ANTIBIOTIC TREATMENT FOR COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN TILL FIVE YEARS OF AGE AT A PRIVATE HOSPITAL IN EKURHULENI

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Research report for MSc (Med) Pharmaceutical Affairs 2021 for submission at University of Witwatersrand

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DECLARATION

University of the Witwatersrand, Johannesburg

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ABSTRACT

Pneumonia is the leading cause of death in children below the age of five years. There are two categories of pneumonia which are community acquired pneumonia (CAP) and hospital acquired pneumonia (HAP). Pneumonia can be prevented through vaccination. However, the prevalence of other causes of pneumonia other than bacterial causes for example, viral pneumonia, is on the rise. The first part of the study introduces CAP as a condition, shows the burden of the disease (statistically) worldwide and in SA as well. The literature review explores epidemiology and aetiology of the disease. Focus was on gathering data of the most prescribed antimicrobials. This report focuses on data collation for the antimicrobials prescribed (which in turn shows trends or doctor prescribing pattern), days spent in hospital, any possible correlation between choice of antimicrobial and duration of admission. The secondary data collected was compared to several other studies that had similar topics to have a point of reference for comparison with the findings of this study under the results and discussion section. It was concluded first that amoxicillin/clavulanate is effective for the treatment of pneumonia infection. Second that ceftriaxone is an effective alternative for treating pneumonia compared to the classic agents. Last the study concluded that the clinical outcomes for children hospitalized with CAP on narrow-spectrum antibiotic are not significantly different from treatment with broad-spectrum antibiotics.

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LIST OF TABLES

ABBREVIATIONS

CAP	Community Acquired Pneumonia
STG	Standard Treatment Guidelines
EML	Essential Medicines List
SATS	South African Thoracic Society
FIDSSA	Federation of Infectious Diseases Societies of Southern Africa
WHO	World Health Organization
UNICEF	United Nations Children's Fund
HIV	Human Immunodeficiency Virus
ICD-10 code	International Classification of Disease
CRP	C-reactive protein
LOS	Length of stay
PCT	Procalcitonin

CHAPTER ONE – INTRODUCTION

1.1 General Introduction

In the whole world, pneumonia is becoming a serious public health problem and a major cause of high disease spread and high deaths. Regardless of efforts in microbiological diagnostic tests, prevention measures and antimicrobial therapies, statistics reveal that many deaths are caused by pneumonia worldwide (World Health Organization, 2016). It is generally assumed that this is due to lack of knowledge, lack of facilities, pneumonia most often misdiagnosed, underestimated and mistreated (Hans Liu, 2017). In addition, the other reason for poor outcome of patients is, they fail to measure and evaluate the severity of the disease and to treat patients on outpatient basis or in a hospital setup or under intensive care. Hans Liu (2017) asserts that in the United States of America, pneumonia coupled with influenza, has been ranked 8th as part of the leading causes of infection related deaths. This raises questions about pneumonia which will be discussed in the next section.

1.1.2 Background to the study

The South African Thoracic Society acknowledges a report by Zar H. J. *et al.* (2005) who purport that CAP is one of the leading causes of mortality and morbidity in South African children. As pointed out in the introduction to this paper, recent research indicates pneumonia was more prevalent in children aged below five years. Reports from UNICEF (2016) indicate that in 2015, the severity of pneumonia resulted in the death of 2500 children aged below five years in a day world-wide. This is 15% of total mortality in children below five years (UNICEF 2016). In a similar report, The World Health Organization reported that in the same year, 16%, to be accurate 920 136 deaths in people aged below five years were due to pneumonia (World Health Organization, 2016).

Health experts argue that the old age in a population and the virulence factors of the causative microorganism is the main reason for the increased deaths in the world is the impact of pneumonia. As indicated in the previous discussion, pneumonia is a

cause of concern. The large number of resistant microorganisms, multidrug-resistant bacteria and the coming in of new pathogens present confusion for hospitals when deciding antimicrobial therapy.

Streptococcus pneumoniae also called (pneumococcus) is the major disease-causing agent for CAP world- wide. (The World Health Organization,2016). The World Health Organization in 2016 in the recent worldwide report of global antibiotic resistance reported that pneumococcus is a bacterium of international concern because the disease is presenting serious resistance worldwide.

Ward Law *et al.* (2006:4), elaborate that pneumonia is caused by bacteria, fungi, and viruses. Studies by Mitike et al. (2001:18) reveal pneumonia in children is caused by bacteria in less developed countries; and viruses are more prominent in the first world countries. Fungal infections affect those who are immunosuppressed mostly.

Margolis (2006) indicates that clinicians do not clearly understand pathophysiology of pneumonia and immune regulation of the inflammatory response to lung infections. It is believed that when the respiratory system is attacked by virus and bacteria, that produces inflammation and initiates the immune response.

Proponents of pneumonia reveal that the symptoms of severe pneumonia are lower chest wall in drawing and hypoxia (Margolis & Gadomski 2006; Lahti 2008; Scott,2008). These characteristics occur since young toddlers have horizontal ribs, poor intercostal muscle development and a soft sternum. In serious infection, the lungs become stiff and inelastic. This is due to degradation products accumulation, cell edema, alveolar epithelial cells loss, and loss of surfactant resulting in lungs to become consolidated, (Margolis & Gadomski 2006; Lahti 2008; Scott,2008).

Furthermore, it is assumed that pneumonia is a respiratory system infection that affects airways below the epiglottis. Findings indicate that it is an acute infection in the lungs which usually results in inflammation of alveoli (air sacs), resulting in fluid and/or pus filling the alveoli (World Health Organisation, 2018; UNICEF, 2018; Hans Liu, 2017; Akter et al., 2015; Sushant et al., 2015). Hans Liu, (2017) concludes that the inflammation of alveoli results in difficulty in breathing due to disruption of absorption

of oxygen.

