FACTORS RELATED TO SEVERITY AND OUTCOME OF PNEUMONIA AMONG CHILDREN AGED 2 – 59 MONTHS, IN DAR ES SALAAM, TANZANIA.

By

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A Dissertation Submitted in Partial Fulfilment of the Requirements for the Degree of Master of Medicine (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences.

Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled: ***Factors related to severity and outcome of Pneumonia among children aged 2-59 months, in Dar es Salaam, Tanzania,*** in partial fulfillment of the requirements for the degree of Master of Medicine, (Pediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Nahya Salim Masoud**, declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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DEDICATION

To My late Mum and Dad, for making me who I am.

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ABSTRACT

Background: Severe pneumonia among children less than five years old is a major cause of morbidity and mortality throughout the developing world. Children with certain risk factors in particular, can develop pneumonia or a more severe disease that requires inpatient attention and is associated with increased risk of death. Improved case management is the main strategy to reduce morbidity and mortality. In developing world, with the risk of malnutrition, HIV-epidemic and the development of antibiotic resistance, pneumonia pattern may have been altered. Therefore there is a need to review management of pneumonia in children in order to define appropriate local approaches to pneumonia management.

Objective: To establish the factors related to severity and outcome of pneumonia among children aged 2-59 months.

Methodology: A cross sectional hospital based study was done prospectively in children aged 2-59 months admitted with clinical symptoms and signs of pneumonia at Muhimbili National Hospital, Ilala, Temeke and Mwananyamala District Municipal Hospitals from March to September 2006. A structured questionnaire was used to capture demographic information, presence of key symptoms and signs of pneumonia, after obtaining a written informed consent from the parent/guardian. Thorough physical examination including oxygen saturation, weight and height were done. Double Rapid test and Polymerase Chain Reaction for HIV, Full Blood Count, ESR and chest X-ray were done. BACTEC machine was used to detect bacteraemia. Children were followed up while in the ward. The outcome recorded as recovery and discharged or death. Data analysis

was done using EPI Info and SPSS (Statistical Package for Social Science) programmes. A p - value of less than or equal to 0.05 was considered significant.

Results: Among the 352 children, 152 (43.2%) were females and 200 (56.8%) were males with the mean age of 12 months. The prevalence of severe pneumonia was 68.8%, significantly affecting younger age group less than 1 year of age. The case fatality due to pneumonia was 22.4%. Mortality was significantly high in children with severe pneumonia with most deaths occurring within 48 hours of admission. The prevalence of hypoxaemia was 25%. Hypoxaemia was significantly associated with severe pneumonia, HIV-infection and high mortality. (p - value = 0.000) Bacteraemia was found in 27.8% of children with pneumonia. *Coagulase Negative Staphylococcus* was the most predominant organism, followed by *Pseudomonas, S. aureus, Klebsiella* and *Streptococcus* species. Most of the bacteria isolated showed less resistance to gentamicin, vancomycin, oxacillin, erythromycin and augumentin. HIV-infection was significantly associated with bacteraemia. A quarter (25%) of children admitted with pneumonia were malnourished based on weight for height Z-score of less than -2SD. Mortality was significantly high among the malnourished children compared to normal nourished children (p - value = 0.012). The prevalence of HIV among children hospitalized with pneumonia was 24.7%. HIV-infection was significantly associated with severe pneumonia and high mortality. (p - value = 0.000)

Conclusions and Recommendations: Considering high mortality associated with pneumonia, development of antibiotic resistance and the short interval between admission and death, early diagnosis, prompt and effective treatment at all health facility levels are required. In the current era of HIV, which is associated with high prevalence of severe pneumonia requiring oxygen therapy, there is a need to improve

monitoring and oxygen supply to children with severe pneumonia. Continued surveillance of bacterial resistance pattern is required to monitor causative organisms and their antibiotic sensitivity patterns in order to guide antimicrobial use.

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ABBREVIATIONS

ARI	Acute Respiratory Infections
ALRI	Acute Lower Respiratory Tract Infections
AIDS	Acquired Immune Deficiency Syndrome
AFB	Acid Fast Bacilli
ART	AntiRetroviral Treatment
CXR	Chest X- Ray
CSF	Cerebral Spinal Fluid
CoNS	Coagulase Negative Staphylococcus
EDTA	Ethyl Diamine Tetra acetic Acid
ESR	Erythrocyte Sedimentation Rate
FBC	Full Blood Count
HIV	Human Immunodefiency Virus
HB	Haemoglobin
IMCI	Integrated Management of Childhood Illness

Ig	Immunoglobulin
LRI	Lower Respiratory Infection
mcg	Micrograms
MTCT	Mother to Child Transmission
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
NIMR	National Institute of Medical Research
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PEM	Protein Energy Malnutrition
PTB	Pulmonary Tuberculosis
PMTCT	Prevention of Mother To Child Transmission
URI	Upper Respiratory Infection
WHO	World Health Organization
WBC	White Blood Cell Count
WHZ	Weight for Height Z-score

DEFINITIONS

- **Pneumonia** was defined as presence of cough and/ or difficult breathing with fast breathing and any of the following signs:

  Flaring of alae nasi, visible lower chest wall indrawing, central cyanosis, inability to breast feed or drink, vomiting everything, convulsions, lethargy or unconsciousness, severe respiratory distress for example head nodding, and/or crepitations.

  Pneumonia was classified according to WHO/IMCI criteria in order to be consistent while recruiting the patients at different hospitals.
- **Fast breathing** is the respiratory rate of more than or equal to 50, or 40 per minute in 2 months to 12 months, 12 to 59 months old children respectively.
- **Hypoxaemia** was defined as an arterial oxygen saturation <90% recorded by pulse oximetry.
- **Bacteraemia** as presence of bacteria in the blood.
- **Malnutrition** defined as Weight for Height Z-score of less than -2SD, according to the National Centre for Health Statistics (NCHS)/ WHO reference.
- **HIV-infection** was defined as:

  Positive Capillus^{TM} HIV 1/HIV 2 (Trinity Biotech USA) and Determine^{TM} (Abbott) for children above 18 months of age.

  Positive HIV DNA-PCR for children aged 18 months and below.

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Background

Pneumonia is an inflammation of the parenchyma of the lungs characterized by presence of cough and/or difficult breathing.[1, 2, 3] Pneumonia often begins after an upper respiratory tract infection (an infection of the nose and throat such as rhinitis, otitis media, tonsillitis, pharyngitis and sinusitis). The upper respiratory tract is separated from the lower respiratory tract at the base of the epiglottis.[3] Acute manifestations of laryngitis, tracheitis, bronchitis, bronchiolitis and lung infection such as pneumonia are among the lower respiratory tract infections (LRI).[3]

Pneumonia can affect one or both lungs, and mostly occurs in infants and under fives. It can be caused by bacteria, viruses and fungi, but can also occur as a result of chemical injury (gastric acid, aspiration of food, hydrocarbon and lipoid pneumonia, and radiation induced pneumonia). The causative agents may reach the lung via the blood stream or from direct inhalation.[4] Bacterial pneumonia progresses rapidly and may have a fatal outcome if not treated promptly and adequately.[5]

The type and severity of the illness are influenced by several factors including age, season of the year, immune status of the host and environmental factors such as overcrowding. Other risk factors include poor immunization status, poor social economic status, and breast feeding and early weaning.[3] Very young children, whose immune systems are not fully developed, are at increased risk of pneumonia. Nearly 75% of pneumonia deaths occur among infants under one year old.

The risk also increases with immunodeficiency states such as HIV/AIDS and malnutrition. The burden of pneumonia among children with HIV is high.[2]

Pneumonia remains a major cause of morbidity and mortality in children under five years of age. The best way to reduce pneumonia related mortality is through improve case management and vaccination coverage. Integrated Management of Childhood Illness (IMCI) strategy, proposed by WHO mid 1990's classify pneumonia into very severe, severe or non-severe based on the clinical features.[6] The classification into one of these grades of severity is extremely useful as it identifies which children require antibiotics, which antibiotics, and who requires hospitalization and supplementary oxygen therapy. The choice of antimicrobials depends on aetiological agents identified. Hypoxaemia; defined as oxygen saturation in arterial blood of less than 90%, is a major predecessor of fatal complication of pneumonia and needs to be assessed.[6] In such cases oxygen supplementation reduces mortality. Furthermore, HIV/AIDS compounds the existing malnutrition problem in the developing world; thus the rate of pneumonia may have been increasing and contributing to the high morbidity and mortality of children among the under fives.

Immunization against measles, diphtheria, and pertussis and more recently against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* serotypes vaccines are among the recognized strategies for the prevention of pneumonia due to these causes.

1.2 Epidemiology

Acute respiratory infections (ARI) in children less than five years old are the leading cause of childhood mortality in the world.[7] The World Health Organization (WHO) in 2004 estimated that the annual number of ARI related deaths in children less than five years old (excluding those caused by measles, pertussis and neonatal deaths) was 2.1 million accounting for about 20% of all childhood deaths.[7, 8, 9] Mortality in developing countries is ten to fifty times greater than in the developed world.[3] Each year about 11 million children die before reaching their fifth birthday mostly from pneumonia, diarrhea, malaria and measles, often with underlying malnutrition.[10] More than 99% of these deaths occur in less developed countries,[11] with 70% caused by infections. Each of these conditions is also associated with malnutrition in more than 50% of the ensuing deaths.[12] Majority of deaths occur in Sub Saharan Africa and South East Asia.[13]

ARI, particularly pneumonia is a major cause of hospitalization and death during childhood in developing areas of the world.[14, 15] ARI account for one third of hospital outpatients and nearly 30% of the ARI cases are being admitted to the hospitals for pneumonia. In any hospital about 90% of deaths in these children with respiratory illnesses are due to pneumonia and its complications.[16] In South Africa, ARI is responsible for 20% of the deaths under the age of five years.[3] In these, acute pneumonia is responsible for about 90% of the fatalities.[3] In Kalabo district, Zambia 81% of the health workers mentioned pneumonia as one of the top five causes of morbidity and 88% mentioned pneumonia as one of the top five causes of mortality.[17] Mothers also confirmed that pneumonia is one of the major causes of death and disease of their

children.[17] In Eldoret, Kenya, a hospital based study revealed that 26.8% of total admissions were due to pneumonia with case specific mortality rate of 20.4%.[18]

Tanzania continues to face serious health challenges. Many positive trends in family planning, child survival and malaria have leveled off or even been reversed in recent years, due in part to the effect of HIV/AIDS and constraints hindering delivery of quality health and service in the country's health care system. The leading causes of infant and child deaths in Tanzania are preventable illnesses such as malaria, pneumonia, diarrhea, malnutrition and HIV/AIDS.[19]

The prevalence of children under five years with symptoms of ARI in Dar es Salaam city as estimated by the Tanzania Demographic and Health Survey of 2004-2005 was 11.9%. The overall prevalence was shown to vary by age, rising to a peak at 6-11 months of age (13 percent) then falling slowly to a low at 48-59 months of age (5 percent).[20]

A study done in children under five years of age in 14 health centers, one referral and four district hospitals in five regions of Tanzania, showed that, 10.5% of all under fives attending these health facilities presented with symptoms of acute respiratory infections. Half (50%) of these children were under one year old. Cough, fever and difficult breathing were the main complaints necessitating seeking medical advice. On examination nearly half of the children had signs of difficult breathing which corresponded to high prevalence of pneumonia (36.8% of all diagnosis).[21]

A study done in Bagamoyo, Tanzania in 1986, found that 25% of deaths among children under five years old were attributed to pneumonia based on "Verbal autopsy"

and 39% of deaths attributed to acute respiratory infections occurred in children less than six months of age.[22]

The annual report of the Muhimbili National Hospital (MNH) in Dar es Salaam, Tanzania, July 2003-June 2004 indicates that there were a total of 4067 admissions in the general pediatric wards. Pneumonia is the second commonest cause of death for all admissions (23.4%) after Malaria (31.6%).[23]

