THE INCIDENCE, AETIOLOGY, AND CHARACTERISTICS OF BACTERIAL MENINGITIS IN YOUNG CHILDREN IN SOUTH AFRICA, 2014-2018: A 5-YEAR RETROSPECTIVE REVIEW

Dr Nkiambi Yannick Kiakuvue

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Infectious Diseases Epidemiology

Johannesburg, June 2022

I, Dr Nkiambi Yannick Kiakuvue, am submitting my research report in partial fulfilment of the requirements of the MSc in the field of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand. This report has not been submitted previously for any degree or examination at this or any other university. I hereby declare that this research report is my own work. Where I have used the thoughts or ideas of others, the required referencing conventions have been adhered to.

Signed:

Date: 22 June 2022

DEDICATION

I dedicate this research report to my mother for all the sacrifices she has made for me to complete my graduate education.

Secondly, I dedicate this research report to all my family members.

Abstract

Introduction: Bacterial meningitis in children is an important public health concern both globally and in South Africa. To date, there are a paucity of nationally representative data examining the incidence as well as associated characteristics of bacterial meningitis (excluding *tuberculosis*(TB)) on the African continent. Further, literature suggests that there has been little attention to the most common pathogens (*Acinetobacter baumannii*, *Klebsiella pneumoniae,* group B streptococcus (GBS), *Escherichia coli, Staphylococcus aureus, Enterococcus faecium)*, as well as the demographic characteristics of children with incident meningitis. Therefore, this study aimed to describe the incidence and the aetiology of bacterial meningitis and to compare these characteristics of children under 1-year-old who tested positive for the two most common pathogens related to their infection.

Methods: To address these gaps in the literature, secondary data from the National Health Laboratory Service (NHLS)Central Data Warehouse (CDW) was analysed to examine the incidence, the aetiology and to compare the characteristics of children who tested positive to the 2 most common pathogens identified during the period. A sample of 2,647 cases of laboratory-confirmed meningitis was used and described by the frequency(n) and percentage (%) tables for the aetiology while Poisson and binary logistic regression methods were employed respectively to calculate the incidence and to compare the characteristics of children who tested positive to the 2 most common pathogens isolated.

Results: The study suggests an increase in the number of cases (358 cases in 2014 to 723 cases in 2018) as well as the annual incidence of most pathogens over the study period. Demographic variables associated with incidence included age (being under the age of 28 days), being male and living in Gauteng . The highest incidence was calculated among neonates (*A. baumannii:* 168.9 per 100 000 persons) while the lowest was calculated in the postneonatal period (*Enterococcus faecalis* 1.01 per 100 000 persons.). *A. baumannii* (19.42%) *followed* by *K. pneumonia (*17.76%), GBS *(*14.51%) were the most common pathogens detected. Regarding the age group, *A*. *baumannii* (23.91*%), K*. *pneumonia* (19.42%) GBS (19.28%) were the most commonly identified organisms among the neonates while

K. pneumonia (15.75%), *S aureus* (14.25%), *A*. *baumannii* (14%) *were* the most commonly organisms isolated in the postneonatale period.

Conclusion: Over the 5-year study period, after the introduction of the Hib vaccine and PCV, there was still an increasing trend in the annual incidence of most pathogens and a change in the leading pathogens with the emergence of pathogens such as *A. baumannii, K. pneumonia,* GBS. In addition to increased uptake of vaccination against common pathogens, prophylactic measures could include prevention of nosocomial and mother to child transmissible pathogens. Among others, these could include antenatal screening for GBS in pregnant women, rigorous hygiene methods for the healthcare giver and cleaning, disinfection, and sterilization of the hospital environment as well as rationalize antibiotic use.

ACKNOWLEDGEMENTS

Firstly, I would like to express my deep gratitude to my supervisors Professor Cheryl Cohen and Doctor Sumaya Mall who used their skills and knowledge to guide me through this project. Being supervised by them was a great honour.

I would like to thank the whole staff in the Division of epidemiology and biostatistics at the University of the Witwatersrand.

I would like to thank professor Nelesh Govender and National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW) for allowing me to use their data. I would like also to thank the National Institute for Communicable Disease (NICD) team particularly Dr Susan Meiring and Rudzani Mashau for their assistance.

I would like also to express my gratitude to my family and friends particularly to Dr Sydney Kasongo, Dr Olivier Mukuku, Richie Kiakuvue, Reuben Kumwimba, Lungile Tshefu and Yaw Awuku-Larbi for the support and encouragement since I enrolled in this master's programme.

TABLE OF CONTENTS

Contents

DEDICATION iv

Abstract v

ACKNOWLEDGEMENTS vii

ABBREVIATIONS x

LIST OF FIGURES xi

LIST OF TABLES xi

LISTE OF APPENDICES xii

1 CHAPITER 1: INTRODUCTION 1

1.1 BACKGROUND 1

1.2 LITERATURE REVIEW 5

1.2.1 Incidence and aetiology of bacterial meningitis in high-income countries: 6

1.2.2 Incidence and aetiology of bacterial meningitis in low- and middle-income countries excluding South Africa: 6

1.2.3 Incidence and aetiology of bacterial meningitis in South Africa: 8

1.2.4 Impact of different vaccines on the incidence and the aetiology of bacterial meningitis in South Africa: 9

1.2.5 Seasonality of bacterial meningitis: 9

1.3 PROBLEM STATEMENT 10

1.4 JUSTIFICATION 11

1.5 AIM AND OBJECTIVES 11

2 CHAPTER 2: METHODS 12

2.1 STUDY POPULATION 13

2.2 DATA SOURCES 13

2.2.1 NHLS CDW 13

2.2.2 Stats SA 14

2.3 DATA COLLECTION 14

2.4 DATA MANAGEMENT 14

2.5 MEASUREMENT 14

2.6 DEFINITION 15

2.7 DATA PROCESSING AND STUDY VARIABLES 15

2.7.1 NHLS CDW dataset 15

2.7.2 Stats SA data set 16

2.8 DATA ANALYSIS 16

2.9 SAMPLE SIZE 18

2.10 ETHICS 19
3 CHAPTER 3: RESULTS 20
3.1 DESCRIPTION OF THE STUDY SAMPLE 20
3.2 AETIOLOGY 20
3.3 INCIDENCE 24
3.4 CHARACTERISTICS OF PEOPLE WHO TESTED POSITIVE FOR THE TWO MOST COMMON PATHOGENS (*A. baumannii and K. pneumonia)*. 28
4 CHAPTER 4: DISCUSSION 32
5 CHAPTER 5: CONCLUSION AND RECOMMENDATIONS 36
REFERENCES 37
APPENDIX 46

ABBREVIATIONS

CSF: cerebrospinal fluid

DTaP-IPV/Hib: Diphtheria tetanus acellular pertussis/inactivated polio vaccine and Haemophilus influenzae type b (Pentavalent)

GBS*:* group B streptococcus

Hib: *Haemophilus influenzae* type b

HIV: Human Immunodeficiency Virus

IPV: Inactivated polio vaccine

LMIC: Low- and Middle-Income Countries

NICD: National Institute for Communicable Disease

NHLS CDW: National Health Laboratory Service Corporate Data Warehouse

PCV: Pneumococcal Conjugate Vaccines

Stats SA: Statistics South Africa

TB: Tuberculosis

LIST OF FIGURES

Figure 1. Diagram presenting attainment of sample 18
Figure 2. Incidence rate of the most common pathogens among children under 1-year-old by year, South Africa, 2014-2018 25
Figure 3. Incidence rate of the most common pathogens detected among children ≥28 days old, South Africa, 2014-2018 25
Figure 4. Incidence rate of the most common pathogens detected among children <28 days old, South Africa, 2014-2018 26
Figure 5. Incidence rate of *A. baumannii* among children under 1-year-old by provinces and year, South Africa, 2014-2018 26
Figure 6. Incidence rate of *K. pneumoniae* among children under 1-year-old by provinces and year, South Africa, 2014-2018 27
Figure 7. Incidence rate of GBS among children under 1-year-old by provinces and year, South Africa, 2014-2018 27
Figure 8. Incidence rate of *S. aureus* among children under 1-year-old by provinces and year, South Africa, 2014-2018 28

LIST OF TABLES

Table 1: South Africa expanded programme on immunization (37) 5
Table 2. Study variables 16
Table 3. Descriptive analysis 17
Table 4. Demographic characteristics of patients with laboratory-confirmed meningitis infection due to pathogens in South Africa, 2014-2018 22
Table 5. Characteristics of people who tested positive to the two most common pathogen (A. baumannii and K. pneumonia). South Africa, 2014-2018.(Univariate analysis) 29
Table 6. Characteristics of people who tested positive to the two most common pathogen (A. baumannii and K. pneumonia). South Africa, 2014-2018.(Multivariate analysis) 31

LISTE OF APPENDICES

Appendix 1: Plagiarism Declaration 46
Appendix 2: Permission to use data 47
Appendix 3: Wits HREC clearance certificate and data user agreement letters 48
Appendix 4: Turnitin report 50
Appendix 5: List of variables 51

1 CHAPITER 1: INTRODUCTION

This chapter presents 1.1. a background section describing the definition, the public health significance, the epidemiology, diagnosis, and treatment of meningitis. 1.2. a literature review which describes the relevant literature on incidence, aetiology and factors that affect incidence and aetiology of bacterial meningitis including among children under 1-year-old. 1.3. the problem statement. 1.4. the justification for the study which highlights the public health importance of the study. 1.5. aims and specific objectives of the study.

1.1 BACKGROUND

- Definitions

Meningitis, a serious inflammation of the meninges, the thin, membranous covering of the brain and the spinal cord is caused by a bacterial, viral, or fungal infection. (1) Meningitis was first recorded in 1661 as an observation of the inflammation of the meninges as well as a concurrent fever. (2) In children, viral meningitis is most common followed by meningitis of a bacterial aetiology. (3,4) In Low-and Middle-Income Countries (LMIC), the bacterial meningitis fatality rate is estimated at 2% in children while it is estimated between 40 and 58% in neonates. (5) Global burden of disease data suggests that LMIC experience a higher burden of bacterial meningitis than high-income countries. (6)

- Public Health significance

Almost 50% of adults and 20% of children who survive meningitis tend to present with short and more long-term neuropsychological sequelae. (7) The former include focal neurological deficit while the long-term effects include permanent deafness, blindness, language disorder, epilepsy, motor delay and cognitive disability after being discharged from the hospital. (8–10) A recent retrospective cohort analysis, albeit from a high-income setting (Denmark), suggested that frequent sequelae among children who had had bacterial meningitis were hearing loss (15%) followed by cognitive impairment (12%) and motor or sensory nerve deficits (9%). A 2009 systematic review focused on African countries corroborated some of the Danish

data. Further, the review suggested that children surviving pneumococcal meningitis and *Haemophilus influenzae* type b (Hib) meningitis had a higher risk of neuropsychological impairment when they were discharged from hospital and that this risk was higher than in meningococcal meningitis cases. These data suggest that it is imperative to understand the epidemiology of meningitis including associated characteristics of neonatal meningitis to later inform prevention and treatment. (9,11) In addition, a cost-effectiveness analysis by Aerts and colleagues in the Sub-Saharan African region suggest that hospitalization and treatment of bacterial meningitis in neonates is costly. Their conclusion is that public health interventions could focus on the prevention of meningitis.

The African continent is disproportionally affected by bacterial meningitis partly due to the West African “meningitis belt”. (12) The Sub-Saharan region commonly referred to as the “meningitis belt” expands from Senegal to Ethiopia and is characterized by seasonal epidemics of meningococcal meningitis(attack rates of 1000 per 100 0000 persons or higher) every 5 or 10 years. South Africa is not part of that belt. (13) Soeters and colleagues who are part of The MenAfriNet Consortium that aims to provide case-based surveillance of meningitis suggest in a 2015 publication that since the introduction of the pneumococcal conjugate vaccine and the Hib conjugate vaccine, the burden of meningitis due to *S. pneumoniae* and Hib has fallen among children aged <5 years around the world. (14,15) However In Africa, the burden of meningitis continues to be high in the central and the western Sub-Saharan regions suggesting there clear value to looking at the reasons for incidence. (6)

- Epidemiology of meningitis

Global epidemiological estimates of the incidence of bacterial meningitis are not entirely conclusive and should be interpreted with caution. Studies sourced yield varying incidence estimates especially between high income and LMIC. For example, in 2016, the overall bacterial meningitis incidence varied from 0.5 per 100 000 persons in Australia to 207.4 per 100 000 persons in South Sudan. This advised caution is due to issues such as the lack of consistency in surveillance systems of different regions as well as the underreporting of cases. (6,16) However, in 2016, 2.8 million cases of bacterial meningitis were recorded in all ages in the world and 56%

of them were among children under 5 years With an estimated annual incidence of 143.6 per 100 000 persons. (17)

The aetiology of bacterial meningitis varies by geographical area and age-group wide world. *Neisseria meningitis* and *Streptococcus pneumoniae* are common in all age groups and all regions. (18) Globally, in the neonatal period, *E. coli,* GBS and *Listeria monocytogenes* are the most common pathogens responsible for meningitis. (19) With almost 25% of all bacterial meningitis, neonates are the most commonly affected, because of the immaturity of the immune system. In the early neonatal period research suggests a vertical transmission from mother to child. (16,20) Beyond this period, the greatest portion of infections is due to a nosocomial infection or community acquisition. (20) Beyond the neonatal period, three pathogens, *S. pneumoniae, N. meningitidis* and *Haemophilus influenzae* are responsible for most of the cases of meningitis reported around the world. (18,19) *N. meningitidis* is known to be a major cause of endemic and epidemic meningitis around the world. (16) Pathogens such as *Micrococcus sp*, *Streptococcus viridans*, *Bacillus sp*, *Pseudomonas sp* are classified as contaminants. (21)

