgei- 0721363032 : P.O Box 20723 KNH Nairobi

Dr Oyatsi D- 0722338345 Lecturer Department of Paediatrics and Child Health, University of Nairobi.

Childhood Pneumonia Study

Consent form

I, being a guardian of _____ (name of child) have had the research explained to me. I have understood all that has been read and had my questions answered satisfactorily. I understand that I can change my mine 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.

Parents/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: _____

Appendix III. Standard Operating Procedures (SOPs)

Standard Operating Procedures for Pulse Oximetry

1.0 Introduction

Pulse oximetry is a non-invasive monitoring system that provides continuous information about arterial oxygen saturation without subjecting the patient to a painful arterial stick. Using light to measure arterial oxygen saturation (SaO2), the pulse oximeter tracks the patient's SaO2 level non-invasively. Pulse oximetry works by placing a pulsating arteriolar vascular bed between a dual light (red and infrared) source and a photodetector. The photodetector records the relative amount of each color absorbed by arterial blood and transmits the data to a monitor, which displays the information with each heartbeat.

2.0 Abbreviations

SaO2 - Arterial oxygen saturation

3.0 Equipment/ Materials

3.1 Portable battery powered pulse oximeter (Nellcor NPB-40)

3.2 Sensor probes of various sizes

4.0   Procedure

4.1 Explain to parent or guardian briefly on pulse oximetry and its value

4.2 Ensure the child is comfortably positioned and calm

4.3 Select an appropriately sized sensor probe for patient age and weight

4.4 Ensure a good capillary refill at a point closest to the selected site

4.5 Attach probe on the selected site (toe, finger or earlobe)

4.6 Hold the probe in position until a steady reading is obtained, observing to ensure a strong pulse wave and a heart rate

4.7 Document the pulse oximeter reading in the questionnaire

4.8 Repeat the measure after one minute and document value

4.9 Record average value of the two readings on the questionnaire.

5.0   References:
Adapted from AACN Procedure manual for Critical Care, Fourth Edition W. B. Saunders 2001

Standard Operating procedures for HIV testing

1.0 Introduction

Rapid testing involves a series of two serological tests done to determine the HIV status of a patient who, in the case of PIDTC has issued informed consent and undergone pre-test counseling either directly or through an a legal proxy.

2.0 Abbreviations

HIV – Human Immunodeficiency Virus

PIDTC – Provider-initiated Diagnostic Testing and Counselling

ELISA – Enzyme-linked Immunosorbent Assay

3.0 Equipment/Materials

3.1 Disposable latex gloves

3.2 Spirit swabs

3.3 Sterile lancet

3.4 Determine HIV-1/2 (Inverness Medical) testing kit

3.5 SD Bioline HIV 1/2 3.0 (Standard Diagnostics Inc.) testing kit

3.6 Chase buffer

4.0 Procedure

After pre-test counseling for HIV and having obtained verbal consent to test, the investigator will glove and wash his/her hands to remove glove powder. The patient's finger is then swabbed with 3 different spirit swabs and the finger pricked using a sterile lancet, the first drop of blood is wiped away and another allowed to gather.

For Determine Assay, 2 drops of blood (50ul) are dripped onto the test pad and 1 drop of chase buffer applied. The test is then allowed to develop for 15 minutes and the results interpreted. A positive result is indicated by the appearance of 2 lines on the test strip and a negative by the appearance of one on the proximal portion. Any other result is invalid and the test is repeated.

For SD Bioline Assay, a 20ul capillary pipette is provided, the open end is immersed in the blood drop and the pressure released to draw blood into the capillary pipette to the black line. The drawn specimen is added into the sample well and 4 drops (120ul) of assay diluent is then added. As the test begins to work purple color is seen moving across the results window at the centre of the test device. The result is interpreted in 5-20 minutes. The presence of only the control line (C) within the results window indicates a negative result. The presence of 2 lines as control line (C) and Test line 1(1) within the results window indicates a positive result for HIV 1. Presence of control line (C) and test line 2 (2) indicates a positive result for HIV 2. the presence of 3 lines; control line (C), test line1 and test line 2 indicates a positive result for HIV 1and/or HIV 2. The absence of a control line (C) within the results window indicates an invalid result.

A test result is considered positive when both tests are positive and negative when both tests are negative. A discordant result will be repeated using ELISA based Vironostika HIV Uni-Form II Ag/Ab test (Sensitivity = 100% and Specificity = 99.9%) manufactured by BioMerieux, Boseind Netherlands.

