AETIOLOGY AND OUTCOME OF PLEURAL EMPYEMA IN CHILDREN ADMITTED TO PIETERSBURG HOSPITAL LIMPOPO, SOUTH AFRICA

Master of Medicine in Paediatrics and Child Health

M Tshamiswe

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AETIOLOGY AND OUTCOME OF PLEURAL EMPYEMA IN CHILDREN ADMITTED TO PIETERSBURG HOSPITAL LIMPOPO, SOUTH AFRICA

by

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DECLARATION

I declare that the mini dissertation hereby submitted to the University of Limpopo, for the degree of Master of Medicine in Paediatrics and Child Health has not previously been submitted by me for a degree at this or any other university; that it is my work in design and in execution, and that all material contained herein has been duly acknowledged.

Tshamiswe , M Dr 21 September 2022

DEDICATION

This work is dedicated to my late grandfather Mr. Sengani Cuthbert Tshikombe, the one person who believed in my academic strengths in all my academic seasons. He knew how to express his love and adoration to me and spoke sense when there seemed to be no hope. May his soul continue to rest in peace.

I also dedicate this work to all my grandfather's grandchildren and the rural boys and girls who dream of changing the world around them.

"Through perseverance and dedication, nothing is impossible".

Dr M Tshamiswe

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ABSTRACT

Introduction: Pleural empyema in children is associated with high morbidity and high mortality. *Staphylococcus aureus* has been shown to be the most common causative organism in developing countries.

Study design: This study applied a retrospective quantitative descriptive study design.

Study population: The population of the study is comprised of children (between 1 years and 13 years) admitted to Pietersburg Provincial Hospital with pleural empyema from January 2016 until December 2020.

Objectives: The study aimed to determine the causative organisms of pleural empyema, the treatment outcomes, and the relationship between pleural empyema, TB, and HIV infection.

Data collection: The National Health Laboratory Services database was used to identify patients who had pleural empyema. A self-generated data collection tool was used to obtain secondary data related to all patients who met the operational definition of pleural empyema during the defined time period.

Results: Eleven participants met inclusion criteria. The mean age of participants was 42 months with 43.8 standard deviation and 64% were males and females were 36% . Of these participants, 40% cultured S. *Aureus* in the pleural fluid, 10% *Streptococcus pneumoniae,* 30% were sterile and 20% cultured other organisms such as *Klebsiella pneumoniae and Haemophilus influenzae.* Cloxacillin was the most prescribed antibiotic. Intercostal drainage was inserted in 91% of the participants of which 18% were successful, no further surgical intervention needed,73% had thoracotomy and VATS was offered to 91% of participants and it was followed by thoracotomy. Fibrinolytics were not offered to the participants in this study. The majority of patients, 55%, were discharged back to their peripheral hospitals and 27% of them died. PCV immunisation status of the children was not documented hence the relationship between pleural empyema and PCV immunisation could not be established. There was a positive correlation between age of patients with pleural empyema and ICU length of stay (r=89%; p=0,01) while another strong correlation was depicted between

HIV status and hospital length of stay (r=88%, p=0,019). Results further show a positive association between outcome and surgery intervention offered (Chi=7,00; p=0,02).

Conclusion: Our study showed that *S. aureus* is the leading cause of pleural empyema, with a predominance of thoracocentesis and thoracotomy offered as surgical interventions.

Key words: Pleural empyema, causative organisms, treatment outcome, children

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DEFINITION OF KEY CONCEPTS

Children: The South African Constitution defines children as any person below the age of 18 years (1). In this study, a child is defined as any person between 28 days of life and 13 completed years.

Clinical Outcomes: Clinical outcomes can be defined as measures chosen to assess the impact of an intervention or treatment (2). In retrospective studies, outcomes have already occurred (3). In this study, treatment outcomes were assessed for all the treatment modalities offered to children with pleural empyema looking at the length of stay, mortality, and complications (bronchopleural fistula, lung abscess and scoliosis) of children treated in our hospital as inpatients.

Pleural empyema - Pleural empyema is defined as an accumulation of pus in the pleural space, usually following bacterial pneumonia, a chest injury, or thoracic surgery (4). In this study, pleural empyema refers to the macroscopic appearance of the pleural fluid with neutrophil predominance or positive culture results of the pleural fluid.

Review – A formal process of assessment, usually with the intention of instituting change if necessary (5). This review is an examination of the files of patients who had pleural empyema with a particular aim to identify causative organisms and the treatment outcomes thereof.

Pneumococcal Conjugate Vaccines (PCV) - vaccines that target *Streptococcus pneumoniae* which cause pneumonia and invasive pneumococcal disease like pleural empyema (6). A conjugate vaccine joins a protein to an antigen to improve its efficacy (7).

Real-time polymerase chain reaction (Real-time PCR) - a molecular diagnostic method used to identify pneumococcal serotypes. Real-time PCR is fast and provides simultaneous identification of more than one serotype (8).

The South African Department of Health "Road to Health Card" (RTHC) booklet - an educational booklet for caregivers and allows the health care providers to document immunisations and clinical findings during encounters with the family or caretaker of the developing child.

Video-assisted thoracoscopy (VATS) - a minimally invasive thoracic procedure that involves introducing an instrument through an incision in the chest wall to visualise the intrathoracic structures. (9).

ABBREVIATIONS

ART	Antiretroviral Therapy
CT Scan	Computerized Tomography Scan
CXR	Chest X Ray
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
NHLS	National Health Laboratory Services
PCR	Polymerase Chain Reaction
PCV 7	Seven-valent pneumococcal conjugate vaccine
PCV 13	Thirteen-valent pneumococcal conjugate vaccine
RTHC	Road to Health Card
TB	Tuberculosis
UK	United Kingdom
US	United States
US CDC	US Centres for Disease Control and Prevention
VATS	Video-Assisted Thoracoscopic Surgery
VATS D	Video-Assisted Thoracoscopic Surgery Decortication

CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1 Background and overview of the study

Pleural empyema accumulates pus in the pleural space, usually following bacterial pneumonia, a chest injury, or thoracic surgery (4). Worldwide incidence in children is reported to be between 0.7 - 3.3 per 10 000 (10). However, incidence of pleural empyema in children appears to have improved in developed countries like the United States (US) and the United Kingdom (UK) with an annual incidence of approximately 3 per 100 000 children. This is attributed to improved diagnosis and use of antibiotics in children with respiratory infections (11).

Data regarding the incidence of pleural empyema in developing countries is limited. For example, a study conducted in Cape Town showed a decreasing trend in the annual incidence of paediatric admissions for pleural empyema (12). However, in Limpopo, we do not have documentation of the numbers of paediatric admissions for pleural empyema.

Over the past years, there have been several cases of children admitted to Pietersburg Provincial Hospital with severe pneumonia, and some were later diagnosed with pleural empyema. Currently, no records of the numbers of empyema admissions are kept at the Pietersburg Hospital. However, the estimated empyema admissions were 30-35 per year, although this is not based on official records.

Pleural empyema has high morbidity and high mortality. *Streptococcus pneumoniae* has been reported to be the main causative organism in developed countries and *Staphylococcus aureus* is commonest in developing countries (12). Pneumococcal infections are the leading cause of death from vaccine-preventable illnesses in children aged <5 years (13). Non-vaccine serotypes could explain the increased incidence in pleural empyema worldwide (14). Other organisms identified in several countries are methicillin-sensitive and methicillin-resistant *S. aureus, Streptococcus pyogenes, Haemophilus influenzae* and

Pseudomonas aeruginosa (14). Therefore, it is crucial to establish whether organisms causing empyema in our setting are similar to those in other developing countries, together with the treatment outcomes.