In South Africa, bacterial meningitis evaluated yearly incidence is 4 per 100 000 persons in all ages groups, 40 per 100 000 per persons in infants less than 1 year and 7 per 100 000 persons in children between 1 to 4 years aged. (22) In 2007, *S. pneumonia* followed by *N. meningitis* and *H. influenzae* were the most common cause of bacterial meningitis among children under 5 years in South Africa. (13) Additionally the epidemiology of meningitis in this country is influenced by the high prevalence of HIV,(23) with HIV infection increasing the risk of all invasive bacterial infections including bacterial meningitis. (24) South Africa also experiences a high incidence of tuberculous meningitis because of the increasing incidence of TB which is in turn associated with the country's high prevalence of HIV. (25) With 3% of all cases of TB reported in 2018 around the world and an HIV prevalence estimated at 13.7% of the national population in 2020. (26,27) The dual effect of HIV and TB on meningitis cannot be ignored in the context of examining aetiology and associated pathogens. A study conducted in Soweto (1997-1999), prior to the Hib vaccine and PCV introduction, found that 42% of children with meningitis were positive for HIV type 1 and that among children HIV type 1 was positive. Further, the results of this study suggested that *S. pneumoniae* exceeded Hib as the first pathogen causing

bacterial meningitis in HIV-infected compared with non-infected children. (28) Another study in Cape Town, found that most of the cases of meningitis tested positive to TB (126 cases), from the 74% of them who were tested for HIV, 12% of them tested positive for HIV. (25)

- Diagnosis

The laboratory examination of the cerebrospinal fluid (CSF) is an important step in meningitis diagnosis. CSF examinations include the following: macroscopic examination, cytological examination, examination of Gram-stained smear, culture, antimicrobial susceptibility testing, latex agglutination test for antigen detection and other diagnostic methods. (29)

In South Africa, differential cell count, glucose, total protein, Gram stain, bacterial culture and sensitivity test of CSF before the initiation of antibiotic treatment is recommended for any suspicious case without delaying the introduction of the antibiotic treatment. (22) From all these tests, the culture of CSF is one most routinely done. It is also the gold standard for the diagnosis of the infectious cause of meningitis, the most specific and the most sensitive. (19,30)

- Treatment and prevention

For bacterial meningitis, an early antibiotics regimen is the most optimal treatment. In most countries, cephalosporin (ceftriaxone) is used as an empirical treatment. (22) Several meningitis vaccines are part of the routine immunisation schedule or are used to control outbreaks around the world. (22) The Hib conjugate vaccine is given in monovalent formulation or combined with other antigens such as diphtheria tetanus pertussis vaccine and or, inactivated polio vaccine(IPV). (31,32) In the case of the meningococcal vaccine, monovalent and multivalent conjugate vaccines are given in response to outbreaks as well as in several national routine immunisation programmes. An *N. meningitidis'* protein-based vaccine is also used in some countries. For *S. pneumoniae*, pneumococcal conjugate vaccines (PCV) covering 10 or 13 of the 95 serotypes of *S. pneumoniae* are used around the world. In South Africa, the Hib vaccine and PCV are part of childhood immunisation programmes. The PCV-7 vaccine (including the serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) was introduced in 2009 replaced by PCV-13 in 2011(containing additional serotype 1, 3, 5, 6A, 7F and 19A). (22,33,34) The Hib vaccine was introduced in 1999 as part of

the national immunisation programme and the Hib vaccine booster dose in 2010. (13,35)Two types of Meningococcal vaccine (a polysaccharide and a protein-polysaccharide vaccine) are available in South Africa since 2014 but they are not part of public South African immunisation programmes. (13,22,36)

Table 1 below presents the South Africa vaccine schedule.

Table 1: South Africa expanded programme on immunization (37)

Vaccine	Age of the children at administration
Pneumococcal Conjugate Vaccine (PCV):c - First dose - Second dose - Third dose	 - 6 weeks, - 14 weeks - 9 months
Hib vaccine (DTaP-IPV/Hib): - First dose - Second dose - Third dose - Booster	 - 6 weeks - 10 weeks - 14 weeks - 18 months

- PCV: Pneumococcal Conjugate Vaccine
- DTaP-IPV/Hib: Diphtheria tetanus acellular pertussis/inactivated polio vaccine and Hib (Pentavalent)

1.2 LITERATURE REVIEW

The literature review below describes the relevant literature on incidence, aetiology of and related factors to bacterial meningitis among children under the age of 1 year.

PubMed/Medline databases were searched for relevant studies from high and LMIC contexts to inform the literature review. The following search terms were used to search the databases: meningitis, children, incidence, high and LMIC countries. Studies sourced were then integrated under the following themes: 1.2.1. Incidence and aetiology of bacterial meningitis in high-income countries. 1.2.2. incidence and aetiology of bacterial meningitis in LMIC 1.2.3. incidence, and aetiology of bacterial meningitis in South Africa.1.2.4. impact of different vaccines on the incidence and aetiology of bacterial meningitis in South Africa. 1.2.5. seasonality of bacterial meningitis.

1.2.1 Incidence and aetiology of bacterial meningitis in high-income countries:

Epidemiological data spanning systematic reviews to observational studies have examined the incidence and aetiology of bacterial meningitis in high and LMIC though this section focuses on high-income country data. (18,38–40) Studies examining the incidence and aetiology of bacterial meningitis have been conducted in high-income countries among adult and children's samples. As far back as the period 1998-2007, Thigpen and colleagues identified cases of bacterial meningitis reported among residents in eight surveillance areas of the Emerging Infections Programs Network in the United States of America (USA). As far back as the period 2006-7, in the United States, the incidence rate in children under two months was 81 cases per 100 000 persons, compared with 0.4 cases per 100 000 persons in children aged 11–17 years. Although these data are dated, they do suggest the importance of examining incidence in neonates. (41)

In Canada, another high-income setting from 2013 to 2014, a cohort study conducted by L.Ouchenir and colleagues among infants under 90 days old examined the epidemiology, management and the outcome of bacterial management. This study found that *E. coli* (37.33%) and GBS (35.31%) were the most common pathogens identified. (42)

From 2011 to 2016, a cross-sectional study conducted by Woll and colleagues among children under 60 days old admitted at the emergence ward of the 11 children hospital (USA), found that GBS (50.8%), *E. coli* (16.9%) and *S. aureus (*.1%) were the most cause of bacterial meningitis in children under 28 days old. (43)

1.2.2 Incidence and aetiology of bacterial meningitis in low- and middle-income countries excluding South Africa:

A systematic review conducted by Ali and colleagues examined and synthesized studies of the incidence and aetiology of bacterial meningitis among children between 1 and 59 months in South Asia, an LMIC country region. The review included 48 articles published between 1987 to 2017 pooling incidence rates of 105

per 100 000 persons. Hib was found to be the most common pathogen associated with almost 13% of all bacterial meningitis cases followed by *S pneumoniae* and *N meningitidis* respectively 10% and 1%.(39).

A study conducted in Oman, from 2000 to 2005, among children < 5 years using surveillance data, after the introduction of the meningococcal serogroup A and C vaccine, pneumococcal vaccine, and Hib vaccine, found that children under 1 year were the most affected. *H. influenzae (*22%) was still the most common pathogen detected however its incidence had significantly decreased followed by *S. pneumoniae* (15%). An important finding was that male children were the most affected. (44)

In Romania, a prospective surveillance study conducted in two districts, between 2000 and 2002, among children < 5 years found that *N. meningitidis* was the most common pathogen with an incidence rate of 22 per 100 000 populations followed by *H. influenzae* (for 13 per 100 000) and *S. pneumoniae* (3.5 per 100 000), 44.6% of cases were children under 1 year. (45)

From 2011 to 2016, a systematic review conducted to examine the epidemiology of *N. meningitis*, *H. influenzae* and *S. pneumoniae* among children < 5 years old included studies from 26 African countries. Laboratory-confirmed data from sentinel surveillance hospitals suggested that over 60.3% of *S. pneumoniae* cases were recorded, making it the most common pathogen detected in all regions of Africa. (46) In Ivory Coast (2010 to 2016), Boni-Cisse and colleagues, described the epidemiological characteristics of bacterial meningitis among children under 5 years. Their study suggest that male children were the most affected and the *S. pneumoniae* (69.5%) was the most common pathogen recorded with a peak among children under 1-year-old, followed by *H. influenzae* and *N. meningitis*. (47)

In Windhoek (Namibia), a study done from January 2010 to August 2014, among children under 5 years old to describe the frequency of bacterial isolated from CSF, found that 28.6% of bacterial meningitis was caused by *S. pneumoniae*, the second cause was *S. aureus* with over 11.% of cases followed by *E. coli* 7.9%. (48)

Another study was conducted among neonates and young children admitted to Kilifi District Hospital in Kenya, from 2001 to 2005 using both microbiological and clinical

symptoms. The study found that only 49% of positive cases were children under 7 days aged and 51% were aged 7 to 60 days,(49) while in Malawi, O. Swann and colleagues. found that 60% of cases were children in the neonate(<7 days) and the most common pathogen found was GBS (45%) followed by *S. pneumonia* (21.7%). (50) In Kenya, A.M.R. Laving found that *E. coli,* GBS *and K*. *pneumonia* were the most common pathogen identified in the neonatal period and male children were the most affected. (51)From the above-synthesized literature, it appears there is a paucity of consistent data in Africa examining both incidence and associated pathogens of bacterial meningitis in children under 1-year-old.

1.2.3 Incidence and aetiology of bacterial meningitis in South Africa:

In South Africa, several observational epidemiological studies have examined the incidence and the aetiology of bacterial meningitis. These are described below.

A study was conducted from August 1999 until July 2002 by Coulson and colleagues to describe the epidemiology of all cases of meningitis due to *N. meningitidis* submitted to the National Institute for Communicable Disease (NICD). Albeit dated, this study findings were useful as they suggested that 76% of meningococcal disease were diagnosed with CSF and blood specimen samples. The incidence rate was equal to 0.64 per 100 000 persons with a peak in infants aged less than one year, the serogroup B of *N. meningitidis* was the most common found in all ages (41%), the study also noticed a high rate of meningococcal disease during the spring and the winter in all ages and Gauteng was the most affected province. (52)

Between 2010 to 2012, a study conducted in the Red Cross War Memorial Children Hospital in Cape Town, using the laboratory database of all CSF analysed over this period found 706 cases of meningitis, 42 cases were caused by a bacterial pathogen excluding TB, 5.5% of cases were children in the neonatal age and 37.4% were children aged between 1 and 6 years. (53) Over 14 years (2003-2016) study, using data from the GERMS-SA national laboratory-based surveillance network on meningococcal disease, Meiring and colleagues, found that the overall incidence of invasive meningococcal disease decreased by 76% and the risk of having invasive meningococcal increased among HIV participants. The study also reported that the

incidence rate of all *N. meningitidis* serogroup was higher among children than all other age groups. (54)

1.2.4 Impact of different vaccines on the incidence and the aetiology of bacterial meningitis in South Africa:

A ten-year study (2005 – 2016), using public and private laboratories-based data of all South Africa to compare the impact of PCV on pneumococcal meningitis to its impact on the total invasive pneumococcal disease, showed that the reduction of pneumococcal meningitis cases and total invasive pneumococcal disease cases were similar among children < 5years old and also showed a direct effect of the vaccine on the reduction of vaccine serogroup disease in the same group age. The incidence of meningitis in children < 5years old decreased from 31.8 per 100 000 persons in 2005 to 7.7 per 100 000 persons in 2016(55)

From 2005 to 2017, the pneumococcal conjugate vaccine, PCV-7 replaced by PCV-13, have reduced the incidence of invasive pneumococcal disease in children <5 years, from 7 per 100 000 persons in 2005 to 4 per 100 000 persons in 2017. (56) In 2017, the GERMS-SA recorded 313 cases of *H. influenzae*, children under 5 years old were the most affected for all serotypes of *H. influenzae*, followed by the age group 25-45 years old age group. The incidence of Hib was estimated at 1.6 cases per 100 000 persons among children < 1 year. The same report showed that in South Africa, the highest burden of meningitis due to *S. pneumoniae* in 2017 was among infants < 1 year with an incidence estimated at 20 per 100 000 persons, while the overall incidence of meningitis due to N. meningitidis in all ages was estimated at 0.24 per 100 000 persons with a peak among children under 5 years. Western Cape was the most affected province by both *N. meningitidis*, *H. influenzae* and *S. pneumoniae* in overall ages. Concerning seasonality, most of the cases of *N. meningitidis* was recorded in the winter and spring months. (56)

1.2.5 Seasonality of bacterial meningitis:

A study conducted by Paireau and colleagues to evaluate whether significant seasonal features are observed in different geographic settings and estimate the timing of seasonal meningitis seasons and among 3 major causes of bacterial

meningitis determine if there is synchronization found that bacterial meningitis has a peak during the winter period regardless the hemispheres (northern or southern).(57) In the Central African Republic, Crellen and colleagues who examined the seasonality of *S. pneumoniae* found that 75.9% of cases were recorded in the dry season.(58) A national wide epidemiological in Iceland using data from 1975 to 2010 found a high number of cases of bacterial meningitis during the spring season.(59) In South Africa in the province of the Western Cape, Donald and colleagues could only identify a seasonality for *N. meningitidis* in winter while they could not identify any seasonality for pathogens such as *H. influenzae* and *S. pneumoniae*. (60)

1.3 PROBLEM STATEMENT

Despite the fact that meningitis is a disease with a high mortality rate and the fact that children under the age of 1 are the most affected population in South Africa, (22,61,62) our literature review has suggested some gaps in the field. Most studies conducted on bacterial meningitis among children in South Africa were mostly conducted among children under the age of 5 years (not specifically in children under 1-year-old) or were confined to a specific region. Further, they may be based on limited pathogens. (52–54) To my knowledge and from my reading of the literature cited above, there were no comprehensive data available encompassing all possible bacterial causes of meningitis (excluding TB) and comparing the age-group, province, season, month, and year's trends of individuals testing positive for the two commonest pathogens over the time of the study in children under 1-year-old in South Africa.

