Beyond fever

Managing children with pneumonia symptoms in malaria endemic Uganda

Helena Hildenwall
Cover photography: father in Iganga/Mayuge Demographic Surveillance Site is taking his febrile infant, carried by an older sibling, for care
To
Jakob & Vera
with love
ABSTRACT

Background: Pneumonia is one of the leading killers of children under five years of age. In sub-Saharan Africa, symptoms of pneumonia often overlap with those of malaria. While many countries have made public commitments to improve malaria management, similar efforts for pneumonia are lacking. The overlap of symptoms between pneumonia and malaria, in combination with more efforts for appropriate malaria management, raises worries that pneumonia cases are being mismanaged. More information is needed on how caretakers and health workers respond to children with pneumonia symptoms.

Main objective: To explore caretakers’ and health care providers’ understanding and response to children with symptoms of pneumonia in order to identify issues that need to be addressed for improved management of children with acute febrile illness.

Methods: A triangulation of a qualitative community study with mothers, traditional healers and health workers (I), two hospital based studies with structured interviews with caretakers of children with symptoms or diagnosis of severe pneumonia (II, IV) and a mixed qualitative-quantitative community study with verbal and social autopsies with caretakers of children deceased in acute febrile illness (III) was done. To compare stated drug use with blood drug concentrations, blood samples were collected on filter papers (IV). Qualitative interviews were analyzed using content analysis (I, III). Blood drug concentrations of sulfamethoxazole, chloroquine and sulfadoxine were analyzed using high performance liquid chromatography methods (IV).

Results: Many terminologies were used to refer to symptoms of pneumonia (I). Mothers tended to interpret any febrile condition as malaria and stated differing preferred care-seeking actions for difficult/rapid breathing in their children (I). Severe pneumonia developed two days after first recognition of difficult/rapid breathing (II). Half of the children diagnosed with severe pneumonia had seen another health care provider prior to arrival at a hospital (II). Barriers to adequate management of a child with fatal acute febrile illness (III) included: “Illness interpretation barriers”- when care was delayed or inappropriate due to caretakers’ interpretation of illness; “Barriers to seeking care” involving gender roles and household financial constraints; and “Barriers to receiving adequate treatment” revealing caretakers’ discontents with providers and possible deficiencies in quality of care. Positive and negative predictive values for caretakers’ reports of drug intake for the child’s acute illness were 67% and 64% for sulfamethoxazole, 69% and 52% for chloroquine and 85% and 62% for sulfadoxine, respectively (IV). Many caretakers could not name the drug given to the child, and more so if treated in a health facility than in the home (RR 2.6 (1.2-5.6)) (IV).

Discussion: There is a need to find ways to encourage caretakers to seek immediate and appropriate care after recognition of key pneumonia symptoms. Ideally, adequate antibiotic treatment should be provided close to where people live and one option is to allow community health workers to diagnose and treat pneumonia in addition to malaria. Quality of care must be improved in the whole health care chain, public as well as private. Health care providers need to be aware of key pneumonia symptoms, appropriate biomedical treatment for these symptoms, and the common co-existence of pneumonia and malaria symptoms.

Key words: pneumonia, malaria, Uganda, healthcare seeking behavior, drug utilization
LIST OF PUBLICATIONS


These papers will be referred to in the text by their roman numerals (I-IV).
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LIST OF ABBREVIATIONS

AB  Antibacterial drug
ACT  Artemisinin-based Combination Therapy
AM  Antimalarial drug
ARI  Acute Respiratory Infection
CHW  Community Health Worker
CQ  Chloroquine
CV  Coefficient of Variation
DRB  Difficult and/or Rapid Breathing
DSA  Demographic Surveillance Area
DSS  Demographic Surveillance Site
FGD  Focus Group Discussion
GAVI  Global Alliance for Vaccines and Immunizations
HBMF  Home Based Management of Fever
HC  Health Center
Hib  Haemophilus Influenza type b
HIV  Human Immunodeficiency Virus
HPLC  High Performance Liquid Chromatography
HSD  Health Sub-District
IDI  In-depth Interview
IMCI  Integrated Management of Childhood Illness
ITN  Insecticide Treated Net
KI  Key Informant Interview
MAFF  Malaria Attributable Fraction of Fever
MOH  Ministry of Health
NGO  Non Governmental Organization
NPV  Negative Predictive Value
OR  Odds Ratio
PPV  Positive Predictive Value
PACU  Pediatric Acute Care Unit
RBM  Roll Back Malaria
RDT  Rapid Diagnostic Test
RS  Respiratory Syncytial (Virus)
RR  Risk Ratio
SA  Social Autopsy Interview
SP  Sulfadoxine-Pyrimethamine
SSA  Sub-Saharan Africa
U5  Children under five years of age
UNICEF  United Nations Children's Fund
USD  American dollars
VA  Verbal Autopsy Interview
VASA  Verbal and Social Autopsy Interview
WHO  World Health Organization
1. BACKGROUND

Almost 10 million children under the age of five died in 2006, half of them in sub-Saharan Africa where the under-five mortality rate remains at 160/1000 live births (UNICEF, 2007). Declines in child mortality are far too slow to reach the fourth Millennium Development Goal to reduce under five mortality by two thirds between 1990 and 2015 (Murray, et al., 2007). After the neonatal period, the main causes of death in sub-Saharan Africa are pneumonia and malaria - both manifesting as acute febrile illness. Antibiotics and antimalarials that are neither very expensive nor very difficult to administer have existed for many years, still the consequences of pneumonia and malaria remain devastating for many families in low income countries. How can this be? How can these rather easily curable diseases take the lives of millions of children every year?

From what is known, the answer is multifaceted. A major decrease in pneumonia and malaria morbidity and mortality occurs when living conditions improve (Mulholland, 2007). A number of preventive measures have been identified. However, once ill, the time it takes for the illness to become too severe to successfully be addressed by any treatment regimen is crucial for intervention. If recovery is to take place, a chain of actions must happen before the critical time period is over; the caretakers must recognize the illness and correctly interpret that the child needs care, then they must have the ability to make the decision to seek and reach a source of adequate care, appropriate care must be available and given at the place where care is sought and the patient must comply to the treatment given. While the care-seeking chain may be quite straightforward in a high income country, caretakers in a low income country are many times confronted with serious barriers when caring for a sick child.

In low and middle income countries, weak health systems are impeding the implementation of major global initiatives for health (Travis, et al., 2004). In the absence of appropriate diagnostic tools, management of childhood illnesses is presumptive and symptom-based under WHO/UNICEF’s Integrated Management of Childhood Illness (IMCI). In these guidelines, fever alone defines malaria while cough and/or difficult breathing with an increased respiratory rate is classified as pneumonia (WHO/UNICEF, 2008). However, overlap between these symptoms is common (Kallander, et al., 2004) and children with overlapping symptoms need to be treated with both antimalarials and antibiotics. Yet many children receive mono-therapy.

While appropriate management of malaria has been encouraged through public commitments by heads of state, community case management programs and the guideline that malaria treatment should be initiated within 24 hours (RBM/WHO, 2000), no similar public commitments for improved management of pneumonia have been made. This has raised concerns that causes of fever beyond malaria are being over-looked when caring for a sick child. This thesis is an attempt to investigate this concern and to understand the difficulties surrounding management of children with symptoms of pneumonia - the forgotten killer of children (UNICEF/WHO, 2006).
1.1 Childhood fevers in sub-Saharan Africa
When a child becomes sick, s/he presents with symptoms rather than diagnoses. Fever is the common presentation of all major child killers in sub-Saharan Africa. While a wide range of mild to severe infectious diseases may present with fever, the most important diseases in terms of childhood mortality are pneumonia, malaria, diarrhea, measles and meningitis. Depending on environmental and socioeconomic circumstances, the burden of disease varies between countries in sub-Saharan Africa. Malaria is thought to be responsible for 6-26% of deaths, diarrhea for 17-26% and pneumonia for 17-26% of deaths among children less than five years. The remaining deaths are due to neonatal disease and HIV/AIDS. Malnutrition as an underlying cause is associated with 53% of all childhood deaths (Black, et al., 2003).

While malaria is commonly the prime suspect in childhood fevers in large parts of sub-Saharan Africa, the malaria attributable fraction of fever (MAFF) is highly variable between 40-97% in under-fives in rural settings (Bejon, et al., 2007) and 0-12% in febrile children in cities (Wang, et al., 2005). The MAFF is highly dependant on transmission intensity and therefore varies greatly between age groups, seasons, altitude and location. In a study from the Ugandan capital Kampala, malaria was responsible for 32% of fever episodes in children between one month and ten years of age (Njama-Meya, et al., 2007). The problem of using fever as a proxy for malaria was highlighted in a review of accuracy of malaria diagnoses where the percentage with a negative blood film among subjects with clinically diagnosed malaria illness ranged from 32-92% (Amexo, et al., 2004). Considering that a child in sub-Saharan Africa may suffer from seven febrile illness episodes every year (Sulo, et al., 2002), the extent of misdiagnosis is potentially enormous if all fevers are treated as malaria alone.

1.2 Pneumonia and malaria – definitions and etiologies

**Pneumonia** is a Lower Acute Respiratory Infection which manifests itself as an inflammation of the lung parenchyma with abnormal alveolar filling with fluid. Recent estimates show that children in low income countries suffer from 0.29 clinical episodes of pneumonia per child-year, compared to 0.05 episodes in high income countries (Rudan, et al., 2008).

Pneumonia is suspected in a patient with cough and difficult breathing with an increased respiratory rate. These symptoms are what usually guide initiation of treatment in low income countries. Other common symptoms of pneumonia include chest pain, chills, and fever. Symptoms vary widely in infants and older people in whom fever and chest pain may be absent. Auscultation of the lungs may guide diagnosis as well as an X-ray of the lungs. For diagnosis, sputum and blood is sampled for specimen cultures in an attempt to identify the organism causing pneumonia. Both X-ray and specimen cultures have low sensitivity for pneumonia diagnosis but are commonly used in high income settings in attempts to confirm pneumonia diagnosis.

In this thesis, difficult and rapid breathing are referred to as pneumonia symptoms as reported by caretakers (Table 1). Since difficult breathing may be used by caretakers to include also an increased respiratory rate, and since caretakers may not be sure about the respiratory frequency, we cluster difficult and/or rapid breathing (DRB) as the operational term for caretakers’ reports of pneumonia symptoms. Pneumonia diagnosis
could be further classified as diagnosed by actual counting of respiratory rate and by clinical diagnosis by a trained physician with chest radiography showing pneumonic consolidations (Table 1).

Pneumonia can be caused by infection from virus, bacteria, fungi or parasites as well as chemical injury to the lungs (chemical pneumonia). In children under the age of five, the most commonly described pathogens are respiratory syncytial (RS) virus, adenovirus, *Haemophilus influenza* and *Streptococcus Pneumoniae*. A virus infection in the respiratory tract may predispose to secondary bacterial infections in the lungs (Jakab, 1977). It is estimated that viruses causes 11-36% of lower respiratory tract infections in low income countries (Weber, et al., 1998) while *S. pneumoniae* have been identified in 30-50% of pneumonia cases, and *H. influenza* in 10-30% of cases (Rudan, et al., 2008). The latter two causative agents, being bacteria, can be managed with antibiotic treatment.

*Streptococcus pneumoniae* is a Gram-positive diplococcus bacterium which frequently resides in the human respiratory tract without causing illness (asymptomatic carriage). Most isolates of *S. pneumoniae* are surrounded by a capsular polysaccharide, which increases the virulence of the bacteria. Up until now, 91 different capsular serotypes of *S. pneumoniae* have been described (Park, et al., 2007), conferring different levels of virulence. Ongoing research to describe the global serotype distribution indicates that seven serotypes are responsible for 66-76% of invasive pneumococcal disease in all regions of the world (1, 5, 6A, 6B, 14, 19F, 23F) (Johnson, et al., 2008). However, serotype distribution remains unknown for most parts of Africa.

*Haemophilus influenza*, also called Pfeiffer’s Bacillus, is a Gram-negative coccobacillus bacterium that exists in encapsulated, unencapsulated, and non-typable, forms. There are six distinct capsular types labeled a-f, with type b (Hib) causing the vast majority of cases of serious *H. influenza* infections. Hib enters the body through the upper respiratory tract and colonizes the pharyngeal mucosa. Asymptomatic carriage is common (Murray, et al., 1998).

*Malaria* is commonly suspected in any fever occurring in a region of malaria transmission, and presumptive treatment is given for fever in absence of diagnostic equipment. However, for diagnosis, malaria parasites should be present in the blood of the patient. This can be checked by microscopy of blood films or by a malaria rapid diagnostic test (RDT) (Hopkins, et al., 2008). Due to the frequent existence of asymptomatic carriage of parasites in semi-immune populations, attempts have been made in various settings to define a parasite count cut-off for malaria diagnosis (Dicko, et al., 2005, Rogier, et al., 1996, Rougemont, et al., 1991).