Limpopo Province is the northern-most province in South Africa and borders on Zimbabwe and Botswana. There are five districts with regional hospitals in all the districts. Pietersburg Hospital is Limpopo's Provincial Hospital and renders tertiary health services to all the province's five districts. Limpopo has a high prevalence of TB and HIV infection. Furthermore, Limpopo had an estimated HIV prevalence of 9,2% among those two years of age and older according to the 2014/15 Limpopo AIDS Council Report compared to the national estimate of 29,5% (Limpopo Provincial AIDS Council, 2016). Tuberculosis is the leading cause of death among all South Africans (8,8%). In Limpopo, the TB death rate was 11,1% in 2014/15, the second-highest rate in the country (15).

Understanding the impact of TB and HIV infection among children admitted to Pietersburg Hospital for pleural empyema is fundamental.

Treatment modalities depend on the clinical stage at which the patient presents (16). The principle of empyema treatment is the prevention of sepsis by evacuation and sterilisation of the pleural cavity (12). Treatment of pleural empyema depends on the organisms cultured and the presence of loculations. Empiric antibiotics should include treatment of likely pathogens of pneumonia and empyema, and should cover both *S. pneumoniae* and *S. aureus* (14). Patients with loculations require advanced treatment modalities such as fibrinolytics and more invasive procedures like thoracotomy.

1.2 Problem statement

In our literature search, we could find no other study that looked at the empyema and treatment outcomes in paediatric patients in Limpopo. However, in Pietersburg Provincial Hospital, antibiotics choice was based on standardised guidelines based on systematic reviews from other settings.

The treatment modalities in the setting of this study include the medical approach as discussed above. In addition, the surgical treatment in our setting includes thoracentesis to drain the pus from the pleural space and thoracotomy with decortication, which is a more invasive surgical procedure that requires postoperative care in the intensive care unit (ICU). The aim of this study is to describe the causative agents and treatment outcomes of children diagnosed with pleural empyema who were admitted to Pietersburg Provincial Hospital.

1.3 Aim, Objectives, and Research Questions of the study

1.3.1 Aim of the study

The aim of this study is to describe the causative agents and treatment outcomes of children diagnosed with pleural empyema admitted to Pietersburg Provincial Hospital over a five-year review period.

1.3.2 Objectives of the study

The objectives of the study are:

- To determine the causative organisms of pleural empyema
- To describe the relationships between pleural empyema, TB, HIV infection and PCV immunisation status at the time of diagnosis
- To review treatment and treatment outcomes of children diagnosed with pleural empyema

1.3.3 Research questions

The research questions for the study are as follows:

- What are the causative organisms of pleural empyema in children admitted to Pietersburg Provincial Hospital?
- What are the treatment options and outcomes of paediatric patients treated for pleural empyema at Pietersburg Provincial Hospital?

1.4 Significance of the study

The results of this study will add to the knowledge of causative organisms of pleural empyema in children admitted to Pietersburg Provincial Hospital. In addition, the study results will demonstrate the relationship pleural empyema has with TB and HIV infection, and PCV vaccination suggesting improved management strategies. Finally, the results of this study will pave the way for future studies looking at pneumococcal serotypes to differentiate between vaccine-preventable disease and non-vaccine-preventable disease. The results of this study will assist in learning about the outcomes of the selected treatment modalities and compare the results with those of other developing countries. This study's results will help provide new insights regarding the causative agents and treatment outcomes in children with pleural empyema in Limpopo.

1.5 Research report layout

This research report consists of five (5) chapters.

Chapter One – This chapter introduces pleural empyema in children, the problem statement, and the aim and objectives of the study. The significance of the study is included in this chapter.

Chapter Two- The literature review of what previous authors have found in their respective studies is detailed in this chapter.

Chapter Three – This chapter presents the research methodology applied in conducting the study.

Chapter Four – This chapter details the data analysis and results interpretation according to the objectives together with the discussion of the results in comparison with the other studies.

Chapter Five – This chapter deals with the discussion of the study, limitations, and recommendations for further study.

1.6 Conclusion

This chapter introduced pleural empyema in children, the importance of the study, and a layout of the research report. The next chapter, Chapter Two, reviews what previous authors found in their studies of pleural empyema in children.

CHAPTER 2: LITERATURE REVIEW

2.1. Introduction

This chapter presents a literature review of research and findings related to pleural empyema in children.

2.2. Epidemiology of pleural empyema

Pleural empyema is defined as pus in the pleural space (17). Pleural empyema can affect any age group, sex, and ethnicity. Over 65,000 patients suffer from a pleural infection each year in the UK and US (18). There are very few studies on the incidence of pleural empyema in Africa, however, a study conducted in Cape Town, South Africa, showed a 50% reduction in pleural empyema between two paediatric cohorts representing the pre- and post-introduction of PCV in 2011 (19).

2.3. Causative organisms

S. pneumoniae has been reported to be the main causative organism in developed countries and *S.s aureus* is most common in developing countries (12). Pneumococcal infections are the leading cause of death from vaccine-preventable illnesses in children aged <5 years (13). Increased incidence of pleural empyema worldwide could be related to non-vaccine serotypes. Other organisms identified in several countries are methicillin-sensitive and methicillin-resistant *S., S. pyogenes, H. influenzae* and *Ps. aeruginosa* (14). In South Africa*, S. aureus* has also been identified as the leading causative organism in a study performed at the Chris Hani Baragwanath Hospital in Johannesburg (20).

Identification of pneumococcal serotypes in empyema plays a pivotal role in reducing the incidence of invasive pneumococcal diseases in children. Real-time PCR is used in developed countries to identify pneumococcal serotypes. Real-time PCR is fast and provides simultaneous identification of more than one serotype (8). The use of PCR for detecting causative organisms has been proved

to be more sensitive and more accurate than bacterial culture (21). Several studies that used molecular diagnostic techniques (real-time PCR) found that pneumococci caused a sizeable proportion of culture-negative empyema in children, mainly serotypes 1, 26, and 32 to 35 (22). A German study identified serotype 3 as one of the commonest in children with invasive pneumococcal disease (23). Gram-negative organisms were limited to infants and were attributed to protein-energy malnutrition (24).

2.4. The impact of the introduction of PCV into paediatric immunisation schedules

PCV targets *S. pneumoniae* which causes pneumonia and invasive pneumococcal disease like pleural empyema (6). Prevention efforts against pneumococcal disease date back to 1977 when the first pneumococcal vaccine, 14 valent polysaccharide (PPSV) was licenced. Later in 1983, nine more serotypes were added to make pneumococcal polysaccharide vaccine (PPSV) known as *Pneumovax 23* (PPV-23).

The polysaccharide vaccine was made of a purified capsular polysaccharide antigen from *S. pneumoniae*. In 2000, a polysaccharide conjugated to a non-toxic *Diphtheria* was licenced with 7 serotypes (PCV 7) (25). As a result, PCV 7, was introduced in South Africa in 2009, followed by the introduction of PCV 13 in 2011 (20).