More signs and symptoms were recorded over several years as follows:
•Cough (usually productive).
•Abnormal rapid breathing (tachypnea).
•Breathing difficulty.
•Accessory respiratory muscle usage.
•Heart rate of more than 100 bpm (tachycardia) or less than 60 bpm (bradycardia).
•Body temperature of more than 38°C (hyperthermia) or less than 35°C (hypothermia); and
•Central cyanosis (bluish colour around lips, tongue, and core) (World Health Organization, 2018; UNICEF, 2018; Hans Liu, 2017; Akter et al, 2015; Sushant et al., 2015).
This raises questions about the dangers of pneumonia in young children below the age of 5 which will be discussed in the next part.

1.1.3 Problem statement

The study discusses antibiotic treatment of CAP in children aged below 5 years who are majorly affected because of the disease. Antibiotic resistance is prevalent in the world, as well as South Africa in a major way. According to Kim *et al.* (2018), the failure to assess whether the infection that is occurring is of bacterial or viral origin is the culprit behind the rise of antibiotic resistance. According to Peyrani *et al.* (2019), antibiotic resistance is defined as the process when a pathogen becomes resilient to the effects of the antibiotic and its working process.

Susceptibility testing along with sensitivity testing is essential for control of antibiotic resistance in bacteria. Furthermore, laboratory and clinical data systems are also not linked in SA, making it difficult to identify bacterial resistance patterns of hospital and community origin (Aliberti *et al.* 2019). Linking of data systems can help in the effective treatment of the disease. Furthermore, due to widespread infection of HIV, the children have weaker immunity and therefore are more prone to the disease. HIV breaks down the body's defense system and renders it defenseless. However, the quantification and the use of proper antibiotics in a private hospital is discussed in this study.

1.2 OBJECTIVES

1.2.1 The Aim of Study

This study aimed at determining the responses of patients to the antibiotics and the relevance of adjunctive therapies in pneumonia management in children below 5 years at a private hospital in Ekurhuleni. The main reason of carrying out this study was to measure and evaluate the use of antibiotics for CAP. It is particularly important to improve the care of community-acquired pneumonia (CAP) patients in South Africa. The main reason is there is a high prevalence of disease and the need to step up the standards of antibiotic prescribing in the face of rising (AMR) antimicrobial resistance.

1.2.2. Objectives

1. To identify the types of antibiotics used for CAP.
2. To measure the effectiveness of antibiotics used for CAP.
3. To analyze the correlation between the antibiotic use and period of stay in the hospital.
4. To evaluate and recommend management of patients (0-5 years) with CAP.

1.2.3 Research Questions

The research questions are as follows:

- Which antibiotics are used for the treatment of young people with CAP aged below five years in South Africa?
- How effective are the antibiotics used for the treatment of children with CAP in South Africa aged below five years?
- How long does it take for children to be treated using antibiotic?
- What is the best possible way to obtain cultures for CAP in young people aged up to 5 years?

1.2.4 Justification for the Study

Pneumonia contributes a lot towards school absenteeism and family disruption in South Africa as portrayed by WHO in 2014. Clinically, pneumonia in children ranges from mild to severe to fatal. Even in non-fatal incidents, pneumonia is a major economic problem in the health care system in South Africa. To reduce the public health menace due to pneumonia, preventive measures are needed to complement efforts directed at early diagnosis and improved case management. This study will help bridge this knowledge gap.

1.2.5 Purpose of the study

The aim of this paper is to render clinicians guidance to assist in management of CAP patients below the age of five years. The research was based on a private hospital in Ekurhuleni, South Africa and thereby has access to resources to quantify the use of antimicrobial drugs so that the proper treatment of the patient is ensured without the risk of developing bacterial resistance. The study further aims to calculate the duration of stay of the children in the hospital and that would provide a considerable idea of the effect of CAP in children. Furthermore, the research question to ascertain the efficacy of CAP treatment this also helps in figuring the sureness of the correct antibiotic being used.

1.3 LITERATURE REVIEW

1.3.1 Introduction

A literature review (Franzel, *et.al*, 2016) involves reading, searching for, evaluating, and summarizing available literature that relates to a research topic both directly and indirectly.

Secondary sources of literature would be used in this study (Franzel, *et.al*, 2016:103). Secondary literature sources will be journals, books, databases and online.
The purpose of review of literature is to:

- Explain the relationship of each work to others under consideration.
- Put each work in the context of its contribution to the understanding of the subject under review.
- Manage conflicts amongst seemingly contradictory previous studies.
- Provide a way forward for further research.
- Reveal, identify, interpret, and shed light on any gaps in, previous research; and
- Enable one to fit original work in the context of existing literature.

1.3.2. The Theoretical Framework

A framework is a set of ideas that you use when you are forming your judgements and decisions. Grant & Osanloo, (2014) indicates that a theoretical framework is one that is based on an existing theory in an area of study that is related and/or rejects the hypothesis of a study. The theoretical framework of this study is Community-acquired pneumonia (CAP) as a main cause of spread and deaths in young South African children.

1.3.3 The Conceptual Framework

The conceptual framework comprises the basis of a research problem (Ranjit Kumar, 2011:53). Luse, Mennecke & Townsend, (2012) argue that the conceptual framework allows the study to define and specify the concepts within the problem of the study. The conceptual framework of this study is the severity, spectrum, and incidence of pneumonia in children which determine the treatment options used. There is an increasing antimicrobial resistance, and this calls for a new developed way to the use of antibiotics in pneumonia management.

