THE EFFICACY OF ZINC AS ADJUNCT THERAPY IN THE
TREATMENT OF SEVERE PNEUMONIA IN CHILDREN ADMITTED
TO MULAGO HOSPITAL

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A dissertation submitted in partial fulfilment of the requirements for the
award of the degree of Master of Medicine (Paediatrics and Child Health),

Makerere University

2007
DECLARATION

I, Maheswari Srinivasan G, hereby declare that the work presented in this dissertation has not been presented for any other degree in any University.

Signed: Maheswari Srinivasan G.

Date: 27/07/2007

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DEDICATION

This book is dedicated to the memory of my parents, late Mr and Mrs. Srinivasan Gurusamy and the twenty-eight children whose lives we could not save during this study.
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♦ I thank God almighty who enabled me to complete this thesis.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEDICATION</td>
<td>ii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENT</td>
<td>iii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>TABLE OF FIGURES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>ix</td>
</tr>
<tr>
<td>OPERATIONAL DEFINITIONS</td>
<td>x</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>xi</td>
</tr>
</tbody>
</table>

## CHAPTER ONE
1.0 BACKGROUND INFORMATION AND LITERATURE REVIEW                       1
1.1. INTRODUCTION AND BACKGROUND                                         1
  1.1.1 Global Situation                                                  1
  1.1.2. Sub-Saharan Africa                                             1
  1.1.3. Pneumonia in Uganda                                             1
  1.1.4. Global Zinc deficiency                                           1
  1.1.5. Zinc status in Uganda                                           2
1.2. LITERATURE REVIEW                                                   2
  1.2.1. Zinc                                                            2
  1.2.2 Zinc and the immune system                                       4
  1.2.3. Zinc and pneumonia                                              5
1.3. DIAGNOSIS OF PNEUMONIA                                             5
  1.3.1 Clinical presentation of pneumonia                             5
  1.3.2 Laboratory diagnosis of pneumonia                             6
  1.3.3 Management of pneumonia in children                           6

## CHAPTER TWO
2.0 STATEMENT OF THE PROBLEM AND STUDY JUSTIFICATION                    7
2.1 Statement of the problem                                             7
2.2 Study justification                                                  7
2.3 Research question                                                    8
2.4 Objective of the study                                               8
  2.4.1 General Objective                                               8
  2.4.2 Specific objectives                                              8
2.5 Study hypothesis                                                     8

## CHAPTER THREE
3.0 METHODS                                                            9
3.1 Study design                                                        9
3.2 Study site                                                          9
3.3 Population                                                          9
  3.3.1 Target population                                               9
  3.3.2 Accessible population                                           9
  3.3.3 Study population                                                10
3.4 Study unit                                                          10
3.5 Selection criteria                                                  10
  3.5.1 Inclusion criteria                                              10
LIST OF TABLES

Table 1: Baseline clinical characteristics of 352 children admitted with severe pneumonia... 19
Table 2: Logistic regression for factors predicting mortality in zinc and placebo group. ...... 27
LIST OF FIGURES

Figure 1 Trial profile for children with severe pneumonia screened and enrolled into the study ................................................................. 17

Figure 2 Kaplan Meier curve for time to normalisation of respiratory rate among children with severe pneumonia ........................................... 22

Figure 3 Kaplan Meier curve for Time to normalisation of chest indrawing in severe pneumonia .............................................................................. 23

Figure 4 Kaplan Meier curve for Time to normalisation of Oxygen saturation in severe pneumonia .............................................................................. 24

Figure 5 Kaplan Meier curve for mortality by treatment group among 352 children admitted with severe pneumonia .............................................................................. 26
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACU</td>
<td>Acute Care Unit</td>
</tr>
<tr>
<td>ALRI</td>
<td>Acute lower respiratory tract infection</td>
</tr>
<tr>
<td>ARI</td>
<td>Acute respiratory tract infection</td>
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<tr>
<td>CMI</td>
<td>Cell Mediated Immunity</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency virus</td>
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<tr>
<td>HMIS</td>
<td>Health Management Information System</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
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<td>PIDC</td>
<td>Paediatric Infectious Disease Clinic</td>
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<td>RNA</td>
<td>Ribonucleic acid</td>
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<td>Th 2</td>
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<td>UDHS</td>
<td>Uganda Demographic Health Survey</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
OPERATIONAL DEFINITIONS

Pneumonia: A febrile illness with cough and respiratory distress with evidence of localised or generalised patchy infiltrates on chest x-ray

Severe pneumonia: Cough or difficulty in breathing, fast breathing and chest indrawing

Very severe pneumonia: Cough or difficulty in breathing, fast breathing, chest indrawing, and cyanosis or inability to feed

Chest in drawing: Continuous subcostal reccessions observed while the child is breathing

HIV Seropositive: Positive (reactive) results following a test for presence of HIV antibodies in blood using the rapid test for children aged 18 months or more, or an RNA PCR test in children less than eighteen months

Positive chest X-ray: Presence of any pathological findings related to pneumonia on chest X-ray regardless of the extent of the disease

Adverse drug effects: Symptoms, signs or laboratory characteristics which are unexpected and related to drug administration

Case fatality rate: The proportion of individuals with a disease who die of that disease

Hypoxaemia: Oxygen saturation of less than 90%

Placebo: Placebo is an inactive pill, liquid, or powder that has no treatment value.

Efficacy: The maximum ability of a drug or treatment to produce a result regardless of dosage.

Effectiveness: The ability of a vaccine or a drug to produce desired beneficial effect.

Adjunct therapy: Another treatment used together with the primary treatment. Its purpose is to assist the primary treatment.
ABSTRACT

BACKGROUND

Acute respiratory tract infection (ARI) is the most common cause of morbidity and mortality in children less than 5 years worldwide. It accounts for 10-30% of all childhood deaths. The burden of lower respiratory tract infections (ALRI) is 2-10 times more common in developing countries than developed countries. In 2004, the World Health Organisation (WHO) documented that pneumonia accounted for 20% of the overall childhood death worldwide and pneumonia was the leading cause of deaths in children under five year. In 2000, ALRI accounted for 23-34% of all admissions in Mulago hospital with case fatality ranging between 10-25%

Zinc deficiency is a global nutritional problem affecting populations of low socioeconomic status in both developing and developed countries. The prevalence of zinc deficiency in Uganda ranges between 20-69 % in children and 21-29% in adults.

Randomised controlled studies from Bangladesh and India by Brooks et al and Dillip et al respectively showed significant improvement with zinc supplementation in severe pneumonia whereas Bose et al from South India found no significance. A recent study recommends further research to clarify the role of zinc as an adjunct therapy in the treatment of severe pneumonia. Its benefit regarding severe pneumonia is still unknown in Uganda.

OBJECTIVES

To determine the efficacy of zinc supplementation as adjunct therapy in the treatment of severe pneumonia in children admitted to Mulago Hospital Paediatric wards.

Study design: A double blind randomised placebo-controlled clinical trail.

Study setting: The Acute Care Unit (ACU) and paediatric wards of Mulago Hospital, Uganda’s national referral and teaching hospital.

Intervention: Either zinc or placebo was given as adjunct therapy to children with severe pneumonia who were followed up for seven days.

Methods: Children aged 6-59 months who fulfilled the WHO case definition of severe pneumonia were randomized to received either zinc or placebo in addition to an antibiotic. Chest x-rays were taken to confirm the diagnosis of pneumonia and to identify complications.
HIV sero-status of the children was established. A blood slide for malaria parasites was done, since severe malaria could simulate pneumonia. The main outcomes included were the proportions of children who showed clinical improvement on time taken for normalisation of respiratory rate, time taken for chest indrawing to disappear and time taken for oxygen saturation to normalise, death and adverse effects.

Results: Three hundred and fifty two children were enrolled into this study, treated and followed up. Each treatment arm consisted of 176 children. The difference in mean time taken for normalisation of respiratory rate, chest indrawing and oxygen saturation in both intervention arms was not statistically significant. Twenty-eight children died, 7 in the zinc group (3.9%) and 21 (11.9%) in placebo group, the difference was statistically significant (P=0.005). Relative Risk (RR) was 0.33 (95% CI of 0.15-0.76). Number needed to treat was 13. This means that we need to treat 13 children with zinc as adjunct therapy to avert one death. Zinc supplementation was well tolerated even though two children developed vomiting initially; subsequent doses were tolerated well.

Conclusion:

1. Zinc given as adjunct therapy in the treatment of childhood severe pneumonia significantly reduced mortality with efficacy of 0.67 as compared to the placebo.
2. There was no difference in time taken for normalisation of respiratory rate, chest indrawing and oxygen saturation in the intervention and placebo arms
3. There were no serious adverse events reported and zinc was well tolerated.