A recent German study showed ongoing changes in the bacterial aetiology of pleural empyema, with *S. pneumoniae* or *pneumococcus*, followed by *S. pyogenes* as the leading causes of empyema after the introduction of PCV 13 into children's immunisation schedules (23). An Argentinian study conducted in 2012 showed a significant reduction of 39,5% in hospital admissions of children with invasive pneumococcal disease during the first two years of introducing PCV 13 into children's immunisation programmes (26).

Another study conducted in the US in 2012, two years after introduction of PCV 13, showed a significant reduction in invasive and non-invasive pneumococcal infection in children under 5-years (27). A 2014 Norwegian study showed less

impact of *pneumococcus* on parapneumonic effusions post-PCV 13 introduction, finding that *Mycoplasma pneumoniae* was the causative organism in a large proportion of the study population (28) .

A large prospective multicentre study was performed in eight French paediatric emergency departments looking at changes in the bacterial causes of community-acquired parapneumonic effusion and pleural empyema in children 6-years of age after PCV 13 implementation. This study showed that *S. pneumoniae* was the leading bacterium implicated before PCV 13 implementation, but its frequency decreased significantly from 79,1% before PCV 13 to 36,4% after the introduction of PCV 13 (29).

In 2015, Zampoli et al. conducted a study during the overlapping period between PCV 7 and PCV 13. They looked at the incidence of pleural empyema in children admitted to a tertiary paediatric hospital in Cape Town, South Africa. The incidence was reduced by 50% in a group who were immunised with PVC 13 compared to those who were immunised with PCV 7 (19). Furthermore, a retrospective study done at Chris Hani Baragwanath Hospital looking at patients admitted with a pleural empyema between January 2017 and December 2019 showed that the most common causes of empyema were *S. aureus*, *S. pneumoniae* and *Mycobacterium* tuberculosis (20).

2.5. Impact of HIV and TB on childhood empyema

A study done in Soweto, Baragwanath Hospital, showed that in South Africa, 43% of a hospitalised children with empyema were started on TB treatment. The presence of HIV infection was also a determining factor for starting TB treatment. Approximately 77% of HIV-positive patients were started on TB treatment (20). Another paediatric study conducted in Cape Town, South Africa, which has one of the highest rates of TB in the world, reported a prevalence of TB empyema of 10 - 14% (19).

2.6. Pleural fluid investigations

A diagnostic pleural tap is done in patients with suspected empyema. Macroscopically the fluid will be turbid and may have frank pus. Pleural fluid is sent for gram staining, microscopy, culture, sensitivity, adenosine deaminase, protein and glucose levels, and tuberculosis studies (12). In developed countries, fluid PCR was found to detect causative agents in 75% of culture-negative pleural fluid; where it is usually a challenge to diagnose the causative agent in patients who had prior use of antibiotics (24).

2.7. Treatment of pleural empyema

Treatment of pleural empyema depends on the clinical stage of the empyema. The three stages are 1.) a simple, exudative stage with no septations; 2.) a fibro-purulent phase with fibrin strands; and 3.)

septation with a multiloculated empyema with thick pleural coating (16). Fibroblasts play a role in transforming the pleural fluid in the pleural cavity into thick non-elastic pleural peels with a resultant “trapped lung” and functionally impaired gaseous exchange (12).

2.7.1. Antibiotic treatment

Empiric antibiotics should include treatment of the likely pathogens of pneumonia and empyema, and it should cover both *S. pneumoniae* and *S.aureus* (14). Children who are less than two months old, are HIV-positive, or who have malnutrition should be treated with ampicillin IVI 50mg/kg 6-hourly, gentamycin 7,5mg/kg stat, then 5mg daily, and cloxacillin 50mg/kg 6-hourly. Children older than two months should be treated with ampicillin 50mg/kg 6-hourly and cloxacillin 50mg/kg 6-hourly. The duration of treatment should be 2-6 weeks, depending on the symptoms and severity. Drug susceptibility patterns of the bacterial culture should guide antibiotic therapy (12).

2.7.2. Surgical interventions and intrapleural fibrinolytic therapy

The use of fibrinolytic therapy has been shown to reduce the length of stay in hospital (30). A 16-year retrospective study showed that ultrasound-guided chest drain insertion with intrapleural fibrinolytics reduced complications with a comparable duration of drain in situ as well as length of stay in hospital (30).

2.8. Treatment outcomes of pleural empyema

In a prospective study done in Canada, long-term outcomes of patients treated with antibiotics and fibrinolytics on initial admission showed that pleural empyema has significant short-term (6 months) sequelae but long-term sequelae were markedly reduced as assessed by follow-up CXR and spirometry (31). In Belgium, the need for surgical intervention remained higher at 20% compared to other reports of children treated medically (antibiotics, chest drain and urokinase) and it was hypothesised to be due to more aggressive pneumococcal disease (32).

Early VATS demonstrated a high success rate in children treated for pleural empyema and reduced the need for open thoracotomy (33). A study conducted in Turkey comparing the efficacy of video-assisted thoracoscopic surgical decortication (VATS D) and intrapleural fibrinolytic therapy in children with empyema showed no statistical difference, however, VATS D showed a reduced length of hospital stay (34). Thoracotomy compared to VATS showed longer operation time and more postoperative complications. However, VATS was associated with longer intensive care unit (ICU) stay postoperatively and mortality rates did not differ between the two groups (35). A systematic review that compared thoracotomy and thoracoscopy showed reduced length of hospital stay in patients who had thoracotomy (4). A study conducted in Pakistan showed that patients who had open thoracotomy as the first line of treatment had shorter stays in hospital (36). An observational study done on Pakistan showed that both VATS and open thoracotomy in experienced hands had fewer post-operative morbidity and mortality when compared with thoracotomy (37).

2.9. Conclusion

This chapter summarised the literature review on the importance of clinical research in improving clinical care and knowledge. Through this chapter, previously published research in developed and developing countries on pleural empyema in children was reviewed.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Introduction.

This chapter outlines how the study was conducted. It highlights the research methodology, research design, data collection, study population and how the sample size was estimated, and data analysis techniques.

3.2 Research design

Research design is defined as the overall strategy the researcher chooses to integrate the different components of the study coherently and logically to ensure that it effectively addresses the research problem. Research design constitutes the plans that guides collection, measurement, and analysis of data (38).

This study applied a quantitative descriptive retrospective study design. In a retrospective study, the outcome of interest has already occurred when the investigation is initiated. A retrospective study typically utilises administrative databases, medical records, or interviews with patients already known to have a disease or condition. This study extracted observational data from the medical records (patients' files) at the Pietersburg Provincial Hospital database and was systematically organised to collect the required data (39).

3.2.1 The population of the study

The population is the whole group of people being studied (40) and from where the sample will be drawn. The study population included all paediatric patients diagnosed with pleural empyema admitted to Pietersburg Provincial Hospital over five years from 1 January 2016 until 31 December 2020.

3.2.2 Study setting

The physical, experimental, or geographical setting where this research was conducted was the Pietersburg Provincial Hospital, a tertiary hospital located in Limpopo Province, South Africa. Pietersburg Hospital is a referral hospital for Limpopo Province where patients are referred from outlying hospitals for specialist services, including a paediatric intensive care unit (PICU) run by paediatric pulmonologists.

Pietersburg Hospital has an eight-bedded paediatric intensive care unit with a nursing staff comprised of one operational manager, six professional nurses with specialty training, six general professional nurses and ten staff nurses. The PICU has two paediatric pulmonologists.