In this thesis, the terms malaria symptoms or IMCI malaria are used for presumptive diagnosis of malaria by observing fever (Table 1).

Malaria in humans is caused by four different species of intraerythrocytic protozoa of the genus *Plasmodium*. These parasites are transmitted by the bite of an infective female *Anopheles* species mosquito. *Plasmodium falciparum* is the most dangerous form of malaria, accounting for around 90% of all malaria deaths. At the end of 2004,
some 3.2 billion people lived in areas at risk for malaria transmission. At least one million deaths occur among the 350 to 500 million clinical episodes of malaria every year. Children, HIV-infected and pregnant women are at highest risk for illness and death. About 60% of the cases of malaria worldwide and more than 80% of the malaria deaths worldwide occur in sub-Saharan Africa (WHO, 2005b).

Table 1: The definitions of pneumonia and malaria in this thesis and their explanations

<table>
<thead>
<tr>
<th>Definition</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia symptom</td>
<td>Difficult and/or rapid breathing as per caretakers’ reports</td>
</tr>
<tr>
<td>IMCI pneumonia</td>
<td>Cough and/or difficult breathing with an increased respiratory rate as per health workers’ assessment</td>
</tr>
<tr>
<td>IMCI severe pneumonia</td>
<td>Cough and/or difficult breathing with IMCI danger signs, chest indrawings or stridor in calm child as per health workers’ assessment</td>
</tr>
<tr>
<td>X-ray pneumonia</td>
<td>Cough and/or difficult breathing with an increased respiratory rate and pneumonic consolidation on X-ray</td>
</tr>
<tr>
<td>X-ray verified severe pneumonia</td>
<td>Cough and/or difficult breathing with chest indrawings or stridor in calm child and pneumonic consolidations on chest radiography</td>
</tr>
<tr>
<td>X-ray verified very severe pneumonia</td>
<td>Cough and/or difficult breathing with chest indrawings or stridor in calm child and pneumonic consolidation on chest radiography and central cyanosis or inability to drink</td>
</tr>
<tr>
<td>Malaria symptoms</td>
<td>Fever as per caretakers’ report</td>
</tr>
<tr>
<td>IMCI malaria</td>
<td>Fever as per health workers’ report</td>
</tr>
<tr>
<td>Malaria</td>
<td>Fever and presence of malaria parasites in blood/positive Rapid Diagnostic Test</td>
</tr>
</tbody>
</table>

Overlap between pneumonia and malaria

Due to lack of diagnostic equipment in many settings in low and middle income countries, children are commonly treated presumptively depending on the symptom presentation. Thus, a febrile child should be treated as having malaria and a child with cough or difficult breathing with an increased respiratory rate should be treated as having pneumonia. However, malaria may also present with rapid and deep breathing, i.e. respiratory distress due to acidosis (English, et al., 1996b), and fever is common in a child with pneumonia. Depending on the setting, studies indicate that 37-80% of children under the age of five meeting the clinical case definition of malaria also meet the pneumonia definition, and that 93-99% of those meeting the clinical case definition of pneumonia also meet the definition of malaria (English, et al., 1996a, Kallander, et al., 2004). Similar overlaps have also been documented at the community level (Kallander, et al., 2005). The co-morbidity underlying the extensive symptom overlap in acute febrile illness is not known.
1.3 Strategies for control

**Pneumonia**

The control of pneumonia requires a combination of preventive interventions combined with rapid and appropriate case management (WHO, et al., 2007). Several environmental and socio-economic preventable factors have been identified. A recent meta-analysis concluded that exposure to indoor air pollution is a proven risk for pneumonia among children that merits attention in interventions aiming at reducing risks for pneumonia (Dherani, et al., 2008). Crowding also increases the risk of pneumonia (Cardoso, et al., 2004). Malnutrition (Caulfield, et al., 2004), lack of breastfeeding (Victoria, et al., 1999) and low coverage of measles vaccination (Perry and Halsey, 2004) can all contribute to a higher risk of developing pneumonia. Micronutrients like vitamin A may decrease the incidence of measles-associated pneumonia (Hussey and Klein, 1990) and the value of zinc in pneumonia treatment is being discussed (Natchu, et al., 2008). Therefore, action against one or all of these factors can help prevent pneumonia.

Vaccines also have the potential to reduce the incidence of pneumonia. The first conjugate *Haemophilus influenza type b* (Hib) vaccine was licensed in the United States in the early 1980s (Lees, et al., 2008). The conjugate vaccine prevents immunized children from asymptomatic pharyngeal carriage for which a considerable herd effect has been seen (Adegbola, et al., 1998). The Hib conjugate vaccine was introduced in Uganda in 2004, and has been highly effective in the Ugandan routine immunization program (Lee, et al., 2008). Several vaccines against *S. pneumoniae* are under development. A nine-valent vaccine showed 16% efficacy against mortality in Gambian children (Cutts, et al., 2005) and it is estimated that global coverage of the seven-valent vaccine would save 480,000 lives every year (Johnson, et al., 2008). However, when serotypes covered by the vaccines are reduced, an increase in non-vaccine serotypes may follow. This serotype replacement may pose a threat to the success of the vaccines (Pletz, et al., 2008). Also, routine use of pneumococci vaccine in most low income countries may be hampered by the high prices in the short to medium term (Peny, et al., 2005). The Global Alliance for Vaccines and Immunizations (GAVI) is working to alleviate costs of new vaccines in low income countries, and recently approved funding to administer pneumococcal vaccines to approximately 2.6 million children in Cameroon, Congo, and Yemen beginning in 2010 (The Global Alliance for Vaccines and Immunizations, 2008).

**Malaria**

The 1980s saw an increase in malaria morbidity and mortality alongside increasing resistance against existing drugs. As a response, the Global Malaria Control Strategy was developed in 1992, aiming at: 1) provision of early diagnosis and treatment, 2) planning of sustainable preventive measures, 3) detection of epidemics and 4) strengthening of local capacities to promote regular assessment of a country’s malaria situation (WHO, 1993). This strategy was further developed in the Roll Back Malaria initiative (RBM) which, in addition to the above strategies, involved attempts to strengthen the health services of affected populations and encourage research for new control tools and their delivery (WHO, 2005b). In 2002 the Global Fund to Fight AIDS, Tuberculosis and Malaria was established. The Global Fund is a partnership between donor and recipient governments, nongovernmental organizations, the private sector,
and affected communities working to make financial resources available to fight the included diseases. So far, the Global Fund has become the largest financier of insecticide-treated bed nets in the world. Prevention efforts through the use of insecticide-treated bed nets (ITNs) have had a great impact on child mortality (Fegan, et al., 2007) and a recent study from Zanzibar suggests a combination of effective drugs and high coverage of ITNs has the potential to even eliminate malaria (Bhattarai, et al., 2007).

Integrated management of childhood illness

Pneumonia and malaria cause 40-50% of all deaths among children less than five years of age (Black, et al., 2003). While previously addressed through disease specific programs, an increased awareness that children may suffer from multiple conditions at the same time resulted in WHO’s first algorithm of the Integrated Management of Childhood Illness (IMCI) in 1993. Three years later, IMCI was presented by WHO/UNICEF as the principal strategy to improve child health (WHO, 1997). IMCI aims at reducing infant and child mortality by:

- Improving the case management skills of health workers
- Improving the health system required for the effective management of childhood illness
- Promoting improved family and community childcare practices

The target group of IMCI is children under five years of age, their overall health status and the diseases that most frequently affect them, namely Acute Respiratory Infections (ARI), diarrhea, malaria, measles and ear infections. HIV has also been included in recent updates (WHO/UNICEF, 2008). Furthermore, IMCI involves assessment and management of malnutrition and immunization status.

During the first IMCI review meeting, it was acknowledged that improved quality of care in health facilities would not reduce childhood mortality and morbidity by itself, since many caregivers do not reach a health facility. Improvements of household and community care of sick children were therefore included as an essential component of IMCI - Community IMCI (CORE, et al., 2004). The focus of c-IMCI is:

- Early childhood development, especially nutrition
- Disease prevention
- Home care for sick, malnourished or injured children
- Treatment of sick children in health facilities when required

Referral is an important component of IMCI and children with severe symptoms should be immediately referred to higher level facilities. However, referral is often difficult. In a study from western Uganda, most caretakers completed referrals from community health workers to health center but delays were common, especially for children with symptoms of pneumonia (Kallander, et al., 2006). Also, rates of compliance with referrals from health facility to hospital may be low due to the difficulties parents face when seeking care for a sick child (Peterson, et al., 2004). Delays to complete referral from a first level health facility may be hazardous for children with possible pneumonia.
or other severe symptoms (Kallander, et al., 2006). In Mexico, inadequate referral had a substantial effect on poor outcomes in children with pneumonia (Reyes, et al., 1997).

**IMCI classifications**

IMCI uses simple clinical signs to facilitate the ability of first-level health workers to classify and treat children. Under IMCI, malaria is defined as fever, while cough or difficult breathing with an increased respiratory rate (≥50 breaths/minute for children 1-11 months old and ≥ 40 breaths/minute for children between 12 and 59 months old) is classified as pneumonia. Severe pneumonia or very severe disease, requiring immediate referral from first level health facilities, is defined by cough or difficult breathing with chest indrawings or stridor - a harsh noise when breathing in – in a calm child or danger signs such as inability to drink or breastfeed, unconsciousness, lethargy and vomiting.

Following evidence that many children with a wheeze, indicative of asthmatic disease or viral infection, were inadequately treated with antibiotics (Hazir, et al., 2004), administration of a rapid-acting bronchodilator to children with simultaneous pneumonia symptoms and wheeze have been included in IMCI-guidelines (WHO, 2005a).

An evaluation of the IMCI diagnostic algorithm accuracy in western Uganda showed 79% sensitivity for the IMCI algorithm for pneumonia when compared to X-ray verified pneumonia. For malaria, the sensitivity of fever was 97% when compared to parasite blood count. The IMCI algorithm sensitivity for severe pneumonia/very severe disease was 53% when compared to medical officer’s assessment and standardized physical examination (Kolstad, et al., 1997). Furthermore, the overlap between IMCI-malaria and IMCI-pneumonia was substantial (Perkins, et al., 1997).

### 1.4 Care-seeking for childhood illness

Care-seeking actions for a sick child depend, among other factors, on the family’s, and foremost the mother’s, interpretation of symptoms, labelling of disease in local terms, and the locally preferred treatment actions (Feyisetan, et al., 1997, Nichter and Nichter, 1994). The *emic* illness concepts - intrinsic cultural distinctions that are meaningful to members of a given society - often diverge from *etic* definitions - concepts that have meaning for the scientific observer (Etkin, 1988), possibly creating misunderstandings between caretakers and health workers. Local understanding of illness may sometimes even lead to harmful practices, as in a case of Ethiopian mothers who would treat a child with pneumonia symptoms by cutting the uvula (Muhe, et al., 1994). While seeking care from traditional healers was previously seen as an important cause of delay to appropriate care, it is now recognized that many caretakers prefer biomedical care in the treatment of suspected malaria (Makemba, et al., 1996). Emic concepts of malaria may have mixed with biomedical information, resulting in a medical syncretism (Hausmann-Muela, et al., 2002). While the emic aspects of the malaria-symptom fever have been explored, (Beiersmann, et al., 2007, Comoro, et al., 2003, Nsungwa-Sabiti, et al., 2004) the emic understanding for the pneumonia symptoms of difficult and rapid breathing have not been as well investigated.

In addition to local understanding of illness, care-seeking for a sick child is constrained by the distance and transport possibilities to a health facility, perceptions and attitudes
towards available health care providers, the resource constraints in the affected family and gender/power roles in the household. As a consequence, home care is widespread and common; e.g., using herbs or drugs bought from a nearby drug shop or left over from a previous illness episode (Lubanga, et al., 1997). Care-seeking outside the home may follow when home remedies have failed and involves a variety of providers; private drug shops and clinics, traditional health care providers, NGO-facilities and public health centers and hospitals. Care-seeking patterns are strongly related to socio-economic status with wealthier households being more likely to seek care or advice outside the home, compared to members of poorer homes (Filmer, 2005). As a consequence, a number of children dying from acute febrile illness may do so without any contact with formal health services during the course of the illness (Breman, 2001).

The implementation of the IMCI strategy has brought some improvements in the number of sick children being brought to a health facility (Arifeen, et al., 2004). Still, in the early 1990s, only 54% of children with pneumonia symptoms in sub-Saharan Africa were taken to a provider where antibiotics are likely to be available (UNICEF/WHO, 2006). Data from 27 low income countries showed that less than 20% of children with pneumonia symptoms, as reported by caretakers, received an antibiotic (Wardlaw, et al., 2006).