Malnutrition is the most important risk factor for the burden of disease in the developing countries, increasing risk of morbidity and mortality.[24] Malnutrition rates are high among Tanzanian children. The onset of malnutrition starts soon after birth and peaks by 12-18 months of age.[20] Indicators of significant chronic malnutrition include the 44% of children who are stunted and 30% who are underweight.[20] The two commonly associated factors for malnutrition in developing countries are inadequate food intake and infections.[19, 25, 26] Food insecurity, inadequacies in frequency of feeding, micronutrient deficiencies (iron, iodine and vitamin A) and frequent illness predispose children to malnutrition. The co-existence of malnutrition and infections has been observed in children to have a synergistic effect reinforcing each other adverse potential in causing malnutrition.[27, 28]

Tanzania is one of the countries in the Sub-Saharan Africa that is seriously affected by HIV/AIDS.[27] HIV/AIDS is considered a significant factor responsible for the reversal of the country's child mortality gains of the 1980s and has become the leading cause of death among adults.[27] Most children are infected by vertical transmission from their mothers.[28] The prevalence of HIV type-1 infection in hospitalized children at Muhimbili

National Hospital (MNH) in Dar es Salaam was found to be 19.2% in a study done by Kawo et al from August 1995 to January 1996, and the mortality rate among these infected children was 21.4%.[29] The three most common diagnoses in HIV-I infected children were ARI (39.4%), malnutrition (38.1%) and tuberculosis (19.3%), while in HIV-uninfected were malaria (47.0%), ARI (25.0%) and malnutrition (16.1%).[29]

A study done in rural Zambia by Smyth et al on the impact of HIV on mortality from acute lower respiratory tract infections found that, 73% of patients had severe or very severe pneumonia using WHO criteria, out of these 16% died.[30] The prevalence of HIV infection in children with acute lower respiratory tract infections was approximately 11%. The study population as a whole was malnourished, but the HIV-positive children were more severely malnourished than the HIV-negative children. The relative risk of death was 2.6 in the HIV-positive group but this was not statistically significant. However, the majority of children survived when they were given simple antibiotic and supportive treatment.[30] A study done in Lusaka, the Zambian Capital by Chintu et al on the seroprevalence of HIV in 1266 children admitted to the hospital, found that the overall prevalence of HIV in paediatric admissions was 28% and the rate was the same among the subgroup of children with pneumonia.[31]

Nathoo et al, in Zimbabwe, found clinical or serological evidence of HIV in 31% of urban children with acute lower respiratory tract infections, and moderate to severe malnutrition in 30%. The case fatality rate was 16% and the risk of death was increased in children who had evidence of HIV-infection.[32]

Another study done by Zwi et al in one of the University Teaching hospital in South

Africa, documented greater proportion of deaths in HIV-infected children with pneumonia compared with HIV-negative and untested children (54.4% versus 12.3%). However, pneumonia was among the most common cause of death in all children irrespective of HIV-status. Case fatality rate was considerably higher for pneumonia in HIV-infected children (19.9%) compared to 3.7% in the HIV uninfected and untested children. For all children, those less than one year had the highest case fatality, and this declined with age. HIV-infected children were more likely than HIV-negative and untested children to have a dual diagnosis.[33]

1.3 Aetiology

Pneumonia is a serious infection or inflammation of the lungs that continues to be a common cause of morbidity and mortality worldwide, even in developed countries where there is good access to antibiotics. It is commonly due to infectious agents, of which bacteria and viruses are the most common.

In developed communities, it is estimated that 90% of pneumonia in children are caused by viral agents.[3] Approximately 50% of documented viral LRTIs in children are caused by *Respiratory Syncytial Virus* (RSV), one quarter by *Para influenza* types 3 and 1, and a smaller number of pneumonia result from *Influenza* A and B or *Adenovirus*. *Rhinovirus* is occasionally implicated.[34] Three of these groups of viral agents (*RSV, Para influenza* and *Influenza*) are seen almost exclusively during the winter months. *Adenovirus* is the most common viral pathogen during the remainder of the year. Such specific seasonal clustering implies a greater likelihood of bacterial causes during the spring, summer and falls.[35] *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*

are common in school aged children, causing the so called atypical pneumonia.[3] Bacteria cause only between 5 to 10% of pneumonia, with *Streptococcus pneumoniae* and *Haemophilus influenzae* being the most common.[3]

In developing communities bacteria are responsible for about 65% of pneumonia. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus* are the organisms most commonly involved.[3, 16] Viral infections are responsible for approximately 40% of pneumonia in children. The same respiratory viruses occur as in the developed world although measles pneumonia is potentially a problem. Other organisms such as *Mycoplasma pneumoniae*, *Moraxella catarrhalis* and *Chlamydophila pneumoniae* occur but their precise role is uncertain.[3]

1.3.1 Viral Pneumonia

Worldwide half of all pneumonia is thought to have a viral aetiology. Although most viruses cause upper respiratory tract disease, some produce pneumonia, especially in children, but most are not serious and last a short time.[36] The most common viruses causing pneumonia include *RSV*, *Para influenza*, *Influenza* and *Adenoviruses*. *RSV* is the most common cause of viral pneumonia, especially during infancy.[1] *Influenza* viruses commonly causes respiratory disease, which can be severe and occasionally fatal. In general, lower respiratory tract viral infections are much more common during the winter months.[36] Unlike bronchiolitis, for which the peak attack rate is within the first year, the peak attack rate for viral pneumonia is between the ages of 2 and 3 years and decreases slowly thereafter.[1] Subsequently, viral pneumonia may be complicated by bacterial infection.[1, 36]

1.3.2 Bacterial Pneumonia

Bacterial pneumonia can affect individuals of any age. People with other respiratory diseases or viral infection and those who have a weakened immune system are at great risk. An underlying disorder should be considered if a child experiences recurrent bacterial pneumonia. The organisms responsible for pneumonia vary according to the age and immune status of the child and where the pathogen was acquired.[3, 16, 34]

The greatest number of potential pathogens is seen in neonates who require prolonged intensive care, particularly those born prematurely.[37] *Group B Streptococci* (*Streptococcus agalactiae*) and gram-negative enteric bacilli particularly *Escherichia coli* are the most common pathogens causing neonatal pneumonia contracted via ascending infection from mother during birth often in association with generalized sepsis.[34, 38] Pneumonia in early months of life is often caused by organisms that do not usually infect older children unless their immune system is suppressed. The clinical signs and symptoms of pneumonia in this age group progresses rapidly and tend to overlap with disease conditions like septicemia and meningitis. Newborns can also have a serious bacterial infection, if they present with deep jaundice and an umbilical cord and/or skin infection. The cause of illness may be fulminant and lead to death in a few hours. *Streptococcus pneumoniae* (the pneumococcus) is the most common cause of bacterial pneumonia in all paediatric age groups after the newborn period, and is one form of pneumonia against which antibiotic therapy and vaccines are available.[36, 38, 39]

World wide, the pneumococcus is the major cause of mortality in children under the age of five.[36, 40, 41] Conditions associated with increased risk of serious pneumococcal

disease include HIV infection, sickle cell anemia, asplenia and a variety of chronic organ failures.[39, 41] Pneumonia is by far the most common cause of pneumococcal death world wide.[41]

The second leading cause of bacterial pneumonia is *H. influenzae*. *H. influenza* type b is an important cause of serious bacterial infection in infants and children who have not received *H. influenzae* type b vaccine. Pneumonia is the second in frequency to meningitis in children with invasive *H. influenzae* disease, most cases occurring during winter and spring.[1, 2, 42]

Other bacteria (*Staphylococcus aureus* and other gram negative bacteria) most often affect newborn and malnourished children.[2] *S. aureus* pneumonia may be primary or secondary. Primary disease is defined as pneumonia with no extra pulmonary site of infection. Secondary pneumonia indicates the presence of one or more non-pulmonary sources of infection. Pneumonia caused by *S. aureus* is a serious and rapidly progressive infection.[1, 2] Blood cultures are positive in 20-30% of patients with primary *S. aureus* pneumonia. The associated pleural effusions if present, should be drained by thoracocentesis or, if large, by a chest tube. Pneumatoceles are also common and are found in 45-60% of patients with *S. aureus* pneumonia.[43]

In 1986, Shann et al reviewed 11 studies of the aetiology of pneumonia in children in the developing world, undertaken since 1974, which had used lung aspiration. Three hundred and fourteen organisms were isolated from 744 patients (42%). Pneumococci comprised 43% of the positive isolates. Subsequent studies undertaken in the Gambia (Wall et al 1986: Forgie et al 1991: Adegbola et al 1994: Uses et al 1998), Papua New

Guinea (Barker et al 1989) and Zimbabwe (Ikeogu 1988) that have employed lung aspiration and/or blood culture have confirmed the dominance of the pneumococcus as a cause of pneumonia in children in these countries.

Other researchers [44-46] found rates of bacteraemia ranging from 7.7% to 9.6% in children with pneumonia, *H. infuenzae* and *S. pneumoniae* were the most common bacterial pathogens identified. Teele and colleagues found that the risk of bacteraemia in children with pneumonia was even higher if the white blood cell count was elevated. In their study of 100 children with pneumonia, the prevalence of bacteraemia was 15% in children with white blood cell counts of 15000 x $10^3/\mu L$ or higher and 5% in children with white blood cell counts less than 15000 x $10^3/\mu L$.[46]

Barkley et al in an observational study based on clinical syndrome approach done at Kilifi, Kenya, found that among children admitted with pneumonia syndrome, 52% had severe disease and 11% had very severe disease.[47] The prevalence of invasive bacterial infection with severe pneumonia syndrome was similar to that with mild pneumonia syndrome, but case fatality was greater. *S. pneumoniae* (38%), *Enterobacteriaceae* (30%) and *H. influenzae* (15%) were the most common isolates.[47] Another study done by Barkley et al on bacteraemia among children admitted to a rural Hospital in Kenya, showed that among infants who were 60 or more days of age, *Streptococcus pneumoniae*, *non typhoidal salmonella species*, *H. influenzae* and *E. coli* accounted for more than 70% of isolates. The proportion of the cases of bacteraemia that were caused by either *S. pneumoniae* or *S. aureus* increased with each year of age.[42] Both HIV infection and malnutrition were associated with an increased risk of bacteraemia among

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children admitted to the hospital, but only 18% of children admitted with bacteraemic illness were infected with HIV, whereas severe malnutrition was present in 37% signifying malnutrition as main cofactor. The correlation of malnutrition with both death and blood stream infection was also showed by Lennox et al in Malawi.[48]

In the study done at the University of Cape Town, South Africa, by Zar et al on aetiology and outcome of pneumonia in hospitalized HIV-infected children found that, 60.4% of the studied population was HIV-infected. Almost 60% of HIV infected children had a prior hospital admission, 60% for a respiratory illness. The incidence and type of bacteraemia (14.3%) were similar in HIV-positive and HIV-negative patients. *S. pneumoniae* and *S. aureus* were the predominant isolates. HIV-infected children with pneumonia had a worse outcome than HIV-negative patients.[49]

1.3.3 Pneumocystis Pneumonia (PCP)

Pneumocystis pneumonia (PCP) is caused by a fungus called *Pneumocystis jiroveci*. PCP is a major cause of severe pneumonia (15-30%) and death (30-50%) in HIV-infected infants.