Patients admitted to this facility represent both the rural and urban areas of Limpopo as it offers services to all five districts of Limpopo and admits patients referred from local primary health care centres and clinics.

3.2.4 Inclusion criteria

- All children aged between 28 days of life and 13 completed years with the operational definition of pleural empyema; This is the age group of paediatric population who are admitted in Pietersburg Hospital.
- Inpatients admitted to the paediatric ward and/or PICU at Pietersburg Hospital between 1 January 2016 and 31 December 2020 who met the criteria for the operational definition of pleural empyema.

3.2.5 Exclusion criteria

- Patients who developed pleural empyema secondary to a surgical procedure or trauma-related pleural empyema because of the possibility of skin flora to be causative organisms.

- Patients diagnosed with pleural empyema before 1 January 2016 and after 31 December 2020 as they fall outside of the time frame of the study. (January 2016 until December 2020)

- Patients less than 28 days of life and older than 13 completed years (Patients younger than 28 days of age were excluded since the causative organisms in the neonatal age reflect that of the mother.)

3.2.6. Data collection

Data collection is defined as “the process of gathering and measuring information on variables of interest, in an established systematic manner that enables one to answer stated research questions, test hypotheses, and evaluate outcomes” (41).

This study is a descriptive retrospective study that involved obtaining secondary data from patients’ medical records from Pietersburg Provincial Hospital’s database. The data were collected using a self-generated template as a data collection tool (Annexure 1). The checklist included demographic data and variables to address the objectives of the study. The researcher obtained permission to access the NHLS database of pleural fluid specimens collected from children of the relevant age group who met the operational definition of 21pleural empyema. The pleural fluid results that included the microorganisms cultured from the fluid was obtained from NHLS. Patients’ medical records were used to obtain demographic information such as HIV status, PCV vaccination status, treatments given, and outcomes which were recorded by the researcher in the self-generated data collection tool. The data captured in a data collection tool were coded and entered onto an excel spreadsheet and then exported to STATA 17 (42) for analysis.

3.2.7 Data analysis

Descriptive statistics have been used to summarise and organise the data as graphs and tables. Ordinal variables and categorical variables were reported as numbers and .percentages Chi-square test was used to determine the

association between pleural empyema, TB and/or HIV infection and PCV immunisation status. Logistic regression analysis was used to describe the data and explain the relationship between the death binary variable and risk factors.

3.2.8 Validity and reliability

The reliability of a measuring instrument refers to how well the instrument consistently yields similar results (39). Each time the data collection tool is used, it will yield the same results according to the variables to be measured. In this study, medical records of patients with pleural empyema as identified by the NHLS have been recorded on the data collection tool in accordance with the study objectives and if repeated, will yield the same results. Validity refers to the extent to which a measurement instrument measures what it is meant to measure. Content validity requires the data collection tool to include all the variables to address the objectives of the study. In this study, the self-generated data collection tool consists of all variables according to the study's objectives (43). Face validity is the extent to which the measure makes sense to those knowledgeable about the subject (43). The researcher works in the hospital's paediatric department and is reasonably familiar with variables to enter on to the data collection tool. The study used scientific quantitative data to analyse the results to draw a valid conclusion regarding the causative organisms of pleural empyema in paediatric patients admitted to Pietersburg Provincial Hospital. This ensured that the results answered the research questions as the study intended.

3.6 Bias

Bias refers to the conduct or design of the study that could lead to invalid results of that particular study (43). There are different types of bias affecting clinical research: information bias, selection bias, and confounding bias. Information bias is a systemic error that occurs in how measurements are taken on participants in the study. In this study, there is potential of information bias in collecting data from NHLS spreadsheet. A 100% quality check of the data received from NHLS was compared to the source documents (patients' medical records) before data analysis. Any errors found were corrected per the source document.

Confounding bias is a systemic error that occurs when third variable results in an apparent association between the exposure and outcome, thus not reflecting true association (43). Confounding bias was addressed to account for confounders such as HIV-predisposition to parapneumonic empyema in younger children.

3.7 Ethical considerations

This study followed ethical consideration in conducting research that include human participants. In this study, the researcher protected the rights of the participants and of the institution, confidentiality and scientific integrity were maintained by the researcher as outlined below.

3.7.1 Protecting the rights of participants

Since this was a retrospective study, only medical records were required. To ensure that patients' data is protected and not subjected to harm in any way, and that respect for the dignity of research participants information is kept confidential, the research protocol was approved by the Turfloop Research and Ethics Committee (TREC) See Annexure B. TREC grants ethical clearance for all human subjects' research conducted under the auspices of the University of Limpopo.

3.7.2 Informed Consent

A waiver of consent/assent was granted by the TREC as this is a retrospective review, the data already exist, there was no impact to the treatment given, and there was no direct interaction with patients or their families.

3.7.3 Confidentiality and Anonymity

Section 14 of the South African National Health Act 61 of 2003 governs confidentiality of patients' medical conditions and treatment thereof. Alpha-numeric codes were used to maintain confidentiality of all the study subjects. Patients' names and file numbers have been stored in a separate secure area that can only be accessed by the researcher and supervisor. Patient confidentiality was maintained by not sharing any subject information with anyone

outside the research team (student researcher, supervisor, research assistant) and was only shared among the research team on a need-to-know basis.

Patient anonymity was sustained by using a subject identifier key. A study number was assigned in lieu of patient name and used on the data collection form and for data entry. A list or identifying key has been maintained by the student researcher for use when going back to the actual patient record to verify missing or investigate erroneous data on an as-needed basis.

3.7.4 Scientific integrity of the research

The researcher has adhered to the highest standards of scientific integrity by faithfully and accurately capturing all data as it is found and by protecting the rights and privacy of the study population by not disclosing or sharing any of their private or personal data outside of the research team. Full acknowledgment of input from colleagues has been observed.

3.7.5 Protecting the rights of the institution

According to the South African National Health Act 61 of 2003, patients' medical records can only be accessed with permission from the head of the health establishment (44). Permission to review hospital patients' records was obtained from the Clinical Executive Manager and the Chief Executive Officer of Pietersburg Provincial Hospital. The NHLS gave permission to view the results of fluid investigations of interest.

3.8 Conclusion

This chapter demonstrated how the study was conducted and the rationale for conducting the study in Pietersburg Provincial Hospital. The chapter also explained the processes followed to perform the study as well as the required ethical considerations when conducting a study with human participation.

CHAPTER 4: RESULTS AND INTERPRETATION

4.1 Introduction

This chapter presents results and interpretation of data analysed through applying methodologies presented from the proceeding chapter.

In this study, 130 fluid/aspirate samples from the NHLS database were identified and retrieved.

From these 130 results, 10 patients had pleural empyema secondary to trauma and were excluded. Sixty sample records turned out to be cerebrospinal fluid, 30 had pleural effusion with no pus, five patients had synovial fluid, and four files were missing. Eleven cases were identified that met the protocol-defined empyema based on macroscopic appearance described as pus by the attending clinician and the culture positive pleural fluid.

This chapter starts by presenting descriptive statistics followed by correlation analysis, then chi-square results.

