PNEUMONIA AMONG HOSPITALIZED CHILDREN AGED 1-9 YEARS
- A prospective and retrospective study at a referral hospital in Northern Tanzania

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Abstract

Objective
The aim was to study epidemiological aspects and identify risk factors for incidence and case-fatality of pneumonia among children aged 1-18 years treated as in-patients at a hospital in northern Tanzania.

Methods
Using the clinical definition and severity assessment of childhood pneumonia by WHO, 140 patients were identified among the 209 children aged 1-9 years treated for pneumonia during June 2010 – July 2011. Patients admitted June 2010 – May 2011 were included in a retrospective study solely based on information in their medical files. The patients admitted during June – July 2011 were included in a prospective study, where information was obtained from the caregiver present regarding socio-economic status, crowding, indoor air-pollution and socioeconomic status.

Results
More patients were diagnosed having non-severe pneumonia at KCMC (67.6%; CI 57.8-77.5%) than would have been according to WHO (40.9%; 95% CI 32.1-49.7), while less many patients were diagnosed as severe and very severe pneumonia at KCMC (32.3%; 95% CI 18-46.6) than would have been according to WHO (59.1%; CI 48-70.2%). The clinical definition and severity assessment of pneumonia in children aged >1 years only identified about 75% of the patients with radiologically confirmed pneumonia. Relapsing infections seemed to be more common among boys (40%; 95% CI 29-51) than girls (21.5%; CI 11.6-31.5). Underlying diseases tended to be more common among relapsing cases (43.2; 95% CI 28.6-57.8) than first-time infections (25%; 95% CI 16.3-33.7). Treatment with parenteral ampicilline and gentamycine was the most common treatment in all the different severity subgroups of pneumonia as defined by WHO. Although malnutrition tended to be more common both among the cases of severe and very severe pneumonia than non-severe pneumonia and among the fatal than the non-fatal cases, there were no risk factors significantly associated with a more severe infection or case-fatality. Crowding was common in the study; however the mean number of family members at home was only slightly higher than the average number in Tanzania. No conclusions regarding possible risk factors for pneumonia and case-fatality inquired in the questionnaire could be drawn due to the low number of participants.

Conclusions
No significant risk factors for pneumonia and case-fatality were identified. Relapsing pneumonia tended to be more common in boys than girls. Underlying disease tended to be more common among the relapsing cases than the first-time infections. Cases of pneumonia were often considered less severe at KCMC than they would have been according to WHO.
INTRODUCTION

Epidemiology

Pneumonia is the leading cause of mortality in children aged less than five years worldwide (Sazawal and Black 2003; Black, Cousens et al. 2010). The incidence of pneumonia in this group is estimated to about 156 million episodes each year, of which approximately 151 million are in developing countries and 35 million in Africa (Rudan, Boschi-Pinto et al. 2008). Estimates indicate that 7-13% of these episodes are possibly life-threatening and require hospitalization (Rudan, Boschi-Pinto et al. 2008). Pneumonia is responsible for about 1.6 million deaths among children aged <5 years, and these occur mainly in Africa and South-East Asia regions (Kabra, Lodha et al. 2010).

Pathophysiology

Pneumonia is defined as an infection of lung parenchyma (alveoli) by microbial agents (Kabra, Lodha et al. 2010). Several pathogens can cause pneumonia (including bacteria, virus, fungi and parasite) and the extent of pulmonary involvement, the onset, pattern and duration of symptoms; as well as the mortality rate depend on both the causative agent and precipitating factors (Duffin 1993). Normally the lower respiratory tract is sterile (Duffin 1993). Organisms that enter the lungs are prevented from colonizing the airways distal to the glottis by mechanical means, such as coughing, or by immune mechanisms (Duffin 1993). If however any of these defense mechanisms are compromised, and when exposed to a highly virulent strain of organism or a high aerosol dose, infection and the resultant inflammation of pneumonia can occur in healthy individuals. Endogenous sources of the microorganisms causing pneumonia are colonization of the sinusitis, pharynx, trachea, gastric tract and hematogenous spread (Alcon, Fabregas et al. 2005).

Community acquired pneumonia (CAP) can be defined clinically as the presence of signs and symptoms of pneumonia in a previously healthy child caused by an infection acquired outside a hospital (Harris, Clark et al. 2011).

Etiology

To establish the etiology of pneumonia among children is important and can help determine which interventions to prioritize, such as the development of specific vaccines and the empiric treatment of the disease. However, this is difficult to study due to the low yield of blood cultures, the difficulty to acquire adequate sputum specimens and the reluctance to perform lung aspiration and bronchoalveolar lavage in children (Harris, Clark et al. 2011). Furthermore, differences between studies regarding e.g. the season, the setting, the age of the children, whether or not the children were admitted to hospital, the local criteria for diagnosis makes it difficult to apply results in published studies to other populations (Harris, Clark et al. 2011). The etiology of pneumonia in high-income countries is different than in low-income countries, including more viral and atypical organisms (Kabra, Lodha et al. 2010). In developed countries studies have shown that viruses are the cause 30-67 percent of CAP and are more frequently identified in children aged less than 1 year than in those aged above 2 years (Harris, Clark et al. 2011). Bacteria are more frequently identified with increasing age, resulting in mixed infections being less common with age (Harris, Clark et al. 2011)
BACTERIA

The knowledge of etiology of pneumonia in low and middle income countries is based on two types of studies: prospective, microbiology-based studies and vaccine trial studies, where indirect evidence of vaccine efficacy for the prevention of pneumonia can be used to estimate the disease burden of each pathogen.

Prospective studies have identified *Streptococcus pneumonia* as the leading cause of bacterial pneumonia among children in developing countries, responsible for 30-50% of pneumonia cases. The second most common is *Haemophilus influenza* type b (Hib; 10-30% of cases), followed by *Staphylococcus aureus* and *Klebsiella pneumonia* (Rudan, Boschi-Pinto et al. 2008). Other bacteria are *Mycoplasma pneumonia* and *Chlamydia pneumonia*, causing atypical pneumonia (Simoes, Cherian et al. 2006); non-typable H. influenza (NTHI) and non-typhoid Salmonella spp (Rudan, Boschi-Pinto et al. 2008). Furthermore, studies of lung aspirate have identified *Mycobacterium tuberculosis* as an important cause of pneumonia (Rudan, Boschi-Pinto et al. 2008).

Pneumococcus

Pneumococci are common members of the normal flora of the upper respiratory tract and can be found in 30-70% of the nasopharynges in pre-school children (Backhaus 2012). Young age, day care center attendance and having young siblings are associated with higher carriage rates among children (Backhaus 2012). Ninety-three different serotypes are known, with difference in virulence, prevalence, and extent of drug resistance. Increased risk for invasive disease includes being <2 years of age (Backhaus 2012)

There are two types of pneumococcal vaccines available; polysaccharide vaccines (PPV) and conjugate vaccines (PCV). The PPV only activates a T-cell independent immune response and thereby fail to evoke memory B-cells; consequently the immunogenicity in children younger than 2 years is poor. On this basis the pneumococcal conjugate vaccines (PCV) were developed. The basic principle is that the capsular polysaccharide of a pneumococcal serotype is conjugated to a carrier protein, which will generate a B-cell response and the production of antibodies against the polysaccharide. To link such proteins and polysaccharides to each other is complicated, therefore only a limited number of serotypes have so far been represented in such a vaccine.

The first PCV contained polysaccharides from 7 serotypes known to be common causes of IPD among children in North America, and was introduced in the childhood vaccination program in the United States in 2000. Since the introduction, the incidence and the overall mortality due to invasive pneumococcal disease (IPD) in both vaccinated children and unvaccinated adults have declined markedly in the USA (Plishvili, Lexau et al. 2010). Also the number of hospitalizations due to pneumonia decreased.