Recommendation

All children aged 6-59 months admitted with severe pneumonia in Uganda should receive zinc supplement as adjunct therapy in order to reduce mortality.
CHAPTER ONE

1.0 BACKGROUND INFORMATION AND LITERATURE REVIEW

1.1. INTRODUCTION AND BACKGROUND

1.1.1 Global Situation
Acute respiratory tract infection (ARI) is the most common cause of morbidity and mortality in children less than 5 years worldwide.\(^1\) It accounts for 10-30% of all childhood deaths. Each year, 10 million children die before their fifth year. Two million of these deaths are due to ARI mainly pneumonia and ninety seven percent occur in developing countries.\(^2\,^4\) The burden of acute lower respiratory tract infections (ALRI) is 2-10 times more common in developing than developed countries.\(^5\,^8\,^6\,^7\) In 2004, the World Health Organisation (WHO) documented that pneumonia accounted for 19% of the overall childhood death. It also stated that pneumonia was the leading cause of deaths in children under five years of age.\(^9\)

1.1.2. Sub-Saharan Africa
Several studies in Africa have shown that pneumonia is the second commonest cause of ill health and it is the leading cause of death among children under five years of age.\(^10\,^12\) One study from Tanzania estimated that the prevalence of pneumonia among children under five years of age was 36.8%.\(^13\) Another study from Botswana showed that the leading cause of death in children less than five years was pneumonia, and in this study the mortality in HIV infected children and non-HIV infected children was 67% and 33% respectively.\(^14\) A study in Zambia on lung disease in children found that more than half (64%) of the cases at autopsy were due to pneumonia.\(^15\) The national mortality figures for Kenya in 1980 showed that ALRI accounted for 19% of childhood deaths. Wafula et al found pneumonia to be the most common cause of childhood death in Kenya.\(^16\)

1.1.3. Pneumonia in Uganda
In Uganda, ALRI accounted for about 10.5% of the morbidity and mortality among children less than five years.\(^17\) In 2000, ALRI accounted for 23-34% of all admissions in Mulago hospital with case fatality ranging between 10-25%.\(^18\,^19\) In a review of all the documented deaths in Mulago hospital general paediatric wards in 1995, Bisase et al reported that ALRI was the leading cause of death accounting for 22.5% of total paediatric deaths.\(^20\)

1.1.4. Global Zinc deficiency
Zinc deficiency is a global nutritional problem affecting populations of low socio economic status in both developing and developed countries.\(^21\) It is one of the ten big factors
contributing to the burden of disease in developing countries and is associated with high mortality. An estimated 68-94% of children are at risk of zinc deficiency.\textsuperscript{21,22} Populations in South East Asia and sub-Saharan Africa are at greatest risk of zinc deficiency because zinc intakes are inadequate for about one third of the population.\textsuperscript{23} In addition, Zinc is the most deficient nutrient in complementary food mixtures fed to infants during weaning.\textsuperscript{24}

Worldwide, zinc deficiency is responsible for approximately 16% of LRTI. A total of 1.4% (0.8 million) of deaths worldwide were attributable to zinc deficiency, with 1.4% of these deaths in males and 1.5% in females.\textsuperscript{25} Research conducted over the past ten to fifteen years by Laura E et al estimated that zinc deficiency in children aged less than five years caused 406,000 pneumonia deaths, 207,000 malarial deaths and 176,000 diarrhoeal deaths.\textsuperscript{26} All these deaths, could have been prevented by public heath action.\textsuperscript{25,26}

1.1.5. Zinc status in Uganda

Uganda is one of many countries with a high prevalence of zinc deficiency.\textsuperscript{22} Bitarakwate in 2000 and Bimenya in 1980, established serum zinc reference values to be 8.9 and 10.1 μmol/l respectively in healthy Ugandan children. They found no significant age or sex difference.\textsuperscript{27-29} Studies of sick children with persistent diarrhoea, HIV positive children and sicklers demonstrated low zinc levels.\textsuperscript{27,30} Bachou in 1998 found low hair zinc levels (less than 1.68 μg/gm) in 90% of rural West Nile adolescents while Kikafunda et al in 1998 demonstrated weight gain in a randomised clinical interventional trial in Kampala preschool children after zinc supplementation, which signified zinc deficiency.\textsuperscript{31,32}

1.2. LITERATURE REVIEW

1.2.1. Zinc

Zinc is an essential micronutrient important for metabolism second only to iron. Zinc is a type two micronutrient and therefore does not have body stores. Physiological requirements of zinc are increased during the periods of rapid growth because it has a significant role in nucleic acid and protein synthesis.

Zinc activates growth (height, weight and bone development) in infants, children and teenagers.\textsuperscript{33} More than half of the body's zinc is found in muscle tissue. This mineral is also found in other parts of the body, which include the bones, eyes, prostate gland, testes, skin and kidneys.\textsuperscript{33,34}
**Dietary source:**
Zinc can be obtained from seafood (oysters), red meat, nuts, poultry products, milk products, fish and cereals. Dietary fibre, particularly phytates, can interfere with the body’s ability to absorb zinc. Excess intake of zinc (from supplements or fortified foods) can impair iron and copper absorption. Zinc found in breast milk is better absorbed than that from formula milk.\textsuperscript{34,35}

**Functions of zinc:**
Zinc is an antioxidant and an important cofactor for the antioxidant-enzyme superoxide dismutase (SOD). It is also a cell membrane stabilizer. It is also essential for protein synthesis, integrity of cell membranes, maintenance of DNA and RNA, tissue growth and repair, wound healing, and cell reproduction.\textsuperscript{25,36,37} It is essential for more than 300 enzymes, structural proteins and hormones.

**Zinc deficiency:**
Clinical features are non-specific in most cases but glossitis, alopecia, nail dystrophy, diarrhoea can occur in young children. Zinc impairs the immune system and decreases resistance to infection.\textsuperscript{22,36,37} In older children, it causes delay in pubertal development and growth retardation.\textsuperscript{38} Low levels of growth hormone, insulin and cortisol were noted in zinc deficient children.\textsuperscript{25,34}

**Zinc requirements:**
Infants require 5mg of zinc, while children require 10mg daily. Requirements for adolescents are a bit higher with male adolescents requiring 15mg while females require 12mg daily.

**Zinc formulations:**
The more easily absorbed forms of zinc are zinc acetate, zinc picolinate, zinc gluconate, zinc citrate, zinc glycerate, Zinc chloride and zinc monomethionine.\textsuperscript{25,34}

**Zinc Toxicity:**
Clinical manifestations of zinc toxicity (doses > 80 mg/day) include:
- **Cardiovascular system:** Hypotension, tachycardia (excessive doses)
- **Respiratory system:** Pulmonary edema (excessive doses)
- **Central nervous system:** Hypothermia (excessive doses)
Gastrointestinal system: Indigestion, nausea, vomiting and diarrhoea (common)

Hematologic: Neutropenia, leukopenia

Hepatic: Jaundice (excessive doses)

Ocular: Blurred vision (excessive doses)

Miscellaneous: Profuse diaphoresis, can interfere with copper absorption and impair immune response.\textsuperscript{35}

Interactions with other micronutrients and drugs

Drug and nutrient interactions:

Drugs that can cause depletion of zinc include oral contraceptives, loop diuretics, thiazide diuretics, H2-receptor antagonists, zidovudine (AZT), D-penicillamine, and ethambutol.

Nutrient and nutrient interactions:

Copper, calcium, and iron compete with zinc for protein-binding sites that regulate absorption. Due to this competition for absorption sites, elevated copper, calcium and/or iron can cause a depletion of zinc.\textsuperscript{35}

1.2.2 Zinc and the immune system

Zinc is an important nutrient for cell replication and function and thus is required for normal functioning of all body systems. The first system to be affected with even mild deficiencies of zinc is the immune system, reflecting its important role in immune function.\textsuperscript{22} As recently reviewed by Sanker and Prasad (1998), zinc deficiency impairs multiple aspects of immune function, including barrier and non-specific immunity, specific immune components (lymphocytes, monocytes, macrophages, neutrophils and natural killer cells), and mediators of immune function such as glucocorticoids, thymulin activity, and cytokine function.\textsuperscript{39,40}

Due to its multiple role in immune function, zinc deficiency is associated with increased risk of morbidity and mortality due to infectious disease.\textsuperscript{22,39}

Lack of zinc is associated with lymphopenia and atrophy of the thymus with a resultant decrease in delayed type II hypersensitivity, and other immune responses mediated by T cells.\textsuperscript{36,37,39} There is an imbalance in the production of T-helper cells with different functions.