1.4. REVIEW OF RELATED LITERATURE

WHO, (2015) maintains that (CAP) community-acquired pneumonia is an acute infection, which is transmitted in the community, of the respiratory system causing either cough or difficulty breathing, tachypnoea or chest-wall indrawing. Respiratory problems are the largest group of disorders comprising more than 30% of acute medical pediatric hospital admissions for which families seek medical attention (Malcolm, 1990). Pneumonia describes the inflammation of the lung. It affects millions of people each year Globally and is a common illness (WHO, 2015). In children, pneumonia is the most important single cause of disease burden and a major cause of child mortality globally (Black, *et al*, 2013). Pneumonia affects all age groups. However, it has been observed that certain groups of people are at more risk of developing the disease than others.

1.4.1. BURDEN OF DISEASE

Epidemiology and burden of disease

Tejada *et al* (2018) state that the epidemiology of the disease refers to the burden of the disease across the world. 19% deaths in children aged less than 5 years are caused by Pneumonia. In developing nations, pneumonia in children is about 0.29 incidences per child-year and 0.05 episodes per year in developed nations. Hospitalization is required in 7-13% of all cases in a community which are life threatening and severe enough to cause an economic harm. Reports show that the pneumonia incidences per child per year are highest in South Asia (0.36 incidences), second Africa (0.33 incidences), third Mediterranean (0.28 incidences), fourth, Pacific (0.22 incidences) fifth, American (0.10 incidences) and sixth Europe (0.06 incidences) (Roomaney *et al.*, 2016).

The increase in CAP cases has seen a drastic rise in the world. In 2017, 12 million children were hospitalized in the world which accounted for about 90% of the cases in the world (ncbi.nlm.nih.gov, 2020). The United states have seen a massive surge in the cases of pneumonia across the decades. In the past decade, the cases have seen an exponential rise which accounted for about 73-85 children among 1000 children

being diagnosed with the lower respiratory tract infection (paediatrics.uct.ac.za, 2020). Among these 45% were found to be diagnosed with CAP and thereby accounted mostly for children aged below the age 2 years. For children aged below 5 years the number was found to be 35-50 per 1000 children. This shows the prevalence of CAP in the states.

A study held in 2012 by The South African National Burden of Disease (SANBD-2), reveals that lower respiratory tract infections (pneumonia included), contributed 12,3% of deaths in children below 5 years nationally. South African Medical Research Council, (2016) postulates that the lower respiratory tract infections were third on list of dangerous diseases. It was reported that lower respiratory system infections were severe in the age group of 0-4 years, causing 13,1% of deaths (South African Medical Research Council, 2016). What follows is a description/outline of the causal agents of pneumonia.

1.4.2 Aetiology

Previous studies reason that pneumococcal pneumonia (*Streptococcus Pneumoniae)*, is a general type of primary pneumonia (Handy L. K *et al.*, 2017). It is characterized by homogenous consolidation of one or more lobes or segments of the lung. The disease occurs in all ages. It is usually a sporadic disease, the mode of spread being by droplet infection. Handy L. K *et al.*, (2017) acknowledge that the other bacteria which may cause primary pneumonia include Klebsiella pneumonia, *Streptococcus Pyogenes, Streptococcus Pyogenes, Haemophilus influenzae, Staphylococcus aureus, Legionella pneumophila* and so-called small bacteria such as *Mycoplasma pneumoniae* and *Chlamydia psittacii.* Fungi and viruses can also cause primary pneumonia. The bacterial aetiology of CAP is changing due to pneumococcal vaccine introduction. The following is a brief report on the diagnosis of pneumonia.

1.4.3. Diagnosis

Scott *et al.* (2008:1299) opines that diagnosis of pneumonia consists of two very important parts; on determination of aetiology by laboratory tests, intensive physical examination should be done with the respiratory system being the main center of attention or focus and to determine the syndrome by history clinical examination and chest radiology. Scholars propose that careful observation can lead to gaining important information (Scott *etal.*,2008:1299). This is of great importance to researchers because disease examination is very difficult in very young children.

1.4.4 Management of Pneumonia

Earlier work reveals that a many effective therapies including antibiotics are available to treat pneumonia, for bacterial infection (Pio, 2003; Qazi, *etal*, 2002). In the further interpretation by (WHO,2016), penicillin has been effective a long period but penicillin-resistant bacterial strains, such as *Streptococus pneumoniae*, are now proving to be a problem in certain regions. Seldom can clinical signs or simple immediate investigations diagnose viral pneumonia with certainty. Thus, antibiotics are useful even before appropriate diagnosis is made. More recent scientific contributions mapping the pneumonia concept underline that, the route of administration depends on how ill the child is, what the suspected aetiology is and what antibiotics are to be used. Looking into the literature on pneumonia, attention should be paid to fluid and electrolyte balance, as severely ill children with pneumonia may retain fluid excessively or may become dehydrated through tachypnoea and fever. Malcolm, (1990) predicts that first, analgesia and antipyretics may be needed. Second, oxygen should be given to those with marked respiratory distress who usually have extensive changes of x-ray. Vaccines remain useful in reducing the number of pneumonia incidence (Gross, 2001).

CHAPTER 2 – METHODS AND MATERIALS

2.1 Introduction

The chapter focused on research philosophy; approach; strategy; design; study population; sampling; collection of data; analysis of data and ethical consideration.

2.2 RESEARCH PHILOSOPHY

There are three perspectives namely objectives, application, and the enquiry process from which research can be viewed. Research being viewed from the application of research, can be applied or pure research.

Franzel, *et.al* (2016:23) elaborates the three dominant research traditions as positivism, interpretivism and critical realism. Positivism was developed by Durkheim: (1859-1917). It aims at finding valid and reliable causal relationships. This study would use the positivist paradigm.

The positivist theory provides the basis for research to be able to explain, predict their occurrence permit the anticipation of phenomena and therefore allow them to be controlled (Creswell, Vicki & Plano,2011). Martins et al. (2006) illustrates that quantitative methodology focuses on collection of primary and secondary data from a group of individual respondents, with an intention of generalizing the results to a wider area. This study used the quantitative approach.