PCP was seen in pre-AIDS era in premature, debilitated infants, children with primary immunodeficiency diseases and children on immunosuppressant drugs.[50] The incidence of PCP is highest during the first year of life and usually peaks at 3 to 6 months of age.[50]

A study done by Stephen et al on clinical presentation and outcome of PCP in Malawian children identified 16 cases of PCP among 150 children with radiologically confirmed severe pneumonia. Children with confirmed PCP had a lower mean age, body temperature, and oxygen saturation than children with bacterial pneumonia and were

less likely to have a focal abnormality on auscultation. Oxygen requirements were much greater in children with PCP than those with bacterial pneumonia. Ten of 16 children with PCP and six of 21 with bacterial pneumonia died. The overall case fatality rate of severe pneumonia was 22%. In addition to a strong association with PCP, a fatal outcome was significantly and independently associated with HIV-infection with age under six months.[51]

Bakeera et al studied the prevalence of PCP, its clinical and radiological features and the outcome in 121 children aged 2-60 months presenting with severe pneumonia over a 2 months period at Mulago Hospital, Uganda. The prevalence of PCP was 16.5% and 12(60%) were less than 6 months of age. The outcome of children with PCP was poor with a case fatality rate of 40% compared with 20% in those without HIV. Radiological findings were non specific. HIV-positivity, AIDS and a clear chest on auscultation were associated with PCP.[52]

1.3.4 Pulmonary Tuberculosis (PTB)

In any child with an unusual or non-responding pneumonia, tuberculosis (TB) needs to be considered, especially if the child has been in contact with an adult with newly diagnosed TB or is from a community with a high incidence of TB. Children of any age can develop TB but it is especially common in children younger than four years of age. Other risk factors for the development of TB are HIV-disease, malignancies, children receiving immunosuppressive treatment, and children with congenital and acquired heart disease.[3]

Most children infected with *M. tuberculosis* do not develop tuberculosis disease. The

development of tuberculosis disease depends on the competence of the immune system to resist multiplication of the *M. tuberculosis*. This competence varies with age, being least in the very young. HIV and malnutrition lower the body's defenses. In the presence of any of these conditions tuberculosis disease can develop more easily.[6]

Children with HIV infection are between 5-10 times more likely to develop TB.[50] Children with dual infection of TB and HIV are four times more likely to die than those with TB alone. The reported seroprevalance of HIV in children with TB ranges from 10 to 60%. The highest prevalence of HIV infection in children with TB has been reported in Southern Africa, the lowest prevalence in West Africa.[50] Diagnosing TB in children was difficult even before the HIV/AIDS pandemic, now it is more difficult because HIV-positive child may have many other pulmonary conditions and HIV related chronic lung diseases that mimic the symptoms of TB.[50] Radiological changes including hilar or mediastinal lymphadenopathy, lobar opacity, cavitations, pleural effusion, and miliary pattern are important features.

1.4 Pathogenesis of Pneumonia

1.4.1 Normal Pulmonary Defense Mechanisms

The lungs are protected by various mechanisms.[53-56] Inspired air is filtered by the nares. Warming, humidification, and filtration occur in the upper airway. The trachea and bronchi are lined with ciliated epithelial cells and goblet cells. The goblet cells and the mucous glands of the airway secrete a mucous layer. The action of the cilia moves the mucous layer toward the pharynx so the mucous layer with entrapped particles can then

be expectorated or swallowed. Particles larger than 10-15 micrograms (mcg) are filtered by the coarse nasal hairs. Particles 5-10 mcg land on the nasal surface and are removed by mechanisms including the ciliary action of the epithelium and by sneezing. Particles 1-5 mcg land on the tracheobronchial mucosal blanket and are removed by ciliary action. Particles smaller than 1 mcg may reach the respiratory bronchioles and air spaces, where some may be exhaled. Particles in the alveoli may be removed by the mucociliary system, phagocytosis by alveolar macrophages, or via the lymphatics or bloodstream. Opsonins and small lymphocytes act to enhance the phagocytosis and killing of living particles. Secretory immunoglobins (Ig), especially secretory IgA, can neutralize some viruses and toxins and assist in the lysis of bacteria. IgG and IgM are secreted when lung inflammation occurs. Other substances including interferon, lactoferrin, and lysozymes may also be a part of the defensive mechanisms of the lung.

1.4.2 Impaired Pulmonary Defense Mechanisms

Any process that adversely affects any of the pulmonary defense mechanisms predisposes to pneumonia.[57, 58] Factors that impair host defenses can be congenital (ranging from anatomic abnormalities to impaired immunity) or acquired (generalized disorders such as human immunodeficiency virus [HIV] or pulmonary diseases such as pulmonary fibrosis) or even iatrogenic (drugs, anesthetics, intubations, and tracheostomy). There are also environmental factors that are associated with an increased incidence and severity of respiratory infections. These include cigarette smoke, crowded living conditions, poverty, malnutrition, daycare attendance, and inhalation of pollutants from wood-burning stoves.[59-61]

In children, probably the most common factor that renders the lung susceptible to pneumonia is a preceding viral infection. At least 50% of the time, a viral upper respiratory infection (URI) precedes the onset of pneumonia.[62] Such a viral URI impairs host defenses by disrupting the normal epithelium of the respiratory tract that impairs the mucociliary system, altering normal secretions, modifying the native bacterial flora, and even inhibiting phagocytosis. Organisms can gain access to the lungs by several routes. Most often, organisms colonizing the upper respiratory tract are aspirated into the lungs, less commonly; organisms access the lung via the bloodstream during a primary bacteraemia or from a distant focus of infection.[63] once the microorganism invades the lung, an inflammatory response occurs. This results in the migration of polymorphonuclear leukocytes, the release of oxidative enzymes and mediators of inflammation, the loss of surfactant, and the leakage of plasma. Bacteria multiply in the alveoli and inflammatory exudates are formed. Scattered areas of consolidation occur, which coalesce around the bronchi and later become lobular or lobar in distribution. There is no tissue necrosis. Pathological process passes from the stage of congestion to red and gray hepatization before the final stage of resolution. These pathophysiologic changes interfere with respiration and lead to the clinical signs and symptoms of pneumonia. The healthy parts of the lungs have to work harder, and this is done by increasing the rate of respiration. The respiratory rate increases because small children are not able to increase their tidal volume. It is more efficient for them to increase their minute volume by increasing their respiratory rate. For this reason tachypnoea is a very sensitive sign of respiratory disease. Study done by Miguel et al on diagnostic value of

tachypnoea in pneumonia defined radiologically showed highest sensitivity 74% and a specificity of 67% and 69% of cases were classified correctly.[64] The sensitivity and specificity of tachypnoea have also been shown by other studies.[65, 66] It is important to note that a slower than normal rate may reflect deterioration, pre apnea, or some central nervous system disease or metabolic disorder. When there is severe respiratory disease, rib and sternal retraction occur. This is due to decreased compliance of the chest wall in small children. Rib and sternal retraction occur with extensive alveolar disease and airway obstruction. Sub costal and lower costal retractions are a result of flattened diaphragm.[3] When large parts of the lung are affected, the oxygen need of the body can not be met, and hypoxia sets in. Sometimes, the pneumonia is not extensive, but the effort of maintaining a high respiratory rate exhausts the muscles involved; and this causes hypoxia too.[3] Prolonged hypoxia causes damage to various organs of the body, and may lead to death. An arterial oxygen saturation of 90% generally corresponds to an arterial oxygen tension of 60-70 mmHg, this relation is affected by factors such as temperature, pH, altitude and age. Below an arterial oxygen tension of 60-70 mmHg the hemoglobin oxygen dissociation curve falls steeply such that further decreases in arterial oxygen tension are associated with greater decreases in arterial oxygen saturation.[67] Tissue hypoxemia is the main fatal complication of pneumonia.[68]

Onyango et al did a prospective observational study to determine the prevalence, clinical correlates and outcome of hypoxia in acutely ill children with respiratory symptoms, in Nairobi, Kenya.[69] They found that, over half (59%) of the children admitted to the hospital were hypoxemic. Ten percent (10%) of all admitted children died whereby

ninety percent (90%) of them were hypoxemic. Children with hypoxemia were 4 times more likely to die than those with no hypoxemia.[69] A Study done in Gambian children with ALRTI on clinical predictors of hypoxemia found that, hypoxemic children were five times more likely to die than non-hypoxemic children.[70]

1.5 WHO /IMCI Classification of Pneumonia

In order to reduce high mortality, the WHO has developed a program for the control of respiratory infections through improved case management of children under five years of age. In mid 1990's this program was included as a component of the Integrated Management of Childhood Illness (IMCI) strategy, being a single and integrated approach to assess, classify and treat children at first level health facilities.

The primary goal is to reduce deaths in children under the age of five. Using this approach, pneumonia is classified as very severe, severe or non-severe, based on the clinical features, with specific treatment for each category of severity.[6] (Refer appendix II). Antibiotic therapy is needed in all cases. Severe and very severe pneumonia require additional treatment, such as oxygen, to be given in hospital. The choice of antimicrobials depends on aetiological organisms identified by microbiological tests. Often these tests are time consuming. Causative organisms are presumed based on the age of the child and epidemiology, clinical and radiological features, extra pulmonary manifestations, and recent drug sensitivity pattern in the hospital.

1.6 Investigations

In a previously normal child, presence of cough with fast breathing is sufficient to make

diagnosis of pneumonia. The following investigations provide more information.

1.6.1 Chest X-ray

Clinical findings that are compatible with pneumonia are most readily confirmed by chest X-ray. It also shows extent of parenchymal involvement and complications of disease. The accuracy of the chest radiograph in predicting the etiologic agent causing the pneumonia varies widely from 42-73% to more than 90%.[70]

Bacterial pneumonia in children is normally characterized by widespread, poorly demarcated, alveolar opacities with air bronchograms. The classical lobar or segmental opacification with air bronchograms is less common. Viral pneumonia, on the other hand causes perihilar streaking, interstitial changes and air trapping. Mucous plugging in viral pneumonia results in lobar or segmental bacterial pneumonia.

Although these features are useful they are not specific enough to differentiate with certainty between viral and bacterial pneumonia on radiological feature alone.

A complete lobar consolidation is not a common finding in infants and children. Severity of disease may not correlate with radiographic findings. A chest roentgenogram assists in the detection of complications of pneumonia, including a large pleural effusion, pneumatoceles, or a lung abscess. Such complications suggest a bacterial infection, particularly *S. aureus* and less commonly *H. influenzae*.

Although a positive chest radiograph is the gold standard for the diagnosis of pneumonia, an occasional patient with clinical symptoms and signs of pneumonia may have a normal chest roentgenogram.[63] The radiographic finding is said to "lag behind" the clinical picture. If a child is dehydrated, especially early in the course of illness, an

initial chest x-ray may be negative while a repeat film after therapy may then become positive.[63] Likewise, the patient may have clinically recovered from the pneumonia, yet still have findings of pneumonia on the chest roentgenogram. Thus, most clinicians will wait 6-8 weeks before repeating the chest roentgenogram in patients with lobar consolidation in order to confirm resolution of the pneumonia.

A study done by Zar et al showed no significant differences in the frequency and type of chest X-ray changes between HIV-positive and HIV-negative children. Hilar or mediastinal adenopathy occurred more commonly in children with tuberculosis. There were no diagnostic features for PCP, but patchy alveolar infiltrates and hyperinflation occurred in 94.4% and 72.2% respectively.[49]

1.6.2 Blood Culture

Bacterial and viral pneumonia cannot be differentiated without microbiological study. Bactec cultures are useful to isolate the organisms. Blood culture prior to antibiotic treatment is extremely valuable in isolating the organism in severe pneumonia, although they isolate the causative organism in about 10-30% of patients with bacterial pneumonia.[18, 33] The causative agent remains unidentified in 30-50% of cases.[71]

A negative blood culture does not exclude a bacterial infection. Organisms cultured from pleural fluid are always pathological. The best source of culture material is a lung aspirate. Published reports have suggested that bacterial pathogens can be isolated in approximately 33% of patients undergoing this procedure.[72]

Such studies have been biased, however, because severe cases were more likely to be enrolled.

1.6.3 White Blood Cell Count (WBC)

With a viral pneumonia, the white blood cell count may be normal or mildly elevated, often with a lymphocytosis. In bacterial pneumonia, there is generally a leukocytosis in the range of 15,000-40,000 x $10^3/\mu L$, with an increased percentage of polymorphonuclear leukocytes and band forms. Leucopenia (WBC < 5000 x $10^3/\ \mu L$), may indicate a poor prognosis. A markedly elevated WBC count (> 30,000 x $10^3/\ \mu L$) almost always denotes a bacterial pneumonia; often with bacteraemia and a higher risk of complication. A normal WBC count is typical of *mycoplasma* or *Ch. pneumoniae.* The Erythrocyte Sedimentation Rate (ESR) and C-reactive protein are usually elevated but are non-specific.[1]

1.6.4 Special Investigations

Invasive diagnostic procedures (transtracheal aspiration, bronchial brushing or washing, lung puncture, or open biopsy) are done in patients who lack a definitive diagnosis and who are deteriorating clinically.