A main problem with PCV-7 is that some serotypes, such as serotypes 1 and 5, known to have a high invasive disease potential in developing countries where the disease burden is the highest, are not included in the vaccine. Therefore, higher-valency vaccines were developed. A Cochrane review in 2009, where more than half of the studies were from African countries, found PCV effective in preventing IPD, radiologically defined pneumonia, and clinical pneumonia among HIV-1 negative and HIV-1 positive children <2 years of age. Furthermore, the impact was greater for vaccine type-IPD than for all serotypes-IPD, and for radiologically defined pneumonia than for clinically diagnosed pneumonia.

These findings show that pneumococcal vaccination has a huge potential to influence childhood morbidity and mortality in developing countries, and great efforts are made today to develop pneumococcal conjugate vaccines accessible where they are needed the most. New PCV’s providing protection against 10 and 13 serotypes, respectively, have recently been approved for marketing.
Today there are three Hib conjugate vaccines available for use in infants and young children (Simoes, Cherian et al. 2006). Several studies have confirmed the efficacy of Hib vaccine in preventing invasive disease (mainly meningitis, but also pneumonia), with equal effectiveness between the vaccine types (Simoes, Cherian et al. 2006). In most industrialized countries that has included the Hib vaccine in their national immunization program, invasive Hib disease have been close to eliminated (Simoes, Cherian et al. 2006). Studies in Bangladesh, Brazil, Chile and Gambia of the effectiveness of the Hib polysaccharide tetanus protein (PRP-T) have shown a 20-31% reduction in radiologically defined community acquired pneumonia in children aged <2 years of age (Mulholland, Hilton et al. 1997; Levine, Lagos et al. 1999; de Andrade, de Andrade et al. 2004). The studies also suggest a significant protection against non-bacteremic pneumonia, as well as invasive disease. These results suggest the importance of further incorporation of the Hib vaccine in developing countries with a high burden of pneumonia.

**VIRUS**

In 40-50 percent of infants and children hospitalized for pneumonia in developing countries, viruses are the causing agent (Simoes, Cherian et al. 2006)

Studies of pneumonia etiology show that RSV is the leading cause of viral pneumonia or bronchiolitis in children admitted to hospital in developing countries, followed by influenza A and B, parainfluenza, human metapneumovirus and adenovirus (Rudan, Boschi-Pinto et al. 2008).

A review of available data found RSV responsible for 27-96 percent of the cases in children hospitalized for acute lower respiratory tract infection where a virus was found (Weber, Mulholland et al. 1998). RSV infection is seasonal in most countries, with peaks typically occurring in the cold season in temperate climates and the rainy season in tropical climates (Weber, Mulholland et al. 1998). The risk of lower respiratory tract infections (LRI) caused by RSV infection is highest among children aged <2 years with the most severe episodes occurring in infants aged 3 weeks to 3 months (Rudan, Boschi-Pinto et al. 2008). A primary infection by RSV increases the risk of secondary bacterial pneumonia. Co-infections with both virus and bacteria is common in young children with pneumonia, found in about 20-30 percent of pneumonia episodes (Rudan, Boschi-Pinto et al. 2008).

Infection of RSV and influenza virus have been shown to increase the binding of both H. Influenza and S. Pneumoniae, which might explain the increased rates of pneumococcal pneumonia that have been found during RSV and influenza epidemics (Simoes, Cherian et al. 2006). Influenza vaccination therefore has a potential to reduce the incidence of pneumococcal disease, and vice versa, pneumococcal vaccination has been advocated as an important intervention to prevent the disease burden caused by both pandemic and seasonal influenza (Klugman 2011)

**Diagnostics**

Diagnostic procedures vary depending on the setting. In a hospital there are numerous investigations available including radiography and microbiological methods, whereas in the community one has to rely mainly on the clinical features of the ill child. The symptoms differ widely between individuals with pneumonia. A child may present with cough, fever and difficult breathing; they may also present with abdominal pain, headache and vomiting (Harris, Clark et al. 2011).

A framework for diagnosing clinical pneumonia has been constructed in the WHO/Unicef IMCI guidelines, Integrated Management of Childhood Illness, to assist health workers in
resource-poor settings in the management of CAP. Table 1 shows the clinical definition of pneumonia and severity assessment in children up to 5 years of age. As shown, pneumonia is divided into non-severe, severe and very severe.

**Table 1.** Definition of clinical pneumonia and severity assessment in children aged 1-5 years according to the WHO (WHO 2005).

<table>
<thead>
<tr>
<th>Non-severe</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Fast breathing (≥40/minute)</td>
<td>■ Fulfilling the criteria of non-severe pneumonia plus at least one of the following signs:</td>
<td>■ Fulfilling the criteria of non-severe pneumonia plus at least one of the following danger signs:</td>
</tr>
<tr>
<td>■ Cough or difficult breathing</td>
<td>■ lower chest wall indrawing</td>
<td>■ central cyanosis</td>
</tr>
<tr>
<td>■ None of the signs of severe or very severe pneumonia</td>
<td>■ nasal flaring</td>
<td>■ inability to breastfeed or drink, or vomiting everything</td>
</tr>
<tr>
<td>■ In addition, other signs of pneumonia may be present on auscultation: crackles, reduced breath sounds, or an area of bronchial breathing.</td>
<td>■ Check that there are no signs of very severe pneumonia</td>
<td>■ convulsions, lethargy or unconsciousness</td>
</tr>
</tbody>
</table>

In a healthcare setting where further diagnostic measurements are available, the care of the child can be based on a more thorough investigation than the clinical picture alone. The WHO guidelines suggest obtaining a chest X-ray in very severe pneumonia cases to identify possible complications (such as empyema and pericardial effusion) and in severe cases that do not respond to treatment, or that are associated with HIV-infection (WHO 2005). Microbiological investigations can be helpful and should be considered in severe cases to determine the causative agent (Harris, Clark et al. 2011). There are a number of investigations available; the British Thoracic Society (BTS) recommendations are to include blood culture, nasopharyngeal PCR/immunofluorescence for viral detection, serology for respiratory viruses, serology for mycoplasma plus chlamydia and investigations on pleura fluid if present (Harris, Clark et al. 2011).

The commonest lower respiratory tract infections in children are bronchiolitis and pneumonia (Simoes, Cherian et al. 2006). The signs and symptoms of bronchiolitis - including rapid breathing and lower chest wall indrawing, wheezing and fever in one-third of cases – overlap with those of pneumonia, thus making it difficult to differentiate between the two diagnoses (Simoes, Cherian et al. 2006). Bronchiolitis is mainly caused by respiratory syncytial viruses RSV’s and occurs predominantly in the first year of life with decreasing frequency in the second and third years (Simoes, Cherian et al. 2006).

**Risk factors**

Risk factors affecting the incidence of childhood CAP in developing countries are categorized by WHO as definite, likely and possible, as shown in table II. The BTS guidelines suggest that children <5 years of age have a higher incidence of severe disease, and that boys have a higher incidence at all ages (Harris, Clark et al. 2011). In developing countries, coal and biomass in the form of wood, dung and crop are commonly used residues for domestic energy. These materials are often burnt in simple stoves with very incomplete combustion. Consequently, young children, who often spend a large amount of time with their mothers doing household cooking, are exposed to high levels of indoor air pollution every day. There is consistent evidence that indoor air pollution increases the risk of chronic obstructive pulmonary disease and of acute respiratory infections in childhood.
(Bruce, Perez-Padilla et al. 2000). Exposure to smoke during cooking and parental smoking has also been associated with an increased risk of death from ALRI (de Francisco, Morris et al. 1993).

