Antibiotic prescribing in treatment of non-severe paediatric Community Acquired Pneumonia at Limbe Health Centre, Blantyre

By

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Submitted as a partial fulfillment for an academic degree in Master of Health Sciences in the discipline of Pharmaceutical Sciences, the School of Health Sciences, University of KwaZulu-Natal, Durban

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ANTIBIOTIC PRESCRIBING IN TREATMENT OF NON-SEVERE PAEDIATRIC COMMUNITY ACQUIRED PNEUMONIA AT LIMBE HEALTH CENTRE, BLANTYRE

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This thesis has been submitted to University of KwaZulu Natal, Westville campus, School of Health Sciences as a partial fulfillment for an academic degree in Master of Health Sciences (Antimicrobial stewardship)

This is to certify that this thesis, contents therein and the research work are the original work of Ernest Matambo.

As the supervisor of the candidate, I have approved this thesis for submission.

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DECLARATION

I, **Ernest Matambo,** do declare that:

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Date ___9th January 2018

DEDICATION

My brothers Brian and Chrispin, my sister Charity and my wife Prisca, you mean a lot to me. I dedicate this study to you.

ACKNOWLEDGEMENTS

I would like to express my heartfelt gratitude to Prof Småbrekke for his commitment, encouragement and tireless effort from the conceptualisation of the research topic, writing the proposal to the writing of the thesis-I have learnt a lot from you. My gratitude should also go to Mr Solomon for the hard work and coordinating with UKZN School of Health Sciences on issues pertaining to the research study where needed be.

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ABBREVIATIONS

ARI	Acute Respiratory tract Infection
ATS	American Thoracic Society
BID	Two times a day
BNF	British National Formulary
BREC	Biomedical Research Ethics Committee
BTS	British Thoracic Society
CAP	Community Acquired Pneumonia
COMREC	College of Medicine Research and Ethics Committee
DHO	District Health Office
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IMCI	Integrated Management of Childhood Illnesses
LHC	Limbe Health Centre
LOS	Length of Stay (in hospital)
MIC	Minimum Inhibitory Concentration
MSTG	Malawi Standard Treatment Guidelines
PIDS	Pediatric Infectious Disease Society
QECH	Queen Elizabeth Central Hospital
SPSS	Statistical Package for the Social Sciences
TFAD	Time for First Antibiotic Dose
TID	Three times a day
UKZN	University of KwaZulu-Natal
USA	United States of America

WHO	World Health Organization

ABSTRACT

Introduction

Pneumonia is one of the diseases with high child mortality worldwide. Appropriate antibiotic treatment is vital for treatment success and minimising emergence of antibiotic resistance. Adherence of prescribers to guidelines in the treatment of non-severe Community Acquired Pneumonia (CAP) is one aspect that can optimise treatment outcome and help mitigate emergence of antibiotic resistance. This study was conducted to investigate antibiotic prescribing patterns of clinical officers and medical assistants in the treatment of non-severe paediatric CAP at Limbe Health Centre (LHC).

Materials and methods

The study was conducted at LHC. Prescriptions of 53 children aged 2-59 months diagnosed and treated for non-severe CAP were reviewed for analysis of demographic and treatment data.

Data collection was conducted from March to May 2017. Prescribed antibiotics by medical assistants and clinical officers were compared using Fischer's exact test. Correctly and incorrectly prescribed antibiotic daily doses in the two groups of prescribers were compared using Chi-square test. In addition, we also analysed demographic and academic qualification data for prescribers.

Results

The 53 prescriptions included were either for cotrimoxazole (n=29), amoxicillin (n=19) or erythromycin (n=5). There was no significant difference in choice of antibiotic for the treatment of non-severe paediatric CAP between medical assistants and clinical officers ($p=0.2$). Based on age or weight of the participant, distribution of correctly and incorrectly prescribed daily doses was not significantly different in the two groups of prescribers ($p>0.5$). Of the 53 participants, 30 (57%) were under-dosed. Ten participants were under-dosed by 33%, while 20 participants were under-dosed by 34-50% of the recommended antibiotic daily dose. Participants were either prescribed a 5-day (n=51) or a 3-day (n=2) antibiotic treatment.

Conclusion

Amoxicillin, cotrimoxazole and erythromycin were prescribed for the treatment of non-severe paediatric CAP at LHC. More than half of the included patients were under-dosed. Antibiotic treatment for paediatric CAP at LHC was either for 3 or 5 days. Understanding antibiotic prescribing patterns is necessary in designing interventions aimied at improving antibiotic treatment and curbing the emergence of antibiotic resistance.

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CHAPTER 1. INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction and background

The World Health Organization (WHO) estimates that 151 million episodes of pneumonia occur in developing countries per year, of which 35 million occur in Africa.[1] In developing countries such as Malawi, 20% of child mortality is due to pneumonia.[2] Viruses are the most common pathogens in Community Acquired Pneumonia (CAP) and most bacterial cases are caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.[3] It is estimated that 70% of deaths among children in developing countries due to pneumonia are caused by *Streptococcus pneumoniae*.[4] Mortality among 6202 children diagnosed with pneumonia in various hospitals of southern Malawi between July 2002 and June 2003 was 9.4%. [5]

Of late, an increasing proportion of strains of *Streptococcus pneumoniae* isolated from patients in Malawi shows resistance to some antibiotics.[6] A study conducted at Kamuzu Central Hospital, found that 33% of the isolates were resistant to chloramphenicol, 10% were resistant to clindamycin, 1.5% to erythromycin, 85.2% to gentamycin, 18.6% to oxacillin, 50.8% to tetracycline and 89.4% to cotrimoxazole.[6]

A ten year surveillance study on resistance of invasive *Streptococcus pneumoniae* to most commonly used antibiotics in Malawi, was conducted at Queen Elizabeth Central Hospital (QECH) from January 2000 to December 2009.[7] The study reported that, "*Streptococcus pneumoniae* had 20-33% resistance to chloramphenicol, above 90% resistance to cotrimoxazole, 2% to erythromycin, 9-18% to phenoxymethylpenicillin, 50-63% to tetracycline and 25-37% resistance to 3 or more antibiotics".[7]

As a way of achieving best therapeutic outcomes and curbing antimicrobial resistance, it is imperative that antimicrobials be prescribed, dispensed and administered correctly. To achieve this, design and implementation of treatment guidelines is considered important[46-47]. The Malawi Standard Treatment Guidelines (MSTG), British National Formulary (BNF) for children and adults, Integrated Management of Childhood Illnesses (IMCI) guidelines and other prescriber's handbooks are being used in Malawi. The MSTG are updated every five years. The Ministry of Health in Malawi produces MSTG to standardize prescribing practice across government hospitals in the country, but recommends the use of specialised publications in clinical conditions requiring specialised attention (page iii).[8]

Limbe Health Centre (LHC) is one of the 25 primary health care facilities managed by Blantyre District Health Office (DHO). LHC is one of the 18 health centres which offer both outpatient and labour ward services. The remaining seven facilities offer outpatient services only. LHC is located close to Limbe market, one of the two major central business districts in the commercial city of Blantyre. As such, urban and semi-urban residential areas and suburbs surround LHC.

In the absence of a secondary level hospital, health centres in Blantyre are overwhelmed with patients visiting the health centre for medical attention. With a nation-wide lack of medical doctors, clinical officers and medical assistants mostly do diagnosis and prescriptions at LHC. Treatment of non-severe paediatric CAP at LHC was based on 2005 IMCI guidelines during the study period.

The 2005 version of the IMCI guidelines recommends treatment of non-severe CAP with cotrimoxazole as first-line antibiotic and amoxicillin as second-line.[9] MSTG, however, recommend treatment of non-severe pneumonia in children with cotrimoxazole or amoxicillin, and erythromycin or doxycycline for non-severe CAP in adults who are allergic to cotrimoxazole or amoxicilin.[8] Hospital guidelines at QECH recommend amoxicillin 15mg/kg TID for 5 days or cotrimoxazole 24mg/kg BID for 5 days in non-severe paediatric CAP treatment .[10]

Many countries have published guidelines for treatment of paediatric CAP. [11-12] Commonly, not all prescriptions are according to the guidelines. "The need to please a patient or the guardian, prescriber's self-confidence, prescriber's preference drugs, training and specialization, prescriber's beliefs, prescribers' motivation, work load, inadequate diagnostic equipment, insufficient knowledge on antibiotic resistance patterns and lack of knowledge on treatment guidelines" are among reasons for non-adherence to treatment guidelines.[13-15]

1.2 Literature review

Worldwide, 2500 children under the age of five died of pneumonia per day in 2015, accounting for 16% of all deaths in this age group.[19] CAP guidelines have emphasized that early initiation of antibiotic treatment, correct antibiotic prescribing and administration, correct categorization of severity of CAP, and timely analysis of cultures are of paramount importance in management of patients.[20] Studies have shown that adherence to CAP guidelines improves clinical outcomes, reduces patient's mortality, emergence of antimicrobial resistance, length of stay (LOS) in a hospital and treatment costs. [21-23]

In 2011, the Paediatric Infectious Disease Society of America (PIDS) and Infectious Disease Society of America (IDSA) published guidelines for treatment of paediatric CAP recommending ampicillin/amoxicillin as first-line antibiotics in the treatment of hospitalized patients. [24] After the publication of the guidelines, studies have shown that there is a positive relationship between adherence to the guidelines and reduced prescription of broad-spectrum antibiotics and increased prescription of narrow spectrum antibiotics. [25-26]

Nevertheless, the decrease in prescription of broad spectrum antibiotics did not result in a decrease in the LOS and proportion of patients readmitted for paediatric CAP in the United States of America (USA).[27] Similarly, the costs associated with CAP treatment did not decrease significantly with the decrease in prescription of broad spectrum antibiotics.[27] Implementation of local hospital CAP guidelines in USA between 2009-11, however, resulted in an increase in the prescription of narrow spectrum antibiotics and decreased prescription of broad spectrum antibiotics.[28]

A secondary data analysis conducted in 12 countries in North America, South America, Europe, Africa and South-East Asia showed that prescribing according to IDSA/American Thoracic Society (ATS) CAP treatment guidelines significantly reduced the in-hospital LOS from a mean of 10 days (for those patients whose prescriptions were not guidelines concordant) to a mean of 8 days (guidelines concordant).[29] However, this study's age group was adults ≥ 65 years.