Tuberculin Skin Test (Mantoux test) and Sputum/Gastric Aspirates/CSF/other body fluids

These investigations are done if the patient does not respond to treatment or has unusual radiological features. Three consecutive early morning gastric aspirates, CSF (if clinically indicated), pleural fluid and ascites fluid can be obtained for microscopic examination of acid-fast bacilli (Ziehl-Nielsen stain) and for culture of tubercle bacilli. Owing to low detection rates by these methods, a positive result would confirm tuberculosis, but a negative result does not exclude the disease.

2.0 RATIONALE

Over two million children die from pneumonia each year and around one in every five death are children under five years old.[73] Severe pneumonia among children less than five years old is a major cause of morbidity and mortality throughout the developing world. Children with certain risk factors in particular, can develop pneumonia or a more severe disease requiring inpatient attention and with an increased risk of death. With co-morbid conditions such as malnutrition, HIV-epidemic and the development of antibiotic resistance, pneumonia pattern may have been altered. To guide therapy, knowledge of the spectrum, burden and attributions of death need to be assessed in order to improve management of pneumonia.

Tanzania is not on track to meet its 2015 targets of reducing under five mortality by two thirds unless urgent actions are taken. According to a UNICEF/WHO press release pneumonia kills more children than any than other illness, and thus any effort to improve overall child survival must make the reduction of pneumonia's death toll a priority.[73] In spite of highest death toll, pneumonia has received little attention especially in Tanzania in terms of research. It is for this purpose that, this study was done to establish the pattern of risk factors related to severity and outcome of pneumonia among children aged 2-59 months in Dar es Salaam, Tanzania.

The study will provide the baseline data on pneumonia which will be useful in defining appropriate local approaches to pneumonia management. The results provide a foundation for more specific and wider studies in future to tackle the major problem of childhood pneumonia.

2.1 Research Question

Does the presence of hypoxaemia, bacteraemia, malnutrition and HIV influence the severity and outcome of pneumonia as classified by WHO/IMCI criteria in children 2-59 months in Dar es Salaam, Tanzania?

3.0 OBJECTIVES

3.1 Broad Objective

To establish the factors related to severity and outcome of pneumonia among children aged 2 – 59 months in Dar es Salaam, Tanzania.

3.2 Specific Objectives

3.2.1 To determine the distribution of pneumonia according to severity pattern as classified by WHO/IMCI criteria according to age and sex.

3.2.2 To determine the prevalence of hypoxaemia in children aged 2-59 months admitted with pneumonia, and its association with severity and outcome.

3.2.3 To determine the prevalence of bacteraemia in children aged 2- 59 months admitted with pneumonia and its association with severity and outcome.

3.2.4 To determine the prevalence of malnutrition among children aged 2-59 months admitted with pneumonia and its association with severity and outcome.

3.2.5 To determine the prevalence of HIV among children aged 2-59 months admitted with pneumonia and its association with severity and outcome.

In this study patients were recruited from the main government hospitals in the city including MNH, Temeke, Ilala, and Mwananyamala. Ilala, Temeke and Mwananyamala are the three District Municipal hospitals which gave a good representative sample of the general population and cases of pneumonia in this study. MNH is a national referral and University teaching hospital in the country where most of the complex cases are managed.

4.3 Study Population

The target population was all children aged 2-59 months inclusive admitted to the general paediatric wards at MNH, Ilala, Mwananyamala and Temeke Municipal hospitals with symptoms and signs of pneumonia.

4.4 Study Duration

The study was conducted from March to September 2006.

4.5 Inclusion Criteria

4.5.1 Age 2 months to 59 months inclusive.

4.5.2A primary clinical diagnosis of pneumonia as classified by WHO/IMCI criteria, which consists of a child presenting with cough or difficult breathing with the following features:

i. Fast breathing

Respiratory rate of more than or equal to 50, or 40 per minute in 2 months to 12months, 12 to 59months of age respectively.

ii. Any one of the following signs

Flaring of alae nasi, visible lower chest wall indrawing, central cyanosis, inability to breast feed or drink, vomiting everything, convulsions, lethargy or unconsciousness, severe respiratory distress for example head nodding, and/or crepitations.[6]

4.6 Exclusion Criteria

4.6.1 Unwillingness of the parents/guardians to participate in this study.

4.6.2 Child known to have congenital/acquired heart disease (cyanotic and acyanotic) or diagnosed at presentation.

4.6.3 Child known to have chronic renal or liver disease.

4.6.4 Child diagnosed or under going treatment for malignancy.

4.6.5 Child with severe anaemia (Hb < 4g/dL)

4.6.6 Child with signs of severe dehydration due to any cause.

4.6.7 Child who was already enrolled in the study, and readmitted with symptoms and signs of pneumonia.

4.7 Sample Size Estimation

The sample size was calculated using a software ***Epi info version 6***.

Using the formula below: [77]

$$n = \frac{N Z^2 P(1-P)}{d^2 (N-1) + Z^2 P(1-P)}$$

Where: **N** = Total population (in this case was the estimated number of admission in general paediatric wards 2003/2004 at MNH which was 4067)[22]

Z = Z value (corresponding to the confidence level 95%)

d = Absolute precision (5%)

P = Expected proportion in the population (in this case malnutrition was considered to be the most prevalent risk factor associated with 50% of all paediatric admissions)

Design effect = 1

The calculated sample size (**n**) was = **352**

4.8 Research Assistants and Training

Four research assistants (medical doctors with experience in clinical practice) assisted in recruitment of study participants, data collection and follow up. They underwent a two days training course conducted by the main researcher. They were trained on the purpose of the study, how to select patients, consent form administration, filling of the questionnaire, standard operating procedures of specimen collection and delivery to the laboratory, and follow up of the recruited children.

4.9 Piloting the Questionnaire

This was done for two weeks prior to actual data collection so as to test the practicability of the questionnaire. Some of the questions were adjusted as research assistants initially misunderstood them. Thereafter, the questionnaire was easily administered and brought up the intended information.

4.10 Recruitment of study Participants

All children aged 2-59 months inclusive admitted to the general paediatric wards at MNH, Ilala, Mwananyamala and Temeke Municipal hospitals with symptoms and signs of pneumonia as classified by WHO/IMCI criteria were recruited into the study. Children were consecutively enrolled into the study as they were admitted after parents/guardians had given written informed consent (Refer Appendix III). Recruitment of patients and sample collection was done during the official working days and hours. On average two to three cases were recruited daily, until sample size of 352 children was realized. All children who met the inclusion criteria and parents/guardians consented were recruited into the study as there was limited number of pneumonia cases during the data collection period.

4.11 Data Collection and Instruments Used

A structured questionnaire designed for the purpose of the study was used. The questionnaire was divided into four different sections. Section A, demographic details including name of the patient, age, sex, residence, site of recruitment, date and time of admission as indicated in Appendix I.

In section B of the questionnaire, parents/guardians were asked about the presence or

absence of key symptoms of pneumonia according to WHO/IMCI guidelines. Symptoms suggestive of PCP and PTB were enquired. They were also asked about drug history particularly to determine previous use of antibiotics for the past 48 hours as most of the admitted children would have taken antibiotics prior to admission. History of the child being tested for HIV, and whether the child was on cotrimoxazole prophylaxis or Antiretroviral Therapy (ART) was enquired to find out those children previously diagnosed and on prophylaxis and/or treatment of HIV infection. A thorough clinical examination was then done to every child according to the principles of paediatric practice and recorded in section C. This included taking patient's weight, height, temperature, respiratory rate for one minute, and pulse oximeter readings. Signs which determine the severity of pneumonia according to WHO/IMCI criteria were assessed. Blantyre Coma Scale was used to assess the level of consciousness.[78, 79] A primary diagnosis according to severity pattern of pneumonia was recorded in section D, with other suspected diagnosis based on clinical features following the standard WHO/IMCI criteria.

Weight

Weight was taken using a 25 kilogram Salter hanging scale (CMS Weighing equipment, High Holborn, London, United Kingdom) with a patient putting on light clothing and removing shoes. Older children who could not fit into the weighing pants were allowed to stand on solar cell SECA weighing scale. Weight was taken to the nearest 100gm. Calibration of the scale was done before each session. For accuracy and consistent data the scales were checked weekly with known weight.

Height/length

Parents/guardians assisted in removing patient's shoes and gently laying the child in supine position on the length board with their heads placed at 90^0 with the head piece while the investigator straightened the legs, to ensure that the feet were at the right angles to the legs and brought the sliding foot piece into contact with the child's heels. For children who were 24 months and above and able to stand height was taken by standing upright on the board and the head piece was placed on the head at 90^0. Height/length was recorded to the nearest 10 millimeters using local height/length boards which were standardized.

Interpretation of nutritional status

Using "Epi Nut" programme on the "Epi Info" statistical package version 6.01, Weight / Height Z-score (WHZ) were calculated.

Z-scores were interpreted as follows: [80]

Z <-1.0 = Mild wasting

Z<-2.0= Moderate wasting

Z<-3.0 = Severe wasting

Pulse oximeter

Child's oxygen saturation was measured with an appropriately sized sensor and a Nellcor pulse oximeter (USA) placed on the toe or finger, while the patient breathed room air. Once a high quality signal was obtained (identified by a clearly pulsatile signal on plethymography) three separate readings over 2-3 minutes were recorded. The interval between each oximeter reading was about 30 seconds. This was done to

minimize the error as movement of the patient causes monitor fault. The mean value was used in all analyses.

4.12 Investigations

4.12.1 Blood Specimen Collection

On admission six milliliters of venous blood were taken from the anterior cubital fossa of each child using a sterile, disposable syringe and needle. The femoral vein was used in those children who were difficult to get the peripheral veins. No immediate complications were associated with the femoral punctures. The child's skin was cleaned with 2% tincture of iodine and a 70% alcohol swab, allowed to dry before blood was drawn for a complete blood count and ESR, HIV testing, and blood culture and sensitivity. Two and a half milliliters of blood was immediately put in the EDTA bottle for FBP and ESR, and PCR later on for those aged less than 18 months who had positive double rapid HIV test. Half a milliliter was put in an empty sterile bottle for double rapid HIV testing.

Lastly three milliliters of blood was inoculated into the peadiatric blood culture bottles (BACTEC^{TM} PĒDS PLUS^{TM} /F culture vials) after the needle had been changed and the top had been cleaned with 70% alcohol and allowed to dry. The volume was marked before and after inoculation to know the exact volume inoculated.

Only one set of blood cultures was drawn for each child before antimicrobial treatment was initiated in the wards. The contaminated needles and syringes were

disposed safely into special boxes. The specimens were placed together with the completed investigation forms, transported to the laboratory as soon as possible and handled to a laboratory technologist.

4.12.2 Determination of Full Blood Count and ESR

The haemoglobin (HB) estimation, total and differential white blood cell count were determined using an ABX Pentra 60 machine (ABX, France). A blood sample in the EDTA bottle mixed up using a mixing machine, and 1ml of blood fed into the machine to determine the above parameters. ESR was done by mixing one ml of blood with 0.25ml of sodium citrate, and sedimentation rate read in the first one hour. This ratio was used to avoid taking much blood to these children.

Quality Control

The machine was regularly checked with the laboratory's standard Quality control samples (high, normal and low) for quality assurance.