T-helper\textsubscript{1} cells (Th1) have a predominately cellular function and are important in defence against viral and intracellular pathogens. T-helper\textsubscript{2} cells (Th2) are involved in the production of antibodies.\textsuperscript{37} Experimentally induced zinc deficiency in animals shows that there is a significant reduction in the production of antibodies and in the function of natural killer cells which leads to 30-80% loss in defence capacity.\textsuperscript{39} Zinc is also required for cell replication
and is thus essential for regeneration, healing of wounds, turnover of epithelial cells, antibody production and phagocytosis. These essential functions of zinc explain why zinc plays such an important role in protection against infections.\textsuperscript{25,39}

1.2.3. Zinc and pneumonia
The high prevalence of zinc deficiency in children in developing countries along with immune impairment, leads to increased susceptibility to pathogens resulting in diarrhoea, pneumonia and malaria.\textsuperscript{22} Apoptosis is also potentiated by zinc deficiency.\textsuperscript{22,25} Impaired antibody production and delayed CMI have been noted in zinc deficiency in several studies, hence it predisposes to infections like diarrhoea and pneumonia in children under five years.\textsuperscript{39,41,42} Zinc is an antioxidant, reduces inflammation, and improves resolution of infection. In addition zinc enhances tissue repair and it acts as a microbicidal agent in high concentration.\textsuperscript{43,44} Other factors associated with increased episodes of pneumonia include malnutrition, immunodeficiency, lack of breast feeding, inadequate vitamin A supplementation and lack of immunisation.\textsuperscript{40,42} Two interventional studies done by Dilip Mahalanabis et al in India- 2004 and Brooks et al in Bangladesh have shown significant improvement in outcome of severe pneumonia with zinc supplementation where as Bose et al from South India found no significance.\textsuperscript{45-47}

1.3. Diagnosis of pneumonia

Pneumonia should be diagnosed based on a careful and detailed history, systematic clinical examination as well as chest x-ray.

1.3.1 Clinical presentation of pneumonia
Pneumonia can be diagnosed clinically in a majority of cases basing on the presenting symptoms and findings on clinical examination. Most children present with cough and or/ difficulty in breathing. The presence of fast breathing and lower chest indrawing has been shown to have a strong association with confirmed pneumonia.

Assessment of respiratory rate identifies over 75% of all cases of pneumonia.\textsuperscript{48} In order to standardize the diagnosis, WHO designed an approach based on respiratory rate and presence /absence of chest indrawing to diagnose pneumonia in children up to five years of age.\textsuperscript{49} (Appendix-I)
1.3.2 Laboratory diagnosis of pneumonia

Chest x-ray for diagnosis of pneumonia

Recognition of pneumonic infiltrates relies critically on radiological appearances, but they are minimal in early stages of disease. Chest x-ray changes usually follow clinical signs by approximately 12 hours.\textsuperscript{40} Radiology is important in establishing the type and extent of the consolidation, the presence of pleural fluid, lung abscesses, Pneumatoceles or Pneumothorax.\textsuperscript{50} A study in Fiji showed that 34\% of all cases of clinical pneumonia could be confirmed by chest x-ray.\textsuperscript{51}

Sputum Analysis

The ability to make a specific diagnosis of pneumonia by analysing sputum is based on collection techniques, preparation and analysis by experienced personnel. The sensitivity ranges from 24-60\%.\textsuperscript{52}

Blood culture

Blood cultures are useful in identifying the causative organism and sensitivity patterns, however the catch rate of organism in the blood of children with clinical features of pneumonia is about 10-30\%.\textsuperscript{53}

Oxygen saturation

Oxygen saturation is very important in a child with pneumonia, the hypoxic children are 4 times more likely to die than those without hypoxemia.\textsuperscript{48,54} The work done by Tumwesigye in Mulago hospital, Uganda showed that 59\% of children with signs of ALRI had hypoxemia.\textsuperscript{54}

1.3.3 Management of pneumonia in children

WHO has defined protocols for management of pneumonia in children up to five years based on classification of the severity of the illness.\textsuperscript{49}

All children with cough or difficulty in breathing should be assessed for pneumonia using two criteria: fast breathing and lower chest indrawing. Two additional signs cyanosis and inability to drink are used to distinguish severe from very severe pneumonia. Children with very severe pneumonia require oxygen therapy.\textsuperscript{9,49} A summary of the WHO protocols for management of pneumonia is presented in appendix II.
CHAPTER TWO

2.0 STATEMENT OF THE PROBLEM AND STUDY JUSTIFICATION

2.1 STATEMENT OF THE PROBLEM

Acute lower respiratory tract infections are the leading cause of morbidity and mortality in children less than five years worldwide.\textsuperscript{1,2} They contribute 10-30% of all childhood deaths 70% of which are in developing countries especially in Sub-Saharan Africa.\textsuperscript{3,4}

In Uganda, pneumonia is the second commonest cause of death among children. It accounts for 25 to 33% of admissions and contributes 30% of deaths in Mulago Hospital. The case fatality rate due to pneumonia ranges from 10 to 15%.\textsuperscript{18,19}

There is in addition a high prevalence (20-69%) of zinc deficiency among children in Uganda.\textsuperscript{27,30-32} In many developing countries, including Uganda the rural diets are mainly plant based so that their contribution to the total dietary intake of zinc is small. Plant based diets often contain high levels of phytic acid and dietary fibre known to inhibit the absorption of dietary zinc.\textsuperscript{34,35}

Two clinical studies have shown that zinc supplementation improves the outcome of severe pneumonia in children by reducing the duration of hospitalisation and complications related to pneumonia.\textsuperscript{45,46}

2.2 STUDY JUSTIFICATION

According to the Uganda National clinical guidelines on management of common conditions 2003, the management of pneumonia includes antibiotics and vitamin A.\textsuperscript{62} Although there is evidence from elsewhere to shown that zinc adjunct therapy is beneficial this has not yet been verified in Uganda.\textsuperscript{45,46} There are no studies on effect of zinc on outcome of severe pneumonia from Uganda. We therefore carried out this study to ascertain whether zinc supplementation would improve the outcome of severe pneumonia in Ugandan children.
2.3 RESEARCH QUESTION

1. What is the effect of zinc as adjunct therapy in severe pneumonia on time taken for normalisation of respiratory rate, O₂ saturation and chest indrawing?
2. What is the effect of zinc supplementation as adjunct therapy in severe pneumonia on mortality?
3. What are the adverse effects of zinc supplementation as adjunct therapy in children with severe pneumonia?

2.4 OBJECTIVE OF THE STUDY

2.4.1 General Objective
To determine the effect of zinc supplement as adjunct therapy in treatment of severe pneumonia in children less than five years admitted to Mulago hospital.

2.4.2 Specific objectives
1. To establish the effect of zinc as adjunct therapy in children with severe pneumonia on time taken to normalisation of Respiratory rate, O₂ saturation and chest indrawing.
2. To determine the effect of zinc supplementation, as adjunct therapy in children with severe pneumonia, on mortality.
3. To describe the adverse effects of zinc supplementation as adjunct therapy in children with severe pneumonia.

2.5 STUDY HYPOTHESIS

Alternate Hypothesis
Zinc as adjunct therapy given orally in a dose of 10mg to children< 1 year and 20mg to children >1 year, aged 6-59 months living in zinc deficient areas who present with severe pneumonia according to WHO criteria will reduce mortality by 36%.

Null hypothesis
Zinc as adjunct therapy does not reduce mortality in children with severe pneumonia.
CHAPTER THREE

3.0 METHODS

3.1 STUDY DESIGN

The study was a randomised double blind placebo-controlled clinical trial.

3.2 STUDY SITE

The study was conducted in the Acute Care Unit and the general paediatric wards of Mulago Hospital. Mulago hospital is a teaching and national referral hospital for Uganda and receives patients from Kampala and referrals from other districts in the country. The acute care unit is run by the Department of Paediatrics and Child Health and it is the emergency unit for sick children up to 12 years with medical conditions. The unit admits about 60 to 80 children daily of whom 10 to 20% of the admissions are due to Acute Lower Respiratory Tract infection.

An average of 23,890 children are hospitalised annually, 4556 of these with pneumonia accounting for 8-20% of admissions. The recommended (WHO) first line treatment for severe pneumonia is intravenous Chloramphenicol 25 mg/kg six hourly for ten days; if no improvement after two days or the child deteriorates, the treatment is switched to second line treatment with Gentamicin 2.5 mg/kg twelve hour plus Cloxicilin 50 mg/kg every sixth hourly for two weeks. However, our children were randomised to receive either IV chloramphenicol or IV ceftriaxone 75mg/kg once daily for seven day. This was another intervention assessing efficacy of IV chloramphenicol and IV ceftriaxone in the treatment of severe pneumonia.

3.3 POPULATION

3.3.1 Target population

All children aged 6 months to 59 months in and around Kampala region.

3.3.2 Accessible population

All children aged 6 months to 59 months attending acute care unit of Mulago National referral Hospital. Our study participants were derived from the population of another intervention of chloramphenicol versus ceftriaxone in treatment of severe pneumonia.
3.3.3 **Study population**
Children presenting with severe pneumonia aged 6-59 months and meeting the criteria for the study.