Recommendation number 31 of the IDSA/ATS guidelines states that, "routine chest radiographs are not necessary for the confirmation of suspected CAP in patients well enough to be treated in the outpatient setting."[12] Some scholars have disagreed with this because "half of the 'high-quality evidence' brought for this assertion (reference 150) is from a single study conducted by Swingler et al. in South Africa".[(30)] The British Thoracic Society (BTS) guidelines for adult patients do not recommend chest radiograph for outpatients.[31] Nonetheless, the absence of CAP confirmation through chest radiograph can lead to antibiotic abuse and overtreatment especially in sub-Saharan Africa.[30]

In Spain, adherence to CAP treatment guidelines reduced mortality and treatment failure.[22] The study was conducted in 13 Spanish hospitals and it recruited 1288 CAP patients. In the study, the authors explored factors that influenced adherence to treatment guidelines and also determined outcomes of adhering to the guidelines. Physicians had a mean adherence to CAP treatment guidelines of 80%. Predictors of adherence to CAP treatment guidelines were the hospital in which the physician was practicing, the physician's confidence, his/her knowledge of both guidelines in

use and drugs recommended by the guidelines and number of years she/he has been practicing medicine.[22] There was, however, a decline in adherence to treatment guidelines when prescribing for patients in the ICU. [22]

Often CAP is associated with comorbidities like asthma, HIV infection and tuberculosis.[33] These comorbidities influence adherence to treatment guidelines, affect choice of antibiotics, increase LOS and costs associated with CAP treatment.[33] A retrospective cohort study from 2007-12 including 25,124 children admitted with pneumonia in American hospitals, 43% were also diagnosed with acute asthma. Those who had asthma co-diagnosis had 5.6% longer LOS and had 11.8% higher cost of treatment.[33]

Few studies on the treatment of CAP have been conducted in Africa. A retrospective cohort study from 2008-10 in Ivory Coast recruited 62 CAP inpatients.[34] The most prescribed antibiotic was amoxicillin + clavulanic acid (42%) followed by netilmicin (35%) and ciprofloxacin (6%). CAP prescriptions mostly involved two antibiotics of amoxicillin + clavulanic acid plus netilmicin (81%). Only 3.6% of the prescriptions were guidelines concordant.[34] However, this study did not report on whether there was a relationship between adherence to guidelines and outcomes of CAP treatment.

A prospective cohort study in Kenya was conducted to determine the extent and pattern of treatment failure in children aged 2-59 months hospitalised for severe and very severe pneumonia.[35] The authors found no difference between guidelines concordant versus non-concordant treatment failure in the very severe pneumonia patient group. Despite reporting that non-adherence to guidelines in children with severe pneumonia was 41.4% and that it was associated with wheezing on first assessment, the study did not report whether treatment failure was associated with lack of adherence to treatment guidelines in this group or not.[35]

There is paucity of data in Malawi on whether prescribers adhere to CAP treatment guidelines or not. A study in a rural clinic in Lilongwe assessed the quality of care clinical officers delivered to children who presented with pneumonia using WHO's Integrated Management of Childhood Illnesses (IMCI) guidelines.[36] The study reported that of all the patients assessed, only 1% was assessed in all the aspects recommended by the guidelines. Despite having all the characteristics for pneumonia diagnosis as stipulated by the guidelines, only 30% (n=76) of 247 of the children were diagnosed correctly.[36] Of the 30%, only 25% (n=19) received correct care. Approximately 41% of

the children diagnosed with severe or very severe pneumonia were not admitted.[36] Reasons for non-adherence to the guidelines were not investigated.

While the study at Lilongwe rural health centre focused on adherence of prescribers to IMCI guidelines when examining patients presenting with signs and symptoms of pneumonia, this study focussed on how antibiotics are being prescribed in treatment of non-severe paediatric CAP at LHC.

1.3 Problem statement

There is paucity of information on how antibiotics are being prescribed in the treatment of non-severe CAP at LHC.

1.4 Aims and objectives

1.4.1 Main objective

To describe antibiotic drug treatment in the management of non-severe paediatric CAP at LHC.

1.4.2 Specific objectives

i. To identify the antibiotics prescribed in the treatment of non-severe paediatric CAP at LHC
ii. To describe antibiotic dosages in treatment of non-severe paediatric CAP at LHC
iii. To compare duration of antibiotic paediatric non-severe CAP treatment at LHC to that recommended by 2005 IMCI guidelines
iv. To compare choice of antibiotics, antibiotic dosages and duration of antibiotic non-severe CAP treatment prescribed by clinical officers to those prescribed by medical assistants

1.5 Case definition of pneumonia

1.5.1 Classification of patients with non-severe CAP

CAP is an acute lung infection that develops in individuals who recently have neither been hospitalized nor been exposed to the health care system. [16-17] LHC is a primary healthcare facility, and only treats outpatients while those who need admission are referred to a secondary or tertiary level hospital. Therefore, all pneumonia patients who had their prescriptions written and dispensed at LHC pharmacy were regarded as coming from their respective homes (CAP patients). 'Non-

severe CAP' classification was assumed to all paediatric patients who were prescribed oral antibiotics only and were not referred to a secondary or tertially level hospital for further treatment.

1.5.2 Definition of pneumonia

According to IMCI guidelines and MSTG, pneumonia presents with cough and/or difficult breathing, fast breathing and fever. A child aged 2-12 months has fast breathing with ≥50 breaths per minute, and a child aged 12-60 months has fast breathing with ≥40 breaths per minute. [8-9]

On examination, a child with cough and/or difficult breathing, fast breathing and fever of ≥37.5° C was diagnosed with non-severe pneumonia. Those who, in addition, were found to have chest indrawing, stridor in calm child and any other danger signs were diagnosed with either severe or very severe pneumonia. Danger signs included vomiting, decreased feeding or drinking, convulsions, lethargy and unconsciousness. This study focussed on non-severe CAP.

The figure 1.1 demonstrates the categorization of severity of CAP.

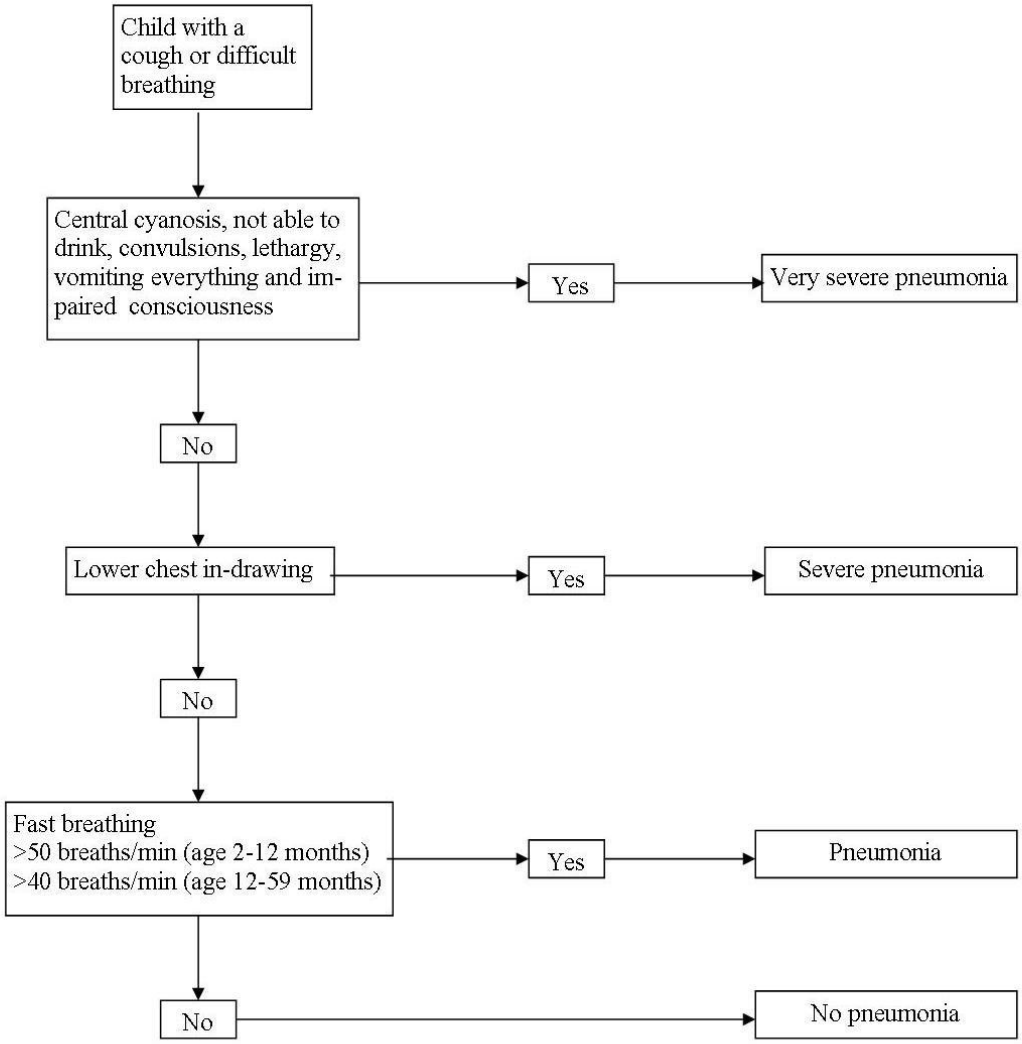

Figure 1.1: An algorithm for categorization of severity of pneumonia. Adopted from The definition of pneumonia, the assessment of severity, and clinical standardization in the pneumonia etiology research for child health study.[18]