Table II. Risk factors affecting the incidence of childhood CAP in developing countries according to WHO (Rudan, Boschi-Pinto et al. 2008)

<table>
<thead>
<tr>
<th>Definite risk factors</th>
<th>Likely risk factors</th>
<th>Possible risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Malnutrition (weight-for-age z-score &lt; -2, &lt;5 years of age)</td>
<td>■ Parental smoking</td>
<td>■ Mother’s education</td>
</tr>
<tr>
<td>■ Low birth weight</td>
<td>■ Zinc deficiency</td>
<td>■ Day-care attendance</td>
</tr>
<tr>
<td>■ Non-exclusive breastfeeding (during the first 4 months of life)</td>
<td>■ Mother’s experience as a caregiver</td>
<td>■ Rainfall (humidity)</td>
</tr>
<tr>
<td>■ Lack of measles immunization (within 12 months of life).</td>
<td>■ Concomitant diseases (e.g. diarrhea, heart disease, asthma)</td>
<td>■ High altitude (cold air)</td>
</tr>
<tr>
<td>■ Indoor air pollution</td>
<td></td>
<td>■ Vitamin A deficiency.</td>
</tr>
<tr>
<td>■ Crowding (defined as ≥5 people per household)</td>
<td></td>
<td>■ Birth order</td>
</tr>
<tr>
<td></td>
<td></td>
<td>■ Outdoor air pollution</td>
</tr>
</tbody>
</table>

Risk factors for fatal pneumonia include poor socioeconomic status, incomplete immunization schemes, malnutrition, late care seeking and inadequate treatment (Rudan, Boschi-Pinto et al. 2008). A multihospital surveillance study in Bangladesh found that infancy, very severe pneumonia, severe malnutrition and a blood culture positive for bacteria was highly associated with death due to pneumonia (Naheed, Saha et al. 2009). Hypoxemia is associated with an increased risk of death from pneumonia (Ayieko and English 2007). In resource-poor settings pulse-oximetry is often unavailable, which has raised concerns to assess the accuracy of clinical signs for detecting hypoxemia. However, studies have found it difficult to identify one single clinical sign that can predict hypoxemia with high sensitivity and high specificity (Ayieko and English 2007).

**HIV**

In recent years, the HIV epidemic has contributed substantially to increase the incidence, severity, and mortality of childhood pneumonia in the developing world, particularly in sub-Saharan Africa (Zar 2004). Pneumonia is a leading cause of morbidity and death in HIV-infected children, and an important cause of hospitalization (Gray and Zar 2009). Children with HIV have a higher risk than immunocompetent children of developing pneumonia, associated with a more severe disease and worse outcome (Gray and Zar 2009; Gray and Zar 2010). Bacterial infection remains a major cause of pneumonia in HIV-infected children, but compared to HIV-uninfected children there is a broader spectrum of organisms (Zar 2004). Gram-negative bacteria and Pneumocystis jirovecii (PCP) are important pathogens, and Mycobacterium tuberculosis is increasingly reported causing acute pneumonia among children from high tuberculosis prevalence areas (Gray and Zar 2010). Polymicrobial infection is common and associated with an increased mortality (Gray and Zar 2009). Furthermore, HIV-exposed, negative children have a higher risk of developing opportunistic infection (Gray and Zar 2010), as well as severe pneumonia and death than HIV-unexposed children (Gray and Zar 2009). In children with HIV there are rising rates of antimicrobial resistance (Gray and Zar 2010).

WHO’s standard case-management guidelines of pneumonia have proven effective in decreasing the morbidity and mortality of childhood pneumonia globally, but despite adherence to these guidelines, pneumonia remains a major cause of morbidity among HIV-
infect ed children (Gray and Zar 2009). Studies suggest the need of adaptation of the guidelines for high HIV-prevalence areas and specific interventions, including antibiotic prophylaxis against PCP, early initiation of antiretroviral therapy and the use of available vaccines (Gray and Zar 2009; Gray and Zar 2010).

**Treatment**

Treatment of pneumonia depends on the age of the child, the severity of illness, the likely causative agents and their resistance patterns.

When managing a child with CAP it is important to decide if treatment with antibiotics is necessary. This is complicated partly due to the difficulty to distinguish bacterial from non-bacterial pneumonia, the latter not benefitting from the use of antibiotics (Harris, Clark et al. 2011). Even if isolation of the causative agent is possible, the child will need to be treated with empirical antibiotics until the result of the culture is available (Kabra, Lodha et al. 2010). The guidelines by the BTS for management of CAP in children recommend that children with a clear clinical diagnosis of pneumonia should be treated with antibiotics (Harris, Clark et al. 2011).

For management of non-severe pneumonia in children, the WHO recommends treating the child as an outpatient, giving oral co-trimoxazole or amoxicillin (WHO 2005). Children with severe pneumonia should be admitted to hospital and treated with benzylpenicillin, switching to oral amoxicillin when the child improves. Oxygen therapy is recommended in children with signs of hypoxia.

For very severe pneumonia WHO recommends ampicillin and gentamicin. When the child improves switch to oral amoxicillin plus intramuscular gentamicin. Alternatively, parenteral chloramphenicol or ceftriaxone intramuscular/parenteral can be given. If the child does not improve within 48 hours, switch to gentamicin and cloxacillin, followed by oral cloxacillin. In children, who are HIV positive or in whom HIV is suspected, with severe and very severe pneumonia, it is recommended to give ampicillin plus gentamicin. If the child does not improve, switch to ceftriaxone. Children aged 12–59 months with very severe pneumonia, and severe pneumonia with clinical signs of PCP, should receive a high dose treatment of co-trimoxazole.

**Tanzania**

Tanzania has a population of approximately 45 million, with a life expectancy at birth of 57 years (The-World-Bank 2012). Tanzania is a low-income country with a GNI per capita of 530 US$, and 33.4% of the population are living below the national poverty line (The-World-Bank 2012).

Between 1999 and 2004 significant improvements were made in Tanzania’s health system, with a more than doubled public expenditure on health, including decentralization and promoting important interventions for child survival, such as insecticide-treated nets, vitamin A supplementation, immunization and exclusive breastfeeding (Masanja, de Savigny et al. 2008).

The effects of these measures were seen in a demographic and health survey in 2005, showing an reduction in mortality in children aged less than 5 years, from 147 deaths per 1000 for 1994-1999 to 112 deaths per 1000 for 2000-04 (Masanja, de Savigny et al. 2008). Another survey in 2011 showed a continuous reduction, estimating the under-5 mortality rate during the period 2006-2010 to 81 deaths per 1,000 birth (National Bureau of Statistics Dar es Salaam 2011).

Pneumonia and malaria are the leading causes of death in Tanzania, both individually responsible for 16% of the total mortality (WHO 2011). Tanzania is among the 15 countries
with the highest estimated number of deaths due to clinical pneumonia with an under-five mortality rate of 52.6 per 10 000 (Rudan, Boschi-Pinto et al. 2008). The prevalence of HIV in Tanzania in 2008 was 62 per 1000 adults aged 15-49 (WHO 2011). Between 2000–2003 HIV/AIDS was responsible for 9% of the mortality among children aged less than 5 years of age (WHO 2006).

METHOD
The study was conducted during June-July 2011 at the Kilimanjaro Christian Medical Center (KCMC) in Moshi, which is the administrative center of the Kilimanjaro Region in Northern Tanzania. Moshi is situated at an elevation of approximately 900 m above mean sea level and has a population of about 144,000, the region inhabits about 1.4 million (Crump, Ramadhani et al. 2011). The climate is characterized by a long rainy period between March-May and a shorter rainy period October-December (Crump, Ramadhani et al. 2011). Malaria transmission is low (Crump, Ramadhani et al. 2011).

KCMC, with its 458 inpatient beds and a catchment area of around 11 million, serves as a consultant referral hospital for several regions in northern Tanzania. Together with the regional hospital Mawenzi Regional Hospital, KCMC is the main provider of hospital care in the Moshi area.

Of the approximately 1500 pediatric in-patients treated at KCMC every year 300–400 are diagnosed with pneumonia (Uriyo, Gosling et al. 2006). The mortality in this group exceeds 10%, which suggests that pneumonia is one of the leading causes of death among children in the region (Uriyo, Gosling et al. 2006).

Guidelines for diagnosis and treatment of pneumonia at KCMC are based on WHO’s clinical definition of pneumonia and severity assessment.