While malaria treatment should be initiated within 24 hours after onset of fever as agreed in a meeting of heads of states in Abudja, Tanzania (RBM/WHO, 2000), the time it takes for life-threatening pneumonia to develop has not been determined, and a timeline for treatment initiation similar to the Abudja target of 24 hours is absent.

1.5 Drug use
The 17th target of the eighth Millennium Development Goal aims at “in cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries” (United Nations General Assembly, 2000). However, access is not sufficient, correct use of drugs is also needed. Yet irrational use of medicines is a major problem worldwide. WHO estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly (WHO, 2006b). Appropriate use of drugs is crucial to achieve adequate treatment, while simultaneously limiting the development of drug resistance, and to avoid wastage of scarce resources and potential health hazards. Correct use can be impeded by inappropriate prescribing practices and low knowledge by providers/pharmacies, by uninformed patients and by circulation of substandard drugs (Bate, et al., 2008).

Many patients in low income countries obtain their drugs outside the formal health sector. Numerous stores sell a range of medicines alongside groceries and household products. In a review of studies of the treatment of childhood febrile illness in Africa, a median 50% consulted the retail sector for treatment (Brieger, et al., 2005). Poorly trained providers may prescribe wrong drugs or fail to offer the appropriate strength and dose of drug (Nshakira, et al., 2002). As unofficial drug shops are responsible for provision of uncontrolled use of antimalarials and antibiotics, they may still be a suitable target for interventions to improve treatment (Goodman, et al., 2004).
Choice of treatment at health facilities is guided by previous drug intake as per patients’ reports. Underreporting of drug intake might be dangerous since repeated treatment with the same drug might cause toxicity or failure to treat resistant strains. Likewise, over-reporting might mislead the health worker in diagnosis and choice of treatment for the illness episode. Studies from Tanzania and Malawi have shown poor correlation between caretakers’ stated intake of antimalarials and measured blood drug levels (Eriksen, et al., 2005, Nwanyanwu, et al., 1996).

**Drug resistance**

Drug resistance is a major threat to successful treatment of pneumonia and malaria (Cars, et al., 2008). While resistance development can be seen as a natural response to the selective pressure of a drug, it is exacerbated by abuse or misuse of drugs, poor patient compliance, and poor quality of available drugs.

To decide what drug to use for different diagnoses at a given time, drug efficacy studies are needed. While drug efficacy studies for antimalarials are numerous (Bukirwa and Critchley, 2006, Dorsey, et al., 2007, Hwang, et al., 2006, Omari, et al., 2005), not many studies of antimicrobial resistance of invasive bacteria in Africa exist. A study from the Ugandan capital Kampala on resistance patterns in *Streptococcus pneumoniae* isolated from healthy children showed 83.5% intermediate resistance to penicillin and 83.5% resistance to the first line antibiotic for pneumonia trimethoprim-sulfamethoxazole (Joloba, et al., 2001). In a recent study of resistance in pathogens isolated from children with severe pneumonia, sensitivity to chloramphenicol, the first line drug for severe pneumonia, was 33% among *Staphylococcus aureus*, 87.4% among *Streptococcus pneumoniae* and 0% among *Haemophilus influenza* (Nantanda, et al., 2008).

Resistance to the first line drug for uncomplicated malaria, chloroquine, approached 40% in Uganda in 2000 (Kamya, et al., 2001, Kamya, et al., 2002), resulting in a change of recommended drugs from chloroquine to a combination of chloroquine and sulfadoxine-pyrimethamine (Uganda Ministry of Health, 2000a, Uganda Ministry of Health, 2000b). However, further studies showed increasing risks of clinical treatment failures for chloroquine and sulfadoxine (Bakyaita, et al., 2005, Sendagire, et al., 2005). In 2005, a study of the effectiveness of artemether–lumefantrine (Coartem) when prescribed under routine outpatient conditions showed a high cure rate (Piola, et al., 2005). Following these results, Uganda changed its policy and adopted Coartem as its first line drug to manage uncomplicated malaria and quinine for complicated malaria treatment.

**1.6 Health systems in resource poor countries**

Health systems provide the interface between life-saving interventions and the people who need them. A well functioning health system is thus of utmost importance for the health of a population. The World Health Report 2000 addressed health system performance as a determinant of health (WHO, 2000). While health systems are defined to “include all actors, organizations, institutions and resources whose primary purpose is to promote, restore or maintain health” (WHO, 2000), the World Health Report 2000 identifies four key functions: 1) service provision, 2) resource generation and development, 3) mobilization and channeling of financing and 4) stewardships.
health system in most countries is a combination of public, private, traditional and informal sectors.

In low and middle income countries, weak health systems are impeding the implementation of major global initiatives for health and attainment of the Millennium Development Goals (MDG) (Travis, et al., 2004). An independent task force convened by WHO has suggested topics where health systems research is needed to advance the functioning of health systems, including: 1) financial and human resources, 2) organization and delivery of health services, 3) governance, stewardship and global management and 4) global influences (Task Force on Health Systems Research, 2004). Human resources are increasingly seen as a key issue in sustainable health systems with task shifting, from more to less trained health workers, being one possible way to reduce the lack of health professionals. Task shifting using lay health workers with no formal professional education for specific tasks in primary health care has shown promising benefits in increasing childhood immunization, promotion of breastfeeding and reducing childhood mortality and morbidity from common childhood illnesses (Lewin, et al., 2006). However, an increased use of community health workers also demands well functioning health systems able to sustain training and supervision (Haines, et al., 2007).

Studies of avoidable deaths can help identify deficiencies in a health system. However, most studies conducted so far have been done in high income countries. While there is a need to define the evaluation criteria for avoidable deaths further and agree on classifications of the avoidable factors examined (Westerling, 1996), these type of studies have the potential to identify where improvement in health care is needed, and can also be performed in low and middle income countries (Westerling, 2001).

1.7 Setting the context: Uganda

The country and the people

Uganda is located in East Africa, landlocked between neighboring Kenya to the east, the Democratic Republic of Congo to the west, Sudan in the north and Rwanda and Tanzania in the south. It covers 241,139 square kilometers, of which 18% is occupied by open water and swamps, and 12% by forest reserves, game parks and mountains. The population in 2008 was 29.6 million people (Uganda Ministry of Finance Planning and Economic Development - Population Secretariat, 2008). With an annual population growth rate of 3.24%, according to the United Nations, the projected population for 2015 is 39,335,000. 51% of Uganda’s population is below age 14 and the life expectancy is 49 years for males and 52 years for women (Uganda Bureau of Statistics (UBOS), 2000-2006). Only two percent of the population is 65 or older. 16% of children under five years of age are underweight and the national under-five mortality rate was 137 per 1000 live births in 2006 (Uganda Bureau of Statistics (UBOS), 2000-2006). An estimated 86 % of Ugandans live in rural areas.

Uganda is among the poorest countries in the world with a per capita gross national income of USD363 per year (WHO/AFRO, 2006). The first draft of a Poverty Eradication Action Plan (PEAP) was formulated in 1997, aiming at reducing the population living in absolute poverty to 10% in 2017. However, income poverty increased from 34% to 38% between 2000 and 2003, partly as a result of slow
agricultural growth and declines in farmers’ prices. Of the 37.7% Ugandans living below the poverty line in 2002/3, half were subsistence farmers (Uganda Ministry of Finance Planning and Economic Development, 2004).

The Ugandan health system

Uganda operates a decentralized health system. Under this system, the health sector structure follows the administrative structure (Fig 1) and the health sector budget is devolved to local district governments through a block grant system. There are currently 80 districts that are further sub-divided into 216 functional zones called health sub-districts (HSDs). Within each HSD there are three different levels of health facilities, which offer a range of health services (health center (HC) II, III, IV).

At the village level, a Village Health Team and various community agents operate under the virtual Health Center I. HC II, at parish level, provides only outpatient care with formally trained health workers, while HC III, at subcounty level, offers maternity care, general ward and laboratory facilities. HC IVs cater to a county and by policy provide surgery and blood transfusions in addition to services given at HC IIs. For purposes of national supervision, coordinating and mentoring the districts have been grouped into eleven service areas based on their geographic location. These services areas are each coordinated by the regional referral hospitals, which are centrally operated by the Ministry of Health.

![Figure 1](image-url)
Private health care providers represent almost 80% of the allopathic health care (Okuonzi and Konde-Lule, 2004). Approximately one-fourth of the health facilities in Uganda are Private-not-For-Profit where a mix of public and private services are offered (Uganda Ministry of Health and WHO, 2004). The total expenditure on health care per capita was USD22 in 2005. Of this, 28.6% was paid by the Ugandan government, 34.4% by private entities, such as non-profit institutions and 37% of the total health expenditure is covered by out-of-pocket household payments (WHO Statistical Information System, 2005).

Rapid improvements have been made in the proportion of people having access to a health facility within five kilometers (from 49% in 2000 to 72% in 2005). Also, more posts are being filled with qualified health workers (from 33% in 2000 to 68% in 2005) since the release of the first National Health Sector Strategic Plan in 2000 (Uganda Ministry of Health, 2005). However, some challenges remain: A study from two Ugandan districts concluded that while the decentralization policy led to increased utilization of health facilities, availability of essential drugs remained inadequate (Anokbonggo, et al., 2004).

**Home based management of fever**

To increase the proportion of febrile children receiving appropriate and prompt malaria treatment, the Home Based Management of Fever (HBMF) strategy was introduced in Uganda in 2003 (Fapohunda, et al., 2004). Under the HBMF, community volunteers are trained for three days on drug distribution and counseling of caretakers on the signs of malaria and drug dosage and administration (Uganda Ministry of Health, 2002). Pre-packaged, color-coded, and easily administered antimalarials should be distributed free of charge to febrile children. Initially, combinations of chloroquine and sulfadoxine-pyrimethamine were used under the name “Homapak” but Uganda subsequently selected artemether-lumafantrine (Coartem) as its new first-line drug in 2005. Coartem has yet to be introduced in the HBMF. Community volunteers should advise caretakers of sick children on how to continue treatment at home. If the child fails to improve after two days of treatment, or if the child has difficulty or rapid breathing or other IMCI danger sign when examined by the community health worker, the child should be referred immediately to the nearest health facility (Uganda Ministry of Health, 2002). The referred child should be given malaria drugs before leaving the community health worker.

Studies on HBMF indicate that it is well appreciated by the community (Nsabagasani, et al., 2007) and improvement in the treatment of IMCI-malaria in relation to correct drug and dose has been achieved (Nsungwa-Sabiti, et al., 2007). However, concerns remain for the impact on management of other febrile conditions and in particular pneumonia, due to the difficulties in distinguishing the two conditions from each other (Kallander, et al., 2004).

A meta–analysis of community management programs similar to the HBMF but for pneumonia - where community health workers are entitled to diagnose pneumonia and administer antibiotics to the sick child - showed a 24-28% reduction of all cause mortality risk under study conditions (Sazawal and Black, 2003). However, while
community management of malaria is spreading over Africa, few African countries have engaged in similar community management programs of pneumonia (Marsh, et al., 2008). Yet, UNICEF/WHO recommend that children presenting with simultaneous symptoms of malaria and pneumonia should receive dual treatment with antibiotics and antimalarials in the community (WHO/UNICEF, 2004).

1.8 Health seeking behavior models
Health seeking behavior models can help to explain how, when, and why people seek care. Two approaches to health seeking behavior have been suggested: health seeking behavior highlights the process of illness response while health care seeking behavior focus on the act of seeking health care (Mackian, et al., 2004).

Models explaining health seeking behavior:
- The Health Belief Model (HBM) initiates with how the person perceives the threat against her/his health; the perceived susceptibility and severity of the illness. This perception may be further affected by a person’s health motivation and consequence beliefs – the perceived benefits and barriers towards performing a certain health seeking action. Through identification of cues to action, a certain behavior could be encouraged (Becker, 1974).
- The Theory of Reasoned Action / Theory of Planned Behavior has been used widely in research about HIV and other sexually transmitted diseases. It looks at external variables that influence the subjective norm, which in turn influences the behavioral intention toward a behavior, together with the attitudes toward behavior and the patients’ perceived control of the situation (Fishbein and Ajzen, 1975).

The criticism of health seeking behavior models is that they tend to focus only on the client as an explanation to success or failure of treatment, and do not consider health care provider factors. Also, they consider neither the emotional aspects in decision making nor the power/gender balance.