1.4 JUSTIFICATION

The research was justified by the fact that despite the introduction of different vaccines (including PCV and Hib vaccine), the ART treatment and the PMTCT programme which reduced the paediatric HIV burden, we still have cases of meningitis in children. Therefore, a better understanding and assessment of the incidence, the aetiology, and the characteristics of children with bacterial meningitis was crucial for the public health action for the prevention of the disease. These data would also help to see if meningitis cases have reduced since the implementation of public health measures to reduce illness and to assess evidence to support continued implementation of these interventions at the national level as well as at the provincial level. The study may also be useful to inform other LMIC countries considering interventions.

1.5 AIM AND OBJECTIVES

This research aimed to describe the incidence rate and the aetiology of bacterial meningitis and to compare the characteristics of children under 1-year-old who tested positive for the two most common pathogens related to their infection.

1. To examine the aetiology of bacterial meningitis by age group, gender, year and province in children under 1-year-old in entire South Africa.

2. To estimate the incidence rate of meningitis for the most commonly identified pathogens in South Africa by age group, year and by province in children under 1-year-old in South Africa.

3. To compare the age-group, province, season, month, and year's trends of individuals testing positive for the two commonest pathogens over the time of the study in children under 1-year-old in South Africa.

2 CHAPTER 2: METHODS

This chapter describes 2.1 The study population. 2.2. the different data sources. 2.3 the data collection. 2.4 the measurement. 2.5 some definition. 2.6. data processing and the study variables. 2.7 data analysis describes different analysis methods presented by each objective. 2.8. sample. 2.9 the ethics.

In our study, secondary data from NHLS CDW and BABY GERMS study was used.

- Primary study

The BABY GERMS is a cross-sectional national surveillance study of neonatal and infant sepsis using secondary data from the CDW. As part of the study, a cross-sectional neonatal baseline survey was conducted at secondary and tertiary hospitals to collect information on the specimen collection methods and different treatments prescribed for neonatal sepsis as well as to calculate the different denominators (number of patients admitted or bed) for the calculation of the different incidences and rates.

BABY GERMS examined both incidence and risk factors (i.e., both fungal and bacterial aetiology and characteristics of the participants) related to neonatal and infant sepsis which includes meningitis as well as bacteraemia and other invasive diseases. (63) The study also included prospective and retrospective laboratory-based surveillance including all infants under 12 months aged in South Africa who attended all public (secondary level and above) and private (hospital and group of the hospital) sectors with blood, urine and/or CSF culture performed. The study was a 5-year retrospective study (2014-2018) plus 2 and half year prospective study (2019-2021).

The primary study had two different populations under its umbrella: one for the neonate units survey which included all neonates ’ from both public (secondary level, regional level and above) and private sector hospitals that have neonatal ward, and one for the national laboratory-based surveillance which included all infant and neonatal population attending any public health sector in South Africa from 2014 to 2021.

- Secondary study

The proposed secondary analysis used a subset of the data available to BABY GERMS and examined only meningitis as the outcome among children under 1 year of age in South Africa and did not examine the additional outcomes available in the GERMS dataset. The study also did not include individuals with other invasive diseases than meningitis. Our study was a retrospective study and analysed only CSF specimens The components are described below.

2.1 STUDY POPULATION

Our study population included any person under the age of 1 year who had a lumbar puncture performed in one of the public sector facilities in South Africa and CSF specimen sent to an NHLS laboratory from January 2014 to December 2019.

- Inclusion criteria: Any person under the age of 1 with CSF culture performed and a bacterial organism considered to be a pathogen that causes meningitis was identified.
- Exclusion: Any person aged ≥ 1 year or any person with missing age with CSF culture performed and bacterial meningitis diagnosed.

For the incidence estimation, as 80% of the population get care from the public sector facilities, (64) our study population for the incidence of meningitis was the number of South African children under 1 year multiplied by 0.8. The number of children under 1 year by year, gender and provinces was estimated using the Statistics South Africa (Stats SA) Sprague table. The number of children < 28 days and ≥28 days to 1 year of age [population was estimated from the under 1-year-old population. For children<28 days old the appropriate estimated 1-year-old mid-year population were divided by 12. For the children≥28 days old (28 days old to 365[days the population was estimated by substracting the under 1-year population from the under 28 days appropriate population.

2.2 DATA SOURCES

2.2.1 NHLS CDW

The NHLS is the biggest South African public health service of pathology diagnostics in all 9 provinces. The NHLS provides laboratory diagnostics for 80% of the population of South Africa. All the demographic and laboratory data from laboratory processed specimens from within the NHLS are archived electronically in the CDW.(64) Data were extracted on all CSF specimens submitted to public sector laboratories from children aged <1 year from 2014 to 2018.

2.2.2 Stats SA

The Stats SA is the national institution that collects, produces and disseminates official vital statistics in South Africa for the collection, production, and dissemination. (65)

2.3 DATA COLLECTION

Permission to use the data was obtained from Prof Govender who was the Principal Investigator on the primary study as well as from the NHLS CDW. My supervisor, Prof Cohen was a co-investigator on BABY GERMS (Appendix 2).

Our data were accessed from Prof Govender via Prof Cohen for the study period of 2014 to 2018.

2.4 DATA MANAGEMENT

The data were entered in Excel file formats as extracted by the gatekeepers and processed/cleaned using Excel and Stata 15.1. The data sets included information on demographics and other variables as shown in Appendix(Appendix 5). Data from the Stats SA was also obtained in Excel file formats.

2.5 MEASUREMENT

The outcome variable was being positive for bacterial meningitis for each CSF sample tested for the descriptive study and being positive for one of the two most common pathogens for the analytic study. The independent variables were age-group, gender, province, year and month of diagnosis, season.

2.6 DEFINITION

A case of laboratory-confirmed bacterial meningitis was defined as any person under 1 year with meningitis diagnosed by culture testing and identification of one of the following pathogens.

Bacterial meningitis positive case was defined as a person with one of the pathogens (*N. meningitidis, H. influenzae, K. pneumoniae,* GBS, *Klebsiella* spp*, S. pneumoniae, E. coli, L. monocytogenes, A. baumannii, Serratia marcescens, Enterobacter cloacae, Klebsiella oxytoca, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, S. aureus, E. faecium, E. faecalis, Streptococcus spp* cultured from CSF.

Any pathogen that is not documented as being a common cause of meningitis and which can commonly contaminate CSF sample (eg: *Micrococcus sp*, *S. viridans*, *Bacillus sp*, *Salmonella enteritidis*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus cohni subsp urealyticus Streptococcus milleri*) was defined contaminant.

As individuals could have multiple CSF specimens submitted during the study period, an episode of illness was defined as all positive samples within 21 days, if a sample is positive > 21 days after a previous episode it was a new episode(laboratory-based surveillance definition) and considered as a new case. (56,66)

2.7 DATA PROCESSING AND STUDY VARIABLES

2.7.1 NHLS CDW dataset

Our data were collected in Excel Format in two Excel spreadsheets, which included the one spreadsheet for samples that tested positive and those that tested negative. The spreadsheet for the positive samples contained 23 demographic and laboratory variables, 10,542 observations while the spreadsheet for the negative samples contained 20 demographic and laboratory variables and 221,325 observations, from the 2 files only few variables were used in our study, and they will be presented in table 2.

2.7.2 Stats SA data set

Data were entered into Excel spread format including the population data by gender, by districts, by age group from 2002 to 2020.

The study variables are presented below in Table 2

Table 2. Study variables

Study variables	Format	Data management process
Age-group	categorical	Encoded as < 28 days = 27.999 days and ≥28 days=28 days to 364.999 days. The age in days was calculated using the variable Detected (the date at which the CSF test was done) – Date of birth
Gender	Categorical	Recoded M= Male, F= Female, U=Unknown
Province	Categorical	Gauteng, KwaZulu Natal, Limpopo, Eastern Cape, Northern Cape, Mpumalanga, North west, Western cape, Unknown
Years of diagnostic	Categorical	A variable year was generated taking the year of the date of the test (Date tested) single year from 2014 to 2018
Month of diagnostic	Categorical	A variable" month" was generated taking the month of the date of the test (Date tested). The values were taken from 1 to 12.
Midyear population	Numerical	A variable generates using the mid-year population of South Africa by age. The variable Midyear population was created using data from the Stats SA under 1 year age population by province, by gender as well as the overall under 1year population was calculated using the Stats SA Sprague table. -For the <28 days population the appropriate estimated under 1-year population were divided by 12. -For the >28days appropriate population was found by using the under 1-year appropriate population – the < 28 days appropriate Midyear population.
Season	Categorical	A variable "Season" was generated using the month of the variable "Date tested" recoded in four seasons as followed and according to the SA meteorological reports: Summer: December, January, February Autumn: March, April, May. Winter: June, July, August, Spring: September, October, November.
Pathogen	Categorical	A variable generates using the variable "organism name" variables. Identical pathogens which were separated into 2 or more, were grouped to create only one pathogen. The label other was created regrouping all pathogens that had few cases.
Actkleb	Categorical	Because *A. baumannii* and *K. pneumoniae* were *the* most common pathogens detected and for the necessity of objective 3, a variable recoded using "Pathogen". recorded 1 if pathogen name is = *Acinetobacter baumannii* and 0 if pathogen =*K. pneumoniae.*

2.8 DATA ANALYSIS

Our descriptive analysis by objectives is presented in the table below.

Table 3. Descriptive analysis

Objective 1	The first objective was to describe the aetiology of bacterial meningitis by age-group, gender, year, and province as well as overall. A descriptive analysis of the aetiology of bacterial meningitis regarding the age-group, the year the gender and the province was done using the frequency(n) and percentage (%) tables. Only pathogens with enough number of cases for provinces and years distributions were included in the study, pathogens with few cases were grouped under "other" pathogen.
Objective 2	The second objective had as its core aim to estimate the incidence rate of meningitis for the most identified pathogens in South Africa by age group, year and by province. Data were collapsed by year and province as well as year and age-group. 3 different Stata files were created and merged with the appropriate population excel data from the Stats SA. The incidences rate of specific pathogens were calculated using a Poisson regression by dividing the age-group, year of the test and provinces positive sample numbers by the appropriate specific mid-year population. As people who attend public facilities represent 80% of the population, the appropriate mid-year population were multiplied by 0.8. Only pathogens with enough cases for the calculation by different distribution were included. The appropriate mid-year population was obtained by using the Stats SA data and estimated using the Stats SA Sprague table for the children under 1-year population. For children<28 the appropriate estimated mid-year population were divided by 12. For the children≥28 days old (28 days old to 365[days the population was estimated by the under 1-year population minus the under 28 days appropriate population. All incidences rates were multiplied by 100 000 persons. Data on the population of the Western Cape province for the year 2014 was not included in any incidence calculation because of the missing CSF data of the same province for the same year. To see if the incidence rate trends were significant, Poisson regression was used. Graphs were done using excel.
Objective 3	The third objective aimed to compare the age-group, province, season, and year's trends of individuals testing positive for the two commonest pathogens over the years of the study. An analytical analysis was done between the two commonest pathogens by age-group, year, month/season, gender, and province. The outcome variable was" testing positive for one of the two pathogens". Variable "Actkleb" was generated recorded as 1 if pathogen name was = *A. baumannii* and 0 if pathogen *was =K. pneumoniae.* As our outcome was binary, a logistic regression analysis was done to check if the associations were significant. Forward stepwise logistic regression analysis was used to test variables associated with being positive for te two most common pathogens (*A. baumannii* and *K. pneumoniae),* all variables with univariate association of <0.1 were included in the model. Univariate logistic regression was done followed by a multivariate logistic regression of the variable age-group, gender, month, province, season and year. Variable with<0.05 were considered as significant. For this part of the study, the sample was the number of all specimens positive for one of the two most common pathogens (*A. baumannii* and *K. pneumoniae).* The two commonest pathogens were chosen as the two pathogens were the highest number of cases over the time of the study. The Goodness of fit test was done to check the fitness of the model. Results showed that the model did not fit the data well, and that could have been due to the low number of variables or the small size of the sample. Because the missing data, data from the year 2014 was not include in this part of the study.