4.12.3 HIV Testing

Screening was done by Capillus^{TM} HIV 1/HIV 2 (Trinity Biotech, USA) and reactive samples were confirmed by Determine^{TM} (Abbott Laboratories, Tokyo, Japan). A sample was considered seronegative if it was non reactive at screening and seropositive when reactive on both assays. A previous study conducted in Tanzania, on an alternative confirmatory strategy in the use of Capillus followed by Dertermine gave a sensitivity of 100% and a specificity of 99.8% for detecting HIV-infection.[81] Positive samples from children 18 months and below were assayed by PCR for proviral DNA following standard protocol with adherence to quality assurance and

quality control procedures. HIV DNA-PCR was also done in those above 18 months with discordant rapid tests. Positive HIV DNA-PCR results were interpreted that the child is HIV-infected and a negative result interpreted that the child is not HIV-infected.

4.12.4 Blood Culture

In the laboratory the blood culture bottles were immediately loaded into the blood culture equipment to ensure performance efficacy. The BACTEC® 9050 system (BACTEC® 9050; Becton Dickinson) was used to process all blood cultures.

The BACTEC® 9050 system monitors carbon dioxide production released by the microorganisms within each bottle. Bottles identified as positive culture were immediately removed from the instrument and an aliquot taken for gram stain and subculture.

Bacterial isolates were identified by conventional procedures. The subcultures were inoculated on solid agars; CLED (Cystene, Lysine, Electrolyte Deficiency), blood and chocolate agars, incubated aerobically at 37^0c for 18-24 hours. After 24 hours of incubation colonies were identified based on characteristic morphology, gram stain appearance and standard commercially prepared biochemical tests as described in Cowan and Steel's manual for identification of bacteria.[82] The isolates were stored on nutrient agar slopes at room temperature and in prepared freezer medium of Tryptone Soya Broth with 15% Glycerol (TSBG) and stored at -70^0C for further identification and testing later on.

Antimicrobial susceptibility of the bacterial pathogens isolated was determined by the

Kirby-Bauer diffusion method according to the National Committee for Clinical Laboratory Standards (NCCLS). Antibiotics tested included Ampicillin 10μg, Penicillin 10μg, Chloramphenical 30μg, Oxacillin10μg, Gentamicin 10μg, cotrimoxazole 25μg, Augumentin 10μg, Erythromycin 15 μg, Cephalothin 30 μg and Vancomycin 30μg.

After 16 to 18 hours of incubation on Muller-Hinton agar, each plate was examined. Zones were measured to the nearest whole millimeter, using sliding calipers or a ruler, which was held at the back of the inverted Petri plate. The Petri plate was held a few inches above a black, non reflecting background and illuminated with reflected light. The zone margins were taken as the area showing no obvious, visible growth that can be detected with the unaided eye. Faint growth of tiny colonies, which can be detected only with a magnifying lens at the edge of the zone of inhibited growth, was ignored. However, discrete colonies growing within a clear zone of inhibition were sub cultured, re-identified, and retested. The results were reported as sensitive, intermediate or resistant to the agents that had been tested according to NCCLS. For convenient interpretation during data analysis intermediate was categorized as sensitive.

Quality Control

Aseptic techniques were observed in all the steps of blood sample collection and inoculation into blood culture bottles to minimize contamination. Commercially prepared BACTEC culture vials type PEDS PLUS^{TM}/F (enriched soybeans-casein digest broth with CO_2) for aerobic cultures were used to support growth of all

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possible organisms causing pneumonia. The BACTEC vials were immediately placed in the BACTEC® 9050 equipment which automatically detects the positive vials to maximize the growth of organisms. All the positive vials were immediately sub cultured, gram stained and submitted for biochemical tests to avoid unnecessary delays and contaminations. All culture media were prepared according to the directions of the manufacturer. Three plates of each batch were incubated at 37^0C for 48 hours to check for sterility and the ability to support growth of the common organisms causing pneumonia was determined by inoculating the media with a typical stock culture. Negative and positive controls were included to validate the biochemical reagents/test kits.

4.12.5 Chest Radiographs

Chest radiographs were done to children who were stable enough, not on oxygen therapy as there was neither portable x-ray machine nor portable oxygen to support them. Anterior posterior view (AP) in supine position was taken. All CXR done were reported by a qualified experienced radiologist.

4.13 End Point/Outcome

All recruited children were followed-up while in the ward until recovery and discharge (following the discharge policy of the wards) or death. Time of death was noted as death within 48 hours and beyond 48 hours of admission.

4.14 Ethical Clearance

Ethical clearance to carry out this study was obtained from the College Research and Publications Committee of MUHAS. Permission to conduct the study was obtained from the respective hospitals involved.

4.15 Ethical Issues/Considerations

The aims of the study were explained to the parents/guardians of the children. Children in the study were identified by a unique study number. Names, places of residence and hospital inpatient numbers were not included in the computerized database, and all data were handled in the strictest confidence. Laboratory results and chest X- ray reports were provided to the admitting clinician, explained to the parents/guardians and/or recorded in the case records to facilitate the appropriate management of these children. HIV pre and post test counseling was provided to the parents/guardians. Children who were found to be HIV positive were referred to a comprehensive infectious disease clinic within the Department of Paediatrics and Child Health for further management, treatment and care. Children of the parents/guardians who did not consent for participation were assured of the same quality of care as any other patient that is their decision would not deny them the right of being treated properly.

4.16 Data Analysis

Data were entered into the computer and cleaned by the main researcher herself. Analysis was done by EPI Info version 6.01 and SPSS (Statistical Package for Social Science) software version 10. Age was grouped into three categories as prevalence of pneumonia varies with age.[20] Children were grouped into two main categories; those having severe form of pneumonia (included severe and very severe pneumonia) and those with non-severe pneumonia for convenient interpretation. The prevalence of hypoxaemia, bacteraemia, malnutrition and HIV were determined using frequency distribution tables. Cross tabulation and Chi square was used to test association between variables. Fisher's exact test was used to compare proportions in two by two tables where expected value in a cell was less than five. P-value of less than or equal to 0.05 was considered significant. Data analysis was done in collaboration with a biostatistician from MUHAS.

4.17 Limitations of the Study

1. Prior administration of antibiotics might have an influence on the positivity of blood cultures.
2. Use of human blood agar and limited availability of laboratory identification tests might have contributed to low yield of the common bacteria causing pneumonia.
3. Unreliable availability of antibiotic disks in the laboratory made antibiotic susceptibility testing erratic.

5.0 RESULTS

During the study period between March and September 2006, 352 children met the inclusion criteria and were recruited into the study. Of these 108 (30.7%) were recruited from Muhimbili National Hospital and 244 (69.3%) were from Municipal Hospitals which included Ilala 33 (37.8%), Mwananyamala 58 (16.5%) and Temeke 53 (15.0%).

From table 1 it is seen that 152 (43.2%) were females and 200 (56.8%) were males. The female to male ratio was 1.3:1 with the overall mean age of 12 months. Ninety nine percent of the information was obtained from the parents and only 1% from the guardians.

Among the acute presentations cough (98.6%), difficult breathing (98.3%) and fever (97.4%) were most common. Inability to drink and/or breast feeding was observed in 19.3% and 17.6% of the acute cases while 11.4% presented with convulsions as signs of severe pneumonia. Most of the children had history of prior treatment with antibiotic (83.2%).

Of the chronic presentations, 10.5% had chronic cough and 9.1% had chronic fever. History of weight loss was the most common symptom among the chronic cases (19.3%). Out of these 5 (1.4%) were on anti TB treatment and 21 (6%) had been diagnosed as HIV- positive before admission to hospital. About 2% of the children enrolled were on antiretroviral therapy and 1.4% were receiving cotrimoxazole as prophylaxis against PCP. (Table1)

Table 1: Patient's characteristics

Variables	N=352	%
Age (months)		
2 - 12	238	67.6
13 - 24	66	18.8
25 +	48	13.6
Sex		
Male	200	56.8
Female	152	43.2
Study site		
Ilala	133	37.8
Muhimbili	108	30.7
Mwananyamala	58	16.5
Temeke	53	15.0
Source of information		
Parent	349	99.1
Guardian	3	0.9
History suggestive of Acute illness		
Fever	343	97.4
Cough	347	98.6
Difficult breathing	346	98.3
Inability to drink	68	19.3
Inability to breast feed	62	17.6
Convulsions	40	11.4
Vomiting everything	6	1.7
Prior treatment with antibiotics	293	83.2
History suggestive of Chronic illness		
Fever > 4 weeks	32	9.1
Cough > 4 weeks	37	10.5
Weight loss	68	19.3
Family history of positive PTB	26	7.4
HIV-positive before admission to hospital	21	6.0
Treatment with ART	6	1.7
PCP prophylaxis with cotrimoxazole	5	1.4
Current TB treatment	5	1.4

More than two thirds, (68.8%) of the admitted children presented with severe form of pneumonia. Children aged less than one year had significantly higher proportion of severe pneumonia (74.4%) compared with the other age groups. ($p < 0.05$)

However, there was no significant difference observed between sexes and the risk of developing severe pneumonia, $p = 0.728$ (Table 2)

Table 2: Severity patterns of pneumonia by Age and Sex

	Non Severe Pneumonia	**Severe Pneumonia**	**Total N=352**	**p - value**
	n (%)	**n (%)**		
Age				
2 – 12	61 (25.6)	177 (74.4)	238 (67.6)	
13 – 24	29 (43.9)	37 (56.1)	66 (18.8)	0.004
25 +	20 (41.7)	28 (58.3)	48 (13.6)	
Sex				
Male	61 (30.5)	139 (69.5)	200 (56.8)	0.728
Female	49 (32.2)	103 (67.8)	152 (43.2)	
Total	**110 (31.2)**	**242 (68.8)**	**352 (100)**	

The overall case fatality due to pneumonia was 22.4%. The mortality was significantly higher among those with severe pneumonia (29.3%), $p < 0.001$.

About half of the children with severe and non-severe pneumonia, died within 48 hours of admission. (Table 3)

All children who had clinical features suggestive of PCP 43 (12.2%), presented with severe form of pneumonia. (Table3) Children with clinical features of PTB had the highest proportion of those presenting with non severe pneumonia (43.5%).

Table 3: Severity patterns of pneumonia by clinical features and association with outcome.

	Non severe Pneumonia		**Severe Pneumonia**		**Total N=352**		**p - value**
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	
Outcome							
Recovered	102	(92.7)	171	(70.7)	273	(77.6)	0.000
Died	8	(7.3)	71	(29.3)	79	(22.4)	
Time of Death							
Within 48 hrs	4	(50.0)	35	(49.3)	39	(49.4)	0.630
Beyond 48 hrs	4	(50.0)	36	(50.7)	40	(50.6)	
Clinical features							
PCP	0	(0.0)	43	(100.0)	43	(12.2)	
PTB	10	(43.5)	13	(56.5)	23	(6.5)	
PAIDS	6	(30.0)	14	(70.0)	20	(5.7)	
Others	81	(36.7)	140	(63.3)	221	(62.8)	

Most of the children recovered regardless of their age though mortality was higher among the children less than one year of age (23.9%). There was no significant difference in mortality according to age. $p = 0.453$. (Table 4)

Table 4: Association between the Age and Outcome

	Recovered		Died		Total N=352		p - value
	n	(%)	n	(%)	n	(%)	
Age							
2 – 12	181	(76.1)	57	(23.9)	238	(67.6)	
13 – 24	55	(83.3)	11	(16.7)	66	(18.8)	0.453
25 +	37	(77.1)	11	(22.9)	48	(13.6)	
Total	**273**	**(77.6)**	**79**	**(22.4)**	**352**	**(100)**	

The proportion of children presenting with hypoxaemia was 25%. Severe pneumonia and HIV infection were significantly associated with hypoxaemia, $p < 0.001$ (Table 5)

Among those who had hypoxaemia, only 58% received oxygen therapy. Oxygen therapy was not shown to improve outcome of those who had hypoxaemia.

Fifty percent of children with hypoxaemia died compared to 13% among the non hypoxaemic group. $p < 0.001$.