Models explaining health care seeking behavior:
- The four As involve the study of Availability, i.e. the geographic distribution of health facilities; Accessibility, i.e. roads and transport etc; Affordability, including the treatment costs for individual households; and Acceptability, relating to cultural and social distance to health care facilities (Hausmann-Muela, et al., 2003).
- Pathway models elucidate the influence of illness perception and significant others for choice of therapy. Nyamongo considers duration of illness, knowledge and expenditure as determinants of therapy choice and therapy switching (Nyamongo, 2002).
- The ‘three delays’ model (Thaddeus and Maine, 1994) has been used in obstetric care as a model for identification of factors that affect the time interval between the onset of obstetric complications and the receipt of appropriate care. Main factors which can delay access to effective care are identified through three consecutive stages during which delays can occur. These are: Phase 1, delay in deciding to seek medical care on the part of the individual or family; Phase 2, delay in reaching a health care facility; and Phase 3, delay in receiving adequate care.
Health (care) seeking behavior is not an isolated event, but the result of a mix of social, personal, cultural and experimental factors (Mackian, et al., 2004). A model thus needs to take into account both the caretakers’ illness response, but also their interaction with the formal as well as informal health system. It is the caretakers’ perceived experiences on both illness and health system that determine health seeking behavior.

1.9 Conceptual framework in this thesis
In this thesis, I wanted to get an understanding of where most delays or barriers to care occur for a child with symptoms of pneumonia. I thus chose to use a modification of the three delays model and combined it with UNICEF’s suggested essential steps in pneumonia management to achieve a reduction of pneumonia mortality (UNICEF/WHO, 2006). These are: 1) Timely recognition of illness by the caretaker(s), 2) Timely care-seeking from an appropriate place, and 3) Timely administration of appropriate drugs in correct dosage. The resulting model uses the key words “recognize”, “seek” and “treat” to identify potential barriers to care at different levels (Fig 2). The subheadings cover the individual decision-making pattern involving recognition of symptoms and cultural interpretations (recognize), barriers to deciding to seek care and to complete care-seeking (seek), and the provision of adequate drugs for treatment (treat). If failing to recognize illness, seeking appropriate care or receiving adequate treatment, the result could be fatal, as indicated by the arrows from each box to a cross. However, it is not clear at which step the mortality occurs, nor how different steps interact to cause mortality in children suffering from acute febrile illness and pneumonia.

Figure 2: Conceptual framework of the thesis, modified after UNICEF (2006) and Thaddeus and Maine’s Three Delays’ Model (1994)

1.10 Rationale for the study
For adequate management of children with symptoms of pneumonia, caretakers and health workers must be familiar with the key pneumonia symptoms and the treatment needed for these symptoms. While little public information about pneumonia exists in Uganda, the frequent symptom overlap between pneumonia and malaria in combination with more public efforts for appropriate malaria management raises worries that possible pneumonia cases are being overlooked by caretakers and health workers. Caretakers and health workers must be able to see beyond the fever and consider difficult or rapid breathing and respond timely and appropriately to these symptoms. To successfully address management of children with potential pneumonia, we need to know and understand the deficiencies in the current management.
First, most interventions fail to address local illness concepts and preferred treatments. While there has been some attention to caretakers’ knowledge, illness concepts and related actions in case of fever, much less is known on these issues for cough and difficult/rapid breathing. We need to know how caretakers currently interpret and prefer to treat children with symptoms of pneumonia.

Second, to guide caretakers and health workers on appropriate timing of treatment initiation, the time to develop severe pneumonia needs to be known. We also need to understand the role of different choices of care-seeking, such as late or inappropriate treatment, in the development of severe pneumonia in malaria-endemic settings.

Third, while local illness concepts may influence the decision of where and when to seek care, it remains to be elucidated to what extent fatal outcomes of febrile illness are caused by inappropriate care-seeking associated with local disease perceptions, or result from care-seeking barriers in the home or in the health system. The barriers to care for a child suffering from severe febrile illness as experienced by caretakers will have to be clarified.

Fourth, routinely we interview caretakers on previous drug intake to guide clinical management and in interview surveys. However, the validity of caretakers’ reports of drug intake is not known. Health workers need to know what drugs a patient has been taking before arrival at the health facility to guide therapy. Also, the accuracy of self reports of drug intake in public health research will guide interpretation of results.
2. OBJECTIVES

2.1 General objective

To explore caretakers’ and health care providers’ understanding and response to children with symptoms of pneumonia in order to identify issues that need to be addressed for improved management of children with acute febrile illness

2.2 Specific Objectives

- To explore local illness concepts involving childhood fever, cough and difficult/rapid breathing and the preferred management of children with these symptoms (I)
- To describe the time to develop severe pneumonia and the care given prior to seeking care at hospital during development of severe pneumonia (II)
- To explore caretakers’ experience of care-seeking for fatal childhood febrile illness to elucidate barriers to adequate care (III)
- To describe caretakers’ reported use of selected antibiotics and antimalarials in children with symptoms of severe pneumonia, and validate these reports against blood drug concentrations of the studied drugs (IV)
3. MATERIAL AND METHODS
This thesis studies all aspects of the suggested conceptual model. Recognition and interpretation of illness is studied in Study I and the influence of the local illness interpretations from Study I on choices of care is explored in Study III. Aspects of care-seeking are investigated in Study II, where the time to develop severe pneumonia is estimated, along with caretakers’ timing and consequences of actions taken after stated recognition of illness symptoms. Barriers to care as experienced by caretakers for a child with acute febrile illness are explored in Study III. Health care providers are studied from caretakers’ reports in Study II, from caretakers’ experience of care-seeking in Study III and in Study IV by investigating how drugs have been used and are reported in children with IMCI-severe pneumonia.

3.1 Study areas and population

Figure 3. Map of Uganda with research districts indicated
The focus of this thesis is children older than one month but less than five years of age and their caretakers. For Study I, caretakers of healthy children were recruited. In Study II and IV, study participants were children diagnosed with severe pneumonia (II) and IMCI severe pneumonia (IV) while Study III involved caretakers of children who had died after an episode of acute febrile illness. Study II and IV were conducted at the Pediatric Acute Care Unit (PACU) at Mulago Hospital in Kampala and Study I and III in Iganga/Mayuge Demographic Surveillance Site (DSS) (Fig 3).

Mulago Hospital is the main public hospital in Uganda, situated in the capital city of Kampala. Mulago hospital serves both as a district and national referral hospital for about 2,000,000 people from the urban and peri-urban populations. While all Ugandan languages are represented in Kampala, the main languages are Luganda and English. Kampala’s under five mortality rate is 94 per 1000 births (Uganda Bureau of Statistics (UBOS), 2000-2006).

The Iganga/Mayuge Demographic Surveillance Site (DSS) is situated 120 km east of the Ugandan capital Kampala. It encloses 65 villages and 67,000 individuals of which some 12,500 are children under five years of age. The main ethnic group is Basoga who speak Lusoga. Malaria is endemic and the region’s under five mortality rate is 116/1000 (Uganda Bureau of Statistics (UBOS), 2000-2006). Economic activities are mainly agricultural with emphasis on millet, maize and sorghum (Rwabwoogo, 2002). Health facilities within the Demographic Surveillance Area (DSA) include Iganga District Hospital with 117 beds situated in Iganga town, eight public health centers, three NGO clinics and some 122 private providers (drug shops and private clinics) and a number of traditional healers.

3.2 Data collection methods
Multiple methods were used in this thesis, including Key Informant interviews (Study I), Focus Group Discussion (Study I), structured interviews (Study II, III, IV), in depth interviews (Study III), and collection of blood on filter papers and High Performance Liquid Chromatography (HPLC) drug analysis (Study IV). Figure 4 illustrates how different data collection methods were used in the studies. The combination of methodologies- method triangulation- allows for greater accuracy and enriches the understanding of a phenomenon by allowing for new and deeper dimensions to emerge (Todd, 1979). Triangulation can be done both through the use of different methods to study the same phenomenon, “between methods”, or through the use of different techniques within a given method to collect and interpret data, “within-method” (Todd, 1979). Three basic types of triangulation exist in addition to method triangulation: 1) the use of a variety of data sources in a study i.e. data triangulation, 2) investigator triangulation– the use of several researchers with different training, and 3) theory triangulation– the use of multiple perspectives to interpret a single set of data (Patton, 1990).

Except for method triangulation, this thesis includes data triangulation with use of different data sources and investigator triangulation. In Study III, within-method triangulation was done through a mixed qualitative (in depth interviews) and quantitative (structured verbal/social interviews) approach.
Focus group discussions
Focus group discussions (FGD) are used to obtain information on concepts, perceptions and ideas of a group, assuming that the participants can and will discuss the subject of interest freely, and add to each other’s comments. While originally used as a tool to assess consumers’ views of new products in market research, FGDs are now widely used in health research. FGDs can potentially produce considerable information in a short space of time (Green and Thorogood, 2004). Some disadvantages with focus groups are that people might narrow the discussions on the most common and acceptable themes, the “social norms”, and the generation of atypical opinions may be deficient (Patton, 2002). It is not a recommended method when the interest concerns personal, stigmatized or possibly embarrassing matters such as sexual preference or activity, disease status etc.

In Study 1, five FGDs were held with mothers of children less than five years of age in order to explore the local illness concepts and their influence on management of childhood fever, cough and difficult/rapid breathing. The FGD participants were recruited by local village leaders in purposely selected locations- two trading centers and three rural places. Each FGD included 8-12 mothers. Two FGDs involved only mothers less than 25 years of age while the other three FGDs involved mothers aged 25 or older, assuming illness perceptions might differ between age groups and increasing number of children. FGDs were moderated by a female social scientist who is native to the area and fluent in the local language Lusoga.

DVD presentation
The presentation of a video/DVD has been shown to elicit more signs dealing with serious illness, respiratory distress and general malaise compared to free listing of terms related to acute respiratory infections (Ryan, et al., 1996).
To get as much information as possible on perceptions of childhood difficult breathing from FGDs with mothers, a DVD showing children with respiratory problems was shown at the end of the session in Study I. The study team initially selected three children from the DVD who resembled children from the community to show to the mothers. However, one of the selected children wore bracelets and other symbolic decorations, which took the mothers’ attention from any illness symptoms. Due to this, results from only two children are presented in study results.

**Interviews**

Interviews are commonly used in health research. A structured interview involves a specific set of questions in a specific order for each interview to generate comparable answers from each respondent (Green and Thorogood, 2004). The kind of data that will be generated is thus pre-determined to a great extent and answers can usually be quantified. When using more open-ended questions, the researcher can decide the topics that will be covered but allow the respondent to decide the kind of information produced and the relative importance of that information.

Structured interviews were done with caretakers of children with X-ray verified or IMCI severe pneumonia in Study II and IV. When asking for drug intake, interviewers first asked an open question about drugs given to the child during the most recent illness episode and then probed for use of trimethoprim-sulfamethoxazole, chloroquine and sulfadoxine-pyrimethamine. Open-ended interviews were performed in Study I and III (below). Study III also used a special kind of structured interview- the Verbal/Social Autopsy (VASA) (Indepth-Network, revised 2003).

**Qualitative Interviews**

In-depth interviews are held with one person aiming to explore more deeply an issue of interest. In-depth interviews can be held with key informants, who can be any member of a community who is particularly knowledgeable about the inquiry setting (Patton, 1990). A key informant can provide in-depth information and help clarify ideas and information. The interview typically allows enough time to develop the informants’ own accounts of the issues most important to them (Green and Thorogood, 2004). A drawback of key informant interviews is that they may overlook the perspectives of collective parts of the community and especially the community members that are least visible.

Key informant interviews were done with eight governmental health workers and eight spiritual healers and herbalists in Study I. Health worker interviews involved four nurses and one nursing aid working at rural health centers and one nurse and two clinical officers working at Iganga Hospital. An interview guide was developed in collaboration with the study team members. The interviews with the healers were done in Lusoga, by a Lusoga-speaking social scientist, while health worker interviews were conducted in English.

In-depth interviews were conducted with bereaved parents in Study III. Parents were asked to narrate the last days prior to the death of their child and if not mentioned spontaneously, probing was done for choices in health care-seeking, encounters with health care professionals and experience of setbacks during the illness leading up to
Verbal and Social autopsies

A verbal autopsy is a method to find out the probable cause of death based on interviews with the relatives of the deceased (WHO, et al., 1999). It is usually applied in settings where civil registration systems are weak in order to find out more about the causes of death. Through gathering of information about symptoms observed in the deceased by the next of kin during the illness preceding the death, a likely diagnosis can be made post-mortem. The Iganga/Mayuge Demographic Surveillance Site uses a locally adapted version of the Indepth Network standardized verbal autopsy questionnaire (Indepth-Network, revised 2003) in order to enable comparison of data with other demographic surveillance sites. An extension of the verbal autopsy is the “social autopsy”, which aims to investigate the health-seeking behavior during the terminal illness. The social autopsy tool could either be a structured multiple-choice questionnaire or open-ended questions with probing for actions taken during the illness period. At the time of the study, Iganga/Mayuge DSS used a locally adapted social autopsy tool originating from Bolivia (Aguilar, et al., 1998) A standardized social autopsy questionnaire for the Indepth sites is under development (Källander, personal communication 2008).