4.2 Descriptive statistics results

4.2.1 Gender

Of the 11 participants, 7 (65%) were males and 4 (36%) were females (Figure 4-1)

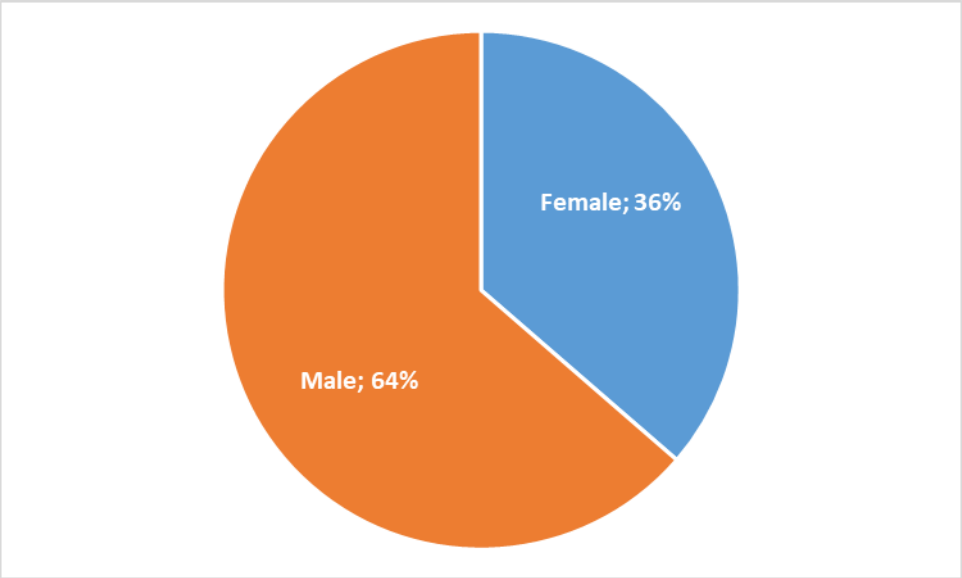

Figure 4- 1. Gender distribution of children admitted with empyema

4.2.2 Age

Infants and children between two and three years had an equal distribution (25%), followed by children aged between three and four years and children aged five years and older. Thus, the most affected age groups were 25-36 months and 0-12 months (Figure 4- 2 and Table 4- 1)

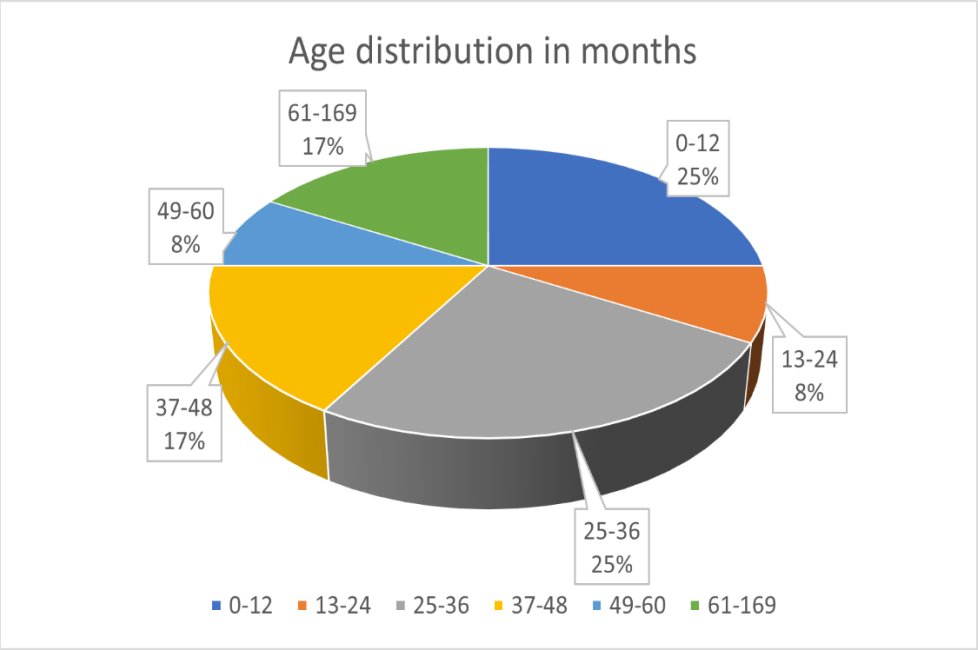

Figure 4- 2: Age distribution of participants with empyema

The mean age of children affected by empyema was 41,7 months, with a range of six months to 140 months (Table 4- 2).

Table 4- 1. Age distribution of children with empyema

	Valid N	Mean	Confidence (-95,000%)	Confidence (+95,000%)	Median	Min	Max	Std Dev	Standard Error
Age (in Months)	10	41,7	10,31647	73,08353	30	6	140	43,8711	13,8733

Table 4- 2: Descriptive statistics of HIV status, viral load, HIV treatment, TB status and pleural fluid culture

Variable	Description	Frequency	Percent (%)
HIV Status	Negative	9	82%
	Positive	2	18%
Viral load	<1 000	1	9%
	>100 000	1	9%
HIV Treatment	Reg 1.1	1	9%
	Reg 1.2	1	9%
TB Status	Negative	5	45%
0	Positive	6	55%
Pleural Culture	Other	3	27%
	Staphylococcus aureus	4	36%
	unknown	3	27%
	Streptococcus pneumoniae	1	9%
	Others	4	36%
	No growth	4	36%

4.2.3 HIV status, viral load, and treatment status

Two of 11 (18%) patients were HIV positive, with both receiving ARVs (Table 4-2). One patient was virally suppressed while the other had not yet achieved this.

4.2.4 TB status

Patients who tested positive for TB were 6 of 11 (55%) tested positive for TB (Table 4- 2)

4.2.5 Causative organisms cultured from the pleural fluid

The results showed that *S. aureus* (40%) was the most common organism cultured from the pleural fluid, followed by a 30% who had a sterile culture, and 10% with S*. pneumonia* (Table 4- 2).

Table 4- 3: Descriptive statistics of HIV status, viral load, HIV treatment, TB status and pleural fluid culture

Variable	Description	Frequency	Percent (%)
HIV Status	Negative	9	82%
	Positive	2	18%
TB Status	Positive	6	55%
	Negative	5	45%
Pleural Culture	Staphylococcus aureus	4	39%
	No growth	4	36%
	Others	4	36%
	Streptococcus pneumoniae	3	27%
	unknown	1	9%

4.2.6 Culture sensitivities

Three of the four (75%) patients cultured S. aureus sensitive to Cloxicillin while one was sensitive to gentamycin, meropenem, and ciprofloxacillin. *Streptococcus pneumomia* was cultured in 9 % which was sensitive to penicillin and erythromycin. Results shows a further 4 of 11(36%) patients were sensitive to others (Table 4- 3).

4.2.7 Medical treatment modalities

The most common treatment given was cloxacillin (63,6%) patients, followed by gentamycin (45%). Other treatments were given to 6 of 11 (54,5%) patients: amikacin (18%) patients, and ampicillin, tazocin, meropenem and ciprofloxacillin were given to 1 of 11 (9%) patients respectively (Table 4- 4). All participants receive a combination of antibiotics to cover both gram negative and gram positive microorganisms.