The aim was to study epidemiological aspects of pneumonia among children aged 1-18 years. This included a prospective study of all the in-patients matching the inclusion criteria during the study period and a retrospective investigation of the journals of all the pediatric in-patients diagnosed with pneumonia between the 1st of June 2010 and the 31st of May 2011.

The inclusion criteria in the prospective study were
• Patients diagnosed with pneumonia during the hospital stay.
• admitted at the Paediatric department 2 at KCMC during June-July 2011
• ≥1 year, maximum 9 years of age

In the retrospective study the inclusion criteria were
• Patients diagnosed with pneumonia in the discharge file admitted at the Paediatric department 2 at KCMC between the 1st of June 2010 and the 31st of May 2011
• ≥1 year, maximum 9 years of age

Pneumonia was defined as according to WHO’s clinical definition of pneumonia and severity assessment. If a patient was admitted more than once during this period with at least one month in between admissions, each admittance was handled separately.

The prospective study was partly based on a questionnaire addressing epidemiological factors (see attached document), which was filled out by the caregiver present. Written and oral information about the study was given to the caregivers before asked to participate and a written consent was obtained. Information was also given that all data was to be handled confidentially and that no compensation was given.

Statistics
Data was collected and analyzed using IBM SPSS Statistics 19. P-value <0.05 were regarded statistically significant. The 95% confidence interval (95% CI) was calculated using the formula:
\[ p \pm 1.96 \times \sqrt{\frac{p(100-p)}{n}} \]

To use the formula the following criteria had to be met:

\[ p \times n \geq 500 \]
\[ p(100-p) \geq 500 \]

(Colton 1974)

\( P \) being the proportion in percent and \( n \) being the number of observations.

**RESULTS**

The number of patients meeting the inclusion criteria between June 2010 – July 2011 was 209.

Based on the signs and symptoms documented in the medical file when admitted, 69 patients did not meet WHO’s clinical definition of childhood pneumonia and were excluded from the study; either because they did not have a respiratory rate \( > 40 \) breaths/minute, or they did have fast breathing but lacked both a history of cough and difficulties in breathing. However, in more than a third of these patients a chest X-ray was suggestive of pneumonia. Six had a positive malaria slide, 2 of which also had a pathological CXR. One patient died during admission.

The remaining 140 patients met WHO’s definition of clinical pneumonia. The most common signs and symptoms presented when admitted/diagnosed are shown in table III.

**Table III**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast breathing</td>
<td>100</td>
</tr>
<tr>
<td>History of cough</td>
<td>95</td>
</tr>
<tr>
<td>Crepitations</td>
<td>84.3</td>
</tr>
<tr>
<td>Difficulties in breathing</td>
<td>77.1</td>
</tr>
<tr>
<td>Chest-wall indrawing</td>
<td>42.9</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>21.4</td>
</tr>
<tr>
<td>Feeding problems</td>
<td>15.7</td>
</tr>
<tr>
<td>History of convulsion</td>
<td>4.3</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>3</td>
</tr>
</tbody>
</table>

* Respiratory rate \( \geq 40 \) breaths/minute.

The commonest primary diagnosis in the medical file among the patients included in the study was severe pneumonia, followed by non-severe pneumonia and malaria. Only 1 was primarily diagnosed in the medical file having very severe pneumonia. When applying WHO’s definition of clinical diagnosis of pneumonia and severity assessment in children aged \( \geq 12 \) months, the 140 cases would have been diagnosed as shown in figure I. Seventeen (12.1%) patients had a positive malaria slide and were therefore considered having coexisting pneumonia and malaria; with similar distribution within the different severity groups.
Figure 1. Diagnosis according to WHO: s definition of clinical diagnosis of pneumonia and severity assessment in children aged ≥12 months in 209 children aged 1-9 years treated for pneumonia at KCMC between June 2010 and July 2011.

Seventy-five (53.6%) were boys and 65 (46.4%) girls. The mean age in months was 35, median 21. Distribution of gender and age are shown in figure II.

Figure II. Age and sex distribution among children aged 1-9 years treated for pneumonia at KCMC between June 2010 and July 2011.

Forty-four (31.4%) of the admissions were relapsing infections. In one case the infection was hospital-acquired. The mean number of nights admitted at the hospital was 7.3, median 6. As shown in figure III, the highest numbers of admissions were in June, March and May 2011, and October 2010. Twenty-nine of the 140 patients included in the study were admitted during June – July 2011 and enrolled in the prospective part of the study.
Investigations
A chest X-ray was performed in 97 (64.3%) patients, 75% were suggestive of pneumonia. In 3 cases pulmonary tuberculosis was also suspected. Blood cultures were taken in 32 patients, the results are shown in table IV. One lumbar puncture was performed, with negative result. There was no data on nasopharyngeal bacterial culture, pleural fluid investigations, serology, urine antigen detection or PCR. There was no difference between boys and girls in the number and results of investigations carried out, except that CXR: s tended to be more frequently carried out among girls than boys (75.4% and 64% respectively). However, this difference was not significant and the percentage of radiologically confirmed pneumonia was similar in boys and girls (75% and 80% respectively).

Table IV. Blood cultures in 32 children aged 1-10 years treated for pneumonia at KCMC between June 2010 and July 2011.

<table>
<thead>
<tr>
<th>Agent</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Aureus</td>
<td>9</td>
</tr>
<tr>
<td>KNS</td>
<td>3</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>3</td>
</tr>
<tr>
<td>SPP</td>
<td>3</td>
</tr>
<tr>
<td>Negative</td>
<td>81</td>
</tr>
</tbody>
</table>

Underlying disease
The underlying diseases among the 140 patients are shown in table V. Nineteen patients were >5 years of age and 15 lacked documentation of weight. Twenty-seven (25.5%) of the remaining 106 <5 years of age patients had malnutrition (weight-for-age <-2 SD). Malnutrition tended to be more common among the cases defined as severe and very severe pneumonia by WHO, however, the difference was not significant. In 96 (68.6%) the patients HIV-status was unknown. Five patients were HIV-positive, of which 3 were diagnosed during admission. Two patients had an HIV-positive mother, but were themselves HIV-negative (“exposed”). In 94 cases the HIV-status of the parents was unknown/not documented.
Table V. Underlying diseases in children aged 1-9 years with relapsing and first-time infections treated for pneumonia between June 2010 and July 2011.

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>Relapsing (N = 44)</th>
<th>First time (N = 96)</th>
<th>All (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>16</td>
<td>2</td>
<td>6.4</td>
</tr>
<tr>
<td>Malnutrition*†</td>
<td>14</td>
<td>7</td>
<td>9.3</td>
</tr>
<tr>
<td>CP + Malnutrition*†</td>
<td>7</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>HIV + Malnutrition*†</td>
<td>5</td>
<td>3</td>
<td>3.6</td>
</tr>
<tr>
<td>CP</td>
<td>2</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>CHD</td>
<td>-</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>CHD + Malnutrition*†</td>
<td>-</td>
<td>-</td>
<td>0.7</td>
</tr>
<tr>
<td>Down’s syndrome + Malnutrition*†</td>
<td>-</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Down's syndrome</td>
<td>-</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>-</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>None</td>
<td>57</td>
<td>72</td>
<td>69.3</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Malaria

Forty-four were diagnosed with clinical malaria in the discharge file: 38 had a malaria slide taken, 17 (45%) were positive. Eleven of the patients with a positive malaria slide had a CXR performed, 8 (73%) were suggestive of pneumonia.

Social/environmental factors

In 122 (87.1%) cases the number of family members at home (including the patient) was documented; in 83 (68%) the household would be considered as ‘crowded’ (≥5 people) - the mean was 5.4. The number of family members is shown in figure IV.

In 22 of the admissions during June 2010-May 2011 the medical file contained information regarding parental smoking; 2 (9%) were reported smoking. In only 1 of the admissions during June-July 2011 the caregiver reported smoking at home.