Verbal/Social autopsy (VASA) interviews were done with 26 caretakers who had lost a child in acute febrile illness for Study III. Interviews took place at the home of the interviewees some 4-6 weeks after the death had occurred. Interviews took between 40-60 minutes to complete and were performed by the Iganga/Mayuge DSS ordinary staff who also were trained to perform in-depth interviews. Since the predictive values of verbal autopsy for determination of cause of death varies between settings (Korenromp, et al., 2003) and has not yet been evaluated in Iganga/Mayuge DSS, we chose to present only reported symptoms.

Filter paper sampling for analysis of blood drug concentrations

Analysis of biological fluids involves handling of potentially infectious material. Capillary blood sampled on filter paper is safe and convenient in rural areas since it reduces the need for equipment, e.g. centrifuge, deep freezer, needles etc (Lindström, et al., 1985). It has been shown that these dried blood samples are often very stable in tropical climates, and that they can be kept at normal working temperatures for long periods of time, facilitating blood sampling in the field (Bergqvist, et al., 1986). Filter paper samples can be sent by ordinary mail without any demands of refrigeration or freezing. The small blood volume needed and the possibility to use capillary blood instead of venous is of great value, especially when sampling children.

In Study IV, blood samples were collected from children under five years of age with IMCI severe pneumonia in order to measure blood levels of the antibiotic agent trimethoprim-sulfamethoxazole and the two antimalarials chloroquine and sulfadoxine-pyrimethamine and validate blood drug concentrations against drug intake histories obtained from caretakers. For each child, a blood volume of 2x100μl was put on two
separate filter papers, dried and put in individual plastic covers for transport to the laboratory at the Department of Chemistry, Dalarna University College, Sweden.

3. 3 Laboratory methods

*High Performance Liquid Chromatography (HPLC)*

HPLC is an analytical method designed to separate and quantify components in a chemical mixture. The sample to be analyzed is introduced in small volume to the stream of a mobile phase which is forced through a column, the stationary phase, by a pump. Separation is done when components interact with the stationary phase and thus are retarded by specific chemical or physical interactions with the stationary phase as it traverses the length of the column. The amount of retardation depends on the nature of the analyte, stationary phase and mobile phase compositions with different compounds retarding passage through the column to a varying degree. The analytes are detected and measured by a UV-detector when leaving the column (Khopkar, 2005).

HPLC methods were used in Study IV to determine blood concentrations of sulfamethoxazole (proxy for trimethoprim-sulfamethoxazole), sulfadoxine (proxy for sulfadoxine-pyrimethamine) and chloroquine from blood sampled on filter papers. Simultaneous measurement of sulfamethoxazole and sulfadoxine was done using a HPLC method developed by Lindkvist et al. (Lindkvist, et al., 2008) while chloroquine was measured in a separate HPLC-method analysis (Lindegardh, et al., 2002).

3. 4 Data analysis

*Statistical measures and methods*

- **Sensitivity:** Measures how often a test turns out to be positive when we test people that we know have the condition we are testing for (Kirkwood and Sterne, 2003). In Study IV sensitivities are calculated for the proportions of children whose caretakers state they have taken a drug out of those who have the drug in their blood (Table 2)
- **Specificity:** Measures how often a test turns out to be negative when we test people that we know do not have the condition we are testing for (Kirkwood and Sterne, 2003), In Study IV specificities are calculated for the proportions of children whose caretakers state they have not taken a drug out of those who have no drug in their blood (Table 2)
- **Negative Predictive Value (NPV):** the proportion of all those who test negative that really do not have the condition we are testing for (Kirkwood and Sterne, 2003). In Study IV, NPV is used to describe proportion of children whose caretakers state they have not taken a drug, who really do not have the drug in the blood (Table 2)
- **Positive Predictive Value (PPV):** the proportion of all those who test positive that really have the condition we are testing for (Kirkwood and Sterne, 2003). In Study IV, PPV is used to describe proportions of children whose caretakers state they have taken a drug, who really have the drug in the blood (Table 2).
Table 2: Relationship between sensitivity, specificity, NPV and PPV

<table>
<thead>
<tr>
<th>Condition (e.g. presence of drug in blood)</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test outcome (caretakers' reports)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>True Positive (a)</td>
<td>False Positive (c)</td>
</tr>
<tr>
<td>Negative</td>
<td>False Negative (b)</td>
<td>True Negative (d)</td>
</tr>
</tbody>
</table>

SENSITIVITY \( a/(a+b) \)
SPECIFICITY \( d/(c+d) \)

The following tests were used to compare differences in data between groups:

- **Student's t-test**: compares normally distributed continuous data for two groups (Ejlertsson, 2003). Used in Study II to compare time since symptoms were noticed.
- **Mann-Whitney U-test**: compares non-parametric (not normally distributed) continuous data or continuous data in small samples (Ejlertsson, 2003). Compares length of home treatment for children with and without DRB in Study III.
- **Chi-square test**: compares proportions of categorical variables between groups (Ejlertsson, 2003). Chi-square test was used in Study II to compare proportions of children who received drugs at different facilities prior to arrival at the hospital.
- **Fischer's exact test**: compares proportions of categorical variables between groups when sample is small or one of the variables includes very few observations (Kirkwood and Sterne, 2003). Applied in Study II to analyze source of drugs for children who had received only antimalarials prior to arrival at the hospital.
- **Test for trend**: used in categorical data analysis when some categories are ordered. For example, doses can be ordered as 'low', 'medium', and 'high' (Kirkwood and Sterne, 2003). Used in Study III to analyze distribution of households between different socioeconomic groups.
- **Logistic regression**: a model used for predicting the probability of occurrence of an event, estimating the effect of several independent variables and possible interactions while controlling for confounding factors. Used in Study II to analyze potential risk factors for Very Severe Pneumonia.

**Content analysis**

Content analysis provides a means to make inferences from verbal, visual or written data in order to describe a specific phenomena (Downe-Wamboldt, 1992). The analysis could be inductive, where categories are created from the data being analyzed, or deductive, where pre-existing theory is validated or extended. All approaches to content analysis require a similar analytical process, including the identification of units of analysis, coding and definitions of categories (Hsieh and Shannon, 2005). There is a distinction being made between manifest and latent content analysis, where the former leaves out all forms of interpretations and only deal with an objective description. However, assuming that there is always some degree of interpretation when reading a text (Graneheim and Lundman, 2004), it might be more appropriate to explain the analysis as being close or not close to the text.

In Study I, inductive latent content analysis was applied on transcripts of focus group discussions (FGDs) and key informant interviews with the individual interviews as the
unit of analysis. A deductive manifest analysis was used in Study III, where content analysis of in depth interviews was performed with pre-determined categories and combined with quantitative analysis of structured verbal/social autopsy interviews.

Data entry and quality control
Structured questionnaires collected at the hospital were checked for completeness on a daily basis. I checked the comprehensiveness of verbal/social autopsy interviews myself during interviewing sessions in about two thirds of interviews. Focus group discussion, key informant and in-depth interviews performed in Lusoga were transcribed and translated by a native Lusoga speaker and translations were cross-checked by the focus group moderator. Key informant interviews with English speaking health workers were transcribed by myself. Data entry was done using EpiData 3.1, followed by exportation to one of the statistical programs R (R Development Core Team, 2006) and/or Stata 9.

3.5 Ethical Considerations
All studies were ethically approved by the Institutional Review Board at Makerere University School of Public Health, Uganda National Council of Science and Technology (HS-32) and Study II and IV also by the Regional Ethics Committee of Karolinska Institutet, Sweden (2005/99-31/1). Informed consent was obtained from all caretakers, health workers and traditional healers who participated in the studies.

The main ethical concerns in this project relate to the discomfort the interview situation may have caused the caretaker, especially when asked to narrate the circumstances preceding the death of their child. Caretakers were approached after a mourning period of 4-6 weeks. Efforts were done to facilitate and make the interview session as comfortable as possible for the caretakers, allowing plenty of time and breaks whenever needed.

Another ethical risk is breach of confidentiality. All interview tools and blood samples were marked only with the study number of the recruited child and study numbers were linked to name of the child only on the first page of the study questionnaire, which was removed shortly after completing the interview. All caretakers were informed and agreed to that filter papers with blood samples would be transported to Sweden.

All caretakers of children who were recruited in the studies and had an HIV-test during hospital admission were counseled before and after testing. Children with a positive HIV-test were referred to the Pediatric Infectious Disease Department at the hospital, for further counseling and follow up. X-rays are not routine for all children with suspected pneumonia and may expose children to some unnecessary radiation. However, radiation exposure from one single X-ray is very limited and X-rays may have contributed to securing the correct diagnosis of the child.

To collect blood samples, vein-puncture was used which is standard hospital procedures but may involve some discomfort. Risks were minimized through careful cleaning of the skin before puncture and bandaging afterwards. Filter papers were destroyed after analysis.
### 3.6 Summary of methods

<table>
<thead>
<tr>
<th>Title of study</th>
<th>Methods</th>
<th>Study population and sample size</th>
<th>Analysis</th>
<th>Study Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Local illness concepts – Implications for management of childhood pneumonia in eastern Uganda</td>
<td>Focus group discussions (FGDs) Key Informant interviews (KIs)</td>
<td>5 FGDs - 2 FGDs with mothers between 15-25 years old - 3 FGDs with mothers &gt;25 years old Governmental health workers (n=8) Spiritual/herbal healers (n=8)</td>
<td>Inductive latent content analysis</td>
<td>November-December 2005</td>
</tr>
<tr>
<td>II. Care-seeking in the development of severe community acquired pneumonia in Ugandan children</td>
<td>Case-series study with structured interviews</td>
<td>Caretakers and their under-fives with severe X-ray verified pneumonia at Pediatric Acute Care Unit, Mulago hospital, Kampala (n=140)</td>
<td>Descriptive statistics, student’s t-test, Chi-square test, Fischer’s exact test, Logistic regressions</td>
<td>January-June 2006</td>
</tr>
<tr>
<td>III. Caretakers’ experience of care-seeking for fatal childhood fevers in rural Uganda – a mixed methods study</td>
<td>Verbal and Social Autopsies In depth interviews</td>
<td>Caretakers who had lost a child between 1-59 months of age due to acute febrile illness</td>
<td>Deductive manifest content analysis, descriptive statistics, Mann-Whitney U-test and Test for trend</td>
<td>March – August 2006</td>
</tr>
<tr>
<td>IV. Low validity of caretakers’ reports on use of selected antimalarials and antibiotics in children with severe pneumonia at an urban hospital in Uganda</td>
<td>Cross-sectional hospital study with structured interviews HPLC of blood sampled on filter papers for drug concentrations</td>
<td>Caretakers and their under-fives with IMCI severe pneumonia (n=139)</td>
<td>Sensitivity, Specificity, PPV, NPV and Chi-square test</td>
<td>January-April 2006</td>
</tr>
</tbody>
</table>
4. KEY RESULTS

4.1 Local illness concepts (Study I)
Local illness concept for symptoms involving fever, cough and difficult/rapid breathing and the preferred actions were explored in Study I.

Figure 5 gives an illustrative presentation of how the different local illness concepts were explained by mothers to involve fever, difficult/rapid breathing and cough, the perceived severity of the concept and the preference for herbal or biomedical treatment.

*Omusudha* emerged as an unspecified concept used for any condition involving fever by caretakers, health workers and traditional healers. Even though the addition of another word would make *omusudha* somewhat more specific, the main cause to any *omusudha* was said to be malaria in focus groups with mothers. Mothers also indicated that a febrile child would urge them to administer antimalarial drugs – suggesting a tendency to interpret any fever as being malaria.

‘Unfortunately *omusudha* is a broad term that our people don’t understand well because somebody can say *omusudha* meaning malaria and somebody can say *omusudha* meaning cough’ (Key Informant, Clinical Officer).

Health workers gave the Lusoga translation of pneumonia; *lubyamira*, and provided some biomedical explanations to the cause and treatment. Some probing was required in focus groups until mothers mentioned *lubyamira*, which was then explained as caused by exposure to cold or a result of untreated *omusudha*.