3.4 **STUDY UNIT**

Children aged 6 – 59 months with a diagnosis of severe pneumonia admitted to ACU in Mulago Hospital and fulfilling the inclusion criteria when parents consent for the study.

3.5 **SELECTION CRITERIA**

3.5.1 **Inclusion criteria**
1. Children aged 6– 59 months admitted to ACU who fulfil WHO criteria for diagnosis of severe pneumonia. (state diagnosis criteria)
2. Written informed consent from the caretaker.

3.5.2 **Exclusion criteria**
1. Children with known heart disease
2. Children on medication with Zinc supplements
3. Children with obstructive air way disease
3.6 SAMPLE SIZE ESTIMATION

A study comparing the effectiveness of zinc as adjuvant therapy in the treatment of severe pneumonia in Bangladesh found that the proportion of children still having signs of pneumonia at 100 hours while on placebo therapy was 68% and for those receiving zinc therapy 50% respectively. With the above estimates, we calculated a sample size of at least 150 patients in each arm with 90% power and 95% confidence level ( = 0.05).

The desired sample size was calculated using the formula by Chris Elwood as shown

\[
n = \frac{(p_1q_1+p_2q_2)K}{(p_1-p_2)^2}
\]

\(n\) = sample size in each arm

\(K = (\alpha + \beta)\)

\(q_1 = 1 - p_1\)

\(q_2 = 1 - p_2\)

\(P_1\) = Proportion in placebo group

\(P_2\) = Proportion in zinc group

\[
(0.68 \times 0.32) + (0.5 \times 0.5) (1.96 + 1.65)
\]

\[
(0.68-0.5)^2
\]

The actual calculated sample size was 300, assuming 10% loss to follow up, the total number of study patients were 333. However, the number of children studied was 352.

3.7 SAMPLING PROCEDURE

3.7.1 SCREENING AND ENROLMENT OF PATIENTS

Children aged 6-59 months with cough, fever and difficulty in breathing accompanied by their parents / caretakers were screened, explained and enrolled for the study. Those screened were recorded in a screening book. Eligible children were consecutively enrolled daily until the required sample size of the 352 children was reached. The principal investigator or a trained research assistant recruited the children who fulfilled the inclusion criteria, after obtaining informed consent from caretakers. Additional consent was sought for HIV testing, although this was not on eligibility criteria. The eligible child was then transferred to the resuscitation room for a detailed history, examination and management. Patient's information
was filled in a pre-tested and pre-coded questionnaire. The oxygen saturation was assessed by pulse oxymetry immediately after admission before oxygen was administered. A blood slide for malarial parasites was taken and HIV also tested.

3.7.2 STUDY DESIGN and RANDOMIZATION

The aim of this study was to determine the efficacy of zinc adjunct therapy on outcome of severe pneumonia while other intervention was to determine the efficacy of chloramphenicol versus ceftriaxone in treatment of severe pneumonia. Therefore, the same study population was used to answer the two research question. Eligible children were enrolled in serial order and randomised to receive oral zinc or placebo, intravenous chloramphenicol or ceftriaxone using a computer-generated list of random numbers.

<table>
<thead>
<tr>
<th>Chloramphenicol</th>
<th>Zn</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>88</td>
<td>88</td>
</tr>
</tbody>
</table>

Random numbers up to 352 were computer generated by an independent person not involved in the study. They were arranged in variable blocks of 4 to 12, matched to treatment codes consistent with the two treatment protocols.

3.7.3 BLINDING

The study comprised of two different treatment arms. In each arm, patients were treated with either oral zinc or placebo and intravenous chloramphenicol or ceftriaxone. The zinc and placebo tablets were packaged and labelled with study identification numbers by a pharmacist not directly involved in the care of the study patients. The study participant number was used to identify the drug package. Zinc and placebo tablets were identical in colour, shape and size. Hence, the study doctor, study nurses, caretakers were masked to the treatment and only the pharmacist had access to the study code.

3.7.4 TREATMENT ALLOCATION

The study used the patients’ study number to identify the drug package and the number on the package was recorded on the patient’s file.
3.7.5 DRUG ADMINISTRATION
The study nurse administered the first dose of intravenous chloramphenicol or ceftriaxone followed by zinc or placebo tablets within 30 minutes after the antibiotics. Children less than one year received the treatment dose of 10mg of zinc or placebo and more than one year 20mg of zinc or placebo as a once daily dose for 7 days. It was a supervised dose (directly observed therapy). Dosing was closely related to the recommended dietary allowance (RDA) for children less than one year (10mg) and above one year of age (20mg).
For children who could not take tablets orally, the tablets were crushed into powder, and placed into the mouth. These were water dispersible tablets which could easily be swallowed once crushed. If vomiting occurred within half an hour, the dose was repeated.
The zinc or placebo was given continuously once daily for 7 days. Stable patients (clinical improvement in oxygen saturation and hydration) were transferred to the general paediatric ward for further management and follow up.

3.8 STUDY VARIABLES. The study variables included:

- Sociodemographic characteristics of the child, age, gender
- Clinical history
- Physical examination- weight, height, respiratory rate, chest indrawing, cyanosis, oxygen saturation and feeding difficulties.
- Radiological investigations – chest X-ray to diagnose pneumonia and its complication

3.9 STUDY PROCEDURE

3.9.1 Clinical history
A detailed clinical history was obtained from primary care taker, which includes social demographic information, patient identification symptoms of severe pneumonia, immunisation, breast-feeding, nutrition history and vitamin A supplementation.

3.9.2 Clinical examination
General and systemic examinations were carried out by the principal investigator / research assistants and the findings were recorded. Body weight, axillary temperature, respiratory rate, grunting, nasal flaring, cyanosis, and oxygen saturations were measured and recorded in the questionnaire.
3.9.3 Laboratory investigations
Blood samples were drawn aseptically from an accessible vein in the cubital fossa using a 23 gauge hypodermic needle and a 5ml syringe. A blood smear was examined for malaria parasites. HIV testing was done using rapid blood tests and those below 18 months old were confirmed using DNA PCR. Remaining sample was centrifuged and serum was stored for zinc analysis.

Radiological examination
Chest X-ray were taken on all study children either first or second day of admission to confirm the diagnosis and rule out the complication of pneumonia.

3.10 Intervention
The study patients were managed in the general paediatric wards with I.V chloramphenicol or ceftriaxone and supportive treatment.
Zinc supplementation: Zinc was administered daily (once a day) orally for a period of seven days. The children aged 6-12 months received 10 mg and those aged 12 to 59 months 20 mg of zinc tablets per day respectively. Those who vomited the drugs with in 30 minutes of administering, the study nurse supplemented the drug again with the help of the caretaker.

3.10.1 Management of study patients
The study children received either I.V chloramphenicol 25mg/kg every sixth hour or ceftriaxone 75mg/kg OD for a total of 7 days. Gentamicin 2.5mg/kg every 12 hours and Cloxicilin 50mg/kg every 6 hrs for a total of two weeks was given as 2\textsuperscript{nd} line therapy for those who did not improve or deteriorated after 48 hours. (Appendix -2)

3.10.2 Supportive treatment
- Nutritional support: The study children who were unable to feed orally were fed by nasogastric tube on milk, porridge and other locally available soups. All children with peripheral oxygen saturation of less than 90% were given oxygen by nasal prongs or catheter
- All children received vitamin A according to IMCI guidelines.
- Rehydration was done according to the hydration status of the patient following WHO guidelines.
3.10.3 Follow up of children

I. All study children were followed up until discharge, death or for a maximum of seven days whichever came first, to monitor clinical course and outcome of the pneumonia. The principal investigator did the clinical review every 6 hours for first 48 hours and there after twice a day, morning and evening with the help of research assistants (medical officers). The clinical review included respiratory rate, chest indrawing, oxygen saturation, chest auscultation findings, fever, cyanosis, and mental status of the child. All children were monitored for GIT disturbances such as vomiting and diarrhoea through history from the caretaker or by observation. All study children were discharged after the 7th day of treatment. Those on the second line treatment stayed in the ward until recovery.

II. A three member independent team comprising of a Paediatrician, epidemiologist and pharmacist regularly and closely monitored the data generated from the study reported to the faculty of medicine Research and Ethics committee for remedial action when necessary.

3.11 Main outcome measures

- The proportion of children who showed clinical improvement indicated by
  Time to normalisation of respiratory rate
  Time to disappearance of chest indrawing
  Time to normalisation of oxygen saturation at 92% or above while breathing room air for 15 minutes.
- Proportion of study children who died during the follow up period.
- Proportion of children who developed drug adverse effects.

3.12 Data management /Data analysis

All the data was entered into EPI-INFO 6.04 computer software package and analysed using SPSS. Chi square tests and Fischer’s exact tests were used to analyse the Categorical data. The results were summarised in tables, piecharts and graphs. To analyse the difference in outcome Kaplan Mier survival curve were used. To determine independent risk factors for poor outcome of severe pneumonia the Cox regression model was used.