1.6 Thesis outline

This thesis has been outlined as follows:

Chapter 2: Is a manuscript, the purposes of which are: to address the objectives of the study and to submit to a peer reviewed journal for possible publication.

Chapter 3: Conclusions. This chapter shows the extent to which the research question and study objectives have been addressed. It also shows the findings of the study in perspective of other

research studies. Recommendations, study limitations and significance of the study have been outlined in this chapter.

CHAPTER 2. MANUSCRIPT

Study results reported in this manuscript are intended for publication in Malawi Medical Journal:

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Contributions:

Mr E Matambo-principal investigator: developed the concept, collected and analyzed data and drafted the manuscript

Prof Lars Smabrekke-co-supervisor: conceptualized the study, designed the study, contributed to data analysis and revised the manuscript

Dr Katundu-co-supervisor: contributed to the writing of the manuscript and data analysis

Mr Vernon Solomon-principal supervisor: reviewed the manuscript

Antibiotic prescribing in treatment of non-severe paediatric Community Acquired Pneumonia at Limbe Health Centre, Blantyre

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2.1 Abstract

Objective: To investigate the antibiotic prescribing patterns of clinical officers and medical assistants in treatment of non-severe paediatric Community Acquired Pneumonia (CAP) at Limbe Health Centre (LHC), Blantyre.

Methods: Data on 53 prescriptions of antibiotics for the treatment of non-severe CAP in children aged 2-59 months were collected from March to May 2017 at LHC. Choice of prescribed antibiotics by clinical officers and medical assistants was compared using Fischer's exact test. Difference in episodes of correctly and incorrectly prescribed antibiotic daily doses in the two groups of prescribers was compared using the Chi-square test.

Results: The 53 prescriptions included were either for cotrimoxazole 54.7% (n=29), amoxicillin 35.8% (n=19) or erythromycin 9.4% (n=5). There was no significant difference in antibiotic choice between clinical officers and medical assistants (p=0.2). Of the 53 participants, 57% were under-dosed (n=30). Ten participants were under-dosed by 33%, while 20 were under-dosed by 34-50% of the recommended antibiotic daily dose. Distribution of correctly and incorrectly prescribed doses was not significantly different in the two groups of prescribers based on either weight or age of participant (p>0.5). Participants were either prescribed 5-day (n=51) or 3-day (n=2) antibiotic treatment.

Conclusion: Cotrimoxazole, amoxicillin and erythromycin were the prescribed antibiotic treatment for paediatric CAP at LHC, and 96% of study participants received treatment for five days. More than half of the paediatric patients who received antibiotic non-severe CAP treatment at LHC during the study period were under-dosed. Understanding antibiotic prescribing patterns is necessary in designing interventions aimed at improving antibiotic treatment and curbing emergence of antibiotic resistance.

2.2 Introduction

In Malawi, the childhood mortality in the age group 0-5 years is approxemately 64/1000, of which 6-40% is caused by Acute Respiratory tract Infections (ARI) including pneumonia.[1] There are variations in the incidence of paediatric ARI in rural and urban areas of Malawi, but the incidence in both areas is highest in the winter season.[1-2] It is estimated that 1000 children died of pneumonia in Malawi in 2010 before the introduction of 13-convalent pneumococcal vaccine in November 2011.[1,3]

Integrated Management for Childhood Illnesses (IMCI) guidelines are the most commonly used guidelines for paediatric CAP management in Malawi. Studies have investigated the adherence of prescribers to the IMCI guidelines and also clinical outcomes associated with the implementation of the guidelines in some parts of Malawi.[4, 5] A study at Lilongwe health centre reported a poor clinical care and low adherence to IMCI guidelines by clinical officers when treating paediatric pneumonia.[4] Despite introduction of IMCI guidelines at Mchinji District Hospital, there was still high proportion of children dying of pneumonia and high occurrence of unknown outcomes among patients from 2004-6.[5] At the time of data collection for this study, LHC was using 2005 edition of the IMCI guidelines.

There has not been any study, to our knowledge, investigating prescribing patterns or adherence of prescribers to IMCI guidelines in the treatment of paediatric CAP at LHC. This study explored how antibiotics are being prescribed in treatment of non-severe CAP in children aged 2-59 months at LHC.

2.3 Methodology

2.3.1 Study design

This was a cross sectional records review study. Patients' prescriptions were reviewed after they had been dispensed at the pharmacy during the study period.

2.3.2 Study site

a. Setting

The study was carried out at LHC which is managed by Blantyre District Health Office. As a common practice in many health centres in Malawi, medical examinations and patient prescriptions were done and written by clinical officers or medical assistants (those with a diploma or certificate

in clinical medicine respectively) while drugs at the pharmacy were dispensed by nurses instead of pharmacists or pharmacy technicians.

b. Examining a child for pneumonia at LHC

When a child with a cough or difficult breathing gets into an examination room, the clinical officer or medical assistant also examines the child for possible pneumonia. Often guardians refer to difficult breathing as noisy, interrupted or fast.[6] IMCI guidelines suggest the following steps when examining a child who presents with a cough or difficult breathing: [6]

i. Ask the guardian for how long the child has had the cough or difficult breathing
ii. Ask the guardian to make the child as calm as possible. If the child is asleep, the clinician will not ask the guardian to wake him/her up
iii. Count number of breaths per minute

A child who is calm, his/her age is between 2-12 months has fast breathing if s/he has ≥ 50 breaths per minute. A child whose age is between 12 months to 5 years has fast breathing if s/he has ≥ 40 breaths per minute. Those who are exactly 12 months have fast breathing if they have 40 or more breaths per minute. If the child is asleep, the clinician will count the number of breaths while s/he is still asleep.

iv. Look for chest in-drawing

The clinical officer or medical assistant will ask the guardian to make the child lie flat facing upwards on the guardian's lap. The child has chest in-drawing if lower ribs (lower chest wall) go in when the child breaths in. Chest in-drawing is an indication for pneumonia if it is clearly visible and is present at in-breath.

v. Look and listen for stridor

Stridor is the harsh noise which can be heard when a child breaths in. The clinician will ask the mother to make the child calm again. Then the clinician will look to see when the child breathes in and will put his/her ear close to the child's mouth. If the child's nose is blocked by mucus, the clinician will ask the guardian to clear it so that wheezing sound of the nose does not mask the stridor if present. Wheezing sound when a child breaths out is not stridor.

A child who has a cough and/or difficult breathing plus fast breathing is diagnosed as having pneumonia. A child who has a cough and/or difficult breathing, fast breathing, chest in-drawing, stridor and other danger signs e.g. decreased feeding, vomiting, lethargy; decreased consciousness has severe or very severe pneumonia.[6]

2.3.3 Study period

Data collection for this study was conducted from March to May 2017.

2.3.4 Inclusion criteria

All children aged 2-59 months diagnosed with and treated for non-severe CAP were included in this study, including those diagnosed with other comorbidities.

2.3.5 Excluson criteria

Those children who were prescribed parenteral antibiotics and those children whose guardians declined to give consent.

2.3.6 Sample size

According to internal records, LHC treats >20,000 "under five" children per year. Among these, approximately 700 are diagnosed with non-severe CAP. Therefore, the yearly periodic prevalence of children diagnosed with non-severe CAP at LHC is between 3.5-4%. Even though data on yearly periodic prevalence of children diagnosed with non-severe CAP at LHC is available, there is no data on antibiotic prescribing patterns in treatment of non-severe CAP at the health centre. A study in rural Lilongwe health centre, Malawi, found that of 247 children who were diagnosed with pneumonia, 25% received correct treatment.[4]

Under the null hypothesis that the proportion of patients receiving correct antibiotic treatment at LHC is the same as that of rural Lilongwe health centre, the alternative hypothesis would be that the proportion of patients receiving correct antibiotic treatment at LHC is different from that of rural Lilongwe health centre. Assuming that the proportion of patients receiving correct antibiotic treatment at LHC is 40%, the sample size was calculated using the formula:

$$n = [a\sqrt{b}(1-b) + 1.96\sqrt{c}(1-c)]2/(\mathrm{b}-\mathrm{c})2$$

Where a= One sided percentage point for the normal distribution corresponding to 100%-power (0.84 for power of 80%), b= proportion of patients assumed to receive correct treatment at LHC, c= null hypothesis proportion i.e. proportion of patients who received correct treatment at rural Lilongwe health centre. Therefore a=0.84, b=0.4 and c= 0.25.

$$n = [0.84\sqrt{0.4}(1-0.4) + 1.96\sqrt{0.25}(1-0.25)]2/(0.4-0.25)2$$

$$n = 53$$

The calculated sample size was 53 (using 2 decimal places for the entire calculation process). Therefore 53 participants were enrolled in the study.