‘It normally comes when the child has some cough; feels pain on breathing and cannot breathe well. It starts as a fever or [child] has a running nose and coughing and later it attacks the chest. The child begins getting difficult breathing’. (FGD, Young Mothers)

According to mothers, *lubyamira* could further develop into *kuziyila*, in which respiratory rate remained normal, but sub- and intercostal chest indrawings were present. Mothers in focus groups never mentioned any names of antibiotics when asked
how they wanted to treat a child with respiratory problems but suggested herbs, paracetamol or immediate care-seeking outside the home. Health workers said that mothers were likely to treat a child with pneumonia symptoms (*lubyamira*) with antimalarials.

*Kinsimbye* (sharp chest/trunk pain) was mentioned by traditional healers instead of *lubyamira* and was explained as an inherited condition that would be exclusively treated with herbs. Health workers said *kinsimbye* affected only adults.

In focus groups, neither *lubyamira* nor *kuziyila* nor any other local term involving pneumonia symptoms were mentioned among the community’s most common childhood illnesses.

*Enhonhi* emerged as a condition which could involve fever, difficult or rapid breathing as well as diarrhea. *Enhonhi* was considered to be quite common and the preferred treatment was herbs. This raises concerns of possible mistreatment of children suffering from pneumonia or malaria due to being classified as suffering from *enhonhi*. Traditional healers had a tendency to explain any problems relating to cough and difficult breathing as being genetic or as part of another illness, e.g. measles.

‘*Enhonhi can be contracted* if you scare the child with a hen or any flying bird [or] even sitting outside in the evening with a child as the birds at this time fly back to their resting places’  (FGD, Older mothers)

Mothers recognized severe respiratory symptoms when showed a DVD with one child with an increased respiratory rate and another child without rapid breathing but with intercostal and subcostal chest indrawings. All mothers agreed to that the presented children were in a severe condition. However, the suggested responses to a child with severe symptoms diverged among mothers; some wanted to seek immediate care at a hospital while others would start treating with herbs or antipyretics at home.

**4.2 Time to develop severe pneumonia and care given prior to hospital (Study II)**

Time since first recognition of illness and care-seeking under the development of severe X-ray verified pneumonia were investigated in Study II.

Of the 140 children included in the study, 23 children were classified as having very severe pneumonia. 18 children died, of whom 11 were classified as having very severe pneumonia. 97% of caretakers to children diagnosed with severe pneumonia had recognized difficult or rapid breathing (DRB), a median of two days prior to arrival at hospital (interquartile range 1-3). First symptoms had been noted a median of seven days prior to arrival at hospital (interquartile range 4-14). Cough was the most commonly reported first symptom of illness (n=103, 74%). Fever had been noted by 88% of caretakers a median three days before hospital arrival.

Altogether 23% of children diagnosed with severe pneumonia were said to have received antibiotics only prior to seeking care at the hospital, 13% had received antimalarials only and 25% reportedly received both antibiotics and antimalarials. Of children with reported symptom overlap of fever and DRB (n=123), 21% had received
only antibiotics, 13% reportedly received only antimalarials and 27% received both. In total, about half (51%) of children diagnosed with severe pneumonia had been taken to a health care provider prior to arrival at the hospital. Most children who were brought outside the home for care had reportedly received some kind of drugs. Of children developing severe pneumonia, 14% of those who sought care outside the home prior to arrival at the hospital reportedly received antimalarial drugs only. Table 3 provides an overview of how care had been sought, and reports of drugs given per place of care, for the 140 children.

Fifty-seven (42%) caretakers responded with giving antibiotics or bringing the child outside the home for care prior to their reported recognition of DRB. Cough (21/46) and fever (11/46) were the two most common symptoms immediately preceding care-seeking outside the home. The majority of children seeking care prior to recognition of DRB sought care at a private provider (40/46).

Children who had been taken outside the home for care prior to the hospital had had key pneumonia symptoms for more time (median 3 days) than children who were taken directly from home to the hospital (median 2 days).

Table 3: Caretakers’ reports of care and drug treatment prior to arrival at the hospital in 140 children diagnosed with severe pneumonia. AB= antibiotics, AM= antimalarials

<table>
<thead>
<tr>
<th>140 CASES</th>
<th>HOME CARE= 90</th>
<th>OUTSIDE CARE WITHOUT PRIOR HOME CARE= 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO CARE  = 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO AM AM &amp; AB= 24</td>
<td>NO AM AM &amp; AB= 8</td>
<td></td>
</tr>
<tr>
<td>AM/AB = 13 AB = 20</td>
<td>AM/AB = 10 AB = 10</td>
<td></td>
</tr>
<tr>
<td>OUTSIDE CARE AFTER HOME CARE = 41</td>
<td>MORE THAN ONE PROVIDER= 3</td>
<td></td>
</tr>
<tr>
<td>NO AM AM &amp; AB= 9</td>
<td>NO AM AM &amp; AB= 0</td>
<td></td>
</tr>
<tr>
<td>AM/AB = 6 AB = 5</td>
<td>AM/AB = 1 AB = 1</td>
<td></td>
</tr>
<tr>
<td>MORE THAN ONE PROVIDER= 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO AM AM &amp; AB= 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM/AB = 0 AB = 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Children were classified as having severe or very severe pneumonia based on the presence or absence of central cyanosis or inability to drink. Chi-square test was done to analyze how being classified as having severe or very severe pneumonia varied depending on the reported drug intake prior to arrival at the hospital. Having received only antimalarials emerged as a risk for being classified as having very severe pneumonia (Table 4). Further analysis with logistic regression of possible predictors, except from previous drug intake, of having very severe pneumonia showed that having received only antimalarials during illness development, compared to having received...
no drugs, or antibiotics alone, or in addition to antimalarials, significantly increased the probability of being classified as having very severe pneumonia (OR 5.5, CI 1.8-16.4).

**Table 4**: Number of children being classified as having severe vs. very severe pneumonia depending on reported drug intake prior to arrival at hospital

<table>
<thead>
<tr>
<th>Drug given</th>
<th>Severe pneumonia, n</th>
<th>Very severe pneumonia, n</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antimalarial and no antibiotics</td>
<td>48</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Antibiotics but no antimalarials</td>
<td>26</td>
<td>6</td>
<td>1.6 (0.4-6.0)</td>
</tr>
<tr>
<td>Antimalarials but no antibiotics</td>
<td>10</td>
<td>8</td>
<td>5.5 (1.4-22.4)</td>
</tr>
<tr>
<td>Antimalarials and antibiotics</td>
<td>33</td>
<td>2</td>
<td>0.4 (0.1-2.4)</td>
</tr>
</tbody>
</table>

4.3 **Barriers to adequate management of childhood acute febrile illness (Study III)**

In Study III, barriers to adequate care for children suffering from acute febrile illness were investigated from the caretakers’ perception and experiences, using UNICEF’s model “recognize”, “seek” and “treat” as sensitizing concepts.

Final categories involving barriers to adequate care were: “Illness interpretation barriers”, “Barriers to seeking care” and “Barriers to receiving adequate treatment”.

**Illness interpretation barriers**

*Omusudha* was the term most frequently used by caretakers to label the illness preceding death in children, despite reported presence of cough, difficult and rapid breathing, or even chest indrawings. 5/8 children labeled with the illness concept *omusudha* reportedly also suffered from difficult/rapid breathing. Of the children with DRB who were labeled with the illness concept *omusudha* (n=5), two reportedly received antibiotics while the others received antipyretics and antimalarials only.

Only one caretaker suggested the deceased child had suffered from *lubyamira*, but the caretaker also said the disease information had been given at hospital. Despite reported difficult/rapid breathing in 16 children, and chest indrawings in ten children, there were no additional reports of *lubyamira* or *kuziyila*.

Two children had symptoms which were explained as *enhonhi*. Both of these children were treated at home and died on their way to the hospital. Table 5 illustrates how treatment preferences for the emerging illness concepts in focus group discussions in Study I relate to the reported actions in Study III.
Table 5: The agreement in treatment of emic illness concepts as explained in Study I and for deceased children reported to suffer from the concept in Study III

<table>
<thead>
<tr>
<th>Local illness concept</th>
<th>Explanation/ symptoms</th>
<th>Treatment preference from Focus Group Discussions (FGDs)</th>
<th>Treatment given in accordance with results from FGDs</th>
<th>Number citing this local illness concept (some caretakers gave more than one illness name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omusudha</td>
<td>Hot body</td>
<td>Herbs, panadol, antimalarial drugs</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Okuwamu omusayi</td>
<td>Lack of blood, pale palms</td>
<td>Blood transfusion</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>Lukunsense</td>
<td>Measles; fever, vomiting, diarrhoea, rash, coated eyes</td>
<td>Herbs</td>
<td>No, went to hospital for care</td>
<td>3</td>
</tr>
<tr>
<td>Lwenyanja</td>
<td>Diarrhea, fever, desquamation of the skin around the private parts</td>
<td>Traditional care. Sometimes in combination with hospital care</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Enhonhi</td>
<td>Cold hands and feet with warm trunk, yellowish diarrhoea, tightness in the chest with difficult breathing</td>
<td>Herbs</td>
<td>Yes, but went to hospital after giving herbs at home</td>
<td>2</td>
</tr>
<tr>
<td>Lubyamira</td>
<td>Difficult breathing</td>
<td>Hospital care/ home care until severe illness</td>
<td>Yes, child put on drugs at home but quickly taken to hospital</td>
<td>1</td>
</tr>
<tr>
<td>Okwesika</td>
<td>Convulsions</td>
<td>Traditional care</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Ebiino</td>
<td>False teeth; vomiting, diarrhoea, high temperature and does not breath well</td>
<td>Traditional care</td>
<td>No, went to hospital for care</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
<td>Different management</td>
<td>6</td>
</tr>
</tbody>
</table>
Barriers to seeking care
Most children (21/26) were taken to more than one healthcare provider. Care-seeking usually started by visiting a nearby provider (public health center n=10 and private clinics n=10) that could be reached on foot or bicycle. Proximity was the most frequently reported reason for choice of first provider in narratives. Most caretakers reported difficulties finding transport to go to the hospital. Care-seeking, or completing referrals, could also be delayed due to the absence of the father. Three mothers gave reports of having to find the father before any decision involving money could be made:

“The health worker said the child needed to be admitted but I told the health worker to first discharge us to go and inform my husband. However, we didn’t find my husband at his work station in town. So we had to wait until evening to go to the clinic.” 18 year old mother of deceased 8 month old boy

Children with reported difficult/rapid breathing had been treated at home for less time before seeking care at an outside provider than children without DRB. Paracetamol and chloroquine were the most commonly used drugs at home.

Barriers to receiving adequate treatment
More discontent emerged about the hospital care than about care provided from nearby facilities. Main issues cited about the care provided at hospital were long queues, rude staff, lack of triage and having to pay for treatment. According to stories told by caretakers, it seemed as if health workers sometimes discharged children who appeared to have needed continued hospital care. Several narratives revealed a lack of drugs and blood at all levels of care, which ultimately may have contributed to the child’s death.

“In the hospital, we stayed in a very long queue but even after enduring, the child was diagnosed and it was found to lack blood. Unfortunately, the child’s blood group wasn’t in stock and we were referred to Nalufenya children’s hospital in Jinja. In Nalufenya hospital, we also stayed in a very long queue. After taking the blood samples, we were also told that the child’s blood group wasn’t in stock. The child was instead put on a water drip.” Grandmother of deceased 7 month old boy

3/15 deceased children with reported difficult and/or rapid breathing and who had sought care outside the home reportedly received an antibiotic from the provider, while 10/15 received antimalarials and antipyretics only.

The underlying theme of the three barrier categories was resource constraints in individual households and at health care providers. 15 of the involved households belonged to the poorest or second poorest socio-economic quintile compared to only one household from the least poor socio-economic quintile (p<0.05). Difficulties to seek care were related to lack of money for paying for transport and care while barriers to receive care involved poorly equipped health facilities.
4.4 Validity of caretakers’ reports of drug intake (Study IV)
We compared caretakers’ reports of intake of the antibiotic trimethoprim-sulfamethoxazole and the antimalarials chloroquine and sulfadoxine-pyrimethamine in their children with drug blood concentrations in the child’s blood.

Paracetamol and chloroquine were the most commonly used drugs at home. About half (53%) of children had been taken somewhere outside the home for care prior to arrival at hospital. Caretakers reporting care in a health facility were more likely not to know the type of drugs given to the child, compared to if the child had been treated at home (RR 2.6, 95% CI 1.2-5.6). Under-reporting of chloroquine intake was more common when the child had been treated at a private health facility than at public facility or at home (RR 3.3, 95% CI 1.4-7.7).

Table 6. Number of children with reported intake vs. detected blood concentrations – above or below therapeutic concentrations - of the three drugs studied given prior to hospital care among 139 children with IMCI severe pneumonia (%). Prophylactic sulfamethoxazole given to HIV positive children, prophylactic chloroquine to children diagnosed with sickle cell anemia.