APPENDIX IV

QUESTIONNAIRE

Please fill ALL sections in by interviewing the patient's caregiver

Questionnaire Serial No.		Patient's Hospital No.		Date (dd/mm/yy)	[___]-[___]-[___]
Data Collector's Code	[1] [2] [3] [4] [5] [6] [7] [8] [9] [10]				

1.0 Patient's Data						
1.1. Personal details						
1.1.1 Gender	[0] Male		[1] Female			
1.1.2 Date of birth (dd/mm/yy) Enter at least year	❑ Don't know		[___]-[___]-[___]			
1.1.4 Time of admission (24 hr clock)	[___]-[___]					
1.1.5 Ward of admission	[1] 3A	[2] 3B	[3] 3C		[4] 3D	
1.1.6 Current body weight in kg						
1.1.7 Immunisation status up to date as per KEPI schedule? Derive from caregiver history and child's card if available Select [0] if not received and [_1_] if received up to appropriate status for age	❑ Don't know OPV 0 OPV 1 OPV 2 OPV 3	[0] [0] [0] [0]	[_1_] [_1_] [_1_] [_1_]	BCG check for scar Pentavalent 1 Pentavalent 2 Pentavalent 3 Measles	[0] [0] [0] [0] [0]	[_1_] [_1_] [_1_] [_1_] [_1_]
1.2 Medical History (present illness)						
1.2.1 Duration of present illness in days	❑ Don't know	[___]				
1.2.2 Cough?	❑ Don't know	[0] No	[_1_] Yes			
1.2.2.1	*If yes indicate the number of days*		❑ Don't know	[___]		
1.2.3 Difficulty in breathing?	❑ Don't know		[0] No	[_1_] Yes		
1.2.4 Fever?	❑ Don't know		[0] No	[_1_] Yes		
1.2.4.1	*If yes indicate the number of days*		❑ Don't know	[___]		
1.2.5 Able to feed/breastfeed?	❑ Don't know		[0] No	[_1_] Yes		
1.2.6 Abnormally sleepy?	❑ Don't know		[0] No	[_1_] Yes		

1.3 Medical History (past)			
1.3.1 Previous hospital admission for treatment of pneumonia?	❑ Don't know	[_0_] No	[_1_] Yes
1.3.1.1	*If yes indicate the number of days*	❑ Don't know	[__]
1.3.2 Has the patient had wheezing or whistling in the chest in the past 12 months? (Demonstrate wheezing)?	❑ Don't know	[_0_] No	[_1_] Yes
1.3.3 Are there any members of the patient's household who are cigarette smokers?	❑ Don't know	[_0_] No	[_1_] Yes

1.4 Pre-admission treatment history			
1.4.1. What was/were the patient's mode(s) of transport to the health facility/facilities attended?	[_1_] Foot [_5_] Private car	[_2_] Bicycle [_6_] Ambulance	[_3_] Bus/*matatu* [_4_] Taxi [_7_] Other (specify)
1.4.2 How long in hours did the patient take to travel from home to KNH?	❑ Don't know	[__]	
1.4.3 Did the patient receive care prior to arrival at KNH? If no, proceed to 1.5	❑ Don't know	[_0_] No	[_1_] Yes
1.4.3.1	*What was the nature of the other care received? Indicate all forms of care reported. If neither sub-district hospital nor private hospital proceed to 1.5*	❑ Don't know [_2_] Private clinic [_4_] Herbalist [_6_] Over the counter drugs (general shop) [_8_] Sub-district/district hospital [_10_] Other (specify)	[_1_] Home-made remedies [_3_] GoK dispensary/health centre [_5_] Traditional healer [_7_] Over the counter drugs (specialist drug store/pharmacy) [_9_] Private hospital
1.4.3.1.1	*Was the patient admitted for any of the above?*	[_0_] No	[_1_] Yes
1.4.3.1.1 1	*If yes,* how many days of in-patient care did the patient receive at all other facilities attended prior to presenting at KNH? (enter the total	❑ Don't know	[___]

	number)				
1.4.3.1.2	*Was the patient referred to KNH?*	❏ Don't know		[_0_] No	[_1_] Yes
1.4.1.1.1	*If yes specify the primary reason for referral*	[_1_] Poor response to treatment	[_2_] Convenience		[_3_] Financial limitations
		[_4_] Severity of the illness	[_5_] Other (specify)		

1.4.2 Treatments given for presenting illness prior to admission *(please request patient for any records including referral note, prescriptions, containers etc)*

1.4.2.1 What kinds of medication did the patient receive?	❏ Don't know	[_1_] cough syrup	[_2_] Antibiotic	[_3_] Antipyretic	[_4_] Antimalarials
		[_5_] Herbal medicines	[_6_] Traditional treatments	[_7_] Anti-histamine	[_8_] Other (specify)
1.4.2.1.1 If antibiotics were given for 1.4.2.1, which one(s)	❏ Don't know	[_1_] Co-trimoxazole	[_2_] Amoxicillin	[_3_] Other penicillin	
		[_4_] Macrolide	[_5_] Cephalosporin	[_6_] Other (specify)	