2.3.7 Data collection tools and methods

Demographic and treatment information were collected from patient's health passports using a data collection form as shown in appendix 1. Academic qualification and prescriber's demographic characteristics were collected using a data collection form as shown in appendix 2.

2.3.8 Data collection process

A medical assistant who was off-duty during the data collection period was recruited and trained as a data collection assistant. The individual was trained on how to collect data from health passports and prescriptions of patients who met the inclusion criteria using the data collection form. The data collection assistant's desk was stationed close to the exit door of the pharmacy to make it easier for guardians of patients to identify him.

After a prescription of a patient had been dispensed, the guardian together with the patient was referred to the data collection assistant. The data collection assistant went through the information sheet as shown in appendices 3 or 4 together with the guardian providing more information about the study.

After going through the information sheet, the data collection assistant and the guardian then went through the consent form as shown in appendices 5 and 6. Then the data collection assistant asked the guardian to give consent by signing or stamping with a thumb print on the consent form before beginning to collect data from the patient's health passport and prescription. Study participants were given consecutive numbers beginning from 1.

All prescriptions should have a signature of the prescriber and the data collection assistant was advised to identify each signature by a unique code on the data collection form.

At LHC pharmacy, there is also a sheet containing names and corresponding signatures for each prescriber. By marrying signatures on prescriptions to corresponding names at the pharmacy, the data collection assistant was able to identify each prescriber.

After collection of demographic and treatment data from patients' prescriptions was completed, the data collection assistant went through the consent form on appendix 7 with each prescriber. When a prescriber gave consent to participate in the study, s/he was asked to state their highest qualification

in medicine. The prescriber's code and highest qualification in medicine were entered on data collection form as shown in appendix 1 while prescriber's code, highest qualification, gender, age and years of practice were entered on data collection form as shown on appendix 2.

To validate the data collection procedure, the researcher visited the data collection site once a week at an unknown time to the data collection assistant.

2.3.9 Data management

Once a week, data collection forms were collected, variables coded and entered on an excel sheet.

Age of patient was calculated by subtracting date of birth from prescription date. Prescribed daily dose was calculated as a product of prescribed dose and times of administration per day. Recommended daily dose was calculated as a product of recommended dose from BNF or IMCI guidelines and times of administration per day.

Excel 2013 computer package was used to create a data base and for storage of coded data. Variables were coded as shown in appendix 8.

2.3.10 Statistical analysis

Descriptive and analytical measures were used to describe and analyze both patients' demographic variables and treatment variables. Demographic and treatment variables which were analysed include: participant's age, gender and body weight, prescribed antibiotic, dosage, duration of treatment, comorbidities, prescriber's age, gender and qualification. SPSS 24 and Stata 12 were used to analyse data. Variables were tested for normality using Skewness-Kurtosis (Jarque Bera) normality test.

Participants' age and weight and prescribed antibiotic were normally distributed whilst participants' gender, dose, duration of treatment and prescribers' qualification were skewed. Both parametric and non-parametric methods were used to analyse the data.

Difference in distribution of prescriptions per each antibiotic in the clinical officers and medical assistants groups was analyzed using Fisher exact test. The null hypothesis was that there was no difference in choice of antibiotics to prescribe in the medical assistants and clinical officers groups. The alternative hypothesis was that there was a difference in choice of antibiotics to prescribe in the medical assistant and clinical officers groups.

Prescribed daily doses were compared to recommended daily doses in IMCI guidelines and BNF for children 2011-2012. How prescribed daily doses and recommended daily doses were calculated from prescribed doses and recommended doses has been demonstrated in the data management section. IMCI recommended doses for amoxicillin and cotrimoxazole are as shown in the Table 2.1.

Table 2.1: Amoxicillin and cotrimoxazole recommended doses

Age or weight of patient	Cotrimoxazole BID for 5 days	Amoxicillin TID 5 days
2-≤12 months (4-<10kg)	240mg	125mg
12-60 months (10-<19kg)	360-480mg	250mg

Adopted from Integrated management of childhood illness in Lahej, Yemen: a qualitative analysis from the perspective of health providers.[6]

Prescribed erythromycin daily doses were compared to recommended daily doses in BNF for children 2011-2012 because recommended doses for erythromycin are unavailable in IMCI guidelines. Recommended doses in BNF for children 2011-2012 are as shown in Table 2.2.

Table 2.2: Erythromycin doses in treatment of non-severe paediatric CAP

Age	Erythromycin QID for 5 days
1≤ 24 months	125mg
24-96 months	250mg

Adopted from BNF for children 2010–2011.[7]

Antibiotics for non-severe paediatric CAP can be prescribed based on age or weight of the patient, especially in children. As such, when comparing prescribed daily doses to recommended daily doses, both the age and the weight of the participant were considered. A prescribed daily dose

would, therefore, be correct if it matches with either recommended weight dependent daily dose or recommended age dependent daily dose or both.

Recommended erythromycin weight dependent doses for non-severe paediatric CAP are not available in BNF for children 2011-2012. As such prescribed erythromycin daily doses were compared to recommended erythromycin age dependent daily doses only.

Correctly and incorrectly prescribed daily doses per antibiotic in the two groups of prescribers were compared using Chi-square test. Since clinical officers did not prescribe erythromycin, only correctly and incorrectly prescribed daily amoxicillin and cotrimoxazole doses were compared in the two groups of prescribers in statistical analyses.

The null hypothesis for comparing the correctly and incorrectly prescribed daily doses was, "no difference between amoxicillin and cotrimoxazole daily doses in the two groups of prescribers". The alternative hypothesis was that correctly and incorrectly prescribed daily doses of amoxicillin and cotrimoxazole were different between medical assistants and clinical officers.

Correctly and incorrectly prescribed daily doses of amoxicillin and cotrimoxazole were also compared using Chi-square test. The null hypothesis was that there was no difference in distribution of correctly and incorrectly prescribed daily doses of amoxicillin and cotrimoxazole while the alternative was that there was a difference in distribution of correctly and incorrectly prescribed amoxicillin and cotrimoxazole daily doses.

Duration of antibiotic treatment was recorded as each prescription was being reviewed.

2.3.11 Ethical consideration

The research proposal was submitted to Malawi College of Medicine Research Ethics Committee (COMREC) for approval before being submitted to UKZN Biomedical Research Ethics Committee (BREC) for a second approval.

The study involved acquiring demographic and treatment information through reviewing of patients' health passports and prescriptions. Consent was sought from guardians of patients before health passports and prescriptions were reviewed. Consent form (appendix 5) was administered to the guardians. The consent form was also translated into Chichewa (appendix 6), for those who preferred vernacular language. Guardians gave consent by signing at the end of the consent form.

Those who were not able to read or write but were able to understand either of the 2 languages (English or Chichewa) had the consent form of which language they were able to understand read out to them. They gave consent by stamping at the end of that consent form with their thumb.

The study also involved acquiring demographic and academic qualifications data from prescribers. Consent from prescribers was sought using consent form in appendix 7. The consent forms and all data collection forms were safely locked up. The CAP database which was created was stored on a computer protected by a password.

2.4 Study findings

2.4.1 Study participants

In this study, 95 children aged 2-59 months were eligible for inclusion. Of the possible participants, 28 were excluded because they were prescribed parenteral in addition to oral antibiotic(s). Guardians of 14 children declined to give consent. Figure 2.1 shows the recruitment into the study.

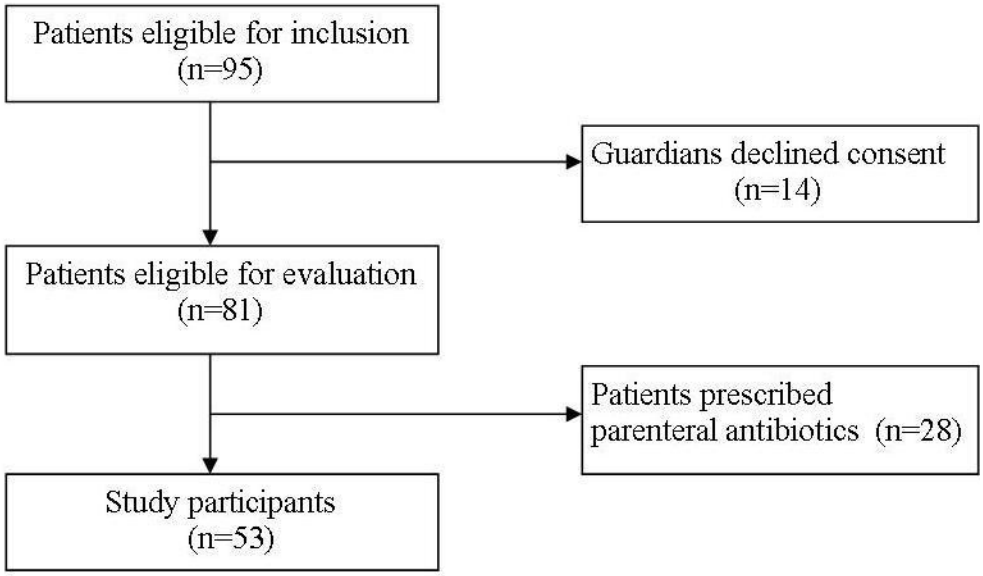

Figure 2.1:Flow diagram of inclusion

Participants' base-line data was analysed based on gender and subgroups of age, weight and presence of other comorbidities. The age of most of the study participants was below 24 months (n=33). Table 2.3 illustrates base-line data for study participants.

Table 2.3: Base-line data for study participants

	Gender		Total
	Girls (n=25)	Boys (n=28)	53
Mean age (SD)	22.2 months (15.8)	19.8 months (14.1)	
≤12 months	7	13	20
13-24 months	9	4	13
25-36 months	5	6	11
37-48 months	2	5	7
49-59 months	2	0	2
Other comorbidities			
Asthma (n=3)	1	2	3
Diarrhea (n=4)	1	3	4
Other (n=8)	5	3	8
Mean weight (SD)	10.9 kg (9.7)	10.1 kg (9.1)	

Six prescribers prescribed antibiotics to the non-severe paediatric CAP study participants during the study period: 4 medical assistants and 2 clinical officers. Table 2.4 gives more information on prescriber characteristics.

Table 2.4 : Prescriber's characteristics

	Female		Male	
	Medical assistant (n=1)	Clinical officer (n=1)	Medical assistant (n=3)	Clinical officer (n=1)
Age in years (SD)	36	29	40 (15.5)	31
Years of practice	8	5	1=21 1=7 1=6	4

2.4.2 Treatment information

a. Prescribed antibiotics

Medical assistants wrote 66% of the prescriptions and clinical officers wrote 34%. Amoxicillin, cotrimoxazole and erythromycin were prescribed for treatment of non-severe paediatric CAP. Of the 53 antibiotic prescriptions, 54.7% (n=29) were for cotrimoxazole, 35.8% (n=19) for amoxicillin while erythromycin was the least prescribed antibiotic with 9.4% (n=5). Table 2.5 denotes prescribing by medical assistants and clinical officers.

Table 2.5: Antibiotic prescribing by clinical officers and medical assistants

	Prescriber's qualification	
Prescribed antibiotics	Clinical officers	Medical assistants
Amoxicillin	6	13
Cotrimoxazole	12	17
Erythromycin	0	5

Clinical officers did not prescribe erythromycin for the treatment of non-severe paediatric CAP. There was no statistically significant difference in choice of antibiotics between clinical officers and medical assistants ($p>0.2$).

b. Prescribed daily doses

Daily doses of the three prescribed antibiotics (amoxicillin, cotrimoxazole and erythromycin) as recommended in IMCI guidelines and BNF were used to categorize prescribed daily doses as either correct or incorrect as shown in tables 2.6 and 2.7.

Table 2.6: Correctly and incorrectly prescribed weight dependent doses

	Prescriber's qualification			
	Clinical officer		Medical assistant	
Prescribed antibiotic	Correctly prescribed daily doses	Incorrectly prescribed daily doses	Correctly prescribed daily doses	Incorrectly prescribed daily doses
Amoxicillin	5	1	8	5
Cotrimoxazole	4	8	4	13

Table 2.7 : Correctly and incorrectly prescribed age dependent doses

	Prescriber's qualification			
	Clinical officer		Medical assistant	
Prescribed antibiotic	Correctly prescribed daily dose	Incorrect prescribed daily dose	Correct prescribed daily dose	Incorrect prescribed daily dose
Amoxicillin	4	2	5	8
Cotrimoxazole	2	10	3	14
Erythromycin	0	0	2	3

Amoxicillin was more frequently correctly prescribed in the weight dependent daily doses (13 of 19 prescriptions) and erythromycin in the age dependent daily doses (2 of 5 prescriptions) then cotrimoxazole in the weight dependent daily doses (8 of 29 prescriptions). Considering either age or weight of the participant, amoxicillin was more correctly prescribed than cotrimoxazole ($p<0.01$).

Of the incorrectly prescribed antibiotic daily doses, none was an overdose. Considering either age or weight of the participant, 30 participants were under-dosed: 10 by 33% of the recommended daily dose and 20 by 34-50% of the recommended daily dose. Cotrimoxazole was the most poorly prescribed antibiotic accounting for 21 under-doses of the 29 cotrimoxazole prescriptions, then erythromycin (2 under-doses of 5 prescriptions) and amoxicillin (6 under-doses of 19 prescriptions). Table 2.8 below demonstrates the under-dose per prescriber's qualification.

Table 2.8 : Under-dose considering either age or weight of the participant

	Prescriber's qualification			
	Clinical officers		Medical assistants	
Under-dose	Under-dose by 33% of recommended daily dose	Under-dose by 34-50% of the recommended daily dose	Under-dose by 33% of recommended daily dose	Under-dose by 34-50% of the recommended daily dose
Prescribed antibiotics				
Amoxicillin	0	1	0	5
Cotrimoxazole	8	0	2	11
Erythromycin	0	0	0	3

Based on both weight and age of the participant, there was no significant difference in distribution of correctly and incorrectly prescribed doses of amoxicillin and cotrimoxazole between medical assistants and clinical officers ($p > 0.5$).

c. Duration of antibiotic treatment

Of all cases in the study, 96% (n=51) were prescribed a 5-day oral antibiotic treatment course. Medical assistants wrote two prescriptions of 3-day antibiotic treatment courses: one treatment with cotrimoxazole and the other with amoxicillin.

2.5 Discussion

2.5.1 Choice of antibiotic

Cotrimoxazole was the frequently prescribed antibiotic during the study period by both clinical officers and medical assistants. This was expected because LHC was using the 2005 IMCI guidelines at the time of the study, which recommend cotrimoxazole as first-line treatment for non-

severe pneumonia.[6] The current 2014 IMCI guidelines recommend amoxicillin as the first-line and cotrimoxazole as the alternative.[8]

WHO released the current guidelines in 2014 and data collection for this study was conducted from March to May 2017. It is not known why LHC was still using outdated guidelines three years after updated guidelines were released. The recommendation of cotrimoxazole as first-line antibiotic for paediatric CAP treatment in the 2005 IMCI guidelines is not supported with references indicating superior outcome of cotrimoxazole.

There may be several reasons leading to that recommendation: for some countries, cotrimoxazole is cheaper and patients are more compliant to cotrimoxazole treatment than amoxicillin.[9] In Malawi, the average price of amoxicillin 250mg capsule is $ 0.057 while cotrimoxazole 480mg tablet is $ 0.045.[10] An adult non-severe CAP treatment of 5-day amoxicillin 500mg TID costs $ 1.71 while a cotrimoxazole 5-day treatment of 960mg BID costs $ 0.9.

There are no published data on prices of paediatric formulations but random market surveillance shows that the average price of a 100mL amoxicillin, 125mg/5mL bottle costs $ 1.16 and a 100mL cotrimoxazole, 120mg/5mL bottle is also being sold at the same average price. Therefore, adult CAP cotrimoxazole treatment is cheaper than amoxicillin adult CAP treatment while the cost of paediatric CAP amoxicillin treatment may be the same as paediatric CAP cotrimoxazole treatment depending on age or weight of participant.

Compliance of patients (2-59 months) to amoxicillin pneumonia treatment has not been studied in Malawi, but one study showed 9.5% non-adherence to cotrimoxazole in pneumonia treatment.[11] The non-adherence was associated with an increase in treatment failure rate (19% versus 14% in the treatment compliant group).[11]

Studies have identified differences in effectiveness of cotrimoxazole versus amoxicillin in treatment of non-severe pneumonia. Some indicate that there is no significant difference in effectiveness of cotrimoxazole and amoxicillin whilst others have shown that amoxicillin is more effective than cotrimoxazole.[9, 12] Studies have also differed on failure rates of cotrimoxazole and amoxicillin pneumonia treatments. While some have reported that the failure rates are the same, studies in India and Vietnam have shown cotrimoxazole treatment to have a higher failure rate.[9, 13] In Malawi, CAP treatment failure rate is also high due to resistant *Streptococcus pneumoniae* and *Haemophilus influenzae* strains. [14-17]

In the early 2000, before the rolling out of the cotrimoxazole prophylaxis against HIV opportunistic infections in Malawi, *Streptococcus pneumoniae* resistance to cotrimoxazole was still significantly high (41-44% of isolates) due to sulfadoxine-pyrimethamine use in treatment of malaria.[19] After rolling out of the cotrimoxazole prophylaxis against HIV related opportunistic infections, *Streptococcus pneumoniae* resistance to cotrimoxazole has significantly increased to 90-96% of *Streptococcus pneumoniae* isolates.[14,16-17]Resistance of *Streptococcus pneumoniae* to amoxicillin on the other hand seems lower than that of cotrimoxazole (9-18% of isolates).[16-17, 20] Therefore the recommendation of the current IMCI guidelines to treat non-severe pneumonia with amoxicillin as first-line instead of cotrimoxazole tallies with local antibiotic resistance patterns.

However, increase in antibiotic resistance is a common trend to almost all antibiotics used in Malawi. This raises concerns of effectiveness of antibiotic treatments in the near future.[15] Alternative treatments will soon be required due to the ineffectiveness of the current antibiotics to treat bacterial pneumonia.[15, 45]

Medical assistants prescribed erythromycin to five study participants. There is evidence that macrolides are as effective as amoxicillin in treatment of pneumonia, and newer macrolides seem to be effective in treatment of non-severe pneumonia caused by multidrug resistant *Streptococcus pneumoniae*.[21-22] However, the IMCI guidelines do not recommend erythromycin as pneumonia treatment and MSTG recommend pneumonia treatment with erythromycin only in adults.[23]

Even though erythromycin is not one of the drugs recommended for treatment of non-severe paediatric pneumonia in IMCI guidelines and MSTG, an erythromycin prescription was not considered as a prescribing error. According to a WHO report on pneumonia treatment, macrolides can be used for treatment of pneumonia as second-line.[24] For the five participants who were prescribed erythromycin in this study, it is unclear if the prescribers had the intention of prescribing a second-line antibiotic therapy.

Eligibility of a participant to second-line therapy was not investigated under this study nor did the study investigate treatment failure associated with amoxicillin or cotrimoxazole treatment. One Canadian study reported that 74% of prescribers chose a macrolide for treatment of paediatric pneumonia which presented with no comorbidities.[25] It is possible that medical assistants infrequently prescribe erythromycin for treatment of non-severe paediatric CAP as first-line antibiotic.

MSTG recommend prescribing erythromycin to pneumonia in adult patients who are allergic to penicillin and cotrimoxazole. MSTG do not give the alternative of administering erythromycin for treatment of non-severe paediatric pneumonia. We did not investigate the presence of allergies to penicillin or cotrimoxazole in the study participants, and so it is unclear whether the five study participants who were prescribed erythromycin were allergic to penicillin and cotrimoxazole.

It should be noted that penicillin allergies are very rare, occurring in 1-5 cases per 10 000 penicillin therapies globally.[26] There is no documented evidence of prevalence of penicillin allergies in Malawi but it is highly unlikely that it is higher than the global estimate.

Since the erythromycin was prescribed by experienced medical assistants, it may be suspected that prescriber's qualification and years of practice had an influence on choice of antibiotic to prescribe in this study. Some literature has shown that prescriber's qualification and years of practice influence choice of an antibiotic to prescribe.[27]

2.5.2 Antibiotic doses

Of the 53 study participants, 10 were under dosed by 33% whilst 20 were under dosed 34-50% of the recommended daily dose. BNF for children 2011-12 indicates that the erythromycin dose for pneumonia treatment and other acute respiratory tract infections should be double the standard dose.[7] WHO revised classification and treatment of childhood pneumonia guidelines state that higher dose (80-90mg/kg/day) amoxicillin is more effective in treatment of both *Streptococcus pneumoniae* and *Haemophilus influenzae* than standard dose (45mg/kg/day). [24]

In this study, all doses which were classified as 'under-dose' were actually standard doses. The objectives of this study were not to identify reasons for prescribing standard doses. It is therefore unknown whether the prescribers at LHC are aware that the recommended doses for amoxicillin, cotrimoxazole and erythromycin are double the standard dose in paediatric pneumonia treatment. A follow up study can be conducted at LHC to investigate treatment outcomes of treating non-severe paediatric pneumonia with either standard amoxicillin, cotrimoxazole or erythromycin doses. An interventional study can also be conducted at LHC to investigate effectiveness of double dose versus stardard dose amoxicillin, cotrimoxazole or erythromycin in treatment of non-severe paediatric CAP.

A higher amoxicillin dose maintains drug serum levels above the Minimum Inhibitory Concentration (MIC) for more than 40% of the dosing interval.[24] Maintaining serum level above

MIC for more than 40% of the dosing interval has been found to be effective against penicillin resistant *Streptococcus pneumoniae* and *Haemophilus influenzae* in otitis media. [24, 28]

It is interesting to note, however, that none of the publications which have been referenced in the revised WHO classification and treatment of childhood pneumonia guidelines in support of higher dose amoxicillin was about pneumonia treatment. In addition, the referenced studies were conducted between the years of 1985 and 1998. [28-34] A more recent clinical trial showed that there is no statistically significant difference in effectiveness between standard dose and high dose amoxicillin in treatment of otitis media.[35] Another recent study has reported that high dose amoxicillin with clavulanate was superior to standard dose amoxicillin in treatment of otitis media only in children of less than 20kg.[36]

As of March 2016, there was no research study or clinical trials in USA or Canada to act as evidence that high dose amoxicillin is superior to standard dose amoxicillin in treatment of paediatric pneumonia. Still, high dose amoxicillin therapy is used in Canada and USA for treatment of paediatric pneumonia as a result of expert opinion.[37]

A study in Pakistan comparing treatment of pneumonia with standard dose cotrimoxazole to high dose cotrimoxazole found that the difference in effectiveness of the two doses was statistically insignificant.[38]

Therefore, there is insufficient evidence from literature to predict that patients who were under-dosed at LHC had increased risk of poor treatment outcomes or that the prescribing patterns influenced emergence of antibiotic resistance. It could, however, be said that the prescriptions were not guidelines concordant in terms of antibiotic doses for amoxicillin, cotrimoxazole and erythromycin in treatment of non-severe paediatric pneumonia. And more importantly, the prescribed doses were not concordant to the most recent IMCI guidelines.

A study should be conducted at LHC to investigate outcomes associated with treatment of paediatric CAP with standard doses. Possibly, a clinical trial should also be conducted to investigate effectiveness of double dose versus standard dose amoxicillin or cotrimoxazole in treatment paediatric CAP in Malawi. Since LHC uses IMCI guildienes, it would be proper to design interventions aimed at encouraging prescribers to prescribe double dose amoxicillin or cotrimoxazole as recommended by the guidelines.

Tables 2.1 and 2.2 give age and weight ranges and their corresponding ideal doses. The recommended ideal dose regimen and age ranges were given to make drug administration easier and also considering the dosage forms which are readily available.[6] These tables have been adopted from the IMCI guidelines (2005 edition) and BNF for children 2011-2012. From that recommended dose regimen, it was possible to precisely calculate the extent of the under-dose and the percentage of the under-dose.

2.5.3 Duration of antibiotic treatment

Of the 53 antibiotic treatments, 2 treatments were for 3 days, and the rest were for 5 days. The 3 day antibiotic treatments were prescribed by medical assistants. IMCI guidelines recommend 5 days duration for treatment with amoxicillin or cotrimoxazole.[6]

There is however some literature which suggests that 3 day amoxicillin treatment is equally effective as the 5 day treatment.[39-40] In both clinical trials, cure rates and failure rates were not significantly different. There was also no difference in effectiveness of 3 day amoxicillin versus 5 day cotrimoxazole in treatment of non-severe pneumonia in another clinical trial.[41] A clinical trial in Indonesia and Bangladesh also reported that there was no statistically significant difference in cure rates and failure rates of 3 day cotrimoxazole and 5 day cotrimoxazole in treatment of pneumonia.[42]

The reasons why the two study participants were prescribed 3 day treatments were not investigated. However, from the literature, there would probably not be significant effects on the cure rate or treatment failure following the 3 day treatments. It may also be investigated as to why it was only medical assistants who prescribed 3 day treatments and not clinical officers.

All the five erythromycin prescriptions were for five days. There are no published studies comparing effectiveness of 3 day erythromycin to 5 day erythromycin in treatment of non-severe pneumonia. One study found no statistical difference in cure rates and treatment failure when total azithromycin dose was spread across 3 days duration and 5 days duration.[43]

2.5.4 Prescribing according to IMCI guidelines

From the study results, it can be said that clinical officers' choice of antibiotics and duration of treatment were more guidelines concordant than medical assistants'. Since clinical officers have a higher qualification than medical assistants, it may be speculated that the academic qualification had an effect on adherence to treatment guidelines by the clinical officers (keeping all other factors

constant).[27] On the other hand, it may be observed from the study results that medical assistants had more years of practice as compared to clinical officers.

Considering academic qualification and years of practice on adherence to treatment guidelines, senior prescribers seem to rely more on experience and personal knowledge than treatment guidelines.[27] Since clinical officers at LHC have a higher qualification but less number of years of practice than medical assistants, it can still be debated as to whether their academic qualification and fewer number of years of practice had an effect on their adherence to treatment guidelines.

It is also possible that the clinical officers were trained in the implementation of the IMCI guidelines on pneumonia treatment whilst the medical assistants were not. It may also be possible that the medical assistants were not aware of the treatment guidelines used for pneumonia treatment at LHC during the study period.

Erythromycin was prescribed by medical assistants only. Prescribers adjust their antibiotic prescribing behaviour according to the clinical groups they identify themselves with.[27] It is therefore not surprising to note that erythromycin was prescribed in the medical assistants group only because a medical assistant would identify themselves with a group of fellow medical assistants.

Lack of adherence to treatment guidelines can also be attributed to lack of pharmacy personnel at LHC. Nurses dispense medicines at LHC due to shortage of pharmacy personnel in Malawi. In other countries pharmacy personnel have been shown to improve adherence to treatment guidelines by ensuring that best drugs available are prescribed and administered to patients correctly . [44-45]

It should also be noted that the data collection forms used to collect data from non-severe paediatric CAP patients and the prescribers were not validated. As such, some important elements or variables may have not been indicated on the forms and consequently such data was not collected. May be the data would have been different if the data collection forms were validated.

2.5.5 Choice of antibiotic therapy in context of antibiotic resistance patterns

In this study, cotrimoxazole was the most prescribed antibiotic (29 of 53 prescriptions). In the wake of increased cotrimoxazole resistant *Streptococcus pneumoniae and Haemophilus influenzae*, it makes more sense to switch to amoxicillin as first-line treatment in non-severe pneumonia treatment.[14-17] Evidence shows that *Streptococcus pneumoniae* and *Haemophilus influenzae* resistance to amoxicillin is lower than cotrimoxazole in the local setting.[14-17, 20]

2.6 Study limitations

The study was not designed to investigate whether categorization of severity of pneumonia diagnosis was correctly done. As such 'non-severe paediatric pneumonia' diagnosis was perceived to all paediatric patients who were diagnosed with pneumonia, treated as outpatients and were prescribed oral antibiotic(s) with no parenteral antibiotic(s).

2.7 Recommendations

Further studies on adherence of prescribers to IMCI guidelines at LHC and other primary health centres in Malawi need to be conducted on non-severe pneumonia treatment. Reasons for non-adherence should be investigated (if they do not adhere to guidelines when prescribing) or what lessons can be learnt from their prescribing behavior (if they adhere to guidelines). Treatment outcomes in the IMCI guidelines adherent and non-adherent groups should also be investigated.

There are also no clear guidelines of prescribing second-line therapy in treatment of non-severe paediatric CAP at LHC and other health centres in Malawi. There are no studies on effectiveness of second-line drugs like erythromycin in treatment of non-severe paediatric CAP in Malawi.

2.8 Conclusion

Cotrimoxazole, amoxicillin and erythromycin were prescribed for treatment of non-severe paediatric CAP at LHC during the study period. There was no difference in prescription of correct and incorrect daily doses of amoxicillin and cotrimoxazole between medical assistants and clinical officers. Clinical officers were more adherent to IMCI guidelines in terms of antibiotic choice and duration of antibiotic therapy than medical assistants. Antibiotic non-severe paediatric CAP treatment was for 3 days or 5 days. Understanding antibiotic prescribing patterns is necessary in designing interventions aimed at improving treatment and curbing emergence of antibiotic resistance.

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CHAPTER 3. CONCLUSIONS

The current study investigated antibiotic prescribing patterns in treatment of non-severe CAP in children aged 2-59 months at LHC. Amoxicillin, cotrimoxazole and erythromycin were prescribed for treatment of non-severe paediatric CAP during the study period. Amoxicillin and cotrimoxazole were prescribed by both clinical officers and medical assistants while erythromycin was prescribed by medical assistants only. Cotrimoxazole was the mostly prescribed antibiotic since it was the recommended first-line antibiotic for non-severe paediatric CAP treatment in 2005 IMCI guidelines which LHC was using at the time of study.[9]

Studies at rural Lilongwe health centre and Mchinji District hospital investigating adherence of prescribers to IMCI guidelines when treating paediatric pneumonia reported poor adherence of precribers to the guidelines.[36, 45] In this study, more than half of the study participants were under-dosed. Both clinical officers and medical assistants prescribed standard amoxicillin and

cotrimoxazole doses instead of double doses for paediatric CAP treatment, however, amoxicillin doses were more correctly prescribed than cotrimoxazole doses. There is no clear basis for recommending amoxicillin and cotrimoxazole double doses to standard doses in paediatric CAP treatment since studies comparing effectiveness of double doses to standard doses have yielded conflicting results.[40-43]

2014 IMCI guidelines recommend amoxicillin as first-line and cotrimoxazole as the alternative.[44] Using amoxicillin as first-line CAP treatment in the local setting can be supported by lower prevalence of amoxicillin *Streptococcus pneumoniae* and *Haemophilus influenzae* resistance[6,37-38] and that amoxicillin was more correctly prescribed than cotrimoxazole in this study.

The duration of antibiotic treatment was either 3 days or 5 days. The shorter 3-day antibiotic treatments were prescribed by medical assistants only. Based on 2005 IMCI guidelines, clinical officers chose antibiotics and prescribed duration of antibiotic therapy more correctly than medical assistants.

Even though paediatric CAP mortality rate is decreasing globally, it still accounts for 4-6% of child mortality in Malawi.[39] Unfortunately, *Streptococcus pneumoniae* and *Heamophilus influenzae* resistance to commonly used antibiotics in Malawi is high.[6-7,37-38] Understanding prescribers' antibiotic prescribing patterns is necessary in designing interventions aimed at improving antibiotic prescribing behaviour, patient management and mitigating emergence of antibiotic resistance.

The present study was not designed to investigate whether categorization of severity of pneumonia diagnosis was correctly done. As such 'non-severe paediatric pneumonia' diagnosis was perceived to all paediatric patients who were diagnosed with pneumonia, treated as outpatients and were prescribed oral antibiotic(s) with no parenteral antibiotic(s). A study should be conducted to investigate adherence of prescribers to IMCI guidelines when examining a child for pneumonia.

Ideally a pilot study should have been conducted to establish antibiotic prescribing patterns in treatment of non-severe CAP at LHC before this study. However, time and resource constraints made it impossible to conduct a pilot study. This study, therefore, can only be used as a pilot study for other major studies in CAP treatment which can be conducted at LHC.

Further studies on adherence of prescribers to IMCI guidelines at LHC and other primary health centres in Malawi need to be conducted on non-severe pneumonia treatment. Reasons for non-adherence should be investigated (if they do not adhere to guidelines when prescribing) or what

lessons can be learnt from their prescribing behavior (if they adhere to guidelines). Treatment outcomes in the IMCI guidelines adherent and non-adherent groups should also be investigated.

There are also no clear guidelines for prescribing second-line therapy in treatment of non-severe paediatric CAP at LHC and other health centres in Malawi. There are no studies on effectiveness of second-line drugs like erythromycin in treatment of non-severe paediatric CAP in Malawi.

As reported in this study, more than half of the study participants were prescribed standard amoxicillin, cotrimoxazole and erythromycin doses despite the double antibiotic dose recommendation. No study, to our knowledge, has been conducted in Malawi to compare effectiveness of double dose to standard dose of these antibiotics in treatment of non-severe paediatric CAP. Another study can compare effectiveness of 3-day versus 5-day non-severe paediatric CAP antibiotic treatment in Malawi.

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APPENDICES

1. Data collection form for non-severe CAP participants

A. Patient demographic data

Case #	Date of birth	Prescription date (day/month/year)	Patient's weight (kg)	Patient's sex

B. Non-severe CAP treatment

Prescribed antibiotic (s)

Drug name:

Strength:

Route of administration:

Times of administration per day:

Duration of treatment:

C. Presence of other comorbidities

Other comorbidities	Yes	No
HIV/AIDS		
Tuberculosis		
Asthma		
Other (Specify)		

D. Prescriber's information

Prescriber's code	Prescriber's highest academic qualification in medicine

2. Data collection form for prescribers

Prescriber's code	
Age	
Years of practice	
Gender	
Qualification	

3. Information sheet

I am Ernest Matambo, a University of Malawi (UNIMA) and University of Kwa-Zulu Natal (UKZN) masters student. As a partial fulfilment to my masters degree, I am conducting a research study aimed at exploring treatment which non-severe paediatric community acquired pneumonia patients receive. I have keen interest in understanding how health practitioners choose which drugs

to prescribe, in what strength and also duration of their usage. I hope this study will provide information to the Malawian health authorities which is vital in maintaining and improving standards of care.

In order to do this research, I will need to have access to prescription information as well as basic demographic information of research participants. The information includes date of birth, gender, body weight, prescribed drug, route of administration, duration of treatment and other diseases which the participant may have been diagnosed with. And so I would like to invite the participation of your son/daughter/ dependant into the study. I would need to have your consent to have access to his/her demographic and treatment information. This will take approximately 10 minutes of your time.

The information acquired will be kept strictly confidential; only accessible to the researcher and his supervisors. All information acquired will be coded. It will be presented in numbers and figures in all out puts e.g. dissertation, conference papers and publications.

The study has been approved by Biomedical Research and Ethics committee (BREC) of UKZN and College of Medicine Research and Ethics Committee (COMREC) of UNIMA. Participation is voluntary: you can turn down the invitation to participate or withdraw your son/daughter/dependant from the study at any point without fear or subjection to any reprisals. Participation is entirely for free and that there are no any incentives to participate. Your consent will be appreciated as it will contribute to knowledge in the field of paediatric community acquired pneumonia treatment.

If you have any questions or concerns related to the study, do not hesitate to contact the researcher on his mobile phone number +265 (0)993 089 868 or on his email address ebmatambo75@gmail.com. You may also direct your concerns to his supervisors on vernonsolomon@gmail.com, lars.smabrekke@uit.no and kkatundu@medcol.mw. Complaints can also be addressed to the chairperson of BREC and COMREC as shown in the addresses below.

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4. Uthenga wakafukufuku

Ndine Ernest Matambo, ophunzira wakusukulu za ukachenjede za University of Malawi (UNIMA) ndi University of Kwa-Zulu Natal (UKZN). Ngati mbali imodzi yokwaniritsa maphunziro anga a masters degree, ndikupanga kafukufuku amene cholinga chake ndikuunikira chithandizo chimene ana odwala chibayo amalandira pa chipatala chaching'ono cha Limbe. Ndili ndi chikhumbokhumbo chofuna kumvetsetsa kuti madotolo amasankha motani mankhwala oti agwiritse ntchito, mulingo wake komanso kutalika kwa kagwiritsidwe ntchito.

Kuti kafukufukuyu atheke, ndikufunika kupeza uthenga wachitandizo chakuchipatala chomwe opanga nawo kafukufukuyu alemberedwa komanso uthenga wamoyo wawo. Uthenga omwe uzafunikire ndi tsiku lobadwa, ngati ali wamwamuna kapena wamkazi, kulemera kwathupi, mankhwala omwe walemberedwa, kalandiridwe kamankhwala nthupi, katalikidwe kachithandizo chakuchipatala komanso matenda ena omwe angakhale apezeka nawo. Choncho ndidzapempha mwana wanu kapena amene mumamusunga kuti alowe nawo mukafukufukuyu. Ndizapempha chilolezo kuti ndithe kupeza nawo uthenga wachithandizo chomwe mwana wanu kapena omusunga walandira kuchipatala komanso uthenga okhudza moyo wake. Zimenezi zidzatenga mphindi pafupifupi khumi za nthawi yanu.

Uthenga omwe udzatengedwe udzasungidwa mwachinsinsi; omwe adzakhale ndimwayi oona uthengawo ndi amene akupanga kafukufukuyu ndiomuyang'anira ake. Udzaikidwa muzizindikiro ndi ziyankhulo zosiyana ndi momwe udzatengedwere. Udzasindikizidwa mu manambala ndi nzithunzi panthawi yotulutsa zosatira zakafukufuku ameneyu.

Chilolezo chopangira kafukufuku ameneyu chaperekedwa ndi nthambi zoyang'anira kafukufuku za Biomedical Research and Ethics Committee ya UKZN ndi College of Medicine Research and Ethics Committee (COMREC) ya UNIMA. Kulowa nawo kafukufukuyu ndikosakakamiza ndipo

mukhonza kunkaniza mwana wanu kapena omusunga kuti asapange nawo kafukufukuyu kapena kumusiyitsira panjira mosachita mantha kapena kulandira chilango. Kuchita nawo kafukufukuyu ndikwaulere ndipo palibe cholowa chilichonse chizaperekedwe.

Ndidzathokoza kwambiri pachilolezo chanu kuti mwana wanu kapena omusunga alowe nawo mukafukufukuyu chifukwa kafukufukuyu adzaonjezera uthenga omwe ulipo kale okhudzana ndi nthenda yachibayo makamaka kwa ana.

Ngati muli ndimafunso kapena chidandaulo chokhudzana ndikafukufuku ameneyu, mutha kulumikizana ndi amene akupanga kafukufukuyu potchaya lamya pa +265 (0)993 089 868 kapena polemba email ku ebmatambo75@gmail.com. Muthanso kunena nkhawa zanu kwa amene akumuyang'anira kafukufukuyu polemba email ku vernonsolomon@gmail.com, lars.smabrekke@uit.no ndi kkatundu@medcol.mw. Chidandaulo chithanso kuperekedwa kwa wapampando wamabungwe amene adapereka chilolezo kuti kafukufuku ameneyu achitike. Chidandaulo chitha kuperekedwa kwa wapampando wa BREC ndi COMREC pa ma email adiresi ali mmusimu.

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5. Consent form 'A'

UNIVERSITY OF KWAZULU NATAL

WESTVILLE CAMPUS

Consent form

Aim

To describe drug choice, dosages and duration of treatment in management of paediatric CAP at LHC.

Researcher: Ernest Matambo

Supervisor: Lars Smabrekke, Vernon Solomon, Kondwani Katundu

I ……. have discussed the risks and the benefits of the study which Ernest Matambo is conducting as a partial fulfillment of his Master's degree in Health sciences. The study is aiming at describing how antibiotics are prescribed in management of paediatric community acquired pneumonia at Limbe Health Centre.

The risk associated with the study is submission of demographic and CAP treatment information for my son/daughter/dependant. I know the researcher as Ernest Matambo whom I can contact if I have complaints on how the study is being conducted or if confidentiality of my son/daughter/dependant is being violated. I am also at liberty to direct my complaints to College of Medicine Research and Ethics Committee (COMREC) or University of KwaZulu-Natal Biomedical Research Ethics Committee using contact addresses as shown at the end of the consent form.

I'm informed that I'm participating in this research voluntarily and that I can refuse to participate or withdraw from the study at any time without being penalized in any way.

I'm informed that by signing below I consent that information about my child or dependant should be used for the purpose of this research only.

…… …….

Signature Date

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6. Consent form 'B'

UNIVERSITY OF KWAZULU NATAL

WESTVILLE CAMPUS

Kupempha chilolezo kuti mulowe nawo mukafukufuku

Cholinga chakafukufuku

Kufotokoza kasankhidwe ka mankhwala, mulingo ndi kutalika kwa nthawi yomwera mankhwala omwe madotolo amalembera ana odwala chibayo kuchipatala chaching'ono chaku Limbe

Opanga kafukufuku: Ernest Matambo

Oyang'anira : Lars Smabrekke, Vernon Solomon, Kondwani Katundu

Ine……..ndakambirana ndi Ernest za kafukufuku yemwe akupanga pokwanilitsa mbali ina ya maphunziro ake a Masters in Health Sciences. Ernest wandifotokozera ubwino ndi chiopsezo chomwe chingakhalepo chokhuzana ndi kafukufuku amene akupangayi yemwe cholinga chake ndi kufotokoza kasankhidwe ka mankhwala, mulingo ndi kutalika kwa nthawi yomwera mankhwala omwe madotolo amalembera ana odwala chibayo kuchipatala chaching'ono chaku Limbe.

Chiopsezo chomwe chingakhalepo chokhuzana ndi kafukufuku ameneyu ndichakuti ndidzapemphedwa kuulula zinthu zina za pamoyo wamwana wanga kapena amene ndimamusamalira kuphatikizapo chithandizo chomwe walandila kuchipatala. Ndikumudziwa akupanga kafukufukuyu ngat Ernest Matambo. Ngati ndili ndi chidandaulo chokhuzana ndimomwe kafukufuku ameneyi akuyendera kapena ngati ndaona kut ufulu wa mwana wanga kapena wayemwe ndimamusalira okhala ndi chinsisi ukuphwanyidwa, ndili ndi ufulu odandaulira Ernest Matambo kapenanso kukadandaula ku College of Medicine Research and Ethics Committee (COMREC) kapena University of KwaZulu Natal Biomedical Research Ethics Committee pogwiritsa ntchito ma adiresi ali kumapeto kwa fomu ino.

Ndikuthanso kumvetsa kuti ndalowa mukafukufukuyu mosakakamizidwa ndipo ndikhonza kukana osapanga nawo kapena kumusiila panjira opanda kulandila chilango chilichonse

Ndikudziwanso kuti poika chisindikizo changa pansipa ndikuvomereza kuti umboni wa moyo wa mwana wanga kapena mwana amene ndimamusamalira ugwiritsidwe ntchito pakafukufuku yekhayu basi.

……. ……...

Chisindikizo Tsiku

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7. Consent form to prescribers

UNIVERSITY OF KWAZULU NATAL

WESTVILLE CAMPUS

Consent form

Aim

To describe antibiotic drug treatment in the management of non-severe paediatric Community Acquired Pneumonia at Limbe Health Centre, Blantyre.

Researcher: Ernest Matambo

Supervisor: Lars Smabrekke, Vernon Solomon, Kondwani Katundu

I ……. have discussed the risks and the benefits of the study which Ernest Matambo is conducting as a partial fulfillment of his Master's degree in Health sciences. The study is aiming at describing how antibiotics are prescribed in treatment of paediatric Community Acquired Pneumonia at Limbe Health Centre.

The risk associated with the study is submission of my demographic and academic qualification information. I know the researcher as Ernest Matambo whom I can contact if I have complaints on how the study is being conducted or if my confidentiality is being violated. I am also at liberty to

direct my complaints to College of Medicine Research and Ethics Committee (COMREC) or University of KwaZulu-Natal Biomedical Research Ethics Committee using contact addresses as shown at the end of the consent form.

I'm informed that I'm participating in this research voluntarily and that I can refuse to participate or withdraw from the study at any time without being penalized in any way.

I'm informed that by signing below I consent that the information I will be provide should be used for the purpose of this research only.

…… …….

Signature Date

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
University of KwaZulu-Natal
Private Bag X 54001, Durban, 4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2602486 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

COLLEGE OF MEDICINE RESEARCH AND ETHICS COMMITTEE
College of Medicine
Private bag 360
Chichiri, Blantyre 3
Email: comrec@medcol.mw

8. Coding of variables

Case number: Consecutive numbers starting from 1

Patient's age: Age in months

Patient's weight: Weight in kg

Patient's gender: Male =1 and female = 2

Prescribed drug: amoxicillin = 1, cotrimoxazole = 2, erythromycin = 3

Daily dose: prescribed daily dose in mg

Duration of treatment: Number of days

Other comorbidities: HIV/AIDS =1, TB = 2, Asthma = 3, other comorbidities = 4, not present = 5

Prescriber's qualification: Certificate in clinical medicine = 1, diploma in clinical medicine = 2

Prescriber's gender: Male = 1, female = 2

Prescriber's years of practice = Number of years of practice