Table 4. 4: Sensitivity and treatment modalities

Variable	Description	Frequency	Percent (%)
Sensitivity	Others	4	36%
	Cloxacillin	3	27%
	Gentamycin	1	9%
	Meropenem	1	9%
	Ciprofloxacillin	1	9%
Treatment given	Cloxacillin	7	64%
	Other	6	55%
	Gentamycin	5	45%
	Amikacin	2	18%
	Ampicillin	1	9%
	Tazocin	1	9%
	Meropenem	1	9%
	Ciprofloxacillin	1	9%

4.2.8 Surgical interventions offered for the management of pleural empyema

Intercostal drainage was inserted in 90% of the participants of which 18% were successful, no further surgical intervention needed,73% had thoracotomy and VATS was offered to 91% of participants and it was followed by thoracotomy. No patient was offered fibrinolytics (Table 4- 5).

Table 4- 5: Surgical intervention offered for management of pleural empyema

Variable	Description	Frequency	Percent
Intercostal drainage	Yes	10	91%
Thoracotomy	Yes	8	73%
	No	3	27%
VATS	Yes	10	91%
	No	1	9%
Fibrinolytics	No	11	100%

4.2.9 Treatment outcomes

Patients were eventually successfully discharged to other facilities were Six (55%) , while three (27%) died and two (18%) patients did not come back fro their

review at the out patient department and were considered to be lost to follow-up (Table 4- 6).

The average length of hospital stay was 22 days and ranged from 3 to 61 days. However, the median hospital length of stay is 15 days due to variation of the patients. (Table 4- 6, Figure 4- 3).

Seven (%) patients went to ICU and the average ICU length of stay stayed was eight days, ranging from one to 23 days (Table 4- 7, Figure 4- 4).

Table 4-6: Treatment outcomes of pleural empyema

Variable	Description	Frequency	Percent
Outcomes	Death	3	27%
	Lost to follow up/Unknown	2	18%
	Discharged to other Facility	6	55%
If discharged w Sequelae	Other	1	9%

Table 4- 7: Hospital length of hospital stay

	Valid N	Mean	Median	Mode	Min	Max	Std. Dev	Standard Error
Hospital Length of stay (days)	11	22,1	15	14	3	61	16,0714	4,8457

Table 4- 8: ICU length of stay

	Valid N	Mean	Median	Min	Max	Std. Dev	Standard Error
ICU Length of stay	7	8,3	6	1	23	7,1581	2,7055

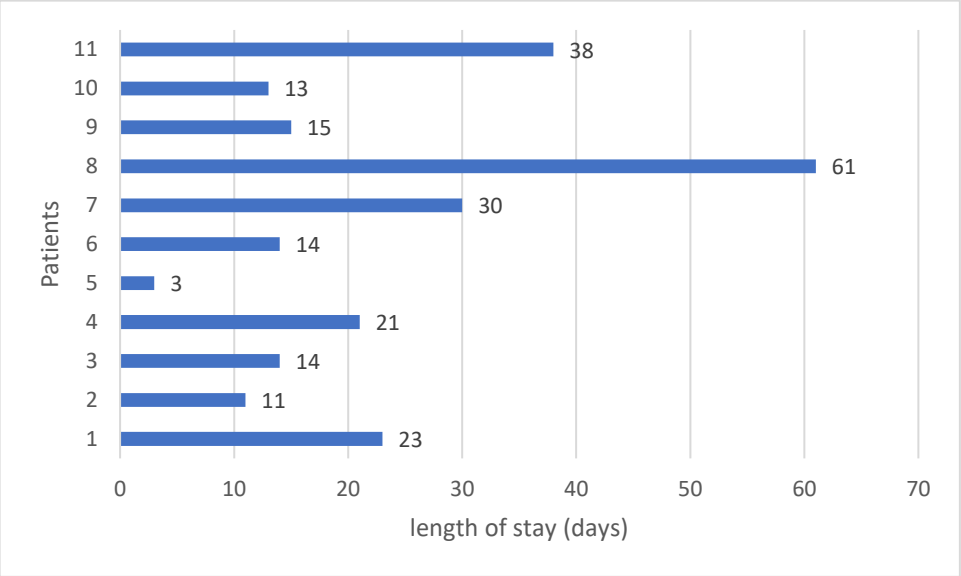

Figure 4- 3: Hospital length of stay

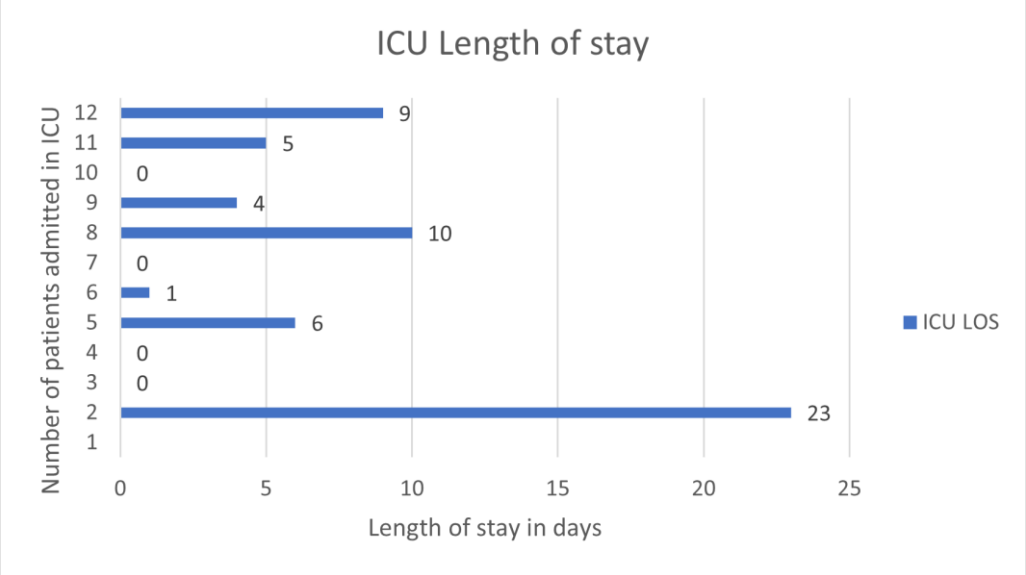

Figure 4.4

4.3 Correlation analysis

There was a significant positive correlation between the age of patients and ICU length of stay (r=89%; p-value = 0,016) (Table 4- 8). Another positive correlation was depicted for hospital length of stay and HIV status (r=88%); p-value =0,019). HIV-positive patients stayed longer on average compared to those with negative status.

There was also a strong association between length of ICU stay and surgical interventions offered (thoracotomy) in patients with pleural empyema (Table 4-9).

Table 4- 9: Correlation analysis for pleural empyema

	ICU LOS	HIV Status	TB Status	Pleural Culture	ICD	Thoracotomy	VATS	Outcomes
Age (in Months)	0,8952 p=0,016	-0,1453 p=0,784	-0,2504 p=0,632	-0,3206 p=0,536	0,2237 p=0,670	0,2237 p=0,670	-0,3021 p=0,561	-0,3323 p=0,520
LOS (days)	0,0435 p=0,935	0,8847 p=0,019	0,2798 p=0,591	0,2642 p=0,613	0,5473 p=0,261	0,5473 p=0,261	-0,1029 p=0,846	-0,2116 p=0,687

P:P-value

ICD: Intercostal drain

Table 4- 10: Level of association between treatment modality and outcome

Outcome	**Treatment**	**Chi-Square**	**Degrees of Freedom**	**p-value**
	Cloxacillin	0,4762	2	0,7881
	Gentamycin	0,2444	2	0,885
	Ampicillin	0,9167	2	0,6323
	Amikacin	3,1574	2	0,2062
	Tazocin	2,9333	2	0,2307
	Meropenem	4,9500	2	0,0842
	Ciprofloxacin	4,9500	2	0,0842
	Intercostal drainage	2,9333	2	0,2307
	Thoracotomy	7,6389	2	0,0219
	VATS	0,9167	2	0,6323

4.4 Conclusion

Chapter Four represented the study results and interpretations according to the methodologies presented in Chapter Three. Descriptive statistics for all the variables of interest in the study were presented. Correlation and Chi-square analyses were also presented to meet the objectives of the study.