1.5 TB/HIV History				
1.5.1 Has the patient ever received prior treatment for TB?	❏ Don't know		[_0_] No	[_1_] Yes
1.5.4 Has the child had diarrhoea lasting >14 days?	❏ Don't know		[_0_] No	[_1_] Yes
1.5.3 Has the patient been diagnosed as HIV positive in the past? If no, proceed to 1.5.4	❏ Don't know		[_0_] No	[_1_] Yes
1.5.3.1	*If yes for 1.5.3, is the patient currently on HAART?*	❏ Don't know	[_0_] No	[_1_] Yes
1.5.3.	*Is the patient currently on cotrimoxazole prophylaxis?*	❏ Don't know	[_0_] No	[_1_] Yes
1.6 Birth History				
1.6.1 What was the patient's birth weight in kg?	❏ Don't know		[___]	

2.0 Caregiver's data				
2.1 Gender	[0] Male	[1] Female		
2.2 Date of birth (dd/mm/yy)	❏ Don't know	[__]-[__]-[__]		
2.3 Administrative location				
2.4 Relationship to patient. If not mother, proceed to 2.5	❏ Non-relative	[_1_] Mother	[_2_] Father	[_3_] Sibling
		[_4_] Grandparent	[_5_] Other relative	
2.4.1 Antenatal History (for the admitted child)				
2.4.1.1	*If mother for 2.4, was ANC attended? If no, proceed to 2.5*	❏ Don't know	[_0_] No	[_1_] Yes
2.4.1.1.1	*If yes for 2.4.1.1, how many times?*		[_1_] Once	[_2_] Twice
			[_3_] >2times	
2.4.1.2 Was a HIV test done during ANC? If no, proceed to 2.5	❏ Don't know		[_0_] No	[_1_] Yes
2.4.1.2.1	*If yes for 2.4.1.2, what was the result? If negative or will not disclose, proceed to 2.5*	❏ Don't know	[_0_] Negative	[_1_] Positive
			[_2_] Will not disclose	
2.4.1.2.1.1	*If positive for 2.4.1.2.1, was PMTCT given?*	❏ Don't know	[_0_] No	[_1_] Yes
2.4.1.2.1.1.1	*Who received PMTCT?*	[_1_] Mother only	[_2_] Baby only	[_3_] Both mother and baby
2.4.1.2.1.2	*Has the patient ever breastfed from the mother?*	❏ Don't know	[_0_] No	[_1_] Yes

2.5 Is the patient's biological mother alive?	❏ Don't know	[_0_] No	[_1_] Yes	
2.6 Is the patient's biological father alive?	❏ Don't know	[_0_] No	[_1_] Yes	
2.7 If caregiver is biological parent, what is his/her marital status?	❏ Don't know	[_1_] Married	[_2_] Single	
		[_3_] Widowed	[_4_] Separated	
2.8 Number of children (including the patient)	❏ Don't know	[__]		

2.9 What is the level of formal education of the child's primary caregiver?	❑ Don't know	[_1_] None	[_2_] Primary not completed	[_3_] Primary completed
		[_4_] Secondary not completed	[_5_] Secondary completed	[_6_] Tertiary and beyond
2.10 Does the caregiver live with the patient?	❑ Don't know	[_0_] No	[_1_] Yes	
2.10.1	*If yes for 2.10, how long in years has the caregiver lived with the patient?*	❑ Don't know	[_|_]	

3.0 Initial clinical Assessment for patients presenting with wheeze

Time after initial assessment / Sign	Pre-bronchodilator therapy	Post-bronchodilator therapy
3.1 Respiratory rate (breaths per minute)	[_|_]	[_|_]
3.2 Heart rate (beats per minute)	[_|_]	[_|_]
3.3 Level of consciousness (AVPU) [_1_] A [_2_] V [_3_] P [_4_] U	[_]	[_]
3.4 Oxygen saturation (%)	[_|_]	[_|_]
3.5 Use of accessory respiratory muscles? [_0_] No [_1_] Yes	[_]	[_]
3.6 Audible wheeze?	[_0_] No	[_1_] Yes
3.7 Auscultatory wheeze?	[_0_] No	[_1_] Yes
3.9 Is there presence of atopic dermatitis?	[_0_] No	[_1_] Yes
3.10 Was bronchodilator therapy administered? If no, proceed to 3.11	[_0_] No	[_1_] Yes
3.10.1	*If yes for 4.2, specify mode of delivery* [_1_] MDI with spacer	[_2_] Nebulizer
3.10.2	*How many cycles of bronchodilator therapy were given?*	[_|_]
3.11 What is the patient's clinical outcome?	[_0_] Admitted	[_1_] Discharged