2.9 SAMPLE SIZE

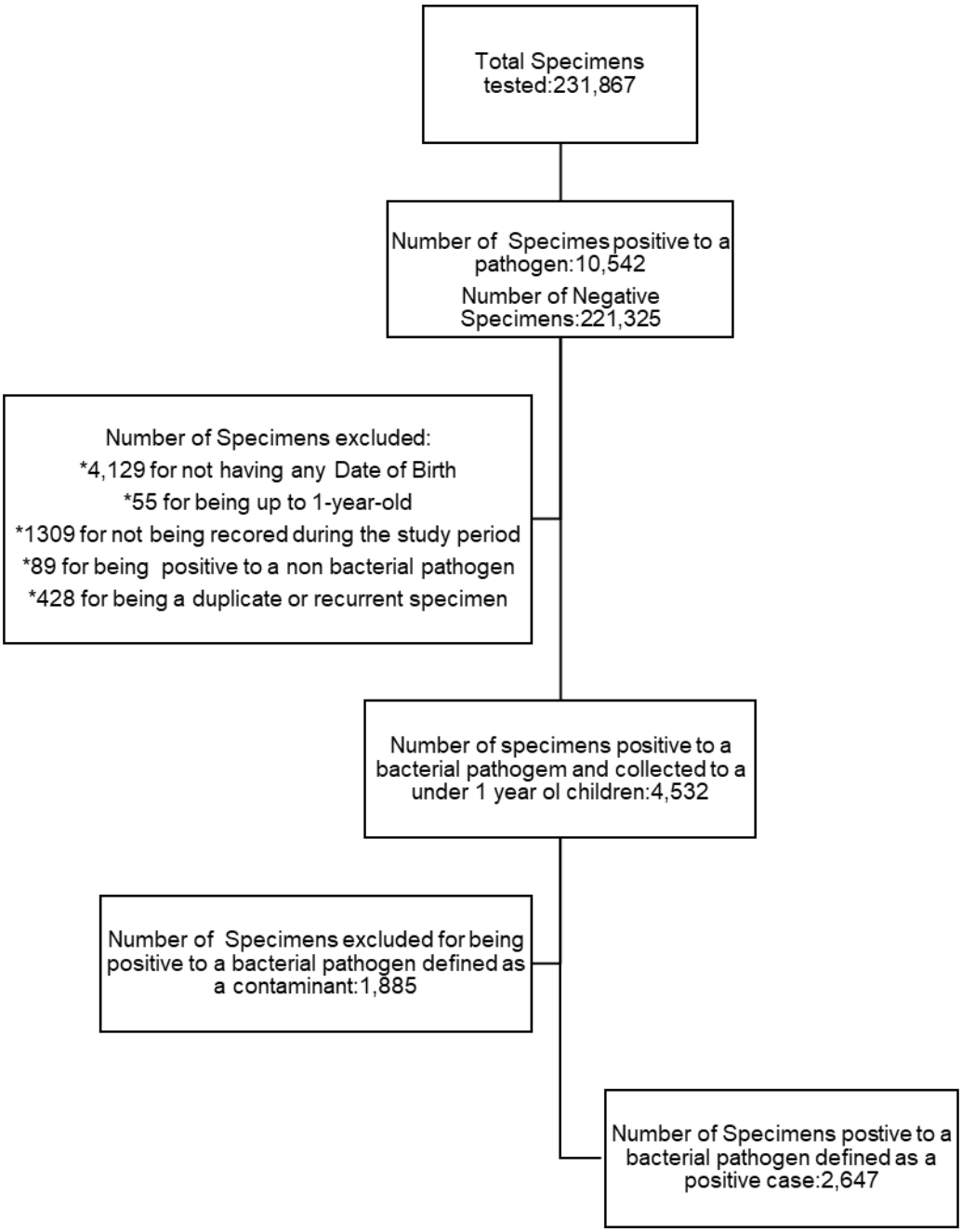


Figure 1. Diagram presenting attainment of sample size

2.10 ETHICS

This study was approved by the University of the Witwatersrand Human Research Ethics (Medical) Committee (HREC). The authorization letters and the clearance certificate (Approval M210110, which can be found in Appendix labelled as Appendix 3). The anonymity of the participant was preserved. All data were kept in password-controlled computers that was only accessible by the researcher and the supervisors.

3 CHAPTER 3: RESULTS

In this chapter, the results of the analysis of data from the NHLS CDW are presented as follows: 3.1. The description of the sample. 3.2. the aetiology of bacterial meningitis, 3.3. the incidence of the most common pathogens isolated. 3.4.the characteristics of children under the age of 1 who have tested positive for the two most common pathogens (*A. baumannii and K. pneumonia)* that are described.

3.1 DESCRIPTION OF THE STUDY SAMPLE

Over the five years of the study, a total of 2,647 cases of laboratory-confirmed bacterial meningitis cases were identified from the 231, 867 CSF specimens tested by the NHLS in entire South Africa.

Of the 2,647 cases, 54.6% were aged in the neonatal group, 51.4% cases were males, 59.46% of cases were recorded in Gauteng province, while 26.8% of cases occurred in spring 26.8%. These data are presented in Table 4 below.

3.2 AETIOLOGY

With regard to the pathogens tested, 514 cases (19.4%) tested positive for the *A. baumannii* pathogen. The second most common pathogen identified was *K. Pneumonia (*470 cases or 17.7% of all cases). GBS was found in (384 cases or 14.5% of all cases) *S aureus* (244 cases or 9.2% of all cases), *E. faecium* (221 cases or 8.3% of all cases), *E. coli (212 cases or 8% of all cases) and E. faecalis (*153 cases or 5.7% of all cases). The other pathogens identified and defined as "others" were *N. meningitidis, P. aeruginosa, H. influenzae, E. cloacae, S. marcescens,* Hib, *S. maltophilia.* These data are presented in Table 4 below

A.baumannii (23.9*%), K*. *pneumonia* (19.4%), GBS (19.2%) were the most common pathogen detected among the neonates while *K. pneumonia* (15.7%), *S aureus* (14.2%) and *A*. *baumannii*(14%) were the most common pathogen detected among those in the post neonate age group (≥28). More than 70% of cases of *A. baumannii* were detected in the neonate group. *A*. *baumannii* was the most common pathogen identified in both male and female children while Assessing by provinces, *A. baumannii* followed by GBS or *K. pneumonia* were the most identified pathogens in most provinces. GBS was the leading pathogen in the provinces of North West,

Mpumalanga, Western Cape. When examining the seasons, *A. baumannii* was the most common pathogen detected in spring (21.69 % of cases) and winter (19.14% of cases) while *K. pneumonia* was the highest in summer (21.55% of cases) and Autumn (17.56% of cases). These data are presented in Table 4 below

Additionally, in our study *S. pneumonia, N. meningitidis* and *H. influenzae*, with respectively 0% (0 cases identified), 2% (53 cases) and 3.1% (82 cases) were not among the most common pathogen recorded and were then dropped under others pathogen categories. 93.9% of *H. influenzae* and 83.02% were common among children aged ≥28 days. Only 9 cases of Hib were recorded over the study period.

Table 4. Demographic characteristics of patients with laboratory-confirmed meningitis infection due to pathogens in South Africa, 2014-2018

Pathogen	***A. baumannii***	***E. faecalis***	***E. faecium***	***E. coli***	***K. Pneumonia***	***S. aureus***	**GBS**	**Others**	**TOTAL**	**p-value**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
TOTAL	514 (19.4)	153(5.7)	221(8.3)	212(8)	470(17.7)	244(9.2)	384(14.5)	449(16.9)	2,647(100)	
AGE-GROUP (days)										
<28	346(67.3)	76(49.6)	120(54.3)	119(56.1)	281(59.7)	73(29.9)	279(72.6)	153(34)	1,447(54.6)	0.001
≥28	168(32.6)	77(50.3)	101(45.7)	93(43.8)	189(40.2)	171(70.)	105(27.3)	296(65.9)	1,200(45.3)	
GENDER										
Female	268(52.1)	90(58.8)	114(51.5)	121(57)	238(50.6)	122(50)	176(45.8)	232(44.5)	1,163(43.9)	0.125
Male	214(41.6)	59(38.5)	98(44.3)	80(37.7)	206(43.8)	115(47.1)	191(49.7)	200(44.5)	1,361(51.4)	
Unknown	32(6.2)	4(6.2)	9(4)	11(5.1)	26(5.5)	7(2.8)	17(4.4)	17(3.7)	123(4.6)	
PROVINCE										
Eastern cape	34(6.6)	1(0.6)	6(2.7)	19(8.9)	43(9.1)	13(5.3)	38(9.9)	48(10.6)	202(7.6)	0.001
Free state	27(5.2)	6(3.9)	8(3.6)	6(2.8)	15(3.1)	8(3.2)	12(3.1)	18(4)	100(3.7)	
Gauteng	359(69.8)	115(75.1)	166(75.1)	118(55.6)	278(59.1)	142(58.2)	196(51)	200(44.5)	1 574(59.4)	
KwaZulu-Natal	39(7.5)	10(6.5)	23(10.4)	28(13.2)	67(14.2)	39(15.9)	52(13.5)	84(18.7)	342(12.9)	
Limpopo	21(4.1)	4(2.6)	5(2.2)	5(2.3)	24(5.1)	11(4.5)	13(3.3)	22(4.9)	105(3.9)	
Mpumalanga	11(2)	0(0)	3(1.3)	2(0.9)	7(1.4)	1(0.4)	13(3.3)	8(1.7)	45(1.7)	
Northern cape	4(0.7)	2(1.3)	4(1.8)	7(3.3)	5(1)	4(1.6)	3(0.7)	6(1.3)	35(1.3)	
North West	2(0.3)	1(0.6)	0(0)	3(1.4)	8(1.7)	1(0.4)	7(1.8)	11(2.4)	33(1.2)	
Western cape	17(0.7)	14(9.1)	6(2.7)	24(11.3)	23(4.8)	25(10.2)	50(13.0)	52(11.5)	211(7.9)	
YEAR										
2014	47(9.1)	18(11.7)	25(11.3)	30(14.1)	62(13.1)	46(18.8)	62(16.1)	68 (15.1)	358(13.5)	
2015	82(15.9)	29(18.9)	46(20.8)	41(19.3)	70(14.8)	41(16.8)	76(19.7)	74(16.4)	459(17.3)	0.001
2016	75(14.5)	37(24.1)	48(21.7)	52(24.5)	90(19.1)	44(18)	66(17.1)	114(25.3)	526(19.8)	
2017	141(27.4)	25(16.3)	34(15.3)	40(18.8)	107(22.7)	51(20.9)	85(22.1)	98(21.8)	581(21.9)	
2018	169(32.8)	44(28.7)	68(30.7)	49(23.1)	141(30)	62(25.4)	95(24.7)	95(21.1)	723(27.3)	
MONTH										
January	37(7.2)	7(4.5)	13 (5.8)	18(8.4)	48(10.2)	18(7.3)	30(7.8)	33(7.3)	204(7.7)	0,054
February	44(8.5)	13(8.5)	10(4.5)	18(8.4)	42(8.9)	15(6.1)	32(8.3)	40(8.9)	214(8)	
March	35(6.8)	11(7.1)	22(9.9)	18(8.4)	51(10.8)	21(8.6)	25(6.5)	35(7.8)	218(8.2)	
April	40(7.7)	12(7.8)	12(5.4)	16(7.5)	34(7.2)	31(12.7)	30(7.8)	35(7.8)	210(7.9)	

May	42(8.1)	22(14.3)	22(9.9)	22(10.3)	33(7)	32(13.1)	33(8.5)	38(8.4)	244(9.2)	
June	36(7)	10(6.5)	22(9.9)	15(7)	29(6.1)	17(6.97)	31(8)	38(8.4)	198(7.4)	
July	34(6.6)	11(7.1)	20(9)	15(7)	36(7.6)	16(6.5)	28(7.2)	36(8)	196(7.4)	
August	46(8.9)	11(7.1)	20(9)	15(7)	37(7.8)	19(7.7)	42(10.9)	22(4.9)	212(8)	
September	41(7.9)	17(11.1)	22(9.9)	18(8.4)	29(6.1)	16(6.5)	33(8.5)	38(8.4)	214(8)	
October	40(7.7)	15(9.8)	27(12.2)	24(11.3)	35(7.4)	19(7.7)	39(10.1)	48(10.6)	247(9.3)	
November	73(14.2)	12(7.8)	15(6.7)	18(8.4)	44(9.3)	21(8.6)	32(8.3)	34(7.5)	249(9.4)	
December	46(8.9)	12(7.8)	16(7.2)	15(7)	52(11)	19(7.7)	29(7.5)	52(11.5)	241(9.1)	
SEASON										
Summer	127(24.7)	32 (20.9)	39(17.6)	51(24)	142(30.2)	52(21.3)	91(23.7)	125(27.8)	659(24.9)	0.012
Autumn	117(22.7)	45(29.4)	56(25.3)	56(26.4)	118(25.1)	84(34.4)	88(22.9)	108(24)	672(25.3)	
Winter	116(22.5)	32(20.9)	62(28)	45(21.2)	102(21.7)	52(21.3)	101(26.3)	96(21.3)	606(22.8)	
Spring	154(29.9)	44(28.7)	64(28.9)	60 (28.3)	108(22.9)	56(22.9)	104(27)	120(26.7)	710(26.8)	

n: frequency; %: column percentage

3.3 INCIDENCE

Results of the Poisson regression suggest that the annual incidence rate of most pathogens increased each year. The annual incidence rate varied by pathogen and by year among children under 1-year-old. The highest incidence was the incidence of *A. baumannii* 10.2 cases per 100 000 persons (CI 8.7-11.9) in 2018 and the lowest was *E. faecalis* 1.1 cases per 100 000 persons (CI 0.6-1.7) in 2014 among children under 1 year. These data are presented below in Figure 2.