Chapter Five will have in-depth discussions of results and compare this study's results to those of studies previously conducted.

CHAPTER 5: DISCUSSION, RECOMMENDATIONS AND CONCLUSION

5.1. Introduction

This study was conducted to establish the causative organisms for pleural empyema in children admitted in Pietersburg Provincial Hospital. The researcher also aimed to determine the relationship between pleural empyema, HIV status and the PCV immunisation status. The researcher was also interested in the treatment modalities and their outcomes in patients admitted to the hospital. This chapter presents discussion and makes a conclusion about the findings of the study based on these objectives. Recommendations, limitations, and further study are also presented in this chapter.

5.2. Discussion of results

5.2.1. Demographics

All the patients in this study were African, 36% of patients were referred from Capricorn District, and none were from the Waterberg District. Gender proportions in this study found that 65% were male compared to 36% females. A study done in CHBAH had similar findings, with males (56.9%) predominately affected. This is also comparable to a study done in Cape Town where males were affected in 57% of cases (20,45). The average age of children in this study was eight years compared to average of four years in a study done in Australia, and 53.2 months in the Soweto but 17.4 months Cape Town studies (14,19,20).

Of the 11 participants, 2 (18%) were HIV positive and already on HAART. One of the HIV-positive patients had been not virologically suppressed, stayed longer in the hospital, and received multiple courses of antibiotics. The CHBAH study had 20% of children who were HIV infected and among those 77 % were started on TB treatment (20).

Results show no association between TB, HIV, pleural culture, and outcome, however, a positive correlation was demonstrated for HIV positive patients with

length of hospital and ICU stay, and patient's age. Thus, the younger the patient, the more likely it is that the patient will have a longer ICU length of stay.

5.2.2. Causative organisms

The common causative organisms cultured from pleural fluid was *S. aureus* (36%), sensitive to cloxacillin. This was followed by *S. pneumoniae* in 10%. Sterile cultures were found in 30% of the pleural fluid sent to the NHLS. This finding is in line with those in developing countries that has *S. aureus* was the commonest organism cultured from the pleural fluid (12). Other organisms cultured included *K. pneumoniae, H. influenza* and *M.* tuberculous; which were similar to the organisms cultured in the CHBAH study, and in Cape Town where *Staphylococcus Aureus* and *Streptococcus Pneumoniae* were found to be the commonest organism in empyema patients (20,45).

5.2.3. Treatment modalities

Patients in this index study were treated according to the three clinical stages of empyema. The three stages are 1.) a simple, exudative stage with no septations; 2.) a fibro purulent phase with fibrin strands; and 3.) septations with a multiloculated empyema with thick pleural coating (16). All the patients received antibiotics. Cloxacillin was administered frequently followed by gentamycin and amikacin. There was no uniformity in the choice of antibiotics. The choice of antibiotics was dependent on the prescriber's discretion. A proportion of patients (54%) were empirically treated for TB at their local hospitals before transfer to the Pietersburg Provincial Hospital and the patients continued with the treatment. The empirical TB treatment was also offered to participants in the CHBAH study (20).

AN Intercostal drain was inserted in 90% of children, thoracotomy was offered to eight and one patient (9%) was offered VATS. The one patient who was not offered ICD stayed in the hospital for three days and eventually died before ICD could be inserted. Fibrinolytics were not offered to patients in this study. Thoracotomy in patients with pleural empyema had an association with being more likely to be discharged to other facilities.

5.2.4. Treatment outcomes

The majority of patients admitted in Pietersburg Provincial Hospital were discharged to other facilities (55 %), but 27% of the children died and 18% were lost to follow up. There were no patients discharged with sequalae among those who could be traced on follow up. The patient who stayed longest in hospital was HIV positive, on HAART, but virally unsuppressed. He received a thoracotomy, and demised after 61 days of admission. Patients with thoracotomies had longer lengths of stay, however statistically we cannot make inferences due to the small population size of the study.

Thoracotomy has been shown to be associated with longer hospital stay, except for a study from Pakistan (37). In this study, patients who were offered thoracotomy had longer hospital and ICU stays. A systematic review that looked at randomized control trials comparing the interventions of pleural empyema in children showed that chest drains with the addition of fibrinolytics were associated with low cost, but no evidence of superiority between VATS and fibrinolytics (46). Fibrinolytics were not offered to any of the participants in this study.

5.3. Study limitations

The study's major limitation was that it was a retrospective study that relied on retrospective clinical data. Immunisation status was missing in the patient medical records, and it negatively impacted achieving one of the objectives set out in the study. The low number of study participants also had a negative impact on the study; associations between the variables could not be proved. The study population included black African children only, and is therefore not necessarily representative of the entire population.

Various reasons could explain the low numbers of study participants in this study. In this study, case definition of pleural empyema was limited to the appearance of pus and a neutrophil predominance in the pleural fluid, as well as a positive pleural fluid culture result. A similar study done in Soweto included patients diagnosed with empyema by visualising purulent material in the pleural space

and radiological investigations like ultrasound and CT scans (20). An American study done in Kentucky also included patients who had empyema confirmed radiologically (47).

In reviewing literature on pleural empyema in children, the number of study participants even in multi-centres had an average of 6 participants per year. This study only had macroscopic appearance of and positive culture in pleural fluid. Poor documentation on requisition forms when submitting the pleural fluid to the laboratory by the clinicians also contributed to the low numbers of eligible participants. Attending clinicians were not requesting the laboratory to count the various cells in the pleural fluid resulting in no documentation of the neutrophil count in the fluid.

The filing system has also proved to be a limitation of this study. Missing files decreased the number of eligible participants identified.

The other challenge is that intercostal drainage is inserted by the cardiothoracic team, who often opt to manage the pleural effusion conservatively. Some pleural empyema could have been missed since the case definition needed evidence pus from the pleural spaces. Several Capricorn District patients that had pleural effusion were not offered intercostal drainage.

5.4. Recommendations

Pietersburg Provincial Hospital has both cardiothoracic surgical and paediatric pulmonology units that would benefit from a management protocol and memorandum of understanding between the two units. Currently we do not have a protocol to manage children who present with pleural effusion and the management is left to the admitting team’s discretion. Therefore, the study recommends that a protocol be developed that will inform the clinicians of the algorithm to investigate and manage patients who present with pleural empyema in Pietersburg Hospital.

Paediatricians are trained to insert intercostal drainage; initial thoracentesis or intercostal drain insertion could be performed prior to referral to cardiothoracic

surgeons for definitive management of those patients who need surgical intervention.