3.13 Quality control

Pre-testing the questionnaire in a pilot study ensured the internal validity of the study, this was done before the study was started and errors were corrected. The research assistants
(medical officers) were trained for data collection procedure. The laboratory tests were done in a standard laboratory. Macleod pharmaceutical Ltd, Mumbai, India manufactured the zinc and placebo tablets (Placebo looked exactly same in shape, size and colour). A pulse-oximeter of the model omeda Biox 3700 with built in automatic calibration was used to measure oxygen saturation. Study children were followed up and monitored twice per day for oxygen saturation, respiratory rate and other danger signs of pneumonia. The principle investigator, research assistant, treatment nurse and patients were blinded to the treatment protocol. Data was checked, edited, and stored by the principal investigator.

3.14 Ethical consideration

Institutional consent was sought from the Department of Paediatrics and Child Health Makerere University, Faculty of Medicine Research Committee and the Uganda National Council of Science and Technology. Free and voluntary consent was obtained from the parents/caretakers of the study children. They were free to withdraw from the study if they so decided anytime during the course of the study, and this did not affect the care of their children while in hospital.

3.15 Study limitation

- Inability to estimate Zinc absorption
- It was not possible to analyse serum zinc levels during the study period. However, the samples were stored to be analysed at a latter date. This is because there was no capacity for zinc analysis in Uganda and another lab outside Uganda has been identified. The samples were stored below 20°C.
- Inability to standardise the diet during treatment
- Inability to retain the patients who have improved up to end of the study

3.16 Disseminations of the study

The results of this study will be availed to the Dept of Paediatrics and Child Health, Albert Cook library and school of Graduates studies Makerere University as well as Ministry of Health Uganda and other concerned bodies. The results will also published in a peer reviewed journal. This study was registered in Clinical Trial. Gov and trial number is NCT00373100.
CHAPTER FOUR

4.0 Results

From September 2006 to March 2007, four hundred and nineteen (419) children with severe pneumonia were screened for the study. Of these 352 children were recruited into the study. One hundred and seventy six children were randomly assigned to receive zinc as adjunct to antibiotic therapy, while 176 received the placebo.

Figure 1 Trial profile
4.1 Description of study subjects

Of the 352 study participants 198 (56.2%) were males while 154 (43.7%) were females. Their ages ranged from six to 59 months with the mean age of 17.89 (SD 12.20) months in the zinc group and 18.13 (SD 11.7) in placebo group. There was no statistically significant difference in the baseline characteristics between the two treatment arms as shown in table 1.
Table 1: Baseline clinical characteristics of 352 children admitted with severe pneumonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zinc group n=176(%)</th>
<th>Placebo group n=176(%)</th>
<th>P- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98(55.7)</td>
<td>100(56.8)</td>
<td>0.63</td>
</tr>
<tr>
<td>Female</td>
<td>78(44.3)</td>
<td>76(43.2)</td>
<td></td>
</tr>
<tr>
<td>Age in months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12</td>
<td>76(43.2)</td>
<td>68(38.6)</td>
<td>0.48</td>
</tr>
<tr>
<td>13-24</td>
<td>64(36.4)</td>
<td>75(42.6)</td>
<td></td>
</tr>
<tr>
<td>25-59</td>
<td>36(20.5)</td>
<td>33(18.8)</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>17.9(12.2)</td>
<td>18.1(11.8)</td>
<td></td>
</tr>
<tr>
<td>WHZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;-2SD</td>
<td>30(17.0)</td>
<td>40(22.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>&gt;-2SD</td>
<td>146(82.9)</td>
<td>136(77.2)</td>
<td></td>
</tr>
<tr>
<td>HIV(n=302)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>27(16.1)</td>
<td>25(14.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>Negative</td>
<td>275(13.9)</td>
<td>277(15.1)</td>
<td></td>
</tr>
<tr>
<td>Malaria(n=343)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>18(10.5)</td>
<td>19(11.0)</td>
<td>0.87</td>
</tr>
<tr>
<td>Negative</td>
<td>153(89.5)</td>
<td>153(89.0)</td>
<td></td>
</tr>
<tr>
<td>Immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully immunized</td>
<td>99(56.3)</td>
<td>105(59.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Partly immunized</td>
<td>77(43.75)</td>
<td>71(40.3)</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever (Temp &gt; 37.5°C)</td>
<td>170(96.6)</td>
<td>164(93.2)</td>
<td>0.48</td>
</tr>
<tr>
<td>Cough</td>
<td>175(99.4)</td>
<td>174(98.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Difficulty in breathing</td>
<td>171(97.2)</td>
<td>165(93.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Grunting</td>
<td>53(30.3)</td>
<td>57(32.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>57(32.4)</td>
<td>44(25.0)</td>
<td>0.157</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ &lt;92%</td>
<td>31(18.1)</td>
<td>31(18.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Tachypenaia Present</td>
<td>161(91.5)</td>
<td>166(94.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Crepitations</td>
<td>140(80.0)</td>
<td>147(84.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>Vitamin “A” supplementation</td>
<td>176(100%)</td>
<td>176(100%)</td>
<td></td>
</tr>
</tbody>
</table>
4.1.1 Clinical Features and Laboratory Indices of study children on Admission
Symptoms

Baseline characteristics of the study children in both treatment arms were comparable and the
difference was not statistically significant. The most common symptoms as reported by the
caretakers on admission were cough in 349 (99%) patients, fever 334 (94%) patients,
difficulty in breathing 336 (95%) patients and diarrhoea in 101 (28.6%) patients. Other
characteristics included HIV and immunization status as described in table 1.

Clinical measurements

Fifty-four (15.3%) children had abnormal oxygen saturation below 92%, 23 (13.7%) in zinc
group, 31 (18.1%) in placebo group. The mean temperature on admission was 38.1°C (SD
1.40) with a mean of 38.19°C (SD 1.17) in zinc group and 38.18°C (SD 1.61) in placebo
group. The mean weight for height Z score (WHZ) in zinc group and placebo group was
-0.448 and -0.661 (median -0.545 and -0.670) respectively. The mean respiratory rate was
64.71 (SD 15.72), with 65.56 (SD 15.09) in zinc group and 63.86 (SD 16.34) in placebo group.
There was no statistical difference between the two arms (P value 0.29). Other signs included
chest retraction, crepitations and grunting respiration as shown in table 1.
4.1.2 Laboratory Parameters of the study participants
The laboratory parameters included blood slide examination for malarial parasites, HIV serology and chest radiographic findings in both arms. Three hundred and two children were screened for HIV antibody test, 52 (17.2%) were found positive. Twenty seven (16.1%) in zinc group and 25 (14.9%) in placebo group had malarial parasites in the peripheral blood. There was no significant difference in two groups.

4.1.3 Chest radiographic findings
Chest x-rays were done on 250 children, 133 in zinc group and 117 in the placebo group. Differences between two groups were not statistically significant. The majority had broncho pneumonia 65 (48.9%) in zinc and 51 (43.6%) in placebo group respectively. The other findings were broncho pneumonia with effusion 26 (19.5%) in zinc group and 35 (29.5%) in placebo group. Children with lobar pneumonia and effusion were more in the zinc group (7; 5.3%) than placebo group (one 0.9%). While the finding of broncho pneumonia with lobar pneumonia was more in the placebo group (5.1%) than zinc group (0.8%). The rest of the children had normal x-ray findin
4.2.1 Time to normalisation of respiratory rate
There was no statistical difference in the median time taken to normalisation of respiratory rate between the two groups as shown in figure 2. The median time for normalisation in zinc and placebo group was 60 hours (95%CI55-65). Fifty percent of children in both intervention arms had normal respiratory rate at 48 hours and 80% at 140 hours (P-value = 0.86).

Figure 2 Kaplan Meier curve for time to normalisation of respiratory rate (hours) among children with severe pneumonia

Log rank analysis showed no significance (P = 0.8662)
4.2.2 Time to normalisation of chest in-drawing

The median time to normalisation of chest in-drawing was not statistically different in the two treatment arms as shown in figure 3. The median time to resolution of chest in-drawing in zinc group was 96 hours (95% CI 92-100) and 108 (95% CI 104-112) hours in placebo group.

Figure 3 Kaplan Meier curve for Time to normalisation of chest in-drawing in severe pneumonia

Log rank test $P=0.1187$ (No significance)

4.2.3 Time to normalisation of Oxygen saturation

The mean time to normalisation of Oxygen saturation was not statistically different in the two treatment arms. However, survival analysis showed that children in zinc group (139 hours 95% CI 137-142) achieved normal oxygen saturation earlier compared to placebo group (141 95% CI 138-143), but this was not statistically significant as seen in figure 4.
Figure 4 Kaplan Meier curve for Time to normalisation of Oxygen saturation in severe pneumonia.