The annual incidence of pathogens was high among children under 28 days old. For certain pathogens, the incidence in the neonates was more than ten times greater than in post neonatal participants. These data are further interrogated below:

The highest incidence rate calculated was the incidence of A. *baumannii* among children in the neonatal period with an annual incidence rate of 168.8 cases per 100 000 persons (CI 139.5-202.5) while the lowest incidence rate calculated was the incidence of *E*. *faecalis among* children in the postneonatal period. These data are presented below in Figure 3 and Figure 4.

The annual incidences rates of almost all the most common pathogens detected in different provinces increase over time except for *S. aureus* and GBS which tended to increase from 2014 to 2017 before slightly decreasing in 2018 in most provinces. The highest incidence rate for all pathogens was observed in the Gauteng province. These data are visually depicted below in Figures 5,6,7 and 8.

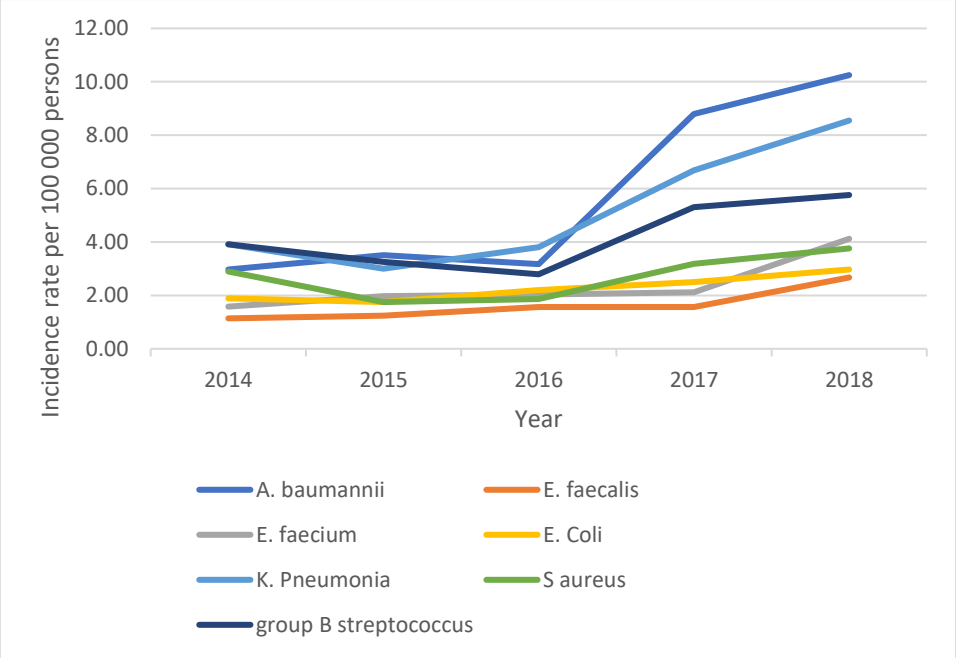


Figure 2. Incidence rate of the most common pathogens among children under 1-year-old by year, South Africa, 2014-2018

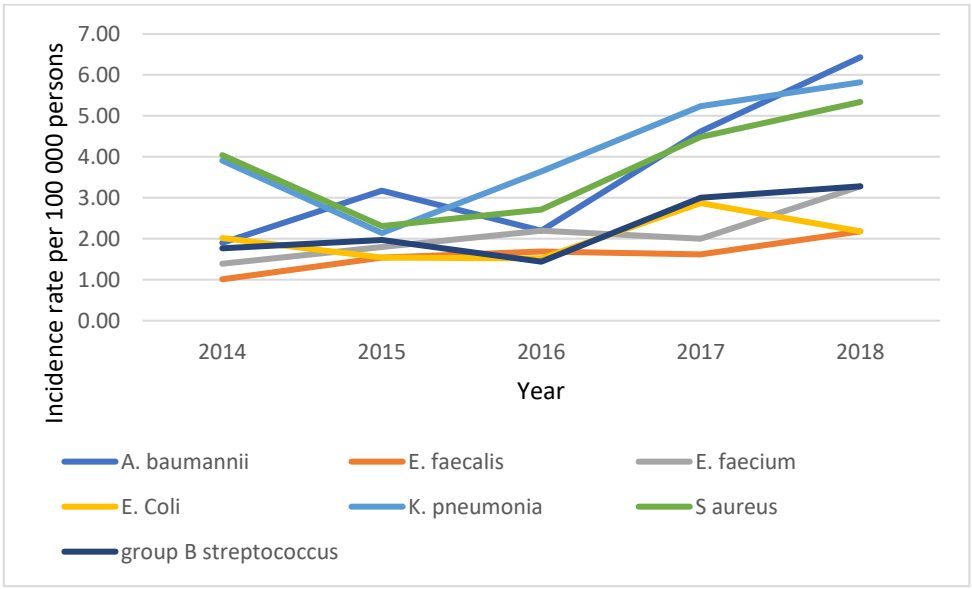


Figure 3. Incidence rate of the most common pathogens detected among children ≥28 days old, South Africa, 2014-2018

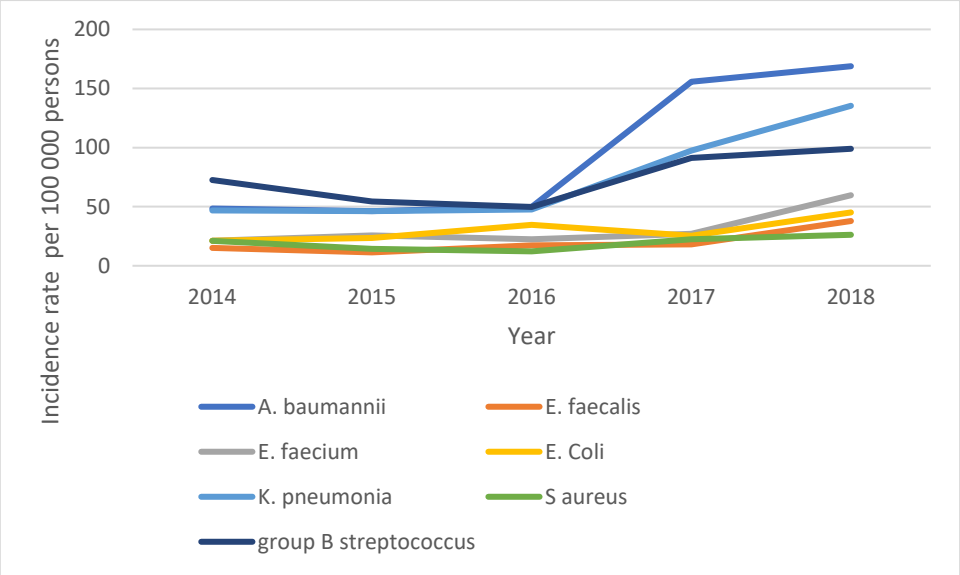


Figure 4. Incidence rate of the most common pathogens detected among children <28 days old, South Africa, 2014-2018

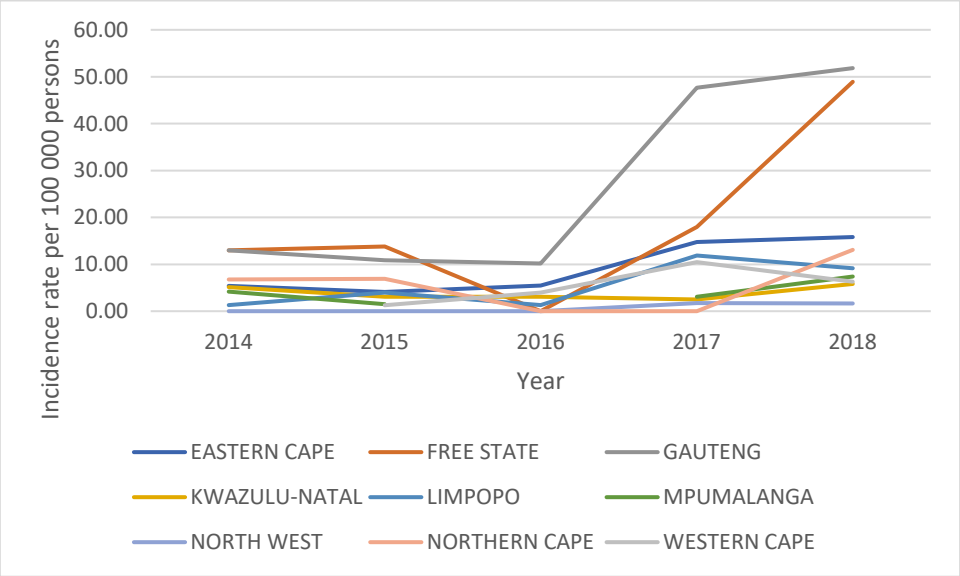


Figure 5. Incidence rate of *A. baumannii* among children under 1-year-old by provinces and year, South Africa, 2014-2018

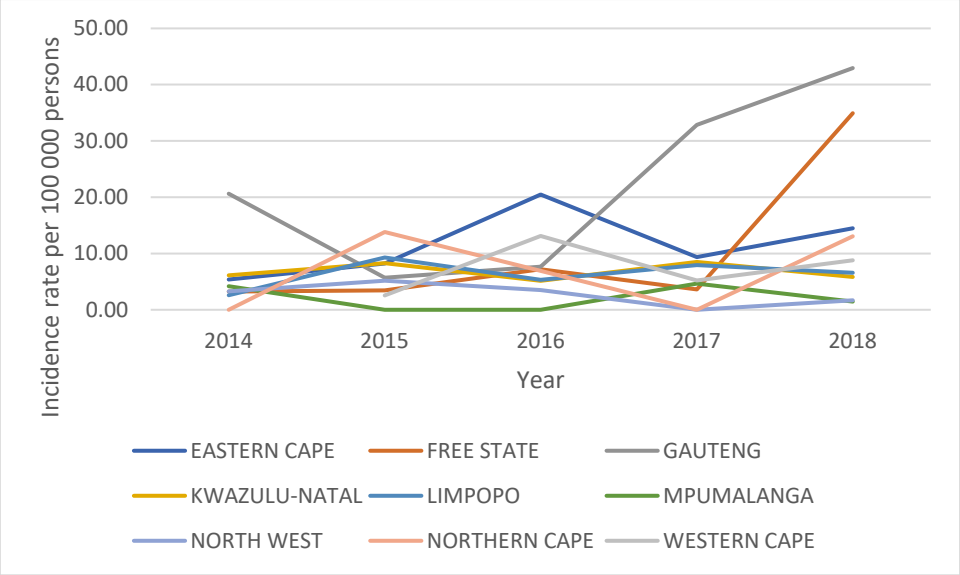


Figure 6. Incidence rate of *K. pneumoniae* among children under 1-year-old by provinces and year, South Africa, 2014-2018

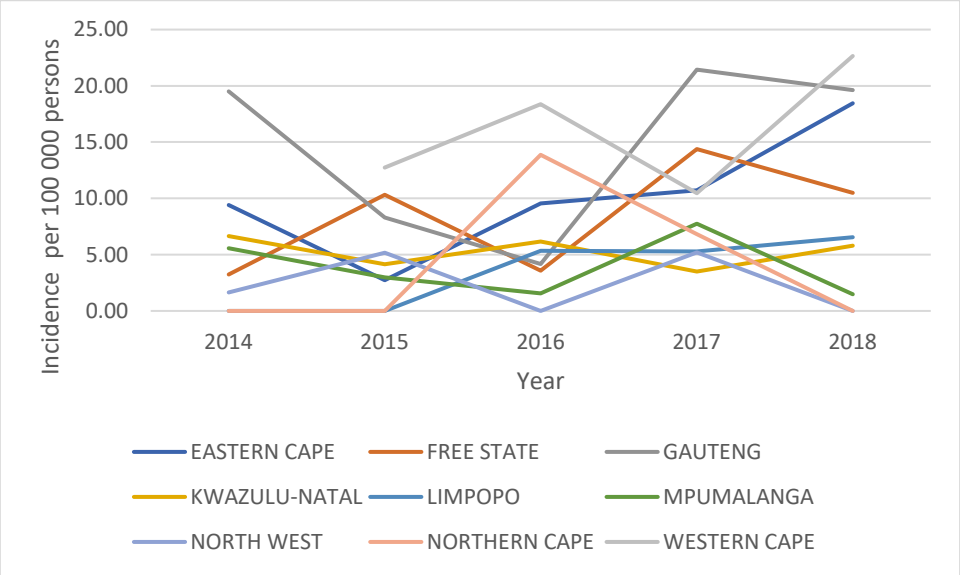


Figure 7. Incidence rate of GBS among children under 1-year-old by provinces and year, South Africa, 2014-2018

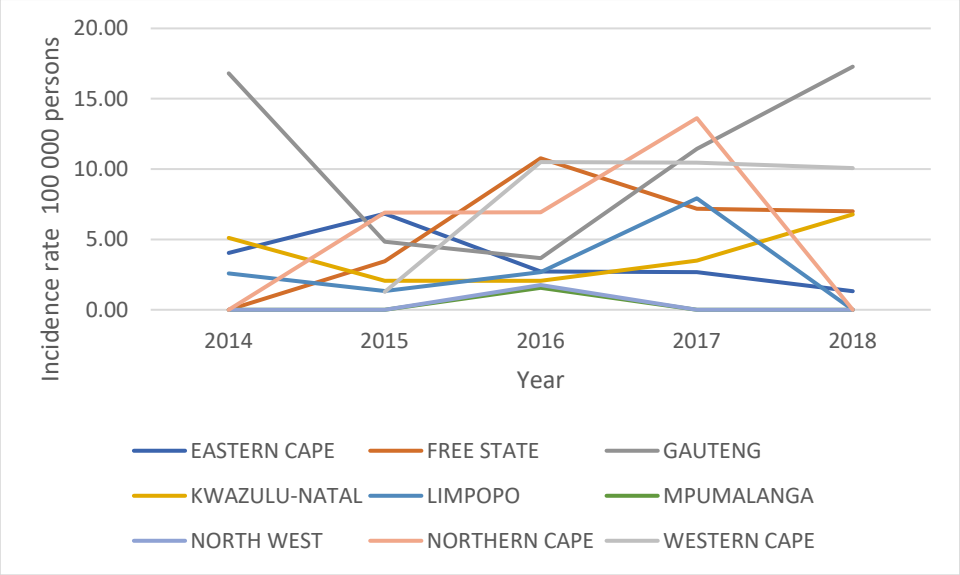


Figure 8. Incidence rate of *S. aureus* among children under 1-year-old by provinces and year, South Africa, 2014-2018

3.4 CHARACTERISTICS OF PEOPLE WHO TESTED POSITIVE FOR THE TWO MOST COMMON PATHOGENS (*A. baumannii and K. pneumonia)*.

About 886 cases tested positive for *A. baumannii* or *K. pneumonia*. 63.4% were aged under 28 days old. Male children constituted 50.9%. 65.4% were recorded in Gauteng province and 26.9% occurred during the summer.