The rate of death did not vary significantly between hypoxaemic and non-hypoxaemic children. $p = 0.562$. (Table 5)

Table 5: Association between Hypoxaemia and selected variables

	Hypoxaemia Present		Hypoxaemia Absent		Total N=352		p - value
	n	(%)	n	(%)	n	(%)	
Severity of Pneumonia							
Non Severe	3	(2.7)	107	(97.3)	110	(31.3)	
Severe	85	(35.1)	157	(64.9)	242	(68.7)	0.000
HIV Status							
Positive	39	(44.8)	48	(55.2)	87	(24.7)	
Negative	49	(18.5)	216	(81.5)	265	(75.3)	0.000
Outcome							
Recovered	44	(50.0)	229	(86.7)	273	(77.6)	
Died	44	(50.0)	35	(13.3)	79	(22.4)	0.000
Time of Death							
Within 48 hrs	23	(52.3)	16	(45.7)	39	(49.4)	
Beyond 48 hrs	21	(47.7)	19	(54.3)	40	(50.6)	0.562
Total	**88**	**(25)**	**264**	**(75)**	**352**	**(100)**	

Bacteraemia was found in 27.8% of children with pneumonia. Among the 98 bacterial strains isolated 57 (58.2%) were gram positive and 41 (41.8%) were gram negative. CoNS comprised 39 (39.8%) of the bacteria isolated. *Pseudomonas* species, *S. aureus*, *Klebsiella* species, and *Streptococcus* species were the common bacteria isolated. Other organisms included *E. coli*, *Salmonella*, and *Acinetobacter* species. More than half of the

organisms were isolated in children less than one year of age (65.3%). Other bacteria isolated and regarded as possible contaminants were *Bacillus* species (6.1%). (Table 6)

Table 6: Blood culture isolates of children with pneumonia by Age.

Pathogen	Age (Months)							
	2 – 12		13 – 24		25+		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Gram Positive								
Streptococcus species	1	(1.6)	0	-	3	(15.8)	4	(4.1)
Staphylococcus aureus	6	(9.4)	2	(13.3)	0	-	8	(8.2)
CoNS	26	(40.6)	5	(33.3)	8	(42.1)	39	(39.8)
Other gram positives	4	(6.2)	2	(13.3)	0	-	6	(6.1)
Gram Negative								
Pseudomonas species	6	(9.4)	3	(20.0)	2	(10.5)	11	(11.2)
Klebsiella Species	6	(9.4)	0	-	2	(10.5)	8	(8.2)
Escherichia coli	3	(4.7)	0	-	0	-	3	(3.1)
Salmonella Species	2	(3.1)	0	-	1	(5.3)	3	(3.1)
Acinatobacter Species	2	(3.1)	1	(6.7)	0	-	3	(3.1)
Other gram negatives	8	(12.5)	2	(13.3)	3	(15.8)	13	(13.3)
Total	**64**	**(65.3)**	**15**	**(15.3)**	**19**	**(19.4)**	**98**	**(27.8)**

Other gram positive included *Bacillus* species (6)
Other gram negative included; *Pasteurella* (2), *Gernella* (2), *Pantoea* (2), *Shigella* (1), *Enterobacter* (1), and gram negative rods not further identified (5)

Antibiotic susceptibility testing using antibiotics such as ampicillin, penicillin, chloramphenical, oxacillin, gentamicin, cotrimoxazole, augumentin, erythromycin, cephalothin and vancomycin was performed on bacteria isolated. Patterns of antimicrobial resistance are shown in table 7. No susceptibility testing was performed on isolated bacteria that were regarded as possible contaminants. A high frequency of resistance to common antibiotics used in treatment of pneumonia like ampicillin, penicillin, cotrimoxazole and to a lesser extent chloramphenical was observed as well as in a third generation cephalosporin, cephalothin. The prevalence of resistance ranged from 50 to 100 percent to most prevalent bacteria isolated. Most of the bacteria isolated showed less resistance to gentamicin, vancomycin, oxacillin, erythromycin, and augumentin.

Table 7: Percentage of Resistance among the most prevalent bacteria

	AMP	PN	C	Ox	Ge	SXT	AU	E	Ce	Va
Bacteria										
Streptococcus	0	50	0	50	0	100	0	50	NT	0
S. aureus	NT	100	0	0	0	100	0	28.6	100	42.9
CoNS	66.7	100	50	57.7	0	81.8	10	64.9	0	14.7
Pseudomonas	100	100	50	50	0	70	87.5	57.1	100	0
Klebsiella	100	NT	40	NT	25	0	37.5	NT	33.3	NT
E. coli	100	NT	100	NT	33.3	100	0	NT	66.7	NT
Salmonella	33.3	NT	33.3	NT	0	0	0	NT	33.3	NT
Acinatobacter	50	NT	100	NT	0	0	50	NT	0	NT

AMP, Amplicillin; **PN**, Penicillin; **C**, Chloramphenical; **OX**, Oxacillin; **Ge**, Gentamicin; **SxT**,Cotrimoxazole; **AU**, Augumentin; **E**, Erythromycin; **Ce**, Cephalothin; **Va**, Vancomycin ; **NT**, Not Tested; **0**, No resistance

A higher proportion of children with non-severe pneumonia had bacteraemia (32.7%) compared to those with severe pneumonia (25.6%). The difference in the prevalence of bacteraemia among the non-severe and children with severe pneumonia was not statistically significant. $p = 0.168$. (Table 8)

About 25% of children were found to be malnourished. Bacteraemia was present in 23% of the malnourished children compared to 29.4% among the well nourished. The difference in the prevalence of bacteraemia among the well and malnourished children was not statistically significant. $p = 0.245$. (Table 8)

A higher proportion of HIV-positive children had bacteraemia (39.1%) compared to those who were HIV-negative (24.2%).The difference in prevalence among the HIV-positive and negative children was statistically significant, $p < 0.05$. (Table 8)

The mean WBC and ESR among children with pneumonia were 15,000 x 10^3 /μL and 42 mm/ in the first one hour respectively. High proportion of children with bacteraemia had WBC ≥ 15,000 x 10^3 /μL (42.9%) and ESR ≥ 30mm/hour (56.1%). The differences between these values among the bacteraemic and non-bacteraemic children were not statistically significant. $P = 0.463$ and 0.174 respectively. (Table 8)

About 24% of children in non-bacteraemic group died compared to 19 % among the bacteraemic children. The difference in the risk of death among the bacteraemic and non bacteraemic children was not statistically significant. $P = 0.393$. (Table 8)

A total of 291 (83%) had chest x- rays. Most of the children with pneumonia had abnormal chest radiographs (96%). The difference of radiographic findings in bacteraemic and non-bacteraemic group was not statistically significant.

Table 8: Association between Bacteraemia and selected variables

	Bacteraemia Present		Bacteraemia Absent		Total N=352		p - value
	n	(%)	n	(%)	n	(%)	
Severity of Pneumonia							
Non Severe	36	(32.7)	74	(67.3)	110	(31.3)	
Severe	62	(25.6)	180	(74.4)	242	(68.7)	0.168
Malnutrition							
Present	20	(23.0)	67	(77.0)	87	(24.7)	
Absent	78	(29.4)	187	(70.6)	265	(75.3)	0.245
HIV Status							
Positive	34	(39.1)	53	(60.9)	87	(24.7)	
Negative	64	(24.2)	201	(75.8)	265	(75.3)	0.007
WBC							
≥ 15,000	42	(42.9)	98	(38.6)	140	(39.8)	
< 15,000	56	(57.1)	156	(61.4)	212	(60.2)	0.463
ESR							
≥ 30	55	(56.1)	122	(48.0)	177	(50.3)	
< 30	43	(43.9)	132	(52.0)	175	(49.7)	0.174
Outcome							
Recovered	79	(80.6)	194	(76.4)	273	(77.6)	
Died	19	(19.4)	60	(23.6)	79	(22.4)	0.393
CXR findings							
Normal	4	(3.7)	10	(4.8)	13	(4.5)	0.488
Abnormal	94	(96.3)	244	(95.2)	278	* (95.5)	
Total	**98**	**(27.8)**	**254**	**(72.2)**	**352**	**(100)**	

* Total Chest radiographs done were 291

Alveolar and interstitial infiltrates were the common radiographic features found, 48.5% and 37.9% respectively. Lobar consolidation, adenopathy, pleural effusion, hyper inflation, cavitations and segmental consolidation were also observed.

Malnutrition was higher among children with severe pneumonia and those who were HIV positive, 27.3% and 29.9% respectively. Presence of malnutrition was significantly associated with high mortality among children with pneumonia, $p < 0.05$. (Table 9)

Table 9: Association between malnutrition and selected variables

	Malnutrition Present		**Malnutrition Absent**		**Total N=352**		**p - value**
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	
Severity of Pneumonia							
Non Severe	21	(19.1)	89	(80.9)	110	(31.3)	
Severe	66	(27.3)	176	(72.7)	242	(68.7)	0.099
HIV Status							
Positive	26	(29.9)	61	(70.1)	87	(24.7)	
Negative	61	(23.0)	204	(77.0)	265	(75.3)	0.198
Outcome							
Recovered	59	(67.8)	214	(80.8)	273	(77.6)	
Died	28	(32.2)	51	(19.2)	79	(22.4)	0.012
Time of Death							
Within 48 hrs	13	(46.4)	26	(51.0)	39	(49.4)	
Beyond 48 hrs	15	(53.6)	25	(49.0)	40	(50.6)	0.699
Total	**87**	**(24.7)**	**265**	**(75.3)**	**352**	**(100)**	

Double rapid tests for HIV were positive in 29.5%, of these 91 (87.5%) were children below 18 months of age. Seventy four (81.3%) were PCR positive and 17 (18.7%) were PCR negative at the time of recruitment. Hence, the true prevalence of HIV among children with pneumonia at the time of study was 24.7%. (Table 10)

Table 10: Distribution of HIV DNA-PCR results by Age

PCR	≤ 18 months	>18 months	Total
Positive	74 (81.3)	1 (16.7)	75 (77.3)
Negative	17 (18.7)	5 (83.3)	22 (22.7)
Total	**91 (100)**	**6 (100)**	**97 (100)**

Eighty percent (80%) of HIV-positive children had severe pneumonia. The difference in the prevalence of severe pneumonia among the HIV-positive and negative children was statistically significant, $p < 0.05$.

Out of those who recovered, 83.4% were HIV-negative. Mortality was significantly higher among the HIV-positive children, $p < 0.001$. (Table11)

Table 11: Association between HIV status and selected variables

	HIV Status Positive		HIV Status Negative		Total N=352		p - value
	n	(%)	n	(%)	n	(%)	
Severity of Pneumonia							
Non Severe	17	(19.5)	93	(35.1)	110	(31.3)	
Severe	70	(80.5)	172	(64.9)	242	(68.7)	0.006
Outcome							
Recovered	52	(59.8)	221	(83.4)	273	(77.6)	
Died	35	(40.2)	44	(16.6)	79	(22.4)	0.000
Time of Death							
Within 48 hrs	8	(22.9)	31	(70.5)	39	(49.4)	
Beyond 48 hrs	27	(77.1)	13	(29.5)	40	(50.6)	0.000
Total	**87**	**(24.7)**	**265**	**(75.3)**	**352**	**(100)**	

6.0 DISCUSSION

Pneumonia is a serious infection of the lungs that continues to be a common cause of morbidity and mortality worldwide. Appropriate management and prevention of childhood pneumonia are key factors for the outcome. Therefore information on clinical presentation, epidemiology, antibiotic sensitivity pattern and other factors such as underlying HIV-infection and malnutrition are relevant in the evaluation and monitoring of various programmes in the prevention of childhood pneumonia. This study involved a highly selected group of children aged 2-59 months admitted with a diagnosis of pneumonia based on symptoms and signs as classified by WHO/IMCI criteria.