Log rank test $P = 0.5074$ (No significance)
4.2.4 Mortality
The total mortality in this study was 28 (7.9%), seven (3.9%) in zinc group and 21 (11.9%) in placebo group. Mortality was lower in the zinc group as compared to the placebo group, and this was statistically significant. Relative Risk (RR) was 0.33 (95% CI of 0.15-0.76). This implies that zinc adjunct therapy is protective hence less likely to be associated with mortality. The Relative Risk Reduction (RRR) was 0.67 (0.24-0.85) while Absolute Risk Reduction (ARR) was 0.0795. The Number Needed to Treat was 13. The efficacy of zinc adjunct therapy for treatment of severe pneumonia was 0.67%, which was statistically and clinically significant.
Figure 5 Kaplan Meier curve for mortality by treatment group

Trend in mortality: Fourteen children died within 24 hours, six at 48 hours and four between 48 hours and 7 days of follow up. Mean time for death in zinc and placebo group was 2.43 and 2.81 hours, respectively as shown in figure 5.

Log Rank test 0.7965
### 4.2.5 Regression analysis

Using the backward Wald model of logistic regression analysis, children who were female, HIV positive or had co-morbid conditions were more likely to die while WHZ scores more than minus two standard deviations and zinc adjunct therapy were protective. Antibiotic therapy did not influence outcome so it was dropped for the model. Details were shown in table 4.

### Table 2: Logistic regression for factors predicting mortality in zinc and placebo group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odd’s ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>0.28</td>
<td>0.09-0.83</td>
<td>0.02*</td>
</tr>
<tr>
<td>WHZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;-2SD</td>
<td>0.26</td>
<td>0.08-0.87</td>
<td>0.03*</td>
</tr>
<tr>
<td>O₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;92%</td>
<td>4.31</td>
<td>1.34-13.81</td>
<td>0.014*</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12</td>
<td>0.87</td>
<td>0.32-2.35</td>
<td>0.79</td>
</tr>
<tr>
<td>13-24</td>
<td>0.00</td>
<td>0.00-2.2</td>
<td>0.75</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4.83</td>
<td>1.64-14.47</td>
<td>0.004*</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6.19</td>
<td>1.199-31.9</td>
<td>0.029*</td>
</tr>
</tbody>
</table>

P-value less than 0.05 considered significant
4.3 Adverse drug events

Two children developed vomiting immediately after administering the first dose of the intervention; one in zinc group and one in placebo group as described in table 5. Subsequent doses were well tolerated. Other adverse events such as indigestion, nausea, diarrhoea, hypothermia, jaundice, cardiovascular and neurological manifestations that occur with excessive doses (Doses > 80mg/day) were not reported in the study patients.

Table -3 Adverse drug events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zinc(n-176)</th>
<th>Placebo(n-176)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1(0.56%)</td>
<td>1(0.56%)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>175(99.43%)</td>
<td>175(99.43%)</td>
<td></td>
</tr>
</tbody>
</table>

P- value less than 0.05 considered significant
CHAPTER FIVE

5.1 Discussion

This study was carried out to determine the efficacy of zinc as adjunct therapy on the clinical outcome of children with severe pneumonia and to identify any adverse effects that may occur with the use of zinc.

5.2 Clinical response of children with severe pneumonia

The main outcome measures in this study were the proportions of children who showed clinical improvement in terms of time taken for normalisation of respiratory rate, time taken for chest indrawing to disappear and time taken for oxygen saturation to normalise, death and adverse effects. The difference in clinical outcomes between the zinc and placebo groups was not statistically significant.

Time taken for respiratory rate to normalise

The median time (60 hours, 95% CI 55-65) for normalisation of respiratory rate in zinc and placebo group was not statistically significant (P=0.86). Two similar studies, one in north India and one from South India showed no significant difference in normalisation of respiratory rate. Contrary to this, the Bangladesh study demonstrated a significant difference in time to normalisation of respiratory rate (40, 48 hours in the zinc and placebo group).

This could be explained by the higher serum zinc levels in the children of south Indian study as compared to those in the Bangladesh study. Serum zinc status was not determined in our study. However, previous studies reported zinc deficiency in Ugandan children.

Time to normalisation of chest indrawing

The median time to normalisation of chest indrawing in our study was 96 hours (95% CI 92-100) in zinc and 108 hours (95% CI 104-112) in placebo group respectively. This was not statistically significant (P value 0.11). The Bangladesh study found a significant difference in zinc (median 40 and 48 hours) and placebo group.

South Indian study reported that their children took longer duration for disappearance of chest indrawing especially in zinc group (median 88.1 hours) compared to placebo group (84.3 hours). Antibiotics used or aetiology of pneumonia could explain the differences in time taken to normalisation of respiratory rate and chest indrawing. These other studies enrolled
children who were wheezing. In addition, most of the children were <12 months (60%) and their children were less sick compared to our children. The other explanation could be differences in the pattern of micronutrient deficiency in the study sites. Zinc supplementation should augment immunological response irrespective of the aetiology of pneumonia whether it is due to viral or bacterial origin.  

**Time taken for normalisation of oxygen saturation**

The mean time to normalisation of oxygen saturation was not statically different in two arms (P 0.507), at seven days. The median hours for oxygen saturation were 60 hours in both intervention arms and this was less than what other studies reported. In south Indian trial, the median time for normalisation of oxygen saturation was 70.7 hours and in placebo 72.3 hours. In Bangladesh study, the mean time to normalisation of oxygen saturation was longer than in this study. The interval at which measurements were done were not stated so it remains unclear whether the outcome could be compared.

**5.3 Mortality**

The overall mortality in this study was 28 (7.9%). Seven children (3.9%) died in the zinc group while 21 children (11.9%) died in placebo group. The difference in mortality rate between two groups was statistically and clinically significant. P value 0.005. Children who were in the placebo group were three times more likely to die as compared to those who received zinc. Relative risk reduction in zinc group (66.67%) was higher than in the placebo group (33.3%). Number needed to (NNT) treat was thirteen. This means that we need to treat 13 children with zinc as adjunct therapy to avert one death. The cost of zinc for one child was 2000 Ugandan shillings (one USD), therefore we need 26,000 Ugandan shillings (13USD) to prevent one death.

A prospective randomized controlled trial by Sunil Sazawal from South India documented that supplementing zinc in small for gestational age infants can reduce mortality from infectious disease which includes pneumonia with a rate ratio of 0.32 (95% CI : 0.12-0.89) 59. Zinc reduces lung inflammation and improves resolution of pneumonia. Pharmacokinetic studies have shown that benefits of zinc can only be demonstrated after 72 hours of supplementation. 35 This late effect might be inherent in the mechanism and pharmacokinetics of the zinc, this probably explains the effect on reduction of mortality. 60 This may explain the difference in mortality in the 2 groups after 48 hours of the intervention in our study.
The factors associated with mortality in the placebo group were age group <12 months, malnutrition WHZ <-2Z score and partial immunization. These are factors associated with decreased immunity, and most likely to be associated with severe infections. For populations where children are deficient in zinc, severe prolonged infections deplete the zinc even further. Prasad et al reported that zinc deficiency impairs the immune system and decreases resistance to infection. Hence, supplementing zinc, reduces inflammation, and improves resolution of infection. In addition, zinc enhances tissue repair and it acts as a microbicidal agent in high concentration, this could explain the clinical recovery and decreased mortality in placebo group.

Fourteen children (50%) died in the first 24 hours. Those who died were seriously ill with severe immunosuppression-associated comorbid conditions. Using the backward Wald model of logistic regression analysis, children who were female, HIV positive or had co-morbid conditions (e.g. Post measles pneumonia, Tuberculosis, HIV and Anaemia) were more likely to die while WHZ scores more than minus two standard deviations and zinc adjunct therapy were protective. Antibiotic therapy did not influence the outcome of our study.

Zinc supplement helps to boost the body's immune response through activating macrophages, lymphocytes and natural killer cells. Children with higher serum zinc levels may have a more robust immune response than those with lower zinc levels. Hence, mortality was lower in zinc group. The children in placebo group with HIV (17.2%, P = 0.029), malnutrition and comorbid conditions (e.g. post measles pneumonia (P= 0.028) were more likely to die. This is more likely to be a high-risk group for zinc deficiency and further more they were assigned to the placebo.

5.4 Adverse drug events

Vomiting was noted in only two children initially, one in the zinc group and another in placebo group (prevalence of vomiting 0.5%). However, subsequent doses were well tolerated by study children. Minor adverse effects similar to others have been reported in other similar studies, although the prevalence was not stated. Zinc was reported to be well tolerated.
CHAPTER SIX

6.1 Conclusion:

1. Zinc given as adjunct therapy in the treatment of childhood severe pneumonia significantly reduced mortality with efficacy of 0.67 as compared to the placebo.
2. There was no difference in time taken for normalisation of respiratory rate, chest in-drawing and oxygen saturation in the intervention and placebo arms.
3. There were no serious adverse events reported and zinc was well tolerated.