In the absence of a protocol, it can be concluded from the results of this index study that patients who present with pleural empyema should be treated with antibiotics that cover the sensitivities of the organisms described, including coverage for *S. aureus*. The empiric antibiotic to be prescribed should be cloxacillin.

Laboratory requisition forms should be fully completed, including the patient's clinical information. The laboratory must discourage clinicians who fill the requisition forms incorrectly by returning them so they can get the most out of the laboratory and proper documentation of the tests requested. The hospital must have a paediatric ICU with paediatric intensive care trained nurses to improve the paediatric intensive care treatment through adequate staff.

The medical record keeping can be improved by introducing electronic records which will be costly to set up but will result in savings in the long run for the Department of Health. Missing medical records also has a negative impact on medico legal suits that the Department face. The electronic data base for medical records will also ease the process of monitoring and evaluating clinicians' work, which will improve the research output for the Limpopo Department of Health. The increased research output for the academic departments will also generate revenue that can be used to purchase consumable items and medical equipment to improve the quality of care rendered to patients.

Research plays a role in generating new knowledge, synthesising knowledge and using the acquired knowledge for developing guidelines for improving quality of care and measuring health care outcomes (48). Research has been the cornerstone of improving patient care services by documenting health deficits and policy inadequacy to ensure the enjoyment of health rights by all (49). Although research is beneficial to the delivery of quality health services, there are barriers in conducting research. Ophthalmologists in Sub Saharan Africa reported lack of time, poor research knowledge, poor research support and lack of interest in

research (50).A study conducted in Sefako Makgatho Medical School recommended the introduction of research-based courses in undergraduate medical studies in order to improve clinicians who treat patients are mostly not research-inclined and the medical recordkeeping is solely for clinical practice without considering the use of the same medical information for monitoring and evaluation of the services rendered in a form of research. Research was viewed as a separate culture from clinical practice demonstrated in a study conducted in Canada. It has shown to be one of the challenges in researching around Corona virus pandemic (51) .

The results and findings in this study should encourage the research culture in Pietersburg Hospital since it is a tertiary hospital of the province and of Limpopo Department of Health. Record keeping should be done in such a way as to consider its later use in research purposes. Admitting clinicians must use the admission book from the Department of Health and complete all the required information which will ease retrospective studies.

Universities should identify and co-appoint individuals who recently passed their dissertations to mentor the upcoming registrars to improve the University's research output. It will also help the university to produce more dissertations. Support could be offered to the supervisors who have not conducted research in their training prior 2010 by offering in-depth compulsory training. Pairing supervisors who have no research experience with co-supervisors with research experience could also relieve the pressure on supervisors with no research background.

5.5. Further study

This was a retrospective study conducted in one centre for a period of 5 years. A South African multicentre prospective study is recommended to provide representation of the whole country. The study should extend the number of years to yield a larger study population that will produce meaningful statistical results. There is a need to know the effect of the change in PCV immunisation schedule on the causative organism of pleural empyema in South African children and thus

the best treatment modality. Future studies could look at pneumococcal serotypes to differentiate between vaccine-preventable disease and non-vaccine-preventable disease. Future studies could also look at the underlying comorbidities like HIV infection and TB infection in children admitted with pleural empyema.

5.6. Concluding remarks

Conducting this research has been one of the most challenging activities I had to endure. It has been a bittersweet journey. Discovering the importance of research in clinical practice has been a great lesson learnt. Contributing new knowledge has been fulfilling. As a first-time researcher, I have come to appreciate the body of knowledge in the medical fraternity. I do believe this journey has laid a firm foundation for quality improvement in our health system. The basic research skills acquired through this mini dissertation will forever be cherished. This dissertation has sensitised me in practicing medicine with research at the back of my mind as a clinician.

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Annexures

Annexure A. Data Collection Tool

Patient allocated research number: _____ (Initials and sequential number: FML+NN)

Date of birth: _____ (YYYYMMDD)

Gender:

1. Male _____
2. Female _____
3. Unknown (missing): _____

District of resident

1. Capricorn
2. Vhembe
3. Sekhukhune
4. Waterberg
5. Mopane
6. South African Non-Limpopo
7. Non-South African

Immunisation status:

Not documented/not available

PCV 7 Date: _____ (YYYYMMDD)

PCV 13 Date: _____ (YYYYMMDD)

Hospitalisation:

Date of Admission: _____ (YYYYMMDD)

Date of Discharge: _____ (YYYYMMDD)

Length of Stay: _____ (DAYS)

Date of ICU Admission: _____ (YYYYMMDD)

Date of ICU Discharge: _____ (YYYYMMDD)

Length of ICU Stay: _____ (DAYS)

Date of Pleural Fluid Investigation (date results posted)

_____ (YYYYMMDD)

Variable	Results
HIV Status	
1.Negative	
2.Positive	
3.Unknown	
If positive	
Viral load	
Cd4 count	
Year of diagnosis (if known)	
Treatment:	
1. Reg 1.1	
2. Reg1.2	
3. Reg 2	
4. Reg 3	
5. Not on treatment	
6. Other	
TB Status	
1. Negative	
2. Positive	
3. Unknown	

Pleural Fluid Investigations	
Culture (can select more than one)	
1. *Streptococcus pneumoniae*	
2. *Staphylococcus aureus*	
3. *Mycobacterium* tuberculosis	
4. Methicillin-resistant *Staphylococcus aureus*	
5. Other	
Sensitivity (can select more than one)	
1. Gentamycin	
2. Ampicillin	
3. Tazocin	
4. Amikacin	
5. Meropenem	
6. Ciprofloxacillin	
7. Others	
Treatment	
Antibiotics *(can be more than one)*	
1. Ampicillin	
2. Gentamycin	
3. Amikacin	

4. Tazocin	
5. Meropenem	
6. Ciprofloxacillin	
7. Others	
Intercostal drainage	
1.Yes	
2.No	
3.Unknown	
VATS	
1. Yes	
2. No	
3. Unknown	
Thoracotomy	
1. Yes	
2. No	
3. Unknown	
Fibrinolytics	
1. Yes	
2. No	
Outcomes	

1. Discharged with sequelae If yes • Bleeding • Bronchopleural fistula • Lung abscess • Scoliosis • Other (describe)	
2. Discharge to other facility	
3. Death	
4. Lost to Follow up/Unknown/No documentation available	

Annexure B. Ethics Certificate

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TURFLOOP RESEARCH ETHICS COMMITTEE

ETHICS CLEARANCE CERTIFICATE

MEETING: 17 August2021

PROJECT NUMBER: TREC/22/2021: PG- Amended

PROJECT:

Title:	Aetiology and Outcome of Pleural Empyema in Children Admitted to Pietersburg Hospital Limpopo, South Africa
Researcher:	M Tshamiswe
Supervisor:	Dr NG Tiva
Co-Supervisor/s:	N/A
School:	Medicine
Degree:	Master of Medicine in Paediatrics and Child Health

PROF P MASOKO
CHAIRPERSON: TURFLOOP RESEARCH ETHICS COMMITTEE
The Turfloop Research Ethics Committee (TREC) is registered with the National Health Research Ethics Council, Registration Number: **REC-0310111-031**

Note:

i) **This Ethics Clearance Certificate will be valid for one (1) year, as from the abovementioned date. Application for annual renewal (or annual review) need to be received by TREC one month before lapse of this period.**

ii) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee, together with the Application for Amendment form.**

iii) **PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.**

Finding solutions for Africa