Among the 352 study children 242 (68.8%) had severe pneumonia. Smyth et al in rural Zambia and Barkely et al at Kilifi, Kenya also reported the predominance of severe pneumonia among the admitted cases.[30, 47] In a hospital based study like this, the predominance of the severe cases was expected. It is speculated that unresponsiveness to earlier treatment, wrong drugs and dosage, and health care seeking behavior might be contributing factors to severe presentation of the disease. Shah et al did a hospital based case control study on risk factors for severe pneumonia in children in South Kerala, India and found that unresponsiveness to earlier treatment and young age were among the significant factors.[83] Fast breathing is the most sensitive and reliable index for evaluating the presence and severity of pneumonia.[84] In this study it was observed that majority of parents/gurdians (>95%) of the admitted children with pneumonia reported fast breathing, cough and fever. Inability to drink and/or breast-feeding as one of the

sign of severe pneumonia was observed in 68 (19%), convulsions in 40 (11%) and about 10% of studied children had features of chronic illness. Cristiana et al in a prospective cohort study on clinical aspects associated with hospitalization or death demonstrated that fast breathing, chest in-drawing, underlying chronic illness and young age were independently associated with hospitalization for pneumonia.[85]

About three quarters (74.4%) of admitted children aged less than one year had severe pneumonia. Significantly high proportions were also observed in other studies done by Mtango et al who studied the magnitude, presentation, management and outcome of acute respiratory infections in Tanzania and as observed in Tanzanian Demographic and Health Survey.[20, 21] High prevalence of severe pneumonia among infants could be attributed by immunological immaturity and anatomical features which predispose them to more severe infections.

More than half (56.8%) of the admitted children with pneumonia were males, among them 139 (69.5%) presented with severe pneumonia. A higher proportion of males was also observed in a community based study of ARI done by Hyam et al in Syria among the preschool children.[86] Biological differences in susceptibility or response to infection could explain this. It is intriguing to speculate that sex difference might contribute to the difference in the severity of pneumonia but further studies in representative population samples are required to confirm this. In this study, the difference between sexes is small and could just be by chance.

Pneumonia is among the top three causes of morbidity and mortality among under fives in most developing countries.[7-9, 10, 11, 14, 15] In the present study case fatality rate of pneumonia was nearly quarter of the study population (22.4%) and time of death was not related to severity of the pneumonia. A retrospective review of medical records in Eldoret District hospital, in Kenya found the case fatality due to pneumonia to be 26.8%.[18] In a community based study on verbal autopsy to assess death among under fives children done in Bagamoyo District, Tanzania in 1986 by Mtango et al established that a quarter (25%) of deaths were ascribed to pneumonia.[22] Similarly the annual report of MNH 2003-2004 indicates mortality of 23.4% being ascribed to pneumonia among the admitted cases.[23] Considering the time of death in relation to severity of the pneumonia found in this study, implies that the management provided did not alter the course of illness. Barriers towards health care seeking behavior, prompt and effective management at health facilities are among the speculated factors to high mortality among cases of pneumonia. Late presentation of patients to hospital as a cause of high mortality rate shortly after admission to hospital in the tropical countries has also been reported in other studies.[18, 87, 88]

The severity of pneumonia was shown to be directly related to PCP and HIV/AIDS.[50-52] The present study found that, all children (12.2%) who had clinical features suggestive of PCP presented with severe pneumonia. Severe pneumonia was significantly associated with higher mortality. It is well known that PCP is a major cause of severe pneumonia and death in HIV-infected infants, with the highest incidence during the first

year of life.[50] It is also possible that the high fatality among those with severe pneumonia was attributed to PCP.

In a prospective study done by Stephen et al on clinical presentation and outcome of PCP in Malawian children, a fatal outcome was significantly and independently associated with HIV-infection and age under six months. [51] Bakeera et al reported similar findings in a prospective study done at Mulago hospital, Uganda.[52] Increase in the prevalence of PCP as a result of acquired immunodeficiency secondary to HIV-infection elucidate the severe cases of pneumonia and high case fatality among the admitted cases.

Children under the age of five years had highest case fatality and mortality declined with age. Zwi et al showed this in a study done on HIV-infection and in-hospital mortality at an Academic hospital in South Africa.[33] In the present study, mortality declined with age, but the trend was lost among the older age groups.

Increases in the prevalence of PCP as a result of acquired immunodeficiency secondary to HIV-infection explicate the severe cases of pneumonia and high case fatality among the admitted cases.

Hypoxaemia is the best indicator of both severe and potentially fatal pneumonia. Prompt recognition of hypoxaemia and supplemental oxygen therapy improves the outcome in severe pneumonia.[69, 70] This study showed that the prevalence of hypoxaemia among children admitted with clinical symptoms and signs of pneumonia were 88 (25%) with significantly higher percentage among those with severe pneumonia 85 (35.1%) and

HIV-infected children (44.8%). The hypoxaemia prevalence found by Onyango et al in a prospective observational study in young Kenya children with acute lower respiratory infection was higher (59%) compared to the findings of this study.[69] The study population may explain the higher prevalence in Kenyan children as it included younger infants less than 2 months of age up to 3 years. This group is more prone to severe disease and hypoxaemia.

Mortality among the hypoxaemic children was 50% compared with 13% among the non-hypoxaemic children. The timing of death was not significantly associated with hypoxic state. Onyango et al observed that 90.4% of those with severe hypoxia died and the risk of death among the hypoxic children were four times more than in those with no hypoxia, however the study population differs. A prospective cohort study done by Usen et al on clinical predictors of hypoxaemia in Gambian children with acute lower respiratory tract infection found a lower prevalence of hypoxemia (5.9%), and a lower mortality among the hypoxaemic group (12.7%) compared to the findings of present study and Kenyan study.[70] The Gambian study was performed on a cohort of children who were under close surveillance for *H. influenza* type b disease, and this may explain partially the low prevalence of hypoxaemia in the study population and lower mortality rate than that observed in present and Kenyan study. As in this and Kenyan study the hypoxaemic child was more likely to die than non-hypoxaemic child.

The outcome of children with acute respiratory tract infection and hypoxaemia correlates with the severity of hypoxaemia [69, 70] and mortality is reduced with oxygen therapy.[69] However; in this study oxygen therapy was not found to improve the outcome. It is

speculated that severe presentation of the disease, inappropriate oxygen delivery and duration of oxygen therapy could be contributing factors. In most areas in developing countries where the case fatality from pneumonia is high, oxygen supply is scarce, expensive and not always freely available. To guide therapy, neither pulse oximeters nor facilities for blood gas analyses are readily available. This study observed that about half of the hypoxaemic children did not receive oxygen therapy because of inadequate oxygen supply and lack of close monitoring to guide oxygen utility.

HIV-positive children were more likely to present with hypoxemia than HIV-negative children (44.8% and 18.5% respectively). It was shown by Kawo et al in a prevalence study of HIV-type I infection, associated clinical features and mortality among hospitalized children in Dar es Salaam, Tanzania that acute respiratory infection was the common diagnosis among the HIV-infected children (39.4%).[29] Mortality rate was also higher (21.4%) in HIV-infected children compared to HIV uninfected children. Zwi et al documented the impact of rapid increase of HIV infection in hospitalized children at Chris Hani Baragwanath Hospital on in-hospital mortality. They found that the rise in in-hospital mortality was most striking in under one year old.[33] This probably caused by high case fatality rates for pneumonia especially in HIV-infected. Given the younger age and higher mortality in these infants with severe pneumonia it is likely that many had Pneumocystis pneumonia presenting with hypoxia. This also indicates that with the HIV epidemic, the burden of severe pneumonia has increased leading to an increased demand for oxygen.

The design and expected efficacy of pneumonia control programmes relying on case management and immunization strategies depend on information on the pattern of aetiology, which may show a considerable geographic variation. Blood cultures are often used to investigate the causative organisms in cases of pneumonia. However, in most settings very few pneumonia cases are bacteremic making this an insensitive test.[89] Bacteraemia often represents a diagnostic challenge in developing countries since most health care centers lack adequate laboratory facilities to do the necessary bacterial cultures or are unable to do so on time. It is well known that blood cultures are insensitive for detecting bacteraemia. Barkley et al looked on bacteraemia among children admitted to a rural hospital in Kenya.[42] They included all acute peadiatric admission below 13 years. Bacteraemia was found in 6.6% of children. Another study done by Nacul et al on aetiology and clinical presentation of pneumonia in hospitalized and outpatient children in Northeast Brazil and risk factors for severity; identified bacteria in 26.7% of cases.[90] Despite the limitations of sufficient availability of culture media, biochemical tests and antibiotic disks, the information gathered in this study is suitable in making a difference in pneumonia care. This study found the prevalence of bacteraemia in 27.8% of children with pneumonia, with the predominance of gram positive bacteria mostly contributed by CoNS. The findings of this study is not in line with others that *S. aureus* was the most common isolate.[48, 49, 91] Under normal circumstances, CoNS are regarded as the normal flora, however they are potential pathogens and therefore they can cause septicemia when they gain access into the blood stream. CoNS are both an important cause of nosocomial blood stream infections and

most common contaminants of blood cultures. Judging the clinical significance of CoNS is vital but often difficult and can have profound impact on blood stream infection rates. For CoNS to be regarded as pathogenic, it must be isolated from at least two separate blood cultures inoculated with different samples collected from the same patient at the same sitting from different sites. A recent study has documented the algorithm for determining clinical significance of CoNS defining as having at least two positive blood cultures within 5 days, or one positive blood culture plus clinical evidence of infection, which includes abnormal white blood cell count and temperature or blood pressure.[92] In this study a single blood culture was done, and 97% of the children presented with fever plus clinical evidence of infection. Positive bacterial cultures were common in HIV-infected children (39.1%). It is likely that the immunosuppression due to HIV predisposes children to bacterial infections. Considering a strong association between bacteraemia and HIV-infection, which is a state of immunosuppression, and the high proportion of CoNS, further studies are needed on bacteraemia and HIV. Contamination during blood specimen collection could also have contributed to high proportion of CoNS.

Other bacteria *Pseudomonas*, *Klebsiella* species and *E.coli* isolated could be contributed by nosocomial pneumonia associated with gastrointestinal flora or hospital environment. The prevalence of bacteraemia found in this study (27.8%) is low compared to that found by Omolola et al on predictors of bacteraemia among febrile infants in Ibadan, Nigeria (38.2%).[93] Recent antibiotic use reduce blood culture yield.

The high incidence of prior antibiotic use (83%) observed in the present study might

have contributed to the negativity of blood cultures especially for agents such as *S. pneumonia* and *H. influenza*, which have been shown to be the common bacteria causing pneumonia in children.[43-46, 93] In the study done by Omolola et al in Nigeria, the high prevalence of bacteraemia found may be because of the differences in study population and the methods used. [93] They involved younger children aged 1-12 months who presented with fever, and also they excluded those who took antibiotics seven days prior to the presentation.

Younger children are at increased risk for bacteraemia.[44, 46, 94] Mc Gowen et al and Teele et al in their studies on bacteraemia in febrile children found that an age of 24 months or less was the epidemiological factor with the highest sensitivity for bacteraemia.[44, 46] Akpede et al in Nigeria, also documented the highest prevalence of bacteraemia in infants aged 1-12 months and the prevalence declined with age.[94] Similarly, the present study showed higher proportion of bacteraemia among the younger children compared to the other age groups (65%).

Barkley et al found similar prevalence of invasive bacterial infection in children with mild and severe pneumonia.[47] As opposed to the findings above, the present study found higher prevalence of bacteraemia among children with non severe pneumonia (32.7%) compared to (25.6%) in those with severe pneumonia. This is probably due to the likelihood of received treatment with antibiotics due to severe nature of the disease or the severe pneumonia could be due to other aetiological agents such as viral or *Pneumocystis jiroveci* especially in children with HIV.

Emerging resistance to antimicrobial drugs increases morbidity and mortality by

hampering the provision of effective chemotherapy making treatment more costly. Exaggerated and irrational use of drugs, availability of antibiotics without prescription, the use of pharmaceuticals of doubtful quality and HIV-epidemic may all contribute to the current worldwide surge of antimicrobial drug resistance. The surge in antimicrobial resistance seen in many low-income countries is potentially disastrous because of the lack of resources for purchasing expensive second line drugs. Resistance to several antibiotics commonly used in the first line treatment of pneumonia has been observed for both gram positive and gram-negative bacteria.