Thompson (2002) identify three types of significance in quantitative research these are practical, statistical, and clinical significance.

First, Onwuegbuzie, Levin, & Leech, (2003) states that practical significance shows the educational value of the results. Practical significance is assessed by finding the use of effect sizes. An effect size are indices that measure the size of a difference or relationship.

Second, economic significance means the economic value of the effect of the intervention. Examples are cost benefit, cost effectiveness, cost-feasibility, cost utility, and cost sensitivity (Leech and Onwuegbuzie (2001).

Third, clinical significance is the level to which (Kazdin ,1999) an intervention causes a real difference to the quality of life of the respondents or encounter.

The aim of enquiry in quantitative research can be exploration, confirmation or quantification. This study is an exploratory, descriptive survey which is quantity driven. The study focuses on the statistical significance between the use of antibiotics and the number of patients treated for CAP under the age of 5 years.

2.3 RESEARCH APPROACH

Research approach is defined as the process and the mindset with which the research has been carried on. It is based on the nature of the problem statement of a research project that is generally described in the introductory section. Researchers need to finalize the exact procedure or approach for a certain research project according to the identified nature of the problem statement to achieve certain research aims and objectives. As per the view of Tuffour (2017), research approach can be categorized into inductive, deductive and adductive research strategies. The study in question has been done with the help of deductive research strategy that helps in deducing the information from the data that has been collected and interpreting them accordingly. This helps in the appropriate effectiveness of the research that has been performed. Therefore, the study uses deductive research approach to analyze the data collected and use them to make a difference in the treatment of CAP.

2.3 RESEARCH STRATEGY

The research strategy used helps in executing the research in the most effective way. It assists researchers to focus on the prime intentions of a research. The study strategy can be of qualitative, quantitative, descriptive, analytical and research action (Metlay et al. 2019). These different research strategies provide different aspects of data collection and analysis such as statistical, in-depth and perspective knowledge along

with description of the existing data without making any modifications. For the analysis of the data regarding CAP that has been obtained an effective research analytical strategy is used. An analytical strategy is used to analyze the data that has been obtained with the secondary methodology of the research. This helps in figuring out which data represents what in the obtained set. This strategy therefore effectively helps in analyzing the data and make progress about the research that has been undertaken.

2.5 THE RESEARCH DESIGN

Research design is a framework, which is used to identify, analyze and gather data leading to a research outcome. A research design is based on different subject matters and also organizing useful studies for a research. Abdulkadiroğlu et al. (2017), distinguish the research design and provide various types such as "Exploratory, Explanatory and Descriptive". All these parts of research design provide different uses of data collection and analysis. It also depends on how gathered data are measured. For this research a descriptive research design is chosen which aims to describe the results and the variations within the results of the CAP treatment in children and their stay in the hospital. This design helps in explaining and also correlating the different data together and form coherent meanings of them. Therefore, effective research design is important for any research to be effectively conducted.

2.6 STUDY POPULATION

The sample size is chosen from the private hospital in Ekurhuleni. Children aged below and up of five years (0-59 months) makes the population of study.

2.6.1 Sampling

The sampling process is used to create a sample size for the study and the study is based on that sample size. Jara-Ettinger et al. (2018), substantiate that sampling method determines the success of the research in a great way. Cases were recruited from children aged 0 to 5 years, sufficiently ill enough to be admitted into the in-patient services of the Ekurhuleni private hospital's children's ward. Since the clinicians at the hospital used different diagnoses to indicate acute pneumonia, all those children admitted with acute respiratory infection, chest infection, bronchopneumonia, lobar

pneumonia, lower respiratory tract infection, respiratory tract infection and pneumonia were further evaluated for pneumonia using the W.H.O criteria (The W.H.O recommends the use of general danger signs, fast breathing and lower chest in-drawing to determine children with pneumonia (WHO, 2015).

Children were first assessed for the presence of any general danger signs i.e. lethargy or unconsciousness, inability to drink or breast feed, vomiting everything, and convulsions. Thereafter they were examined for chest in drawing and the presence of stridor (in a calm child). The observations to determine the respiratory rate was measured by observation of the child's chest for exactly one minute when the child was awake, while breastfeeding, asleep, and while being quiet. If coughing interrupted this, the measurement was started again. Fast breathing was defined as a respiratory rate of ≥ 50 per minute in children less than 12 months and ≥ 40 in children aged 12 months to 5 years (WHO, 2015). Other clinical findings e.g. presence of crackles on auscultation and new infiltrates on chest radiographs were documented. The sample size is 287. Sample size was calculated using the Creative Research Systems sampling size calculator at 95% confidence level and the confidence interval of 5. The formula used by the research system calculator was ss =Z 2 * (p) * (1-p)/c*2
Where: Z = Z value (1.96 for 95% confidence level)
p = percentage picking a choice, expressed as decimal
c = confidence interval, expressed as decimal
This formula is used to calculate the sample size. The sample size was also based on the International Classification of Diseases Code-10. This code contains more than 70000 diseases (Martins et al. 2018).

2.7 DATA COLLECTION

Data collected includes patient's demographic information, type of pneumonia diagnosed, investigations and antibiotic and adjunctive therapies of the study subjects. The antimicrobials were grouped by pharmacological class, e.g. penicillin, cephalosporin, antivirals, macrolides, carbapenems, aminoglycosides, glycopeptides and antifungals for further analysis. The dosage appropriateness was tallied with the prescribed dosage and the high, low, marginalized prescriptions were analyzed most appropriately.

The data were collected based on the following criteria:

- Age (in months)
- Blood cultures done and outcome
- CRP (C-reactive protein) level which helps in measuring the amount of c reactive blood protein. The blood protein gets released as a part of the body's defense against infection.
- Antimicrobials (antibiotic, antifungal or antiviral) prescribed.
- The dose of antimicrobials.
- Lengths of hospital stay (LOS) (which in the case of this study was calculated from the first day of admission until the day of discharge all inclusive).
- Immunization status, either up to date or not up to date.
- Patient weight (in kilograms).