<table>
<thead>
<tr>
<th></th>
<th>Sulfamethoxazole</th>
<th>Chloroquine</th>
<th>Sulfadoxine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥37.5 μg/ml</td>
<td>&lt;37.5 μg/ml</td>
<td>Not detected</td>
</tr>
<tr>
<td><strong>Reported non-prophylactic use</strong></td>
<td>2 (1.4%)</td>
<td>8 (6%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td><strong>Reported prophylactic use</strong></td>
<td>4 (3%)</td>
<td>7 (5%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td><strong>No intake reported</strong></td>
<td>10 (7%)</td>
<td>30 (22%)</td>
<td>70 (50%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>16 (12%)</td>
<td>45 (32%)</td>
<td>78 (56%)</td>
</tr>
</tbody>
</table>

1 Two caretakers reported use of sulfamethoxazole both prophylactically and for the current illness and are therefore included in two rows.
2 One caretaker reported use of prophylactic chloroquine as well as for the current illness and is therefore included in two rows.
Table 6 shows the numbers of children whose caretaker reported intake of trimethoprim-sulfamethoxazole, chloroquine and sulfadoxine-pyrimethamine where drugs were measured in therapeutic levels, under therapeutic levels or not at all detected. Sensitivities of caretaker’s reports of drug intake for the acute illness were 20% for sulfamethoxazole, 31% for chloroquine and 19% for sulfadoxine (Table 7), indicating caretakers underreport drugs given to the child. While some of the under-reporting may be explained by the studied drugs’ long halftimes, many children had therapeutic concentrations of the drugs in their blood even when their caretakers did not report prior drug intake.

Of caretakers stating intake of trimethoprim-sulfamethoxazole for the acute illness in their child, 67% had the drug detected in blood. Positive Predictive Values for intake of chloroquine and sulfadoxine-pyrimethamine during the acute illness were 69% and 85%, respectively. Of children whose caretaker gave negative reports of trimethoprim-sulfamethoxazole intake, 64% had no drug detected in blood. Negative Predictive Values for chloroquine and sulfadoxine-pyrimethamine were 52% and 62%, respectively (Table 7).

Table 7. Sensitivities, specificities, PPVs and NPVs for caretakers’ reports of drug intake for the acute illness compared to blood drug concentrations of the studied drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfamethoxazole</td>
<td>20%</td>
<td>93%</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>31%</td>
<td>85%</td>
<td>69%</td>
<td>52%</td>
</tr>
<tr>
<td>Sulfadoxine</td>
<td>19%</td>
<td>98%</td>
<td>85%</td>
<td>62%</td>
</tr>
</tbody>
</table>
5. DISCUSSION
This thesis points out four major issues in the management of children with possible pneumonia: 1) caretakers’ knowledge of symptoms and biomedical treatment of pneumonia is limited, 2) development of severe pneumonia occurs rapidly but recognition of difficult and/or rapid breathing does not prompt any specific care and could involve care at home and/or at private or public providers, 3) many children who died in acute febrile illness were brought to a health care provider during the illness, but still failed to improve, possibly due to insufficient quality of care, and 4) caretakers’ unguided reports of previous intake of antibiotics and antimalarials may have limited validity.

5.1 Caretakers’ recognition and interpretation of difficult/rapid breathing
Caretakers recognize difficult breathing but do not associate it with pneumonia (I, III). A variety of terminologies were used for difficult and/or rapid breathing (DRB) (I). Even though mothers in focus groups said difficult breathing is a threatening condition, the fact that mothers and traditional healers did not list any local illness concept involving respiratory problems among most common childhood illnesses implies the perceived risk of getting pneumonia is low (I). This was further demonstrated in Study III, where only one caretaker suggested pneumonia as a possible cause of death despite many children reportedly suffering from DRB, and even chest-indrawing. This could be due to low knowledge about pneumonia as a common childhood killer, similar to what has been described in Ethiopia (Muhe, et al., 1994). In focus groups, probing was required before mothers mentioned “lubyamira” (pneumonia) as related to difficult breathing (I). This indicates both that awareness of pneumonia as a common childhood killer is low, and points to a need to raise caretaker awareness and responsiveness to key pneumonia symptoms and appropriate care-seeking. This could be done either by emphasizing “lubyamira” as a common and serious condition, or by separating symptoms from illness concepts and encourage immediate care-seeking after recognition of DRB, independent of local illness classification.

While knowledge of pneumonia symptoms and pneumonia seemed low, awareness of fever as a sign of malaria appeared high (I). Hot body emerged as a well-known symptom to mothers and would be interpreted as malaria. Health workers said both “okukolola” (cough) and “lubyamira” (pneumonia) could be ascribed to malaria by caretakers (I), and several children who died in acute febrile illness were labeled as suffering from “omusudha” despite reports of difficult and/or rapid breathing (DRB) (III). Children reported to suffer from “omusudha” were reportedly most commonly treated with antipyretics and/or antimalarials, independent of presence or absence of DRB (III). Caretakers’ acceptance of biomedical drugs for “omusudha” may reflect how biomedical information about malaria has merged with pre-existing emic concepts rather than displaced them, similar to a study in Tanzania where people had a preference for biomedical care despite a prevailing non-biomedical understanding of the cause (Hausmann-Muela, et al., 2002). The agreement between caretakers, health workers and traditional healers on symptoms and preferred treatment was large regarding “omusudha”, but decreased for other local illness concepts (I). As in previous studies from Uganda, it seems any symptom combination involving a hot body may be interpreted as “omusudha” (Kengeya-Kayondo, et al., 1994), and that there is a need to improve caretakers’ understanding and response to symptoms beyond fever.
Caretakers did not talk about children suffering from more than one illness at a time, but rather viewed the illness as a changing condition (I). When the child gets cough and later develops a hot body, the hot body issue tended to take the attention of the mothers off the cough, similar to what has previously been described for western Uganda (Kallander, et al., 2005). Mothers said untreated “omusudha” could develop into “lubyamira” but gave no clear difference between ”omusudha with cough” and “lubyamira”.

The emic concept “enhonhi” was thought to be caused by birds scaring the child and was explained to present with simultaneous symptoms of hot body, difficult breathing and diarrhea. The concept of a spirit bird causing illness has been described elsewhere in sub-Saharan Africa, also presenting with similar symptoms (Hill, et al., 2003). “Enhonhi” was treated with herbs at home but care would be sought outside the home if no improvement was seen (I). Two children in Study III who had symptoms of “enhonhi” were treated at home and died on their way to the hospital. “Enhonhi” may thus be an emic concept of the frequent etic symptom overlap between malaria and pneumonia (Kallander, et al., 2004). Since overlap between symptoms of pneumonia and malaria and also diarrhea are common, caretakers may need to be informed of the possibility of co-existence of two or more diseases, and the need for different simultaneous treatments in these cases. Also, immediate care-seeking for “enhonhi” should be encouraged.

5.2 Responding to illness symptoms – choices of care
The development of severe pneumonia occurred rapidly - two days after first recognition of difficult and/or rapid breathing (DRB) (II). While other studies have pointed at modest caretaker ability to recognize DRB and poor recognition of severity signs (Simiyu, et al., 2003, Uwaezuoke, et al., 2002), in our study the majority of caretakers of children diagnosed with severe pneumonia stated they had recognized DRB (II). Mothers in focus groups also identified a child with difficult breathing when showed children with respiratory problems on DVD (I). However, recognition of DRB did not lead to any specific care giving action (II, III). Less than half of the caretakers of children diagnosed with severe pneumonia had responded with some kind of care-giving action within one day after having recognized DRB, and many had taken action prior to recognition of these pneumonia symptoms (II). Thus, despite adequate recognition of DRB, caretakers may interpret it in a way which does not prompt biomedically adequate care (Mull, et al., 1994) and local illness categorization may lead to preference of herbs (Kauchali, et al., 2004) or otherwise inappropriate practices.

Preferred treatments for a child with pneumonia symptoms emerged as pluralistic and changed between herbal, traditional and biomedical private and public care (I, II). As in other settings, preference of treatment changed as illness interpretations changed in response to symptom progression and outcomes of treatment attempts (Kamat, 2006, Nyamongo, 2002). Some children in Study III received traditional care outside the home during the fatal febrile illness episode. While it has been suggested that traditional care is no longer a risk for delayed hospital care of children with malaria in Tanzania (de Savigny, et al., 2004, Makundi, et al., 2006), local illness concepts have been shown to strongly influence treatment and choice of provider in Burkina Faso and
Tanzania (Beiersmann, et al., 2007, Comoro, et al., 2003). Our findings in children diagnosed with severe pneumonia at the hospital (II) confirm community findings from focus group discussions (I) that some caretakers respond inadequately to key symptoms of pneumonia. This calls for a need of further attention to communication with the community on when and where caretakers need to seek care for a child with pneumonia symptoms.

5.3 Health care providers and perceived quality of care

Half of all children diagnosed with severe pneumonia had been brought to an allopathic health care provider prior to arrival at the hospital (II). Of the 26 children in Study III, all but three reached at least one allopathic health care provider during the final illness. Still, they failed to improve and progressed to develop severe pneumonia (II) or died (III). Except from seeking care too late, children who failed to improve after receiving treatment at a health facility may have suffered from the disease due to resistant pathogens or underlying complicating conditions such as HIV-infection. Yet, ¾ of the children in Study II were not HIV-infected but nevertheless developed severe pneumonia. Apart from drug resistance, there is also a possibility that some of the failures to improve were due to low suspicion and/or ability to recognize pneumonia among health care providers, as previously described in Zambia (Stekelenburg, et al., 2002) or inappropriate prescribing practices at health facilities (Graham, et al., 2008, Ogwal-Okeng, et al., 2004). A study from seven low income countries demonstrated inadequate knowledge and practice for the management of childhood pneumonia among 56% of doctors and nurses (Nolan, et al., 2001). Previous studies have revealed low knowledge of etiology and danger signs of acute respiratory infections among private drug providers in Uganda (Tumwikirize, et al., 2004), possibly explaining health care providers’ low suspicion of pneumonia. An acceptable quality of care at public as well as private facilities must be promoted in all sectors (Graham, et al., 2008).

The interpretation that low quality of care could explain some of the failures to improvement of sick children in Studies II and III were supported by caretakers’ reports in Study III. Long waiting times, reported harshness from staff and lack of necessary drugs/equipment were major problems at the hospital according to caretakers seeking care for a fatally ill child (III). Quality of treatment for febrile children has been shown to be sub-optimal in several sub-Saharan African countries (Zurovac and Rowe, 2006). Health worker attitudes may influence decisions regarding how soon and where to treat the child (Gross and Howard, 2001), as well as caretakers’ eventual compliance to treatment (D’Souza, 2003). While resource constraints can explain some of the poor quality of care, absence of or poor adherence to hospital protocols contributes to further deterioration of quality of care. Decreased mortality at hospital following introduction of case management protocol for pneumonia has been reported from Zambia (Smyth, et al., 1998). Quality of care could be further improved through supervision and training of staff (Rowe, et al., 2005).

Some children with simultaneous symptoms of difficult/rapid breathing and fever were reportedly treated with mono-therapy of antimalarials or antibiotics when seeking care outside the home during the development of severe pneumonia (II). This is despite the fact that children suffering from difficult and/or rapid breathing and fever should be
dually treated with antibiotics and antimalarials under national and IMCI policy (WHO/UNICEF, 2008). If correctly implemented, integrated approaches to management of the sick child have the ability to produce significant improvements in quality of care (Arifeen, et al., 2004, Armstrong Schellenberg, et al., 2004). In resource constrained settings, integrated syndrome-based management may even help to rationalize admission policy and standardize pediatric care at the hospital level (English, et al., 2003).

In Study III, financial constraints at the individual level and resource constraints in the health system appeared as the greatest barriers to adequate care of fatally ill children. Concentration of deaths in the poorest quintiles (III) may reflect an inequity pattern with less-poor children receiving more appropriate care than the poorest (Schellenberg, et al., 2003). Results indicate an urgent need to increase public health expenditure to the recommended minimum of USD28 per capita per year (WHO, 2006a) and work for strengthening of health systems with limited resources (Travis, et al., 2004).

5.4 Utilization and reporting of antibiotics and antimalarials

Caretakers appeared to have a lower awareness of antibacterial drugs compared to antimalarials. Mothers in focus groups never referred to any brand names or generic names of antibiotics when asked how to treat a child with symptoms of pneumonia, but used the general term ‘tablets’, or specified paracetamol (I). In Study II and IV, some caretakers knew the child had been given an antibiotic but could not tell the name of the drug. This could possibly imply that knowledge of the use and benefits of antibacterial drugs is limited, similar to Botswana where antibiotics had low labeling and knowledge scores among patients (Boonstra, et al., 2003) but contradicting findings from Viet Nam, where mothers had good knowledge of antibiotic names (Halfvarsson, et al., 2000). The fact that some children reportedly received antibiotics, but still failed to improve or recover, merits further investigations about etiologies and resistance patterns in this setting.