Time after initial assessment / Sign	0 hours (1st review) Note: Post broncodilator therapy for wheezers Date: Time:	24 – 48 hours 2nd review. Date: Time:	48 hours 3rd review. Date: Time:
4.1 Respiratory rate (breaths per minute)	[__]	[__]	[__]
4.2 Temperature (°C)	[___]	[___]	[___]
4.3 Oxygen saturation (%)	[___]	[___]	[___]
4.4 Cough [0] No [1] Yes	[__]	[__]	[__]
4.5 Wheeze audible/auscultatory [0] No [1] Yes	[__]	[__]	[__]
4.6 Crepitations [0] No [1] Yes	[__]	[__]	[__]
4.7 Lower chest wall indrawing [0] No [1] Yes	[__]	[__]	[__]
4.8 Nasal flaring [0] No [1] Yes	[__]	[__]	[__]
4.9 Level of consciousness (AVPU) [1] A [2] V [3] P [4] U	[__]	[__]	[__]
4.10 Central cyanosis [0] No [1] Yes	[__]	[__]	[__]
4.11 Grunting [0] No [1] Yes	[__]	[__]	[__]
4.12 Head nodding [0] No [1] Yes	[__]	[__]	[__]
4.13 Ability to drink [0] No [1] Yes	[__]	[__]	[__]
4.14 Neck stiffness [0] No [1] Yes	[__]	[__]	[__]
4.15 Severe pallor [0] No [1] Yes	[__]	[__]	[__]
4.16 Sunken eyes [0] No [1] Yes	[__]	[__]	[__]
4.17 Capillary refill [1] <2sec [2] 2 – 3sec [3] ≥3sec	[__]	[__]	[__]

5.0 Investigations done					
5.1 Haemogram					
5.1.1 Total WBC count (10^9 cells/L)	[___|___|___]				
5.1.2 Neutrophil count (10^9 cells/L)	[___|___|___]				
5.1.3 Lymphocyte count (10^9 cells/L)	[___|___|___]				
5.1.4 Haemoglobin (g/dL)	[___|___.___]				
5.1.5 Platelet count (10^9 cells/L)	[___|___|___]				
5.2 HIV test results					
5.2.1 Rapid test done?					
5.2.1.1	*If no for 5.2.1, indicate reason and proceed to 5.3*	[0] Consent not granted	[1] Kit unavailable	[2] Other reason (specify)	
5.2.2 Determine®	[0] Negative	[1] Positive			
5.2.3 Biloline® assay. If both 5.2.1 and 5.2.2 are negative, proceed to 5.3	[0] Negative	[1] Positive			
5.2.3.1	*If 5.2.2 and 5.2.3 are discordant, report Vironostika ELISA results.*	[0] Negative	[1] Positive		
5.2.4 Patient's age >18 months?	[0] No	[1] Yes			
5.2.4.1 If no for 5.2.3, report result for HIV viral DNA	[0] Negative	[1] Positive			
5.2.5 Patient's HIV status. If negative, proceed to 5.2.5	[0] Negative	[1] Positive			
5.2.5.1	*If positive for 5.2.5, report CD4 count (10^9 cells/L)* [___|___|___]				
5.2.5.2	Report the CD4/TLC % [___|___]				

6.0 Treatment prescribed **in the ward. Indicate** appropriately
[_0_] Not prescribed [_1_] **Prescribed**

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
6.1 Xpen	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.2 Gentamicin	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.3 Chloramphenicol	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.4 Cloxacillin/ flucloxacillin	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.5 Co-trimoxazole low dose (OD)	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.6 Co-trimoxazole high dose (TDS)	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.7 Macrolide	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.8 Ceftriaxone	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.9 Ceftazidime	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.10 Amikacin	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.11 Fluconazole	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.12 Anti-TB	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.13 Anti-retroviral drugs	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.14 Other anti-microbials (specify)	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.15 Bronchodilators	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.16 Antipyretics	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]	[__]
6.17 Was the patient prescribed any other drugs not listed above while admitted?	[_0_] No (specify)				[_1_] Yes				

7.0 Treatment outcome

7.1 What was the outcome of inpatient treatment?	[_1_] Patient discharged	[_2_] Patient died	[_3_] Patient absconded	[_4_] Patient's whereabouts unknown
7.2 Indicate days of in-patient treatment received				

8.0 Caregiver/ Nursing treatment record for Xpen administered over first 24 hours of admission (To be issued to caregiver upon admission and collected after 24 hours)

8.1 Questionnaire Serial No.			Date of admission (dd/mm/yy)	[___]-[___]-[___]
8.2 Indicate if dose is given at the respective hours after admission by selecting [_1_] and if not given by selecting [_0_]	1st dose (0 hours) [_0_] [_1_]	2nd dose (6 hours) [_0_] [_1_]	3rd dose (12 hours) [_0_] [_1_]	4th dose (18hours) [_0_] [_1_]

Request the caregiver to tick below the appropriate box upon administration of the injectable treatment (Xpen)