All the data collected were tabulated in excel.

2.8 DATA ANALYSIS

The effectiveness of the treatments was measured using the time of stay on admission, and the overall health status and wellbeing of patients after pneumonia therapy. Safety of antibiotics was assessed with reports of adverse reactions. These data were then fed into Statistica® version 13.5.0.17, a statistical software. Stata® version 14.0 was used as an additional statistical software for data analysis. Descriptive tests and t-tests were used to present the data. This presentation takes care of the contrasting treatment of the children in the sample size and helps in predicting them based on the antibiotics used.

2.9 Ethical Consideration

The present research study has been conducted by having some essential ethical considerations. The study was solely based on secondary research; no informed consent was needed. However, it has been confirmed that all the gathered data have been used only for academic purposes; the research has not focused on any commercial purposes. Moreover, the collected information has been kept confidential and secure according to the law of data protection.

Permission to continue with the research was given a green light to proceed by the University of Witwatersrand Human and Research Ethics Committee. A Clearance certificate was issued Certificate number M180524.

2.10 SUMMARY OF THE CHAPTER

The chapter examined various aspects of the methodology that has been used to conduct the research in the most appropriate manner. The chapter dealt with the research approach, design, philosophy and strategy that have been considered while doing the research. The sampling process has been described along with the method of data collection. The chapter further described how the data was collected and how to analyze the data obtained.

CHAPTER THREE: RESULTS AND FINDINGS

3.1 Introduction

The chapter deals with the research that has been conducted and the analysis of the data that has been found. The chapter discusses the results and findings and interprets them in accordance with CAP and its pattern in the country. The discussion on the antimicrobial resistance patterns and the aetiology of the bacteria and the viruses involved are described in detail. Therefore, this chapter is of importance in the long run.

Table 3.1: The age of the children under study

Age group	Number of children	Percentage
0-24 months	158	55.05
24-36 months	48	16.72
37-48 months	30	10.45
48-50 months	51	17.78
Totals	**287**	**100**

Table 3.1 shows that the average age of the children under was 39.5 months. The highest number of children hospitalized was 158 from the age group of 0-24 months and the lowest was 30 from 37-48 months' age group.

3.2. Prescribing trends of antimicrobials used for CAP treatment.

The trend for the prescription of the antibiotics in the study cohort consisted of a list of antibiotics:

- 1.Cephalosporins (e.g. ceftriaxone) used - 45%.
- 2.Penicillins such as amoxicillin/clavulanate used - 25%
- 3. Antivirals such as acyclovir used - 19%
- 4.Aminoglycosides (e.g. gentamicin) used- 5%

- 5. Macrolides such as azithromycin used- 3%
- 6. Antifungals such as fluconazole used - 2%
- 7.Carbapenems such as imipenem used - 1%

The most important antimicrobial group according to prescribing trends of antimicrobials used for CAP treatment was cephalosporin e.g. ceftriaxone which was prescribed at 45% rate. The second most important group was penicillin such as amoxicillin/clavulanate which were prescribed at a rate of 25%.

3.3. Antimicrobial usage based on age.

The antimicrobial agents that have been used for the children have been categorized based on the age group. These groups of age of children are divided based on the type of antimicrobial agents that they have received.

The use of antimicrobial agents varied based on the child as follows:

- In most cases penicillin was used for children in the age range of 0-24 months along with antiviral drugs. This accounted for about 66% of the cases.
- Out of the remaining cases the cephalosporin and macrolides made up most of the dosages for children agedf 0-24 months.
- The cephalosporin alone accounted for about 60 percent and macrolides about 1% of the cases.
- The use of antifungals was mostly limited to the age group of 36 to 48 months. Use of aminoglycosides and carbapenems is limited in most age groups.

Table 3.2: Time of hospital stay (admission duration)

Length of stay in days	Number of children	Percentage
One day	51	17.77
Two days	44	15.33
Three days	77	26.83
Four days,	51	17.77
Five days	38	13.23
More than five days	**26**	9.05
Totals	**287**	**100**

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Table 3.2 reflects that among the 287 children who were included based on the inclusion criteria of the study the average hospital stay was 3-4 days with a standard deviation of 1.38. The release of the patients from hospital was based on the lowering of the symptoms of CAP.

3.4. The relationship between immunization and length of stay

The relationship between the length of hospital stay and immunization is based on the form of data which has been acquired. The data is of two types as shown in the table below:

Table 3.3. Immunization status table

Immunization status	Mean length of stay	Standard deviation	Percentage	P value
Up to date	4.27	0.101	76.49	0.6911
Not up to date	4.38	0.186	18.43	0.6911

A sample t test was performed on the group of children amidst the 287 children to see the mean difference in the hospital stay for age groups based on the mean time in days that the children spent in the hospitals. The regression on the duration in days spent in hospital decreased by only 0.11 for children who had been immunized previously compared to those who had not been immunized. The P value remained constant at 0.6911 which showed that there is no statistical difference between the immunized and the non-immunized children when it comes to length of hospital stay.

3.5. Cultures: blood cultures and/or sputum cultures

Table 3.4 CRP level percentage analysis

CRP levels	N=287	Percentage
High	120	41.81%
Normal	140	48.78%
No lab test	27	9.41%
Totals	**287**	**100**

Table 3.4 indicates that the infection markers from the laboratory tests carried out, out of the 287 patients who were treated for CAP were done for 91% of the cases. The infection markers which were used to treat the patients were CRP and, in some cases, PCT levels were added.