The binary logistic regression analysis results suggest a range of interesting findings. First, cases *A. baumannii* were significantly more likely to be from the Free State(6.6% p<0.028) and the Gauteng province(71.3% p<0.018).Second, they were significantly more likely to be recorded during the month of June(7.7% p<05), October(9.2% p<02),November(14.3% p< 0.007). Third, they were significantly more likely to be isolated in Spring (30.9% p < 0.002). Furthermore, the multivariate analysis suggested that cases of *A. baumannii* were significantly more likely to be identified during spring (30.9% p <0.002) while they were significantly more likely to be from the Gauteng province (71.3% p<0.027). These data are presented below in table 6.

The Characteristics of people who tested positive for the two most common pathogens (*A. baumannii* and *K. pneumonia)* are presented in the table below.

Table 5. Characteristics of people who tested positive to the two most common pathogen (A. baumannii and K. pneumonia). South Africa, 2014-2018.(Univariate analysis)

	TOTAL n (%)	***A. baumannii* n (%)**	***K. Pneumonia* n (%)**	**Unadjusted OR (95% CI)**	**p-value**
Characteristics					
Age-group (Days)					
<28	562(63.4)	310 (65.9)	252 (60.6)	1.2(0.95-1.65)	0.097
≥28	324(36.6)	160 (34,1)	164(39.4)		
Sex					
Male	451(50.9)	241(51.3)	210(50.5)	1.07(0.81-1.40)	0.612
Female	387 (43.7)	200(42.6)	187(44,9)		
Unknown	48 (5.4)	29(6.2)	19(4.6)	1.42(0.77-2.63)	0.255
Provinces					
Eastern Cape	72(8.1)	31(6.60)	41 (9.9)		
Free State	40(4.5)	26(5.53)	14 (3.4)	2.4(1.10-5.46)	0.028
Gauteng	579 (65.4)	335(71.3)	244 (58.7)	1.8(1.10-2.97)	0.018
KwaZulu Natale	84 (9.5)	28(6)	56 (13.5)	0. .66(0.34-1.26)	0.213
Limpopo	42 (4.7)	20 (4.7)	22 (5.3)	1.2(0.55-2.58)	0.637
Mpumalanga	12 (1.4)	8 (1.7)	4 (1)	2.6(0.72-9.58)	0.139
North West	8(0.9)	2 (0.4)	6 (1.4)	0.4(0.083-2.33)	0.336
Northern Cape	8(0.9)	3 (0.6)	5 (1.2)	0.79(0.17-3.57)	0.763
Western Cape	41(4.6)	17 (3.62)	24 (5.8)	0.93(0.430- 2.03)	0.869
YEAR					
2015	156(17.6)	86(18,3)	70 (16.8)		
2016	169(19.1)	76(16.2)	93 (22.4)	0.66(0.42-1.03)	0.068
2017	249(28.1)	139 (29.6)	110 (26.4)	1.02(0.68-1.53)	0.891
2018	312(35.2)	169 (35.9)	143 (34.4)	0.96(0.65-1.41)	0.844
MONTH					
January	81 (9.1)	35(7.5)	46(11.1)		

February	77 (8.7)	38(8.1)	39(9.4)	1.28(0.68-2.39)	0.439
March	78 (8.8)	31 (6.6)	47(11.3)	0.86(0.46-1.63)	0.658
April	66 (7.5)	34(7.2)	32(7,7)	1.39(0.72-2.68)	0.316
May	64 (7.2)	34(7.2)	30(7.2)	1.48(0.77-2.87)	0.236
June	60(6.8)	36(7.7)	24(5.8)	1.97(1.0- 3.88)	0.050
July	65(7.3)	34(7.2)	31(7.5)	1.44(0.74-2.77)	0.275
August	75(8.5)	42(8.4)	33(7.9)	1.67(0.88-3.15)	0.111
September	61(6.9)	35(7.5)	26(6.3)	1.76(0.90-3.46)	0.096
October	69 (7.8)	43(9.2)	26(6.3)	2.17(1.12-4.18)	0.020
November	106(11.9)	67 (14.3)	39(9.4)	2.25(1.25-4.07)	0.007
December	84(9.5)	41(8.7)	43(10,3)	1.25(0 .67-2.31)	0.471
SEASON					
Summer	242(27.3)	114 (24.2)	128 (30.8)		
Autumn	208 (23.5)	99 (21.1)	109 (26.2)	1.01(0.7- 1.47)	0.918
Winter	200 (22.6)	112 (23.8)	88 (21.1)	1.42(0.98-2.08)	0.063
Spring	236 (26.6)	145 (30.9)	91 (21.9)	1.7(1.24-2.57)	0.002

n: frequency; %: column percentage

Table 6. Characteristics of people who tested positive to the two most common pathogen (A. baumannii and K. pneumonia). South Africa, 2014-2018.(Multivariate analysis)

	TOTAL n (%)	***A. baumannii*** **n (%)**	***K. Pneumonia*** **n (%)**	**Adjusted OR (95% CI)**	**p- value**
Province					
Eastern Cape	72(8.1)	31(6.60)	41 (9.9)		
Free State	40(4.5)	26(5.53)	14 (3.4)	2.18 (0.97- 4.9)	0.057
Gauteng	579 (65.4)	335(71.3)	244 (58.7)	1.74 (1.05- 2.87)	0.029
KwaZuluNatale	84 (9.5)	28(6)	56 (13.5)	0.63 (0.32- 1.21)	0.170
Limpopo	42 (4.7)	20 (4.7)	22 (5.3)	1.32 (0.61- 2.87)	0.473
Mpumalanga	12 (1.4)	8 (1.7)	4 (1)	2.54(0.69- 9.31)	0.157
North West	8(0.9)	2 (0.4)	6 (1.4)	0 .45(0.08- 2.4)	0.352
Northern Cape	8(0.9)	3 (0.6)	5 (1.2)	0.80(0.17- 3.67)	0.784
Western Cape	41(4.6)	17 (3.62)	24 (5.8)	0.86 (0.36- 1.00)	0.723
Season					
Summer	242(27.3)	114 (24.2)	128 (30.8)		
Autumn	208 (23.5)	99 (21.1)	109 (26.2)	1.0(0.74- 1.59)	0.661
Winter	200 (22.6)	112 (23.8)	88 (21.1)	1.4(0.98- 2.12)	0.061
Spring	236 (26.6)	145 (30.9)	91 (21.9)	1.7(1.22-2.58)	0.002

n: frequency; %: column percentage

4 CHAPTER 4: DISCUSSION

This study has found a number of important findings. These findings are elaborated and reflected upon below**:**

- Increase in the annual incidence of most pathogens over the study period

We found an increased (annual) incidence in most pathogens over the study period which is not always corroborated by previous studies. Several studies have reported a decreasing trend in the incidence of bacterial meningitis as well as in their causative pathogens worldwide after the introduction of different vaccines.(67,68) In South Africa, studies on bacterial meningitis among adults or studies conducted on more frequent pathogens such as *S. pneumoniae*, *H. influenzae* and *N. meningitidis* have shown the same trend. (13,32,54,55,66)

Surprisingly the present study showed an increased trend although different vaccine programmes. We could not find a recent study on bacterial meningitis among children under 1 year in South Africa to compare this finding to. The increasing trend cannot be attributed only to a failure of different vaccines programmes given the low number of cases of Hib (9 over the 5 years of the study) and the absence of any cases of *S. pneumoniae* which are part of South African national immunisation programme, but could be explained by improvements in laboratory technique and the quality of NHLS CDW data collection and the treatment of data as well as an increase in the number of sample testing, the change in the denominators(population) for the calculation of the incidence rate over the time of the study, as well as the deterioration of the public health system.

- Most common pathogens detected over the study period

Second, we found that *A. baumannii* followed by *K. pneumonia,* GBS was the most common pathogens detected over the study period. The findings in the present study suggest a high proportion and predominance of pathogens such as *A. baumannii, K. pneumoniae, S. aureus,* GBS which can be categorised in “healthcare-associated infection (nosocomial)” and “mother to child transmissible” pathogen (mostly for GBS). Factors such as poor infection control programmes or bacterial infection

management (poor hygiene method for the healthcare provider and poor environmental cleaning, a lack in disinfection and sterilization in the hospital, antimicrobial resistance, inadequate antibiotic administration and prolonged antibiotic administration), prolonged hospital stay, immunosuppression, immunosuppression, a lack of antenatal screening and education for GBS in pregnant women, unhygienic behaviours in the delivery rooms and neonatal intensive care units and a high number of premature babies… could explain that predominance. (63,69–71)

The leading causes of bacterial meningitis in our study were different to what has been suggested by previous studies, also from LMIC. For example, in a study conducted in the Gulf region in Oman, the introduction of meningococcal serogroup A and C vaccine, pneumococcal vaccine, and Hib vaccine did not seem to impact the leading pathogens. *S. pneumoniae*, *H. influenzae* and *N. meningitidis* were still the 3-leading cause of bacterial meningitis among children under 1 year.(40) That could be due to the fact that in the Oman study they used the neutrophilic pleocytosis, latex agglutination test for antigen as well as culture test of CSF to define a case of bacterial meningitis while our study included only the culture test of CSF.

In a Kenyan study by Laving and colleagues found that *E. coli*, GBS, *and K*. *pneumoniae* were the most common pathogens isolated in neonates. Once again the leading causative pathogens were different to what we found.(51) Their results were different from our findings. That may be due to the fact that this study was located in one hospital while our study was a nationwide study. Similarly, a Namibian study tracking infants identified *S*. *pneumonia, Haemophilus sp* and *Streptococcus sp* as the 3 most common pathogens isolated in the postneonatal period also starkly different to what we found.(72) This could be attributable to differences in the two contries' healthcare programmes. In South Africa, another study conducted by Velaphi and colleagues in Soweto identified almost the same pathogens as our study as causes of sepsis in the neonate. However, the most common pathogens were not the same. (73) The difference could be explained by the fact the Velaphi and colleagues examined molecular and culture CSF, blood as well as respiratory (nasopharyngeal and oropharyngeal swabs) specimen samples while our study only examined CSF culture.

- Gender, province and seasons with the highest number of cases

The finding that male children were more likely to test positive was similar to findings suggested by a number of previous studies. (40,47,51,53) That may be explain by some genetic and endocrine effects on their immune system and physiology. (74,75)

The fact that Gauteng was the most affected is quite understandable since Gauteng is the most populated province, with 25.3% of the national population living in this province for the year 2018 and the most developed province with better access to care and laboratories testing. (52,76)

The highest number of cases were recorded in Spring which was similar to the findings in Iceland. (59) That may be the result of some damage on mucosal defences of patients due to environmental conditions caused during dry seasons. (77)

- Characteristics of people who tested positive for the two most common pathogens (*A. baumannii* and *K. pneumonia*)

When we compare the characteristics of the 2 commonest pathogens identified (*A. baumannii* and *K. pneumonia*), the study suggests that *cases* of A. *baumannii* were significantly more likely to be identified in the Gauteng province This could be due to a lack of infection control programs and management of bacterial infection including factors such as a high antimicrobial resistance rate, inappropriate antimicrobial use as well as the non respect of different antibiotic control policy, non-adequate use of antibiotics. Other factors such as a high incidence of preterm birth, , and long hospital stays since *A. baumannii* is a nosocomial pathogen.(78) Regarding the seasonality, in our study cases of meningitis due to A. *baumannii* were significantly more likely to be recorded in spring, the results are not corroborated by those of previous studies on A. *baumannii* which have shown that A. *baumannii* is more likely to be recorded in summer(warm and humid season), as well as the Paireau and colleagues findings on the seasonality of bacterial meningitis in general (57,79)

- Strengths and limiatation

- Strengths and limitations

The study had several strengths: The study included all bacterial pathogens (other than TB) and included data across South Africa. Although the study only included CSF culture, it provided a clear distribution of aetiology and incidence of bacterial meningitis over a 5-year period using data from the largest public health service for pathology diagnostics with the best facilities for microbiological testing and procedures, which serves 80 % of the total population of South Africa.