The results from the questionnaire handed out to the caregivers of the patients enrolled in the study during June-July 2011 are shown in table VI. All the 29 caregivers filling out the questionnaire were women. None of the differences regarding socio-economic status, indoor air pollution and crowding were statistically significant.

Figure IV. Number of family members at home among 122 children aged 1-9 years treated for pneumonia at KCMC between June 2010 and July 2011.

Relapsing infections
Thirty of the boys (40%; 95% CI 29-51) and 14 of the girls (21.5%; CI 11.6-31.5) had a relapsing infection. There was no difference in number of family members at home compared to first-time infections. In none of the relapsing cases were parents reported smoking, however, documentation on parental smoking was low. The case fatality rate was similar among relapsing infections and first-time infections.

An underlying disease was reported in nineteen (43.2%; 95% CI 28.6-57.8) of the relapsing cases and 14 (25%; 95% CI 16.3-33.7) of the first-time infections. None of the differences between relapsing and first-time infections in each of the underlying diseases were significant.

**Table VI.** Information from questionnaires answered by caregivers to 29 children aged 1-9 treated for pneumonia at KCMC during June – July 2011.

<table>
<thead>
<tr>
<th></th>
<th>Relapsing Infections (N = 9)</th>
<th>First time infections (n = 20)</th>
<th>All (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illiteracy</td>
<td>33%</td>
<td>50%</td>
<td>41%</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Urban</td>
<td>67%</td>
<td>53%</td>
<td>55%</td>
</tr>
<tr>
<td>- Rural</td>
<td>33%</td>
<td>47%</td>
<td>45%</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Finished primary school</td>
<td>78%</td>
<td>70%</td>
<td>73%</td>
</tr>
<tr>
<td>- Finished secondary school</td>
<td>11%</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>- University degree</td>
<td>11%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Housewife/unemployed</td>
<td>67%</td>
<td>56%</td>
<td>58%</td>
</tr>
<tr>
<td>- Employed/self-employed</td>
<td>33%</td>
<td>44%</td>
<td>42%</td>
</tr>
<tr>
<td>Similar cases of ARI in the family</td>
<td>44%</td>
<td>10%</td>
<td>22%</td>
</tr>
<tr>
<td>Cooking over open fire indoors, no chimney</td>
<td>44%</td>
<td>45%</td>
<td>48%</td>
</tr>
<tr>
<td>Shared bedroom</td>
<td>33%</td>
<td>36%</td>
<td>33%</td>
</tr>
</tbody>
</table>

**Treatment**

Treatment with antibiotics was given in 137 (97.9%) cases, as shown in table VII. The commonest regime was the combination of ampicilline and gentamycine, followed by single treatment of ampicillin and ceftriaxone respectively. A second-line treatment with antibiotics was given in 39 (27.8%) cases; single treatment with parenteral ceftriaxone was most common, followed by parenteral cloxacilline. There were no significant differences in the choice of antibiotics between the first- or second-line treatment in the cases defined by WHO as non-severe, severe and very severe pneumonia.

Three (2%) patients were given a third-line of parenteral antibiotics. Six (4.3%) patients were treated with oral antibiotics only, all received amoxycilline. Five of these cases were defined as non-severe pneumonia, 1 as severe pneumonia.

Eleven (8%) patients were shifted from parenteral to oral antibiotics during admission and in 74 (53%) cases home treatment with oral antibiotics was prescribed after discharge; single treatment with amoxycilline was most common.

There was no significant difference in treatment between boys and girls.
Table VII. Treatment with parenteral or oral antibiotics in children aged 1-10 years treated for pneumonia between June 2010 and July 2011.

<table>
<thead>
<tr>
<th></th>
<th>n = 137</th>
<th>n = 39</th>
<th>n = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Treatment</td>
<td>2nd Treatment</td>
<td>3rd Treatment</td>
</tr>
<tr>
<td>Ampicilline + Gentamycine iv</td>
<td>54.7%</td>
<td>Ceftriaxone iv</td>
<td>23%</td>
</tr>
<tr>
<td>Ampicilline iv</td>
<td>16.8%</td>
<td>Cloxacilline iv</td>
<td>13%</td>
</tr>
<tr>
<td>Ceftriaxone iv</td>
<td>8.8%</td>
<td>Gentamycine</td>
<td>10%</td>
</tr>
<tr>
<td>Ceftriaxone + Cloxacilline iv</td>
<td>5.8%</td>
<td>Ceftriaxone + Cloxacilline</td>
<td>10%</td>
</tr>
<tr>
<td>Amoxycilline po</td>
<td>4.4%</td>
<td>Amoxycilline po</td>
<td>8%</td>
</tr>
<tr>
<td>Ampicilline + Chloramphenicol iv</td>
<td>3.6%</td>
<td>Cloxacilline + Metronidazole iv</td>
<td>8%</td>
</tr>
<tr>
<td>Chloramphenicol iv</td>
<td>1.5%</td>
<td>Chloramphenicol iv</td>
<td>8%</td>
</tr>
<tr>
<td>Other</td>
<td>4.4%</td>
<td>Other</td>
<td>21%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>Total</td>
<td>100%</td>
</tr>
</tbody>
</table>

Outcome and evaluation of diagnosis
Of the 140 cases were 126 (90%) discharged from the hospital, 10 (7.1%) of the patients died and in 4 cases the outcome could not be established. Two of the patients were still admitted when the study was ended and 8 did not have a discharge file, resulting only 130 patients having a final diagnosis documented in the medical file upon our departure. All of the 130 patients were diagnosed having a lower respiratory tract infection; non-severe pneumonia was most common, followed by severe pneumonia, while only 2 patients were diagnosed with very severe pneumonia. Eight were diagnosed with bronchiolitis in addition to pneumonia, 2 with Pneumocystis jirovecii (both HIV-positive) and 1 with pulmonary tuberculosis. Furthermore, many patients received more than one and sometimes up to four different diagnoses; the most common after non-severe and severe pneumonia was malaria, followed by acute watery diarrhea, septicemia and malnutrition.

As suggested by table VIII, the diagnoses given at KCMC were in many cases considered less severe than according to the diagnosis by WHO’s guidelines. When excluding 13 cases in which the severity of pneumonia was not assessed in the medical file, more patients were diagnosed having non-severe pneumonia at KCMC (67.6%; 95% CI 57.8-77.5%) than would have been according to WHO (40.9%; 95% CI 32.1-49.7), while less patients were diagnosed as severe and very severe pneumonia at KCMC (32.3%; 95% CI 18-46.6) than would have been according to WHO (59.1%; 95% CI 48-70.2%)

As shown in figure V, most patients were between 1-2 years of age. There was no significant difference in severity in relation to the age of the patient, nor between boys and girls. There was no difference in the length of stay between the severity subgroups defined by WHO, nor between boys and girls.
Table VIII. Severity of infection in children aged 1-9 years treated for pneumonia at KCMC between June 2010 and July 2011.

<table>
<thead>
<tr>
<th></th>
<th>According to WHO</th>
<th>Diagnosis in discharge file</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 140</td>
<td>n = 127*</td>
</tr>
<tr>
<td>Non-severe pneumonia</td>
<td>39.3</td>
<td>67.7</td>
</tr>
<tr>
<td>Severe pneumonia</td>
<td>35.7</td>
<td>30.7</td>
</tr>
<tr>
<td>Very severe pneumonia</td>
<td>25</td>
<td>1.6</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Ten of the 140 patients did not have a diagnosis in the discharge file, 2 were only diagnosed with “PCP” and 1 with “TB”; they were therefore excluded when comparing the severity of infection.

Figure V. Severity assessment shown in percent of the 140 children aged 1-9 years treated for pneumonia between June 2010 and July 2011 that met the diagnostics criteria for pneumonia according to WHO’s guidelines.