Table 3.5 Bacterial Aetiology in study cohort

Age group	Number of children =287			Percentage =100		
	Positive	Negative	No test	Positive	Negative	No test
0-24 months	22	116	20	7.67%	40.41%	6.97%
24-36 months	5	40	3	1.74%	13.93%	1.05%
37-48 months	8	22	0	2.78%	7.66%	0%
48-60 months	4	43	4	1.39%	15.00%	1.39%
Totals	**39**	**221**	**27**	13.59%	77.00%	9.41%

Table 3.5 details that only 13.58% that is (39/287) patients had confirmed bacterial aetiology. While 77.00% did not have a positive bacterial culture growth and 9.41 % represent bacterial culture growth tests not carried out.

Table 3.6 Viral Aetiology in study cohort

Age group	Number of children			Percentage		
	Positive	Negative	No test	Positive	Negative	No test
0-24 months	130	8	20	45.29%	2.78%	6.97%
24-36 months	45	0	3	15.67%	0%	1.05%
37-48 months	30	0	0	10.45%	0%	0%
48-60 months	46	1	4	16.04%	0.035%	1.39%
Totals	**251**	**9**	**27**	**87.46%**	**3.13**	**9.41%**

Table 3.6 summaries that 251 children tested positive to viral pneumonia based on the PCR results which consisted of 87.46% accounting for (251/287) children, while 9

children tested negative to viral pneumonia thus 3.13 % and 9.41% about 27/287 children were not tested for viral aetiology.

Table 3.7 Mixed infections

Age group	Number of children	Percentage
0-24 months	16	61.54
24-36 months	3	11.54
37-48 months	6	23.08
48-60 months	1	3.85
Totals	**26**	**100**

Table 3.7 shows data on the mixed infection group which consisted of the children that had both bacterial and the viral agents affecting the health of the children. The mixed infections too were more prevalent in children between the age group of 0-24 months and accounted for about 61.54% cases as compared to 3.85% in those aged 48-60 months.

Table 3.8 Guideline on dosage

The dosage appropriateness refers to the dose of the antimicrobial agents that were given to the children as per appendix 1.

Dosage according to weight	Percentage
Low	30.28
High	9.16
Appropriate	50.60
Inappropriate	3.19

Table 3.8 reveals that only 50.60% of dosages were appropriate in terms of the guidelines that are set for the treatment of CAP. However, 9.16% of cases recorded high doses of strong antimicrobial agents which can cause potential side effects in the children. Furthermore, the low doses which were as high as 30.28% results in antibacterial resistance which is the primary cause for the recurrence of the CAP among kids in the South African belt.

3.6. Frequently prescribed antimicrobials versus STG 1st choice

The guidelines for the treatment of the disease in South Africa clearly prescribed penicillin to be the number choice. It is followed by the cephalosporin for treatment of children who are older than 60 days. Most treatments for children between 0-59 days include a combination of penicillin and aminoglycosides. The major reason behind the use of this combination is that most bacterial agents causing pneumonia are ineffective against the group of beta lactam drugs. The combination with aminoglycosides helps in the prevention of the antibiotics to be ineffective against the bacteria. However, cephalosporin was prescribed at a rate of 45% as a lot of patients were above two months of age. The rate of prescription of penicillin was 25%. This shows that the prescribing patterns were a mere adjustment of the age of the children suffering from CAP.

3.7 DISCUSSION

Scott et al. (2008: 1291) accent that pneumonia has clear signs and symptoms and treated in developed nations but in less developed countries pneumonia usually leads into high morbidity and mortality due to several predispositions. Scott et al. (2008: 1291) emphasize that pneumonia research can be highly effective if pneumonia is being isolated and accorded a serious response and be dealt with thoroughly as one.

Results reveal that pneumonia has a link with malnutrition and poverty these are pneumonia risk factors. When introducing strategies for child survival where effective management through the community programs that has proven difficult to achieve, it is very important monitoring how each of these factors is contributing to pneumonia (Mulholland, 2008:399).

Scott (2008: 1299) infer that worldwide child deaths from pneumonia are a huge problem. Clinicians need to understand and have information that is intensively detailed about aetiology and pathophysiology of pneumonia when implementing new guides to tackle this disease. More importantly good results can yield if this disease is dealt with comprehensively as one disease.

An investigation by Madhi (2008: 365) informs that child mortality rate can be reduced by using common bacterial vaccines. In developing countries with low-income, this has revealed to be effective and safe to use in prevention of pneumonia. Furthermore, he reasons that vaccines have the ability to help children in developing countries with low-income who might not have access to health care facilities (Madhi 2008 :372).

More so, Dawson et al. (2008:339-343) instils that community management of CAP has resulted in mid-term solution during strengthening of the efforts to curb this leading cause of childhood deaths. To improve the management of pneumonia in poor countries lacking health skills is one of the major approaches to reduce child mortality rates from pneumonia

3.7.1 Prescribing trends of antimicrobials used for CAP treatment

The trends for prescribing antimicrobials for the study showed a preference for cephalosporin and then penicillin. The MAREA guidelines preferred ampicillin or amoxicillin for the treatment of CAP. However, cephalosporins were also used for a large amount in the monotherapy treatments of the study. As per the studies conducted in the countries like India, Brazil, Italy cephalosporins were the primary anti-microbial agent that is most effective against CAP. The trend observed in this study clearly indicates that cephalosporins were the most sought-after drug to be effective against CAP followed by penicillin, macrolides and aminoglycosides. The use of broad-spectrum cephalosporin is the key in ensuring the effective treatment for CAP especially if a specific causative organism is not identified.

3.7.2 Length of hospital stay (admission duration)

The length of the hospital stay varied in different regions and in different hospitals across the continent. As per reports most hospitals like the Cincinnati hospital record an average stay of 9 days while a study in Brazil demonstrated that the length of

duration in the hospital remains the same at an average of 7 days. The treatment for pneumonia usually takes about 7-10 days as it is an acute infection and chances of relapse can also be severe. In this study the average period of hospital stays accounted for about 4 days in average which is less that the prescribed 7 days. This raises the question if the infection has been effectively removed. However, according to the studies in hospitals in Asia the average stay of 4 days has been recorded same as the one in this study.