It was observed that gram-negative bacteria showed frequent resistance to common and inexpensive antibiotics such as ampicillin, penicillin, cotrimoxazole and to a lesser extent chloromphenical. Pseudomonas species further showed resistance to infrequently used antibiotics such as augumentin and cephalothin.

Gram-positive bacteria showed resistance to penicillin and cotrimoxazole. Oxacillin, gentamicin, erythromycin and vancomycin remained useful to the treatment to bacteremia in children with pneumonia.

These results are consistent with the study done by Blomberg et al in 1998, who did a surveillance of antimicrobial resistance from blood cultures and Aboud et al who studied a collection of bacteria isolated from blood culture specimen from 1995-2004, in a similar setting as the present study, from inpatient and outpatient specimens examined at MNH, Department of Microbiology and Immunology.[95, 96] They found high rates of resistance to ampicillin and cotrimoxazole in gram negative bacteria. Gentamicin and third generation cephalosporins remained useful for parenteral therapy.[95]

High proportion of children with bacteraemia showed elevated levels of WBC ≥ 15,000 x $10^3/\mu L$ and ESR ≥ 30 mm in the first one-hour, though this was not statistically significant. A total WBC > 15,000 x 10^3 /μL have been shown by several studies to be a predictor of bacteraemia.[44, 46, 93] Mc Gowan et al and Teele et al reported that the incidence of bacteraemia rose with increasing WBC count and was greatest in patients with WBC count > 20,000 x 10 /μL.[44, 46] The actual cut off point differs from study to study. The specificity is reasonably high depending on a cut-off point choosen, but its sensitivity is low.[97] ESR is a non-specific indicator of infection, and is usually elevated in children with alveolar consolidation compared to those with interstitial pneumonia.[97] However, there is considerable overlap in values between the two groups. Moreover the timing of obtaining the sample in relation to onset of illness affects the ESR.[98] This makes it difficult to define a cut-off that would make it a useful adjunct in diagnosing bacterial pneumonia. This was also observed in prospective study done by Virkki et al in Turku, Finland, undertaken to investigate the differential diagnostic role of chest radiographic findings, total WBC, ESR and serum C reactive protein of varying aetiology. WBC and ESR were shown to add very little to the differential diagnosis of pneumonia.[99]

In the present study most of the children had abnormal chest radiographs with the predominance of alveolar and interstitial infiltrates. This may be explained by the possibility that these children had mixed viral-bacterial infection as interstitial infiltrates are seen in both viral and bacterial pneumonias. It is possible that the initial viral infection after denuding the epithelial respiratory cover during replication of the virus

facilitated the adherence of bacteria and their consequent invasion in the respiratory system.[100]

The observation is clinically important because half of children in the present study had alveolar infiltrates on the chest radiograph and lobar consolidation accounted for 10% of the observed findings, with almost 40% having interstitial infiltrates. It is possible that most the pneumonia cases are bacteremic. Virkki et al also observed that most children who had alveolar pneumonia, especially those with lobar infiltrates, had laboratory evidence of a bacterial infection.[99]

Several studies have suggested that bacterial pneumonia cannot be differentiated from non-bacterial pneumonia on the basis of the chest radiograph. Turner et al studied the chest radiographs of 37 paediatric outpatients with pneumonia and documented viral or bacterial infection. Alveolar infiltrates were found in 38% of the cases with bacterial pneumonia and in 67% of those with viral pneumonia.[101] Courtoy et al found alveolar infiltrates in 67% of 24 viral pneumonia and 42% of 12 bacterial pneumonia, the rest having interstitial infiltrates.[102] Korppi et al studied radiological findings of 61 children with microbiologically verified pneumonia. Alveolar pneumonia was associated with bacterial infection in 74% and with sole viral infection in 26% of the cases.[103]

It is difficult to get a comparison from these studies because the descriptive terms of the radiological findings vary widely and no generalized conclusions can be drawn.

An X-ray should be interpretated by comparing it with the clinical findings but its high cost in developing countries dictates priority for complicated cases and those with access to hospitals or clinics where the resources are available. Even in those areas where the

resources are available chest X-rays are not easily accessible especially to severely sick children on or not on supportive care like oxygen therapy.[100] In this study, 17% of children had no chest X-rays. These were the seriously sick children who could not be sent for chest radiographs and those who died early that is few hours post admission. The observation that consolidation was present in 95% of cases where a chest radiograph was taken suggests that the clinical diagnosis was correct in most cases.

In the present study bacteraemia was not associated with increased risk of neither malnutrition nor death as observed by others.[47, 48] This could be due to different definitions of malnutrition used and low yield of bacteria.

Weight for height play an important role in delineating children on adequate, possibly excess and those on lesser yet apparently satisfactory food intakes. As intake bears a direct relationship to growth, assessment of nutritional state using only weight for age is unsatisfactory.[104] The ratio of weight for height more accurately assess body build and distinguishes wasting (acute malnutrition) from stunting (chronic malnutrition). [104, 105]

This study utilized WHZ score to assess acute malnutrition in children admitted with pneumonia. The prevalence of malnutrition was 25%. In a study done by Nacul et al on aetiology and clinical presentation of pneumonia in hospitalized and outpatient children in Northeast Brazil and risk factors for severity, the prevalence of malnutrition was found to be 13%.[90] This is low compared to the findings of the present study. The difference could be due to the difference in methodology used. They included outpatient children who normally present with mild disease and utilized weight for age z- score as

indicator of malnutrition. Their study was also part of a randomized, double blind, placebo controlled trial of vitamin A in the treatment of childhood pneumonia.

The present study also observed that, high proportion of malnourished children had severe pneumonia. Impaired local and systemic immunity in malnourished children is a likely explanation for the increased severity of pneumonia in these children.

The synergism between malnutrition and infection is widely acknowledged, and various studies in developing countries have shown that malnourished children have an increased case fatality rate of pneumonia.[106-108] Similar findings was observed in this study. Malnourished children had significantly higher mortality (32%) compared to well nourished children (19%) with almost 50% of children with pneumonia dying within 48 hours of admission.

The prevalence of malnutrition in HIV-infected children was about 30% compared to 23% in HIV-uninfected children. Malnutrition was not found to be associated with HIV infection. Previous studied showed malnutrition to be a common finding in children with HIV infection.[29, 109] In this study, the small number studied could be contributing to the small difference between the two groups.

The present study employed the polymerase chain reaction (PCR) to determine the prevalence of HIV in children aged 18 months and below admitted with pneumonia. In the first year of life, the possibility of trans-placental transmission of antibodies to HIV makes the use of HIV serology unreliable. Even those children who had escaped contracting HIV in utero or during delivery little chance exist for them to escape it

postnatally due to lack of enough interventions to prevent Mother to Child Transmission (MTCT) as a result some of these children will be HIV positive by the time they reach 18 months. Breast feeding is the norm in resource-poor settings, formula feeding may be culturally unacceptable, and indirectly reveal a mother's HIV status and expose her to stigma. Protecting these babies from contracting HIV-infection from their mothers by replacement feeding is difficult in many African communities due to poverty as most people can not afford to buy breast milk substitutes. In the study area, babies are usually fed some other types of food like meal porridge on top of breast feeding assuming the child is not getting enough from breast milk, further increasing the chance of HIV transmission. Although 75% of infants will lose maternal antibody to HIV by 1 year of age, a significant proportion of children who become antibody negative will be infected with HIV.[110] HIV-PCR represents a more reliable way of making the diagnosis of HIV-infection in young children.

Incidentally this study found a high prevalence of HIV infection among exposed children aged 18 months and below admitted with pneumonia (81.3%). This calls for attention in prevention of MTCT (PMTCT) of HIV. Efforts are made to increase the coverage and utilization of voluntary counseling and testing services during the antenatal period but there is a delay in making a diagnosis of HIV in children. In our setting, PCR facilities are not readily available and this contributes to a puzzlement delay in making a diagnosis of HIV infection to these young children. Prolonged exposure to breast milk with or without mixed feeding, failure to link PMCTC with care and treatment services, weak postnatal care and follow up services for HIV exposed children could be

attributing factors to high HIV infection rate among young children. Transmission of HIV-1 through breast feeding was found to be high among women in Dar es Salaam, Tanzania, as shown by Fawzi et al.[111]

The present study shows that 6% of the mothers/guardians knew the serostatus of their children before admission, only 1% of children were on PCP prophylaxis and approximately 2% were on ART at the time of recruitment. Considering that more than two third of the studied population were 2-12 months old, this means that most of the children were not screened for HIV early in life contributing to late interventions. These predispose them to infection. HIV-infected children had increased risk of developing severe pneumonia and more likely to die after 48 hours of admission than non-infected HIV children. The prevalence of HIV infection among the studied children admitted with pneumonia was 24.7% with a mortality of 40%. Higher pneumonia related mortality has been reported among children with supportive evidence of HIV-infection than among those without.[29, 30, 32, 33, 49, 112]

Nathoo et al in Zimbambwe, found clinical or serolological evidence of HIV in 31% of urban children with acute lower respiration tract infection.[32] The case fatality rate was 16% and the risk of death was increased over three fold in children who had evidence of HIV-infection.[32] The rate of HIV-infection was unexpectedly high (62%) and the outcome was severe among the HIV-infected children diagnosed by PCR. Grahams et al showed this in a study done in Malawi on clinical presentation and outcome of Pneumocystis pneumonia.[51] The high prevalence could be explained by the fact that they involved children with severe pneumonia, targeting those more likely to have PCP and

hence HIV-infected. HIV-infection was also seen to be a strong risk factor for mortality in Tanzania, among children who were hospitalized with pneumonia. Villamor et al showed this in a prospective study among children aged 6-60 months of age who were admitted to hospital with pneumonia.[112]

Several factors may account for this; more rapid progression of pneumonia, inability to mount an effective immune response and less aggressive medical management such as reluctance to ventilate HIV-infected children, failure to diagnose and intervene early in infancy and late treatment seeking behavior. Other studies also showed the susceptibility of HIV-infected children to morbidity and mortality.[29, 30, 32, 33, 49, 112]

7.0 CONCLUSIONS

1. The prevalence of severe pneumonia was found to be high among the hospitalised cases of pneumonia.
2. The young age group is at high risk of developing severe pneumonia, which also accounts for most death that occurred early after admission among children admitted with pneumonia.
3. Hypoxaemia was the presenting feature of children with severe pneumonia and those who were HIV-infected. It was significantly associated with high mortality in children with severe pneumonia.
4. *S. pneumoniae* and *H. influenza* which are the fastidious pathogen causing pneumonia in children were not commonly isolated.
5. Most of the isolated bacteria showed high resistance to ampicillin, penicillin, cotrimoxazole and to a lesser extent chloramphenical. Gentamicin, vancomycin, oxacillin, erythromycin and augumentin are safe options for the treatment of bacteraemia among children admitted with pneumonia.
6. Malnutrition among children with pneumonia was associated with high in-hospital case fatality rate.
7. The prevalence of HIV among hospitalized cases of pneumonia was higher in severe cases of pneumonia and significantly associated with high mortality.
8. High proportion of children aged 18 months and below admitted with pneumonia were PCR positive for HIV.

8.0 RECOMMENDATIONS

1. Early diagnosis, prompt and effective treatment at all health facility levels are required in order to reduce death due to pneumonia.
2. In the current era of HIV which is associated with high prevalence of severe pneumonia requiring oxygen therapy, there is a need to improve monitoring and oxygen supply to children with severe pneumonia.
3. A continued surveillance of bacteraemia is required to monitor changes in causative organisms and their antibiotic sensitivity to generate valuable information on antimicrobial resistance, which can be used to prepare locally applicable recommendations on antimicrobial use. This can also function as a quality assurance tool bringing attention to methodological issues in identification and susceptibility testing so as to improve patient management.
4. Effective interventions on malnutrition and HIV are needed in order to reduce the burden of childhood pneumonia. Effort should be done to diagnose children with HIV-infection early in order to start effective preventive interventions such as PCP treatment and prophylaxis and ART.
5. HIV DNA-PCR facilities should be available at all health facilities running PMCTC services to facilitate early diagnosis of HIV-infection in children aged 18 months and below.

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