We have also identified some limitations. These included the lack of information on the Hib vaccine and HIV status. We also experienced missing data for the entire Western Cape province in 2014; the missing of the date of birth for 4129 specimens and the fact that all cases of Coagulase-negative staphylococci were considered as contaminants because of the difficulty of defining a case of Coagulase-negative staphylococci by only one positive CSF. There was also no data on TB status, which can be relevant in meningitis analyses**.**

5 CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

Despite the introduction of the Hib vaccine and PCV, the different incidence of different pathogens tended to increase during our study period. However, no case of *S. pneumoniae* was recorded and only 9 cases of Hib were recorded of the 5 years. *A. baumannii K. pneumonia* and GBS were the leading causative pathogens in children in the neonatal period and children under 1 year while in the postneonatal period, *K. pneumonia*, *S aureus*, *A. baumannii* were the most common identified. Overall, this study suggests a predominance of nosocomial pathogen and mother to child transmissible pathogens as the cause of bacterial meningitis. Data suggest that different public health programmes should not only be focused on vaccination (immunisation) programmes. Consideration should also be given to national and provincial prophylactic measures(infection prevention programme) such as rigorous hygiene methods for the healthcare provider and cleaning, disinfection, sterilization of the hospital environment, antenatal screening for GBS in pregnant women and hygienic practice in the labour room and intensive care units as well as a rationalize antibiotic use to prevent nosocomially and mother to child transmissible pathogens. (20,71,78) Further, studies could collect clinical variables for a more accurate diagnosis of bacterial meningitis as well as the vaccine status for children.

REFERENCES

1. van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, et al. ESCMID guideline: Diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016;22:S37–62.
2. Tyler KL. Chapter 28: a history of bacterial meningitis. Handb Clin Neurol. 2010;95:417–33.
3. Logan SAE, MacMahon E. Viral meningitis. Bmj. 2008;336(7634):36–40.
4. Mount HR, Boyle SD. Aseptic and Bacterial Meningitis: Evaluation, Treatment, and Prevention. Am Fam Physician. 2017;96(5):314–22.
5. Furyk JS, Swann O, Molyneux E. Systematic review: Neonatal meningitis in the developing world. Trop Med Int Heal. 2011;16(6):672–9.
6. Zunt JR, Kassebaum NJ, Blake N, Glennie L, Wright C, Nichols E, et al. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(12):1061–82.
7. Hsu MH, Hsu JF, Kuo HC, Lai MY, Chiang MC, Lin YJ, et al. Neurological complications in young infants with acute bacterial meningitis. Front Neurol. 2018;9(OCT):1–10.
8. Singhal K, Singhal J, Muzaffar J, Monksfield P, Bance M. Outcomes of Cochlear Implantation in Patients with Post-Meningitis Deafness: A Systematic Review and Narrative Synthesis. J Int Adv Otol. 2020 Dec;16(3):395–410.
9. Svendsen MB, Ring Kofoed I, Nielsen H, Schønheyder HC, Bodilsen J. Neurological sequelae remain frequent after bacterial meningitis in children. Acta Paediatr. 2020 Feb;109(2):361–7.
10. Zainel A, Mitchell H, Sadarangani M. Bacterial meningitis in children: Neurological complications, associated risk factors, and prevention. Microorganisms. 2021;9(3):1–12.
11. Ramakrishnan M, Ulland AJ, Steinhardt LC, Moïsi JC, Were F, Levine OS.

Sequelae due to bacterial meningitis among African children: A systematic literature review. BMC Med. 2009;7:47.

12. World Health Organization. Neisseria meningitidis, Streptococcus pneumoniae, Diagnosis of Meningitis caused by Laboratory Methods for the and Haemophilus influenzae: WHO manual,2nd Edition. World Heal Organ [Internet]. 2011;3. Available from: http://apps.who.int/iris/bitstream/handle/10665/70765/WHO_IVB_11.09_eng.pdf?sequence=1

13. von Gottberg A. Bacterial meningitis in the era of paediatric vaccination against the encapsulated pathogens. Contin Med Educ. 2010;28(6):252.

14. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. Lancet Glob Heal [Internet]. 2018;6(7):e744–57. Available from: http://dx.doi.org/10.1016/S2214-109X(18)30247-X

15. Soeters HM, Diallo AO, Bicaba BW, Kadadé G, Dembélé AY, Acyl MA, et al. Bacterial Meningitis Epidemiology in Five Countries in the Meningitis Belt of Sub-Saharan Africa, 2015-2017. J Infect Dis. 2019 Oct;220(220 Suppl 4):S165–74.

16. Agrawal S, Nadel S. Acute bacterial meningitis in infants and children: Epidemiology and management. Pediatr Drugs [Internet]. 2011;13(6):385–400. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011577682

17. Lukšić I, Mulić R, Falconer R, Orban M, Sidhu S, Rudan I. Estimating global and regional morbidity from acute bacterial meningitis in children: Assessment of the evidence. Croat Med J. 2013;54(6):510–8.

18. Oordt-Speets AM, Bolijn R, Van Hoorn RC, Bhavsar A, Kyaw MH. Global etiology of bacterial meningitis: A systematic review and meta-analysis. PLoS One. 2018;13(6):1–16.

19. Brouwer MC, Tunkel AR, van De Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev. 2010;23(3):467–92.

20. Ku LC, Boggess KA, Vohen-Wolkowiez M. ..Bacterial Meningitis in the Infant-authors copy. Clin Perinatol [Internet]. 2015;42(1):29–45, vii–viii. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4332563/pdf/nihms638514.pdf

21. Lessing MPA, Bowler ICJ. The Value of Cerebrospinal Fluid Enrichment Culture in the Diagnosis of Acute Bacterial Meningitis. Eur J Clin Microbiol Infect Dis. 1996;15(1):79–82.

22. Boyles TH, Bamford C, Bateman K, Blumberg L, Dramowski A, Karstaedt A, et al. Guidelines for the management of acute meningitis in children and adults in South Africa. South African J Epidemiol Infect. 2013;28(1):5–15.

23. Johnson LF, Dorrington RE, Moolla H. Progress towards the 2020 targets for HIV diagnosis and antiretroviral treatment in South Africa. South Afr J HIV Med. 2017;18(1):1–8.

24. Molyneux EM, Tembo M, Kayira K, Bwanaisa L, Mweneychanya J, Njobvu A, et al. The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi. Arch Dis Child. 2003;88(12):1112–8.

25. Wolzak NK, Cooke ML, Orth H, Van Toorn R. The changing profile of pediatric meningitis at a referral centre in Cape Town, South Africa. J Trop Pediatr. 2012;58(6):491–5.

26. Van der Walt, M; Moyo S. The First National TB Prevalence Survey. South Africa. 2018;25.

27. Statistics South Africa (Stats SA). STATISTICAL RELEASE P0302: Mid-Year population estimates 2021 (Embargoed until 19th July 2010 10:00). 2021;(July). Available from: www.statssa.gov.za/?page_id=1854&PPN=P0302&SCH=72983

28. Madhi SA, Madhi A, Petersen K, Khoosal M, Klugman KP. Impact of human immunodeficiency virus type 1 infection on the epidemiology and outcome of

bacterial meningitis in South African children. Int J Infect Dis. 2001;5(3):119–25.

29. Seehusen DA, Eisenhower DD, Medical A. Cerebrospinal fluid analysis. 2014;(October 2003).

30. Brouwer MC, Thwaites GE, Tunkel AR, Van De Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. Lancet [Internet]. 2012;380(9854):1684–92. Available from: http://dx.doi.org/10.1016/S0140-6736(12)61185-4

31. Johnston JW, Apicella MA. Haemophilus Influenzae. Encycl Microbiol. 2009;153–62.

32. von Gottberg A, De Gouveia L, Madhi SA, Du Plessis M, Quan V, Soma K, et al. Impact of conjugate Haemophilus influenzae type b (Hib) vaccine introduction in South Africa. Bull World Health Organ. 2006;84(10):811–8.

33. Madhi SA, Cohen C, von Gottberg A. Introduction of pneumococcal conjugate vaccine into the public immunization program in South Africa: Translating research into policy. Vaccine [Internet]. 2012;30(SUPPL.3):C21–7. Available from: http://dx.doi.org/10.1016/j.vaccine.2012.05.055

34. von Gottberg A, Cohen C, de Gouveia L, Meiring S, Quan V, Whitelaw A, et al. Epidemiology of invasive pneumococcal disease in the pre-conjugate vaccine era: South Africa, 2003-2008. Vaccine. 2013 Aug 28;31(38):4200–8.

35. Quan V, Mccarthy K. Communicable diseases surveillance and outbreak investigation in South Africa 10. 2005;87–98.

36. Meiring S, Hussey G, Jeena P, Parker S, Von Gottberg A. Recommendations for the use of meningococcal vaccines in South Africa. South African J Infect Dis [Internet]. 2017;32(3):82–6. Available from: http://doi.org/10.1080/23120053.2017.1359939

37. L.Baker. Immunization-New Vaccines, Schedules, Catch-Ups and Contra-Indications. South African Med J. 2012;102(11):845–7.

38. Di Mauro A, Cortese F, Laforgia N, Pantaleo B, Giuliani R, Bonifazi D, et al. Neonatal bacterial meningitis: a systematic review of European available data.

Minerva Pediatr. 2019 Apr;71(2):201–8.

39. Ali M, Chang BA, Johnson KW, Morris SK. Incidence and aetiology of bacterial meningitis among children aged 1-59 months in South Asia: systematic review and meta-analysis. Vaccine. 2018 Sep;36(39):5846–57.

40. Dash N, Panigrahi D, Al Khusaiby S, Al Awaidy S, Bawikar S. Acute bacterial meningitis among children under 5 years of age in Oman: a retrospective study during 2000-2005. J Infect Dev Ctries. 2008;2(02).

41. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med. 2011 May;364(21):2016–25.

42. Ouchenir L, Renaud C, Khan S, Bitnun A, Boisvert A-A, McDonald J, et al. The Epidemiology, Management, and Outcomes of Bacterial Meningitis in Infants. Pediatrics. 2017 Jul;140(1).

43. Woll C, Neuman MI, Pruitt CM, Wang ME, Shapiro ED, Shah SS, et al. Epidemiology and Etiology of Invasive Bacterial Infection in Infants ≤60 Days Old Treated in Emergency Departments. J Pediatr. 2018;200:210-217.e1.

44. Dash N, Panigrahi D, Al Khusaiby S, Al Awaidy S, Bawikar S. Acute bacterial meningitis among children < 5 years of age in Oman: a retrospective study during 2000-2005. J Infect Dev Ctries. 2008 Apr;2(2):112–5.

45. Luca V, Gessner BD, Luca C, Turcu T, Rugina S, Rugina C, et al. Incidence and etiological agents of bacterial meningitis among children <5 years of age in two districts of Romania. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol. 2004 Jul;23(7):523–8.

46. Mwenda JM, Soda E, Weldegebriel G, Katsande R, Biey JNM, Traore T, et al. Pediatric Bacterial Meningitis Surveillance in the World Health Organization African Region Using the Invasive Bacterial Vaccine-Preventable Disease Surveillance Network, 2011-2016. Clin Infect Dis. 2019;69(Suppl 2):S49–57.

47. Boni-Cisse C, Jarju S, Bancroft RE, Lepri NA, Kone H, Kofi N, et al. Etiology of Bacterial Meningitis among Children <5 Years Old in Côte d'Ivoire: Findings of Hospital-based Surveillance before and after Pneumococcal Conjugate

Vaccine Introduction. Clin Infect Dis. 2019;69(Suppl 2):S114–20.

48. Haimbodi EL, Mukesi M, Mtambo O, Moyo SR. Frequency of Bacterial Organisms Isolated from Cerebrospinal Fluid (CSF) of Children under Five Years in Windhoek from 2010 to 2014. Open J Med Microbiol. 2016;06(03):125–32.

49. Mwaniki MK, Talbert AW, Njuguna P, English M, Were E, Lowe BS, et al. Clinical indicators of bacterial meningitis among neonates and young infants in rural Kenya. BMC Infect Dis [Internet]. 2011;11(1):301. Available from: http://www.biomedcentral.com/1471-2334/11/301

50. Swann O, Everett DB, Furyk JS, Harrison EM, Msukwa MT, Heyderman RS, et al. Bacterial meningitis in malawian infants <2 months of age: Etiology and susceptibility to World Health Organization first-line antibiotics. Pediatr Infect Dis J. 2014;33(6):560–5.

51. Laving AMR, Musoke RN, Wasunna AO, Revathi G. Neonatal bacterial meningitis at the newborn unit of Kenyatta National Hospital. East Afr Med J. 2003 Sep;80(9):456–62.

52. Coulson GB, Von Gottberg A, Du Plessis M, Smith AM, De Gouveia L, Klugman KP. Meningococcal disease in South Africa, 1999-2002. Emerg Infect Dis. 2007;13(2):273–81.