Responses of antibiotics

Carboxypenicillins - Clinical study to assess the efficacy of ticarcillin/clavulanate for severe pneumonia. The clinical efficacies of ticarcillin/clavulanate for dangerous pneumonia (both CAP and HAP) in 11 patients were studied in an open controlled trial. With infections due to *Pseudomonas aeruginosa*, amikacin was added. Seventy-three percent of patients improved with pathogen eradication in all patients except in 2 cases with *Pseudomonas aeruginosa* superinfection.

Penicillins are bactericidal. (Amoxicillin)- Clinical study to assess the effectiveness of oral amoxicillin for the treatment of pneumonia. Failure rate of 9% (26/287) was observed. Three deaths occurred. It concluded that community case management of pneumonia with oral amoxicillin is more effective than WHO recommended treatment with first dose oral co-trimoxazole followed by referral (Abdul Bari, et al, 2013).

Cephalosporins- Narrow-spectrum and broad-spectrum antibiotics

The Clinical study to assess the effectiveness of narrow-spectrum antibiotic therapy for severe to very severe pneumonia resulted in the median length of stay for the group recorded as 3 days.

The mean duration of treatment for azithromycin group was 3.6 days in the clinical study done to compare the effectiveness of azithromycin with cefuroxime alone or cefuroxime plus erythromycin. A treatment failure of 16.8% was recorded for amoxicillin group compared to 18.9% for the co-trimoxazole group. Clinical study comparing the efficacy of co-trimoxazole with amoxicillin for the treatment of pneumonia

3.7.3 Relationship between immunization and length of stay

The relationship between immunization and the length of hospital stay have been observed in the study. A regression of about 0.11 has been found in the children who were immunized prior to their admission in the hospital. This showed that there is a very little deviance in the time in hospital and immunization status. However, a 2-sample t-test and linear regression analysis showed that the reduction in length of hospital stay in the group of children with immunization that was up to date; compared to the group with immunization that was not up to date was not statistically significant in this cohort. Hence, other studies in the future could explore the relationship between immunization and length of hospital stay.

3.7.4 Cultures: blood cultures and/or sputum cultures

The guidelines set by the South African Thoracic Society clearly state that microbial testing is necessary for the treatment of the patients suffering from pneumonia. Identification of the causative organism would further aid the treatment and would be beneficial for the society as well. Identifying causative agents also is beneficial as it contributes to the public health where epidemiology could be better understood if there's data available and driving the public health focus, if issues of potential threat can be identified. The tests have been performed extensively to test the levels of white blood cells and C-reactive blood protein. The C-reactive blood protein is a marker for infection and can be relied on to justify antimicrobial use while further investigations are carried out.

The CAP guidelines indicate that microbiological diagnostic test in low to mild cases of CAP is recommended and in special situations it should be selected. In severe cases of CAP, clinicians are encouraged to do sputum staining, blood cultures, sputum culture, and the urinary antigen test for Legionella and pneumococcus.

Liu *et al.* (2013) and Hohenthal *et al.* (2009) attest that there are some special situations where microbiological tests should be applied:

- Hospitalized patients with positive urinary antigen test for pneumococcus;
- Cavitary infiltrates;
- Outpatients with failure of antibiotic therapy;
- Severe obstructive lung disease: sputum culture;

- Active alcoholism;
- Epidemiological factor or specific risk factors suggesting pathogen;
- Pleural effusion;
- Severe CAP admitted to intensive care unit (ICU) (Liu *et al.*,2013).

Microbiological diagnosis of CAP continues to be based on respiratory samples or blood culture.

(Liu *et al.*,2013) concludes that the main problem with conventional methods are the low yield and long turnaround time and that previous antibiotic use affects microbiological results (Hohenthal *et al.*,2009)

3.7.5 Culture yield

The yield of the cultures showed presence of causative organisms that were present in the cultures. Blood cultures are requested with the aim of identifying the causative agent to assist in choosing the appropriate treatment. Positive blood cultures have been obtained at a rate of 1,5% - 7,1% in children with CAP in other studies. Bacterial aetiology of CAP is changing due to pneumococcal vaccine introduction. However, *Streptococcus pneumoniae* has remained the leader in the causative agents list of CAP, hence the reason why guidelines suggest *Streptococcus pneumoniae* as the target organism for most CAP treatment.

3.8 Guideline adherence

3.8.1 STG guidelines

The guidelines showed that outpatients with less severe pneumonia are treated with amoxicillin for 3 days. While patients with severe pneumonia have been treated with amoxicillin for a period of five days. The dosage for the children has been discussed in the appendix of the study.

3.8.2 SATS guidelines 2017 + FIDSSA guidelines summary

There have been findings that physician adherence to guidelines was 43,6%. This figure is a concern and triggers need for further investigations to improve the outcome or rather, a need for engagement with prescribers to find out the reasons for below 50% adherence. The 25% adherence rate presented in this study is a motivating factor to look at prescriber – pharmacist engagement to establish the reasoning behind the

prescription pattern presented and to develop platforms that contribute to better patient care. The care for bacterial resistance and the dosage of the antimicrobial drugs are considered.

3.8.3 Resistance pattern (2010-2014)

Resistance rates for *Streptococcus pneumoniae* are very significant for macrolides and penicillin, which is of great concern because macrolides were considered 1st choice in CAP empiric treatment at the time of the referred study. For the period of 1998 – 2009, ceftriaxone susceptibility rate of *Streptococcus pneumoniae* reduced from 97,4% to 87% and 5%. *Mycobacterium pneumoniae* has shown macrolide resistance rates varying with geographical location between 7% and 50% in Seattle and New Jersey, respectively. The variation of antimicrobial resistance patterns and causative agents' epidemiology necessitate the need for local treatment guidelines; since these factors affect patterns of susceptibility and local aetiology; resulting in the need for locally specified empiric antimicrobial CAP treatment.

3.9 Summary of the chapter

The chapter shows the results and findings; and interprets them in accordance with CAP and its pattern in the country.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusion

Cephalosporins- The study concluded that the clinical outcomes for children hospitalized with CAP on narrow-spectrum antibiotic are not significantly different from treatment with broad-spectrum antibiotic (Derek JW, et al, 2013).

It is a great advancement that 96,02% of the cases underwent laboratory testing to ascertain CAP aetiology. However, it is concerning that 49,4% of the children who received antimicrobials, did so at inappropriate doses for weight. The doses were either low or higher than the recommended ranges. This is where CAP treatment guideline implementation would be useful because the dosing considerations would be readily available both for the prescriber and for the pharmacist or anyone issuing the medicine, for example, nurses in the emergency cupboard when the pharmacy is closed. Guideline implementation can also be used as a tool to influence outcomes (directly or indirectly); specially to bring out efficient practices for the benefit of the population since the information available will be based on current trend analysis.

In turn, this addresses potential risks of antimicrobial resistance as irrational exposure due to under-dosing would hopefully be eliminated or reduced. It would also be interesting to state at this point that the most prescribed antibiotic group in this study, was the 2nd line regimen recommended in the STGs. The 1st line regimen was prescribed at 25% rate which is a huge concern as most patients were treated with a broad-spectrum antibiotic. Perhaps, with guideline use enforcement or encouragement, the distribution of percentages of antimicrobials prescribed would probably have been different, which is a trend analysis that can be studied in the future. It can also be a trend to show that the antimicrobials prescribed were merely an adjustment due to the age of the children as per STG recommendation.

New STGs and EMLs were published during the course of the study. A study to check how quickly prescribers adopt new strategies would also be valuable to determine the relevance of the treatment options at any given time. The results of this study were variable when compared to other similar studies done elsewhere, which can be

attributed to the limited sample size and population distribution as only a small group was considered for this study. However, it is in support of the findings of the Department of Health which was made the basis of establishing an antimicrobial stewardship programme to enable data pooling. Initiatives in the future can look at standardizing data collection methods across the South African healthcare system for availability in one database to enable efficient and effective reporting, as well as trend analysis. Considering NHI, this would be beneficial as it could be a framework for future initiatives to standardize processes.

4.2 RECOMMENDATIONS

- It will be of great interest to implement a clinical practice guideline and compare its cost-effectiveness and clinical outcome trends to the periods where there was no enforced set guideline on CAP management in a hospital setting.
- Guidelines would also be useful in addressing issues of antimicrobial resistance and also preventing misuse by guiding antimicrobial choice. Issues of dosage appropriateness according to weight, can also be addressed using guidelines as all dosing references would be readily available.
- Further studies with a bigger sample and more study sites would also be an interesting venture to see trends of practices across the private hospital groups. Another factor to investigate would be the readiness to receive and implement the guideline by prescribers.

4.3 Object Linking

The objective linking of the study is effective as it helped acquire the knowledge about the use of different antibiotics for the treatment of children in a private hospital in Ekurhuleni. The objective to ensure that the appropriate dosage of antimicrobial drug for the disease was the objective this study. A relationship between the length of hospital stay and the duration of the treatment of CAP is also established in this study. The study takes care of all these details in a great way.

4.4 RESEARCH LIMITATIONS

1. The reader should bear in mind that the study is based on CAP only for children aged 5 years and below.
2. Due to practical constraints, this paper cannot provide a comprehensive review

of pneumonia because of reverse bias: breastfeeding and nutritional status may change because of pneumonia.

3. The study was done in one-year cases only; it would have been better to conduct the study for at least two to five years to cover all the seasons.

4.5 FUTURE RESEARCH

- This study focused on CAP in children under the age of 5 years only in one province and one private hospital. The study can be duplicated to cover more provinces and government hospitals to allow generalization of results.
- Scholars can also advance and probe on the factors that promote and affect the effectiveness of antibiotics on the same age group.
- More research is needed in the prevention of CAP since most studies have been focusing on treatment.
- The same study can be done on all age groups and compare the effects of the same antibiotics for CAP treatment on patients of different age groups and gender but in a similar or same environment.

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APPENDIX 1: DOSE CALCULATION REFERENCES:

Ceftriaxone - once daily dose: 80mg/kg/day

- Twice a day dose: 50mg/kg/dose

Amoxicillin-clavulanate – 30mg/kg/dose of amoxicillin component.

Clarithromycin- 7.5mg/kg/dose twice a day

Azithromycin – 10mg/kg orally on day 1 then 5mg/kg orally from day 2-5

Erythromycin – 10mg/kg/dose, up to 15mg/kg

Cefazolin – 150mg/kg/day

Amikacin – 15 to 22mg/kg once daily

Ertapenem (3 months- 12 years) – 15mg/kg twice a day

Ampicillin: less than 20kg – 12,5mg to 25mg/kg/dose

Over 20kg – 250mg to 500mg 6 hourly

Cefotaxime – 200mg/kg/day divided into 8 hourly doses

Fluconazole – 10mg/kg/dose

Acyclovir – 10mg to 20mg/kg/dose intravenously every 8 hours

Oseltamivir for influenza A and B for 5 days:

Children 2 weeks old to less than 1 year

– 3mg/kg orally twice a day

Children above 1 year

- less than 15kg: 30mg orally twice a day
- 15-23kg: 45mg orally twice a day
- 23-40kg: 60mg orally twice a day

Oseltamivir for H1N1:

- 3-5 months – 20mg orally once a day for 10 days
- 6-11 months – 25mg orally once a day for 10 days