In contrast, antimalarial drugs like chloroquine were repeatedly suggested as the drug of choice for any febrile condition (I) and 13% of children diagnosed with severe pneumonia were reported to have received antimalarial drugs only during the development of disease (II). Health workers in Iganga/Mayuge stated that community members prefer antimalarial drugs even for respiratory problems (I), a situation which has been previously described for western Uganda (Kallander, et al., 2005). This exemplifies how mothers possibly have received more information about malaria and the benefits of antimalarial drugs than for antibiotics. The fact that no caretakers at the hospital reported administration of “unknown” antimalarials during the course of the illness (II, IV) supports community findings from focus group discussions that caretakers possess more knowledge about antimalarials than about antibiotics (I). Still, some children with reported fever alongside difficult/rapid breathing in Study II had reportedly received mono-therapy with antibiotics.

Caretakers’ reports of drug intake in their children had limited validity when compared to drug concentrations found in the blood. Study IV thereby challenges the reported drug intakes in Study II and III. The lower sensitivities than specificities indicate a larger under-reporting than over-reporting of all studied drugs. While under reporting
of antimalarial drugs has previously been described in Malawi (Nwanyanwu, et al., 1996) and Tanzania (Eriksen, et al., 2005). Study IV demonstrates a similar under-reporting for the antibiotic sulfamethoxazole. The implication of this finding is that more children than reported in Studies II and III may have received drugs.

Less than half the children with severe pneumonia in Study II were reported to have received antibiotics. If the Negative Predictive Value (NPV) of 64% and Positive Predictive Value (PPV) of 67% for sulfamethoxazole (IV) are generalized to all antibiotics, the 48% of children with reported intake of antibiotics in Study II may be re-estimated to 51%, indicating under-reporting is bigger than over-reporting. Similar estimations can be made for antimalarials, but will give higher proportions of under-reporting, since NPVs are lower than for sulfamethoxazole. While there is thus considerable misclassification of drug intake in the individual patient, at group level the overall treatment levels of antibiotics and antimalarials are less affected. Furthermore, even in spite of misclassification the finding remains that monotherapy with antimalarials or antibiotics is common in children with difficult and/or rapid breathing and fever. This can not be accepted practice. Even in the case of a positive malaria blood slide, withholding antibiotics is not justified in a child presenting with simultaneous pneumonia symptoms (Berkley, et al., 2005). Efforts to provide dual treatment with both antimalarials and antibiotics as recommended by Integrated Management of Childhood Illness (WHO/UNICEF, 2004) need to be increased.

When care had been sought outside the home, caretakers were less aware of the drugs given compared to when treated at home. 16/140 children diagnosed with severe pneumonia had been treated outside the home with drugs where even the type of drug remained unknown to the caretaker (IV). While this finding may help explain the limited validity of the caretakers’ reported drug intake, it also suggests health workers’ counseling of caretakers on treatment is poor, as previously described (Pariyo, et al., 2005). Inaccurate prescribing of drugs combined with inadequate examination practices may hamper compliance and thus recovery and reduce caretakers’ trust in providers (Boonstra, et al., 2005). Good patient knowledge of the medicine prescribed is one of the essential prerequisites for patient compliance. Quality of labeling, the time spent informing the patient and the communication skills of the dispenser can therefore affect compliance rates as well as ability to recall the treatment.

Low validity of caretakers’ reports of drug intake may increase risk of incorrect management of the child at health facilities. If clinicians are unaware of drugs given prior to arrival at the health facility, they may chose to administer the same drug already given to the child without improvement. This may contribute to further delays of appropriate treatment and also allow toxic levels of drugs to accumulate (Bjorkman and Phillips-Howards, 1991). The positive and negative predictive values for drugs given during the ongoing illness episodes limit the value of caretakers’ reports to guide further treatment.

Interviewing caretakers on previous care-seeking and drug intake is commonly done in both clinical practice and public health research and major international surveys like the Demographic and Health Survey (ORC Macro, 2006, Schellenberg, et al., 2003, Wardlaw, et al., 2006). The validity of self-reported or interviewed drug intake has
been found wanting in studies from high income countries (Cummings, et al., 1984, Garber, et al., 2004, Prado, et al., 2007) and in e.g. antiretroviral care in low income countries (Minzi and Naazneen, 2008). However, this appears less studied for intake of antimalarials and antibiotics in children (Eriksen, et al., 2005, Nwanyanwu, et al., 1996).

5.5 Methodological consideration

All study tools were pre-tested and revised before use. For Study II and IV, a pilot study was conducted before the study started to train study staff and to streamline study procedures. Efforts were made to ensure quality of information through supervision of interviewers and regular questionnaire completeness checks. A subset of chest radiographs were interpreted by two radiologists, blinded to each others’ results, to check for inter-observer agreement: this showed a substantial agreement of interpretations (kappa value 0.78).

To increase qualitative credibility, several months were spent in each study setting during data collection. Peer debriefing, defined as "a process of exposing oneself to a disinterested peer in a manner paralleling an analytic session and for the purpose of exploring aspects of the inquiry that might otherwise remain only implicit within the inquirer's mind" (Lincoln and Guba, 1985), was done through frequent discussions between co-researchers throughout the course of the study, discussing the analysis and emerging categories and themes of the studies.

Setting and sampling

The urban study setting in Studies II and IV may result in recruited children having received more care from different sources compared to what would be the case in a more rural setting. It is also worth highlighting that all studied children actually managed to reach the hospital. This may affect the study in that caretakers of children who never reach a hospital would not report such high numbers of recognition of difficult and/or rapid breathing or seek care in a different manner. Also, children not reaching the hospital may lack access to adequate care and thus suffer from additional barriers to care compared to the included children. Alternatively, children ending up at the hospital may represent more severe or complicated diagnoses than children who recovered from primary treatment. Malaria transmission and the availability of different health care providers are other variables that may differ between Kampala and more rural settings.

Study II and IV may have been further affected by recruiting only during daytime, since more severe cases or children from farther away may seek care out of office-hours. HIV infection and wasting can possibly cause bias in that known HIV-positive children may have different pathogens, have a longer history of disease and possibly come for treatment earlier when symptoms get worse, compared to HIV-negative children. However, HIV-infection and wasting were controlled for in multi-variate analysis in Study II and by excluding symptoms reported to have been recognized more than 30 days ago when analyzing time to develop severe pneumonia. Study IV would have benefited from inclusion of more than three drugs since the urban study-setting exposes caretakers to a variety of easily accessible drugs. This may limit generalizability to more rural communities.
The studied areas represent two of many different malaria endemicities and two ethnic groups in areas with relatively good access to health care. Findings may thus not be generalizable to all of Uganda.

**Information bias**

Recall bias may threaten validity as well as reliability and may be a source of bias in Study II, III and IV, as in most studies involving interviews on morbidity and drug use (Kroeger, 1985). Severe symptoms are remembered longer than mild ones (Linder, 1965) but short recall periods have been shown able to capture even mild problems accurately (Roberts, et al., 1996). Recall may be more complicated for drug use where accuracy is affected by type of drugs used, duration of drug use, time since last prescription and number of drugs used (Paganini-Hill and Ross, 1982, Van der Brandt, et al., 1991, West, et al., 1995). Socially desirable bias may also have been introduced if caretakers over-reported desirable behaviors and under-reported undesirable behaviors (Bowling, 2005).

The long illness episodes reported by some caretakers in Study II and III may reflect the belief that one illness disappears and reappears over a long time period (Hausmann-Muela, et al., 2002) or e.g. underlying HIV-infection. Discontent with providers may have been under-reported due to worries it might have consequences for future possibilities to receive healthcare.

In study IV, except from being affected by simple forgetting and confusion about the names of the drugs (McCombie, 2002), caretakers may have given what they perceived to be socially desirable answers regarding drugs, for example if they were concerned that the care of the child at the hospital could be negatively influenced if they told health workers about prior treatment given. Validity was possibly further impaired by the way prior drug use was asked for. Interviewers asked open questions about what drugs had been given to the child during the illness and then probed for use of trimethoprim-sulfamethoxazole, chloroquine and sulfadoxine-pyrimethamine. Directed recall, for example by probing for specific drugs, is demonstrated to give better sensitivities compared to only using open-ended questions (Klungel, et al., 2000). Under-reporting of drug intake could also have appeared due to misunderstanding of questions, if caretakers did not understand the drug types and names asked for, and validity could possibly have been improved if drugs had been demonstrated to the caretakers during interviews.

**Blood sampling and drug analysis**

Drug analysis could have been affected by contamination of samples or if an incorrect blood volume was sampled on filter papers. However, all sample volumes were carefully measured using an Eppendorf pipette dispensing 100 µL of blood from a venous sample of blood, taken for the purpose of another study (Nantanda, et al., 2008). Contamination was avoided by use of gloves, disposable pipette tips and by putting the sample in an individual plastic cover immediately when dry. Neither transport, length of storage, nor tropical temperatures affect chloroquine and sulfadoxine content in blood sampled on filter papers (Bergqvist, et al., 1986). The coefficients of variation (CV) for quality control samples of sulfamethoxazole at 3.8
µg/ml and 152.0 µg/ml were 5.3% and 3.7% respectively. CV for sulfadoxine were 5.7% and 3.8%, at 4.6 µg/ml and 186.2 µg/ml during the assays. Lower limits of quantification for sulfadoxine and sulfamethoxazole were 1.6µg/mL and 1.3µg/mL (Lindkvist, et al., 2008) and for chloroquine 32ng/mL (Lindegardh, et al., 2002).

The pharmacokinetic properties of the analyzed drugs may have influenced the results. The very long half life of especially chloroquine, 30-60 days (Ducharme and Farinotti, 1996), may be one explanatory factor to caretakers’ under-reports of drug intake, since the drug may have been given for a previous illness episode.

**Triangulation**

In Study I, we used a triangulation of methods (focus group discussions and key informant interviews), informants (mothers, health workers and traditional healers) and researcher-professions (public health professionals, medical doctors, an anthropologist and a social scientist) to check for consistency and disagreement between different respondents. The use of a DVD showing children with respiratory problems produced information additional to the focus group discussions and confirmed mothers’ perceptions through the practical perspective. Results were triangulated between Study I and Study III, where stated treatment preferences were compared to reported treatment during actual illness episodes. Also, results between caretakers’ stated action for a child with difficult and/or rapid breathing (DRB) were triangulated with results from Study II, where caretakers were asked what they did for an actual episode of DRB. The same kind of triangulation was done between Study I and Study III. The validation of drug intake in Study IV triangulated reported drug intake from Study II and III.
6. CONCLUSIONS AND POLICY IMPLICATIONS

- Caretakers have limited awareness of the appropriate biomedical treatment of symptoms of pneumonia (I, II, III)

- Local illness concepts for difficult and/or rapid breathing have limited influence on choices of care in the studied setting (I, III)

- Progression to severe pneumonia occurs rapidly: two days after recognition of difficult or rapid breathing (II)

- Recognition of difficult and/or rapid breathing does not prompt any particular care but a multitude of care is used - at home and from private and public health care providers (I, II, III)

- Children with acute febrile illness may be brought to health care providers but still fail to improve/recover (II, III)

- Caretakers’ reports on the child’s prior drug intake may be of low validity, especially when treatment has been given at a health facility (IV)

Implications of findings

Findings indicate a need to improve caretakers’ as well as health care providers’ awareness on the symptoms and biomedical treatment of pneumonia. Due to the tendency to interpret and treat any febrile condition as malaria, there is a further need to emphasize pneumonia as a separate, but equally serious, condition from malaria. Since a variety of local illness concepts can include symptoms of difficult and/or rapid breathing, there may be reason to encourage caretakers to respond on key pneumonia symptoms rather than to any specific illness concept.

Since severe pneumonia develops rapidly, there is a need to define and implement guidelines encouraging caretakers to seek immediate appropriate care after recognition of difficult and/or rapid breathing. Ideally, adequate antibiotic treatment should be made available close to where people live and one option would be to allow community health workers to diagnose and treat pneumonia in addition to malaria. However, satisfactory quality of care is as important, and may be as hard to achieve, in a community health worker program as it is in already existing facilities. Since many children in the included studies were brought to at least one health care provider during the illness, improved quality of care at public as well as private facilities may advance the management of children with pneumonia. Efforts are needed at all health care levels to provide dual treatment with antibiotics and antimalarials in children with simultaneous difficult/rapid breathing and fever.

Due to the possibly low validity of caretakers’ reports of drug intake when interviewed with probing, interview methods to elicit valid and reliable information on previous drug intake need to be developed.
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