The fatal cases
Table IX compares the fatal with the non-fatal cases regarding age, gender, crowding, underlying disease and length of stay; none of the differences shown were statistically significant.
There was no information regarding parental smoking among the fatal cases. All had radiologically confirmed pneumonia. Six had a blood culture taken, all with negative results. Six had a malaria slide taken, one was positive. There was no proven difference in the severity of pneumonia as defined by WHO, nor in treatment with antibiotics between the fatal and non-fatal cases.
None of the 10 patients who died were admitted between June – July 2011.
Table IX. The fatal cases compared to the non-fatal among 140 children aged 1-9 years treated for pneumonia at KCMC between June 2010 – July 2011.

<table>
<thead>
<tr>
<th></th>
<th>Fatal N = 10</th>
<th>Non-fatal n = 126</th>
<th>All n = 140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Boys</td>
<td>70%</td>
<td>51.6%</td>
<td>53.6%</td>
</tr>
<tr>
<td>- Girls</td>
<td>30%</td>
<td>48.4%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Age in months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean</td>
<td>23.4</td>
<td>36.3</td>
<td>35</td>
</tr>
<tr>
<td>- Median</td>
<td>14.5</td>
<td>21.5</td>
<td>21</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cerebral palsy</td>
<td>22%</td>
<td>4%</td>
<td>6.4%</td>
</tr>
<tr>
<td>- HIV</td>
<td>10%</td>
<td>4%</td>
<td>3.6%</td>
</tr>
<tr>
<td>- Malnutrition (≤5 years of age) †</td>
<td>78%</td>
<td>16.2%</td>
<td>25.5%</td>
</tr>
<tr>
<td>Family members</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean</td>
<td>6.3</td>
<td>4.8</td>
<td>5.4</td>
</tr>
<tr>
<td>- Median</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>CXR suggestive of pneumonia*</td>
<td>100%</td>
<td>75%</td>
<td>78%</td>
</tr>
<tr>
<td>Length of stay (median days)</td>
<td>1.5</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

*Of performed/documentated  
† Weight-for-age < -2 SD

**DISCUSSION**

**Case fatality**

There were no fatal cases included between June-July 2011. However, the median length of stay among the fatal cases was only 1.5 days and the ward was only attended once every morning Monday-Friday. The cases with a fatal outcome admitted between June 2011 – July 2011 may therefore not have been included. When excluding the 29 patients admitted during this period, the case-fatality rate among the 111 patients admitted between June 2010 – May 2011 would have been 9%, compared to 7.1% among all the 140 patients in the study. A case fatality rate of 9% would imply that approximately 2-3 children would have died between June-July 2011.

In a study in Bangladesh of pneumonia among children aged <5 years hospitalized for pneumonia, the case-fatality rate was 4% (Naheed, Saha et al. 2009), which was similar to 3.2% found in a study in Papua New Guinea (Duke, Wandi et al. 2008). A retrospective study in Fiji of children aged between 1 month and 5 years with LRTI found a case-fatality rate of 2.8% in all children with LRTI, and 6.8% in those with CXR-confirmed pneumonia (Magree, Russell et al. 2005).

The case-fatality rate in the actual study could not be linked to the severity of pneumonia defined by WHO. However, studies in India and Kenya of children aged up to 5 years hospitalized with clinical pneumonia as defined by WHO, found an association between the severity of pneumonia and a higher case fatality rate (Sehgal, Sethi et al. 1997; Berkley, Maitland et al. 2005). The case-fatality rates in the studies were 10.5% and 4% respectively. This was also found in a study in Bangui (Central African Republic) using the WHO algorithm of identifying patients at higher risk of death, however, the ‘very severe disease’ definition did not predict death when used in children who did not also meet the criteria for severe pneumonia (Pepin, Demers et al. 2001). As previously shown in table I, a child must...
not fulfill the definition of severe pneumonia to be considered having very severe pneumonia according to WHO.
The length of stay seemed to be shorter among the fatal cases, which may be associated with late care seeking. As mentioned earlier, late care seeking is a risk factor for fatal pneumonia, however, due to the low number of fatal cases no conclusions could be drawn.

**Underlying/concomitant disease**
An underlying disease tended to be more common among the relapsing infections. However, 7 of the 19 relapsing cases with an underlying disease had asthma, sometimes difficult to differentiate from pneumonia, which could have created a “false” correlation.

**Malnutrition**
Malnutrition has been identified as a significant and independent risk factor of death from pneumonia (Naheed, Saha et al. 2009) (Sehgal, Sethi et al. 1997). Although malnutrition tended to be higher among the fatal than the non-fatal cases admitted June 2010 – May 2011, this could not be verified statistically, probably due to the low number of fatal cases. Furthermore, malnutrition could not be linked to the severity of pneumonia, nor with relapsing infection. Twenty-five percent of the patients had malnutrition, which can be compared to results from a demographic and health survey carried out in Tanzania in 2010, where the percentage of children aged 12-59 months with a weight-for-age Z-score <2SD ranged from 16-20.5% (National Bureau of Statistics Dar es Salaam 2011). This might indicate that malnutrition was a risk factor for acquiring pneumonia in this study, however, the difference was small. A control group would have been useful to assess this relationship.

**Malaria**
Forty-four patients were diagnosed having malaria in the discharge file. Although the possibility that children with pneumonia may have coexisting malaria has been recognized (O'Dempsey, McArdle et al. 1993), a clinical overlap has been suggested; two studies in Gambia and Malawi found that many children with malaria satisfied the WHO criteria of pneumonia but had no other clinical or radiological evidence of an ALRI (Acute lower respiratory tract infection) (Redd, Bloland et al. 1992; O'Dempsey, McArdle et al. 1993). This may indicate that some patients in the actual study were diagnosed having pneumonia according to WHO, when in fact they only had malaria. However, of the patients diagnosed with malaria, only 39% had a positive malaria slide, which instead could suggest an over-diagnosis of malaria. A study in north-east Tanzania found that malaria is commonly overdiagnosed in adults and children presenting with severe febrile illness, especially in those living in areas with low to moderate transmission (Reyburn, Mbatia et al. 2004). However, 82% and 73% of performed CXRs among the patients diagnosed with malaria and the patients with a positive malaria slide respectively, were suggestive of pneumonia; similar to 77% of performed CXRs among all the 140 patients in the study.

**HIV:**
Only 6 patients were HIV-positive in the study and HIV-infection was neither associated with severity, nor a fatal outcome. Many patients were not tested for HIV and the HIV-status of the parents was often not documented, however, the reason for this might simply have been a low suspicion of HIV-infection.
Social/environmental factors
Although most of the households in Tanzania use solid fuel for cooking (National Bureau of Statistics Dar es Salaam 2011), due to the low number of patients admitted between June-July 2011 in our study, cooking food over an open fire indoors without a chimney could not be evaluated as a risk factor for acquiring pneumonia and a higher case-fatality. Only one of the caregivers to the patients admitted June-July 2011 reported smoking at home, and the documentation of parental smoking was too low among the patients admitted between June 2010 – May 2011 to draw any conclusion of the impact of parental smoking on the incidence and case-fatality of pneumonia.
Crowding, defined as ≥5 people per household, seemed to be common. However, the mean number of family members in Tanzania is 4.9 (National Bureau of Statistics Dar es Salaam 2011), which is only slightly less than 5.4 in this study. It is therefore difficult to evaluate crowding as a risk factor for pneumonia in this study.
Seventy-three percent of the caregivers of the patients admitted June-July 2011 had finished primary school, which was somewhat higher compared to 57.1% in the region (National Bureau of Statistics Dar es Salaam 2011). However, the literacy rate was only 61% in our study, which is slightly lower than the 73% in Tanzania as a whole (National Bureau of Statistics Dar es Salaam 2011).
The level of employment was 42% among the caregivers of the patients admitted June-July 2011, which is lower than the 56.1% among women in northern Tanzania and the 71.6% in the Kilimanjaro region (National Bureau of Statistics Dar es Salaam 2011). The reason for this might be that unemployed family members are more likely to be able to accompany the ill child to the hospital and remain during the daytime when the ward was visited. Furthermore, since the relationship to the patient was not inquired, in many cases the adult present might not have been the mother of the child.