53. Jansz L, Buys H, Van Dijk M, Rohlwink UK. The profile of meningitis in a tertiary paediatric hospital in South Africa. South African J Child Heal. 2018;12(1):15.

54. Meiring S. Declining Incidence of I nvasive Meningococcal Disease in South Africa. Clin Infect Dis [Internet]. 2018; Available from: https://academic.oup.com/cid/article-abstract/69/3/495/5142640

55. Kleynhans J, Cohen C, McMorrow M, Tempia S, Crowther-Gibson P, Quan V, et al. Can pneumococcal meningitis surveillance be used to assess the impact of pneumococcal conjugate vaccine on total invasive pneumococcal disease? A case-study from South Africa, 2005–2016. Vaccine [Internet]. 2019;37(38):5724–30. Available from:

https://doi.org/10.1016/j.vaccine.2019.04.090

56. Meiring S, Cohen C, Gouveia L De, Plessis M, Kleynhans J, Quan V, et al. Germs - Sa Annual Surveillance Report for Laboratory - Confirmed Invasive Meningococcal , Haemophilus Influenzae and Pneumococcal Disease , South Africa , 2017. 2017;16(2):78–90.

57. Paireau J, Chen A, Broutin H, Grenfell B, Basta NE. Seasonal dynamics of bacterial meningitis: a time-series analysis. Lancet Glob Heal. 2016 Jun;4(6):e370-7.

58. Crellen T, Rao VB, Piening T, Zeydner J, Siddiqui MR. Seasonal upsurge of pneumococcal meningitis in the Central African Republic. Wellcome Open Res. 2018;3(0):134.

59. Snaebjarnardóttir K, Erlendsdóttir H, Reynisson IK, Kristinsson K, Halldórsdóttir S, Hardardóttir H, et al. Bacterial meningitis in children in Iceland, 1975-2010: A nationwide epidemiological study. Scand J Infect Dis. 2013;45(11):819–24.

60. Donald PR, Burger PJ, Becker WB. Paediatric meningitis in the western Cape. A 3-year hospital-based prospective survey. South African Med J. 1986;70(7):391–5.

61. Bradshaw D, Pillay-Van Wyk V, Laubscher R, Nojilana B, Groenewald P, Nannan N, et al. Cause of death statistics for South Africa: Challenges and possibilities for improvement. 2010;(November).

62. Ntuli ST, Malangu N, Alberts M. Causes of Deaths in Children under-Five Years Old at a Tertiary Hospital in Limpopo Province of South Africa. 2013;5(3):95–100.

63. Zaidi AKM, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries. Pediatr Infect Dis J. 2009;28(SUPPL. 1):10–8.

64. Graham BJM. South Africa’s health. Bmj. 1995;311(7010):947.

65. STATS SA [Internet]. Available from: http://www.statssa.gov.za/

66. Britz E, Perovic O, Von Mollendorf C, Von Gottberg A, Iyaloo S, Quan V, et al. The epidemiology of meningitis among adults in a south African province with a high HIV prevalence, 2009-2012. PLoS One [Internet]. 2016;11(9):2009–12. Available from: http://dx.doi.org/10.1371/journal.pone.0163036

67. Wong CH, Duque JR, Wong JSC, Chan C man V, Lam CSI, Fu YM, et al. Epidemiology and Trends of Infective Meningitis in Neonates and Infants Less than 3 Months Old in Hong Kong. Int J Infect Dis [Internet]. 2021;111:288–94. Available from: https://doi.org/10.1016/j.ijid.2021.06.025

68. Chapoutot AG, Dessein R, Guilluy O, Lagrée M, Wallet F, Varon E, et al. Impact of the 13-valent pneumococcal conjugate vaccine on the incidence of pneumococcal meningitis in children. Epidemiol Infect. 2016 Feb;144(3):607–11.

69. Heath PT, Yusoff NKN, Baker CJ. Neonatal meningitis. 2003;(September 2002):173–8.

70. Dramowski A, Whitelaw A, Cotton MF. Burden, spectrum, and impact of healthcare-associated infection at a South African children's hospital. J Hosp Infect [Internet]. 2016;94(4):364–72. Available from: http://dx.doi.org/10.1016/j.jhin.2016.08.022

71. Khan HA, Baig FK, Mehboob R. Nosocomial infections: Epidemiology, prevention, control and surveillance. Asian Pac J Trop Biomed [Internet]. 2017;7(5):478–82. Available from: http://dx.doi.org/10.1016/j.apjtb.2017.01.019

72. Mengistu A, Gaeseb J, Uaaka G, Ndjavera C, Kambyambya K, Indongo L, et al. Antimicrobial sensitivity patterns of cerebrospinal fluid (CSF) isolates in Namibia: implications for empirical antibiotic treatment of meningitis. J Pharm policy Pract. 2013;6:4.

73. Velaphi, S.C. Westercamp M, Moleleki, M. Pondo T, Z. D, N. W, A. von G, N. S, et al. Surveillance for incidence and etiology of early-onset neonatal sepsis in Soweto, South Africa. PLoS One. 2019;14(4):1–18.

74. Peltola H. Burden of Meningitis and Other Severe Bacterial Infections of Children in Africa: Implications for Prevention. Clin Infect Dis. 2002;32(1):6475.

75. Muenchhoff M, Goulder PJR. Sex differences in pediatric infectious diseases. J Infect Dis. 2014;209(SUPPL. 3).

76. S.A S. Stats SA Mid-year population estimates 2017. 2018;(July):1–22.

77. Trotter CL, Greenwood BM. Meningococcal carriage in the African meningitis belt. Lancet Infect Dis. 2007 Dec;7(12):797–803.

78. Dellinger EP. Prevention of Hospital-Acquired Infections. Surg Infect (Larchmt). 2016;17(4):422–6.

79. Doughari HJ, Ndakidemi PA, Human IS, Benade S. The ecology, biology and pathogenesis of acinetobacter spp.: An overview. Microbes Environ. 2011;26(2):101–12.

APPENDIX

Appendix 1: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I, Dr Nkiambi Yannick Kiakuvue (Student number: 2252788) am a studentregistered for the degree of MSc in Epidemiology in the academic year 2019-2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: Date: 22/06/2022

1

Appendix 2: Permission to use data

3 March 2021
The Human Research Ethics Committee (Medical)
3rd Floor, Room 306, Philip Tobias Building
Cnr York Road and 29 Princess of Wales Terrace,
Faculty of Health Sciences, Parktown, Johannesburg

Dear Mr Rhulani Mkansi,

Permission to use data

I am the Principal Investigator (PI) of the Baby GERMS-SA study that aims to improve neonatal and child health. This study aims to develop a deeper understanding of the burden and aetiological factors of neonatal sepsis in urban and rural sub-Saharan Africa through development of a two-tiered surveillance programme.

I grant permission for Nkiambi Yannick Kiakuvue to use the Baby Germs dataset for his Msc in Infectious Disease Epidemiology, supervised by Professor Cheryl Cohen (a co-investigator). Mr Kiakuvue will use the data for a secondary analysis to examine the incidence and aetiology of bacterial meningitis and to compare the characteristics of children aged under 5 years who tested positive for the two most common pathogens related to their infection. He will comply with all ethical considerations including appropriate sharing of his report with the Baby GERMS-SA investigators.

Please contact me should you require any further information about the study or Mr Kiakuvue's proposed analysis.

Your sincerely,

Nelesh Govender, NICD centre head
Neleshg@nicd.ac.za | 011 555 0353

Appendix 3: Wits HREC clearance certificate and data user agreement letters

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Postgraduate Affairs)

TO: Dr NY Kiakuvue and Professor C Cohen
School of Public Health
Division of Epidemiology and Biostatistics
Medical School
University

E-mail: yannkiakuvue@gmail.com

CC: Supervisor: Dr S Mall
<sumaya.mall@gmail.com>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2021/04/26

REF: R14/49

PROTOCOL NO: **M210110** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *The incidence, aetiology and characteristics of bacterial meningitis in young children in South Africa 2014-2018: a 5 year retrospective review*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr NY Kiakuvue and Professor C Cohen

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210110

NAME: (Principal Investigator)	Dr NY Kiakuvue and Professor C Cohen
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*The incidence, aetiology and characteristics of bacterial meningitis in young children in South Africa 2014-2018: a 5 year retrospective review*
DATE CONSIDERED:	2021/01/29
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M190320
SUPERVISOR:	Dr S Mall
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/04/26

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

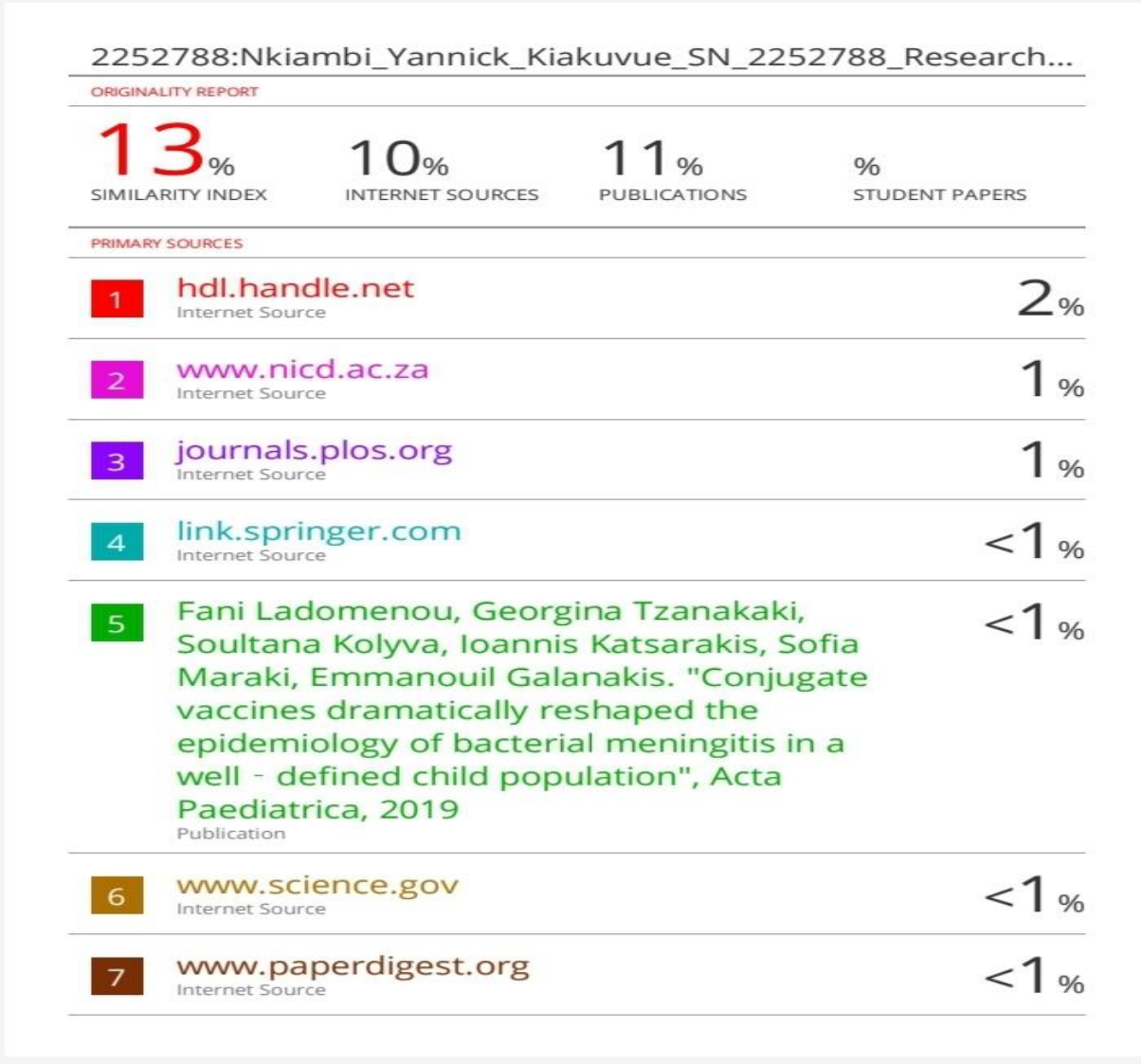
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **January** and therefore reports and re-certification will be due in the month of **January** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

Appendix 4: Turnitin report



2252788:Nkiambi_Yannick_Kiakuvue_SN_2252788_Research...

ORIGINALITY REPORT

13%	10%	11%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	hdl.handle.net Internet Source	2%
2	www.nicd.ac.za Internet Source	1%
3	journals.plos.org Internet Source	1%
4	link.springer.com Internet Source	<1%
5	Fani Ladomenou, Georgina Tzanakaki, Soultana Kolyva, Ioannis Katsarakis, Sofia Maraki, Emmanouil Galanakis. "Conjugate vaccines dramatically reshaped the epidemiology of bacterial meningitis in a well - defined child population", Acta Paediatrica, 2019 Publication	<1%
6	www.science.gov Internet Source	<1%
7	www.paperdigest.org Internet Source	<1%

Sumaya Mall

Dr Sumaya Mall

Appendix 5: list of variables

List of variables.

The following information (variables) about the patients were collected by the National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW):

Age tested in year
Age tested in month
AST results
Date of birth
Date reviewed
Date of specimen collection
Date of testing
Episode number
Facility name
Folder number
Gender
Health district
Health sub-district
Organism name
Organism ID
Province name
Referring lab
Testing lab
Test set name
Unique ID number
Specimen type
Ward name