6.2 Recommendation

All children aged 6-59 months admitted with severe pneumonia in Uganda should receive zinc supplement as adjunct therapy in order to reduce mortality.
References


### WHO Case Definition of Pneumonia

<table>
<thead>
<tr>
<th>Pneumonia</th>
<th>Cough or difficult breathing or fast breathing (RR &gt;60 bpm in children 1 week – 2 months, &gt;50 bpm in children 2 – 12 months and &gt;40 bpm in children (12 – 59 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe pneumonia</td>
<td>Cough or difficult breathing, fast breathing plus lower chest indrawing</td>
</tr>
<tr>
<td>Very severe pneumonia</td>
<td>Cough or difficult breathing, fast breathing, lower chest indrawing, cyanosis and / or inability to feed</td>
</tr>
</tbody>
</table>
### WHO guidelines for management of severe pneumonia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>IV/IM chloramphenicol 25mg/kg every hour until the child improves then continues with oral chloramphenicol for a total of 7-10 days. If no improvement after 2 days or deterioration, switch to gentamicin 2.5mg/kg every 12 hrs plus cloxacillin 50 mg/kg every 6hrs for a total of 2 weeks. Give oxygen by nasal catheter.</td>
</tr>
<tr>
<td>Severe pneumonia</td>
<td>IV/IM chloramphenicol 25mg/kg every hour until the child improves then continues with oral chloramphenicol for a total of 7-10 days. If no improvement after 2 days or deterioration, switch to gentamicin 2.5mg/kg every 12 hrs plus cloxacillin 50 mg/kg every 6hrs for a total of 2 weeks. Give oxygen by nasal catheter.</td>
</tr>
<tr>
<td>Very severe pneumonia</td>
<td>IV/IM Ampicillin 100mg/kg/day + Gentamycin 2.5mg/kg/day for 14 days. Give oxygen by nasal catheter.</td>
</tr>
</tbody>
</table>
APPENDIX-3

WHO Treatment Guidelines for Severe Pneumonia in HIV infected / suspected children

<table>
<thead>
<tr>
<th>Severe pneumonia</th>
<th>2-11 months</th>
<th>IV/IM Ampicillin 100mg/kg/day + Gentamicin 2-5mg/kg/day for 7 - 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>If no improvement after 48 - 72 hrs, switch to ceftriaxone 75 – 100 mg/kg/day for 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCP therapy with IV cotrimoxazole or suspension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe pneumonia</th>
<th>12 – 59 months</th>
<th>Ampicillin / Penicillin + Gentamicin (as above)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>If no improvement after 48 – 72 hrs, switch to ceftriaxone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCP treatment if clinically indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Steroids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Very severe pneumonia</th>
<th>2 – 11 months</th>
<th>Treat as in severe pneumonia</th>
</tr>
</thead>
</table>

| Very severe pneumonia | 12 - 59 months | Treat as in severe pneumonia |
APPENDIX-4

Consent Form

Introduction
We are carrying out a research study on children with severe pneumonia admitted to Mulago Hospital. The aim of the study is to find out if supplementing zinc with standard antibiotics will affect the outcome in affected children. We are requesting your child to participate in this study.

The reason we are carrying out this study is that severe pneumonia is one of the main causes of childhood sickness. Hence it is important to find out supplementing zinc along with other antibiotics can help children improve from sickness. If the children improve from this study it will help us to reduce the complications and deaths from severe pneumonia.

Methods
If your child is recruited for the study, we shall discuss with you about the symptoms of pneumonia in your child and treatment given. We shall do the following investigation:

- We will take blood samples from the site after cleaning the site with alcohol (70%), which kills the germs on the site. About 2ml of blood from your child’s arm or groin and a drop of blood from finger for malarial parasites.
- HIV test will be done. This will help us to know whether zinc supplement can help HIV associated pneumonia.
- Chest x-ray will also be done to confirm the diagnosis. Your child may exposed to radiation, but the effect will be small for single exposure.

You will not be paid any incentive for your child’s participation, we shall pay all the money for investigation which will be done by us.

If the HIV test become positive, you will be offered counselling and care for your child at a special clinic (Paediatric infectious Disease clinic). The results will be kept confidential. The other members of the family also counselled and advised.

The Risks and benefits
- There may be little pain while collecting the blood.
- Occasionally the study tablet may produce vomiting.

The patients’ right
Your child’s participation will be voluntary, and you have the right to refuse participating in the study or withdraw the study at any time. But it wouldn’t affect your child’s management. The results of investigation that will be useful to be communicated to your doctor for further management. The information from your child and you will be kept
confidential and will be used for research purpose only. If you have more question and any information you may clarify them at any time, please contact

Dr. Maheswari Srinivasan
Prof. J.K. Tumwine
Dr. Grace Ndeezi
Dr. Sarah Kiguli
Dept of paediatrics and child health Mulago Hospital
Tel: 0712404079.

Statement of consent

The purpose and nature of this study has been explained to me, and I understand that my child’s participation in this study is voluntary and that no consequences will result if I refuse to participate. I am free to withdraw from the study at any time. I have the rights to know the results of the laboratory tests. The child will be referred to paediatric infectious disease clinic if he/she is positive for further management.

I……………………………………………………………………………… (parent/guardian)
do hereby consent for my child to participate the above study.

Name of the
parent/guardian……………………………………………………Signature……………………

Investigator/Assistant………………………………Signature……………………

Date……………………
Appendix 5

Questionnaire

ZINC OR PLACEBO AS ADJUNCT THERAPY WITH CEFTRIAXONE/CHLORAMPHENICOL IN THE TREATMENT OF SEVERE PNEUMONIA IN CHILDREN AGED 6-59 MONTHS ADMITTED TO ACU MULAGO HOSPITAL

A. Study Identification
1. Serial number: .................................................................
2. Study Identification number: ...........................................
3. IP Number: ..........................................................
4. Date of Admission: ..............................................................
5. Date of Discharge/Death/Ran away: ...........................................
6. Duration of Hospital stay (days): ...........................................

B. Socio-Demographic Details
7. Name of patient: ..........................................................
8. Date of Birth: ..............................................................
9. Age (months): ..........................................................
10. Sex
    1. Male  2. Female  [  ]
11. Relationship of Caretaker/Parent to patient
    1. Mother
    2. Father
    3. Grandmother  [  ]
    4. Aunt
    5. Other
12. District of origin
    1. Kampala
    2. Wakiso
    3. Mukono  [  ]
    4. Mpigi
    5. Luweero
    6. Other
C. Symptoms of present illness and duration

14. Drug used for treating the patient
   1. S  2. T  [ ]

15. Cough
   1. Yes  2. No  [ ] Duration (days): ......................

16. Fever
   1. Yes  2. No  [ ] Duration (days): ......................

17. Difficulty in breathing
   1. Yes  2. No  [ ] Duration (days): ......................

18. Grunting respiration
   1. Yes  2. No  [ ] Duration (days): ......................

19. Inability to feed on solids/breast feed/formula feeds
   1. Yes  2. No  [ ] Duration (days): ......................

20. Convulsion/seizures
   1. Yes  2. No  [ ] Duration (days): ......................

21. Vomiting
   1. Yes  2. No  [ ] Duration (days): ......................

22. Diarrhoea
   1. Yes  2. No  [ ] Duration (days): ......................

D. Past Medical History

23. Recurrent cough
   1. Yes  2. No  [ ] Duration (days): ......................

24. Cardiac disease
   1. Yes  2. No  [ ] Duration (days): ......................

25. Use of study antibiotics in the last one month
   1. Yes  2. No  [ ] Duration (days): ......................

   Specific antibiotic(s) used if any
   1. Chloramphenicol  2. Ceftriaxone  3. CAF  4. Other  [ ]

26. Use of study antibiotics in the last 24 hour
   1. Yes  2. No  [ ] Duration (days): ...
Specific antibiotic(s) used if any
1. Chloramphenicol 2. Ceftriaxone 3. CAF 4. Other [ ]

27. HIV sero-status
1. Positive 2. Negative 3. Unknown [ ]

28. Immunization status
1. Fully immunized 2. Partly immunized 3. Not immunized [ ]

29. Card available
1. Yes 2. No [ ]

Which vaccines:

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>B</th>
<th>Poli</th>
<th>Penta</th>
<th>Penta</th>
<th>Penta</th>
<th>Poli</th>
<th>Poli</th>
<th>Poli</th>
<th>Measle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>o</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>s</td>
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<tr>
<td>G</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