Information about socioeconomic status, indoor air-pollution etc. was not regularly documented in the medical files, and the importance of these factors for disease development could therefore not be assessed in the patients admitted June 2010 – May 2011. Since only a few of the relapsing infections and none of the fatal cases were admitted between June 2011 – July 2011, the possibility of an association with a higher risk of relapsing infection and death from pneumonia could not be evaluated.

Diagnostics - WHO case management
Of the 209 patients originally considered for the study, 101 (73.2% of performed) had radiologically confirmed pneumonia. The clinical definition of pneumonia by WHO only identified 75 (74.3%) of these patients, which raises questions about the accuracy of these guidelines when diagnosing children with symptoms of ALRI.
Studies have found the fast breathing-criteria as defined by WHO, to detect about 85% of children with pneumonia and to have specificity around 80% (Simoes, Cherian et al. 2006). A study in Mexico of children with radiologically confirmed pneumonia found that tachypnea used as the only clinical sign is useful for identifying pneumonia in children, with no significant variations for age (Palafox, Guiscafre et al. 2000). However, during the first three days of disease, the sensitivity, specificity, and percentage of correct classification were significantly lower. Furthermore, in children with low weight for age, tachypnea had higher sensitivity, but lower specificity.
A Gambian study in an outpatient clinic found that fast breathing defined by WHO as ≥40 breaths per minute in children aged 1-5 years, predicted pneumonia equally well in malnourished as well-nourished children. However, the respiratory rate cut-off required should be about 5 breaths per minute less in malnourished children to achieve similar
sensitivity and specificity as in well-nourished children (Falade, Tschappeler et al. 1995). Furthermore, lower chest wall indrawing was less common among malnourished children, and suggested being a less sensitive predictor of pneumonia in malnourished children. Pneumonia was defined as radiological pneumonia or probable radiological pneumonia associated with crackles on auscultation.

In the actual study malnutrition based on weight for age could be assessed in 46 of the 69 patients that did not meet WHO's clinical definition of pneumonia and thereby were excluded from the study; when adjusting the threshold for fast breathing from 40 to 35 breaths/minute only 2 with malnutrition would have been considered having pneumonia.

A study in the UK investigating which symptoms and clinical features that identified serious respiratory infection in children aged between 3 months and 12 years, found that tachypnea offered little discriminatory value, whereas tachycardia and decreased oxygen saturations were better predictors of serious respiratory infection (Blacklock, Mayon-White et al. 2011). Respiratory distress was the best predictor.

Radiographic confirmation of pneumonia is a subject for debate. It is commonly used in scientific studies as a golden standard (Harris, Clark et al. 2011), but the value in diagnostics within the clinical practice is questioned. There is a poor relationship between clinical pneumonia and X-ray findings, a low concordance between viewers and an inability to determine the etiology based on radiographic findings (Harris, Clark et al. 2011). It should not be used as a routine investigation in children suspected to have pneumonia (Bourayou, Zenkhri et al. 2011).

In a study from Pakistan of 1848 X-rays taken in children aged 2-59 months diagnosed with non-severe pneumonia using the WHO case definition, 82% were normal (Hazir, Nisar et al. 2006). Furthermore, of those with radiographic evidence of pneumonia, 96% had fever, 99% cough and 89% had difficulties in breathing. Of those without radiographic evidence of pneumonia, 94% had fever, 99% had cough and 91% had DIB (Hazir, Nisar et al. 2006), which indicates a poor agreement between clinical signs and chest radiographs. However, a study in Canada in children 1-16 years found that patients with focal infiltrates were more likely to have a history of fever, tachypnea, tachycardia, retractions, grunting, or auscultatory findings suggestive of pneumonia (Lynch, Platt et al. 2004).

**Treatment and severity of pneumonia**

Although many cases of pneumonia were considered less severe at KCMC than according to the clinical definition and severity assessment of childhood pneumonia by WHO, non-severe pneumonia was the most common diagnosis, followed by severe pneumonia. The commonest treatment with antibiotics in the different severity subgroups was the combination of parenteral ampicilline and gentamycine, and in only a few cases oral antibiotics was the first-line treatment.

A Cochrane review of antibiotics in childhood pneumonia from 2010 suggests that in children hospitalized with severe CAP without hypoxia, treatment with oral amoxicillin has the same cure rate as parenteral penicillin and may be an alternative (Kabra, Lodha et al. 2010). The studies included mostly used the case definition of pneumonia given by the WHO, and were mainly from low-income countries with age groups below five years. Although hypoxemia was not examined in the actual study, this may imply a use of parenteral antibiotics with an unnecessary broad antimicrobial coverage in children treated for non-severe and severe pneumonia at KCMC.

KCMC is a referral hospital where many patients already have received medical care at local clinics prior to admission. Treatment failure with oral antibiotics prior to admission at KCMC, and the lack of identification of causing pathogens and their antimicrobial resistance pattern.
due to the low yield of blood cultures etc., may therefore affect the choice of antimicrobial treatment, with a stronger tendency towards broad-spectrum parenteral antibiotics.

The spread of isolates of bacteria such as pneumococci and S. aureus with decreased susceptibility to several antibiotics compromising effective therapy is a universal problem (Willems, Hanage et al. 2011). Some in vitro tests have shown resistance to co-trimoxazole in more than 50 percent of respiratory isolates of S. pneumoniae and H. Influenza, and pneumococcal resistance to penicillin is increasing worldwide (Simoes, Cherian et al. 2006) as well as macrolide resistance (Harris, Clark et al. 2011). The consumption of antibiotics, both in the population and in the individual, has been associated with nasopharyngeal carriage of penicillin-resistant pneumococci in children (Arason, Kristinsson et al. 1996). Resistance is more common among isolates from carriage and non-invasive disease compared to invasive disease (Backhaus 2012).

The impact of antimicrobial resistance on the clinical outcome in children with pneumonia is not clear. One study in the US of pneumococcal pneumonia and one study in South Africa of bacteremic pneumococcal infections showed no difference in outcome between penicillin-resistant and penicillin-susceptible infections treated with beta-lactam antibiotics (Friedland 1995; Tan, Mason et al. 1998). Although increased macrolide use is associated with pneumococcal resistance (Dias and Canica 2008), resistance and treatment failure has not yet been demonstrated in children (Harris, Clark et al. 2011).

Antibiotic treatment in children with fast breathing has been shown to reduce mortality (Sazawal and Black 2003). However, the low specificity of the fast breathing criterion as mentioned earlier, may result in an overuse of antibiotics (Simoes, Cherian et al. 2006) and consequently stimulate an unnecessary development of antimicrobial resistance in bacteria causing pneumonia.

Girls and boys

Although relapsing infections tended to be more common among boys, there were no significant differences in treatment, investigations carried out, severity of pneumonia, risk factors for pneumonia or case fatality between boys and girls.

Vaccine

The national vaccine program in Tanzania includes BCG, DPT (diphtheria, pertussis and tetanus), measles and since 2009 Hib, but not a PCV. An introduction of a PCV could lead to a substantial reduction of childhood pneumococcal disease in Tanzania. However, before implementing a PCV in the national vaccine program, which serotypes to include in such a vaccine is an important question. Natural occurring differences in serotype carriage and disease burden between Tanzania and countries, such as the US, where the PCV has been introduced need to be considered. Furthermore, the prevalence of underlying diseases with immunocompromising effects, such as malnutrition and HIV, could affect the efficacy of a vaccine. Even if the important serotypes responsible for pneumococcal disease in the region were to be covered, other serotypes with a low disease capacity in healthy children might be able to cause opportunistic infections in immunocompromised children.

Two double-blind placebo controlled randomized trials of a nine-valent conjugate vaccines (PCV-9) were performed among children younger than one year in Soweto and Gambia respectively. The study from Soweto showed a reduction of radiologically confirmed pneumonia, and the incidence of vaccine-serotype and antibiotic-resistant IPD was reduced both among HIV-negative and HIV-positive children (Klugman, Madhi et al. 2003). The Gambian study also showed efficacy against radiologically confirmed pneumonia,
furthermore, a significant efficacy against all-cause admissions and all-cause mortality was found (Cutts, Zaman et al. 2005).

The effect of malnutrition on the efficacy of available PCV: s has yet not been thoroughly investigated.

Following the success with the introduction of PCV-7 in USA and other countries, concerns have been raised about the change in clonal distribution among both carried and invasive pneumococcal strains following the introduction of the vaccine. Serotype replacement is known to have occurred, with a substantial decrease of vaccine serotypes from carriage and the replacement with non-vaccine serotypes (Singleton, Hennessy et al. 2007; Hanage 2008). This is likely due to the possibility for non-vaccine types to expand in an ecological niche previously occupied by vaccine types. The spread of resistant clones promoted by antibiotic pressure may also have influenced the serotype distribution (Black 2008).

The incidence of pneumococcal disease caused by non-vaccine serotypes is increasing (Hicks, Harrison et al. 2007). However, to evaluate the effects of serotype replacement it is important to compare the increase of IPD caused by NVTs to the decrease in vaccine type IPD. A study in the US seven years after the introduction of the PCV-7 found a dramatic reduction in the overall IPD incidence, and although IPD rates caused by non-PCV7 serotypes had increased, they remained low relative to decreases in PCV7-type IPD (Pilishvili, Lexau et al. 2010). The demonstration of replacement invasive pneumococcal disease emphasizes the importance of ongoing surveillance and development of expanded valency vaccines.

CONCLUSIONS

Our main findings and conclusion were:

- There were no risk factors significantly associated with the severity of pneumonia or case fatality. However, malnutrition tended to more common among cases of severe and very pneumonia than non-severe pneumonia, and among the fatal than the non-fatal cases.

- The clinical definition and severity assessment of pneumonia in children aged >1 years only identified about 75% of the patients with radiologically confirmed pneumonia.

- Cases of pneumonia were often considered less severe in the medical files than according to the clinical definition and severity assessment of childhood pneumonia by WHO.

- Underlying diseases tended to be more common among relapsing cases than first-time infections. Relapsing infections tended to be more common among boys.

Limitations/improvements

Patients considered for the study were either patients with pneumonia as a working diagnosis during admission or being diagnosed with pneumonia in the discharge file. In many cases the patients received more than one diagnosis in the discharge file, where pneumonia sometimes was the third or the fourth diagnosis, and often without confirmation by CXR or blood culture etc. Furthermore, the selection of patients was based on the signs and symptoms documented in the medical files upon admission. Hence, the initial clinical judgment was made by several
different clinicians, in many cases medical students. Together, this might have created arbitrariness in the selection and assessment of the patients in the study. Due to the low number of patients included in the prospective study and the lacking of documentation of this in the medical files, there was little data gathered about socio-economic status and risk factors such as indoor air pollution. Furthermore, a control group would have been useful in order to draw any conclusion about these factors. When investigating socio-economic status, it would have been useful to inquire if the family owned a car, if there was electricity and a radio in the household etc. instead of only asking about the level of education and employment, literacy etc. Hypoxemia could have been very useful to examine in our study to more properly assess the severity of respiratory infection. However, the pulse-oximetre that was brought malfunctioned. To better evaluate the risk factors investigated, it would have been useful to examine other key risk factors for the incidence and mortality of pneumonia, such as non-exclusive breastfeeding the first months of life and low birth weight. There were few microbiological examinations performed in the patients, which could have helped to better evaluate the diagnosis and establishing the etiology of the infections. Vaccine-coverage would also been vital information, which many of the medical files lacked documentation of. Furthermore, the answers to the questions regarding this in the questionnaire were inconclusive; probably because the caregivers lacked knowledge thereof or because they did not understand the questions. Treatment with antibiotics before admission at KCMC should have been documented to better evaluate the treatment given at KCMC and the severity of infection.

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References


Lunginflammation bland barn i Moshi, Tanzania

I vår studie studerades lunginflammation enligt WHO:s definition bland barn mellan ett till nio år. Följande slutsatser kunde dras:
* Ingen ökad risk för insjuknande och dödlighet i lunginflammation kunde associeras med trångboddhet, förorenad luft i hemmiljön, socio-ekonomiskt status eller underliggande sjukdomar.
* Blåna patienter med återkommande lunginflammation verkade fler vara pojkar än flickor. Förekomsten av en underliggande sjukdom, som t.ex. undernäring eller ett medfött hjärtfel, verkade även vara vanligare bland dessa.
* Barnen ansågs ofta ha en lindrigare grad av lunginflammation i patientjournalerna jämfört med diagnostiken enligt kriterier uppsatta av WHO.
* De flesta av patienterna i studien var mellan ett och två år gamla, vilket är en ålder då kroppens immunförsvar fortfarande utvecklas mycket och man ännu inte förväntar den motståndskraft mot många bakterier och virus som äldre personer har. Införandet av nya vaccin bland barn i Tanzania har en potential att dramatiskt minska sjukdomsbördan och dödsheten i lunginflammation i landet.

Varje år dör omkring 1,6 miljoner barn under fem år i världen i lunginflammation. Merparten av dessa dödsfall sker i Afrika och regioner i Sydostasien. Lunginflammation definieras som en infektion i lungvävnaden och orsakas av antingen virus, bakterier, parasiter eller svampar. Vanliga symptom är hosta och en snabbare andning. Vilken typ av mikroorganism som orsakar infektionen är viktigt information eftersom det är avgörande för behandlingen: t.ex. kan antibiotika vara mycket effektivt mot bakterier, medan det är verkningslöst mot virus. Ett växande problem i världen är en ökande förvärvad motståndskraft hos flera bakteriearter mot vissa typer av antibiotika. Detta beror till stor del beror på en överbehandling med antibiotika i fall där det är onödigt eller verkningslöst, såsom en vanlig förkylning. Vidare behandlas många infektioner med antibiotika som har en onödigt bred täckning och därmed en effekt på flera andra bakterier i kroppen som inte är orsaken till sjukdomen.

Kunskapen om vilka mikroorganismer som orsakar lunginflammation är även viktigt ur ett samhällsperspektiv, eftersom det påverkar vilka preventiva åtgärder som är lämpliga, såsom specifika vaccin. Införandet av vaccin i flera länder har dramatiskt minsatt sjukdomsbördan av vissa virus och bakterier och därmed minskat den totala dödsheten i lunginflammation i dessa länder. Det är därför en mycket viktig uppgift att introducera tillgängliga vaccin i länder som dödsheten i lunginflammation är som störst.

Det finns flera olika riskfaktorer för att insjukna i lunginflammation, viktiga är t.ex. undernäring, förorenad luft i hemmiljön, lägt socioekonomiskt status och trångboddhet. Förekomsten av andra underliggande sjukdomar, som t.ex. HIV, kan negativt påverka kroppens immunförsvar och därmed öka risken för att insjukna och dö i lunginflammation. HIV-epidemin har på senare tid starkt bidragit till att öka antal fall av lunginflammation och dödsheten i fattiga länder, framför allt i Afrika söder om Sahara.

Studien genomfördes sommaren 2011 på The Kilimanjaro Christian Medical Center (KCMC) i Moshi, Tanzania. Deltagarna var alla inlagda med misstänkt lunginflammation på sjukhuset. Studien var delad i två delar: en del gick ut på att studera patientjournaler till de barn som behandlats för lunginflammation på KCMC ett år bakåt i tiden, en annan del omfattade de barn som vårdades under juni-juli 2011. I den senare gruppen svarade även den närvarande föräldern/vårdföreningen på ett formulär efterfrågandes information om ett par riskfaktorer, såsom socioekonomiskt status,
trångboddhet, vaccination etc. De patienter som inkluderades i studien skulle alla uppfylla kriterierna för lunginflammation hos barn definierade av Världshälsorganisationen (WHO).