1. Yes
2. No [ ]

E. General examination

30. Pallor

31. Jaundice
1. Yes 2. No [ ]

32. Dehydration
1. None 2. Some 3. Severe [ ]

33. Grunting
1. Yes 2. No [ ]

34. Cyanosis
1. Yes 2. No [ ]

35. Extremities
1. Warm 2. Cold [ ]

36. Capillary refill time (seconds/minute): .........................

F. Respiratory system examination

37. Respiratory rate (breaths/minute): .........................
38. Flaring of alae nasi
   1. Present  2. Absent  

39. Chest retractions
   1. Present  2. Absent  

40. Percussions

41. Air entry
   1. Normal  2. Reduced  

42. Crepitations/rales
   1. Yes  2. No  

43. Bronchial breathing
   1. Yes  2. No  

G. Cardiovascular system

44. Pulse rate (beats/minute)  

45. Heart sounds
   1. Normal  2. Abnormal  

46. Murmurs
   1. Yes  2. No  

H. Central nervous system

47. Consciousness
   1. Abnormal  2. Normal  

48. Behaviours
   1. Abnormal  2. Normal  

49. Lethargy
   1. Present  2. Absent  

50. Seizures
   1. Yes  2. No  

I. Abdominal examination

51. Hepatomegally
   1. Yes  2. No  

52. Tenderness
   1. Yes  2. No  

46
J. Skin examination

53. Rashes
   1. Yes  2. No  [  ]

54. Other lesions
   1. Yes  2. No  [  ]

K. Pulse Oximetry (%)

L. Laboratory investigations

55. Thin blood film
   1. No malaria  2. Malaria  [  ]

56. Hb Level (g/dl)  

57. Differential counts (initial/final)
   Neutrophils (%) 
   Lymphocytes (%) 
   Monocytes (%) 
   Basophils (%) 
   Eosinophils (%) 

58. Chest radiograph appearances
   a. Date when radiograph appearances were taken 

   b. Chest X-ray findings
      1. No Pneumonia
      2. Broncho pneumonia  [  ]
      3. Lobar pneumonia
      4. Lobar pneumonia and pleural effusions
      5. Broncho pneumonia and pleural effusions

M. Diagnosis

59. Diagnosis
   1. Severe Broncho pneumonia
   2. Lobar Pneumonia
   3. Pneumonia and Malaria
   4. Pneumonia and Diarrhoea
   5. Pneumonia and HIV  [  ]
   6. Pneumonia and Anaemia
   7. Pneumonia and Post measles
   8. Pneumonia and TB
9. Pneumonia and Malnutrition
10. Pneumonia, Malaria and Anaemia
11. Pneumonia and Others

60. Other treatments administered other than Chloramphenicol or Ceftriaxone

1. Analgesia
2. Oxygen
3. Anti-malarial
4. Blood transfusion
5. ORS
6. Vitamin A
7. Dextrose
8. Other

61. Other treatments administered other than Zinc

Vitamin A

1. Analgesia
2. Anti-malarial
3. None

62. Classification of the severity of the pneumonia

1. Severe pneumonia  2. Very severe pneumonia

63. Outcome of treatment

1. Treatment success
2. Treatment failure
3. Death
4. Ran away

64. Treatment failure

(i) Clinical complication
1. Yes  2. No

(ii) Nature of clinical complication

(iii) Death
1. Yes  2. No

(iv) Date of death: ....................

(v) Cause of death
1. Respiratory failure  2. Severe pneumonia

(vi) Second line drugs
1. Yes  2. No
N. Nutrition

Dietary history: Feeding

<table>
<thead>
<tr>
<th>Breast feeding</th>
<th>Breast/complementary feeding</th>
<th>Solid feeding</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12 months</td>
<td>1. Yes 2. No [ ]</td>
<td>1. Yes 2. No [ ]</td>
<td>1. Yes 2. No [ ]</td>
</tr>
</tbody>
</table>

Appetite improved

1. Yes 2. No [ ]

Vitamin A supplementation

1. Yes 2. No [ ]

O. Physical examination

Nutritional assessment

- Birth weight (kgs)
- Weight today (kgs)
- Length/height (cms)
- Mid upper arm circumference (cms)

Assessment of Micronutrients status

Skin rashes

1. Yes 2. No [ ]

Signs of vitamin A deficiency

1. Yes 2. No [ ]

- Axillary temperature (°C)
- Respiratory rate (beats/min)
- Pulse rate (beats/min)
- Oxygen saturation (%)

P Laboratory and CXR results sheet

Laboratory investigations

HIV Anti body

1. Positive 2. Negative [ ]

DNA PCR

1. Positive 2. Negative [ ]
Appendix 6

Follow up

<table>
<thead>
<tr>
<th>Day/Parameter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>am</td>
<td>pm</td>
<td>am</td>
<td>pm</td>
<td>am</td>
<td>Pm</td>
<td>am</td>
</tr>
<tr>
<td>Temperature (axillary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oxygen saturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grunting</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (b/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest indrawing</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NB: Observations will be done twice a day (12 hrly)

Outcome

- Clinical improvement (oxygen saturation, respiratory rate, chest indrawing and improvement in feeding in infants)
- Clinical complication (specify)
- Death Date of death: ..................
## Appendix 7

**Treatment Sheet**

<table>
<thead>
<tr>
<th>Days of Rx</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day-1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Time of dose</td>
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<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2 saturation</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Day-2</td>
<td></td>
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</tr>
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<td>Time of dose</td>
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</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>O2 saturation</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days of Rx</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day-3</td>
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</tr>
<tr>
<td>Time of dose</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Temperature</td>
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<td></td>
</tr>
<tr>
<td>RR</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>O2 saturation</td>
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</tr>
<tr>
<td>Day-4</td>
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<tr>
<td>Time of dose</td>
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</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RR</td>
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<tr>
<td>O2 saturation</td>
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</table>

<table>
<thead>
<tr>
<th>Days of Rx</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
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<tr>
<td>O2 saturation</td>
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<table>
<thead>
<tr>
<th>Days of Rx</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
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<td>Temperature</td>
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<td></td>
</tr>
<tr>
<td>RR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2 saturation</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
CONSENT FOR HIV SEROLOGY

I am a counsellor from the department of Paedics and Child Health Makerere Medical School. I am conducting a study for Dr Maheswari G. Srinivasan to find out whether Zinc supplementation will improve severe pneumonia in children less than 5 years. Other investigations to be done include HIV screening using a blood sample. I will talk to you about doing the HIV test, why it’s done, the benefits and risks. You will also be allowed to ask any questions on this subject and I will respond to them accordingly.

Benefits
Knowing the HIV status of your child is beneficial in terms of future management and follow-up of the child and family.

Risks
The child will feel slight pain when the blood is being obtained with a needle. You and your child may have some psychological trauma.

Confidentiality
The results obtained shall be confidential. Any other person other than the principal investigator, counsellor and research assistant will not know them. The doctors and nurses participating in the care of your child will not know them unless we see that by doing so it will aid in the management of your child and you have accepted us to release this information.

Statement of consent
The purpose and nature of the HIV test has been explained to me. I am aware that the results of the test will be confidential but I have a right to know them. I therefore sign below as proof of my consent.

.................................  .................  ................................
Study Identification No  Date  signature of caretaker

.................................  .................  ................................
Name Counsellor  Date  signature of counsellor
APPENDIX - 9

ADVERSE EVENT REPORT FORM

THE EFFICACY OF ZINC AS ADJUNCT THERAPY IN THE TREATMENT OF SEVERE PNEUMONIA IN CHILDREN ADMITTED TO MULAGO HOSPITAL

Day 1 □ 2 □ 3 □ 4 □ 5 □

Patients Initials: _______________ study Id no _______________ Date: __ / __/2006
Investigator: Name _______________ Signature: _______________ Serial number _______________

Adverse drug experience form

➢ Describe the event. ____________________________________________________________________

➢ Date of onset. __________/_____/2006

➢ Day of onset. Day 1 □ Day2 □ Day3 □

4. Duration of event. (To date). ________ days.

5. Maximum intensity

☐ MILD. (awareness of signs or symptoms, but easily tolerated)

☐ MODERATE. (Causes interference with usual activity)

☐ SEVERE. (Incapacitating, inability to do usual activity)

➢ Was the adverse effect serious?

☐ NO: Any mild or reversible adverse events.
Includes changes, which produce no Hazard to health, will not hinder the patient in continuing their normal life; and will not lower the patient's life expectancy.

☐ YES: Any adverse event which is a definite hazard to the patient’s well-being. In general, vital organ-system, functional or physicochemical impairment which at the time of diagnosis appears irreversible or is known to be reversible for a significant period of time.

Action taken

☐ Patient withdrawn. (Fill out patient withdrawal form)

☐ Patient continued.

☐ Other. (Any temporary cessation of treatment).
Follow-up:

- [ ] Patient recovered – no residual effects observable
- [ ] Adverse experience still present – no treatment
- [ ] Adverse experience still present – being treated

Details:

Residual effects present – no treatment/being treated

Details: