UNIVERSITY OF THE WITWATERSRAND
FACULITY OF HEALTH SCIENCES
SCHOOL OF PATHOLOGY

# CONTRIBUTION OF VACCINE-PREVENTABLE DISEASES (VPDS) TO THE HOSPITALIZATION IN CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL, JOHANNEBURG, SOUTH AFRICA

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A research report submitted to the faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of the Master of Science in Medicine in the field of Vaccinology

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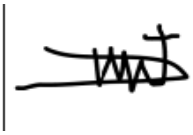
## Declaration

I, Zinabu Temesgen Melsebo, declare that this research report is entirely my own work. It is intended for submission to the University of the Witwatersrand, Johannesburg, South Africa, for the award of Master of Science in medicine degree. It has never been submitted either in part or fully to this or any other university for examination or award of any academic qualification.

Signature..  .....

Research Report for Master of Science in Medicine in the field of Vaccinology

## Dedication

I dedicate this work to my wife, Addisalem and to my parents, Amarech and Temesgen.

# Abstract

**Problem and Purpose**

Despite improvements in global vaccination coverage, the burden of vaccine-preventable diseases (VPDs) remains high and causes annual death of 1.5 million under five years children globally, of these deaths more than 500,000 were from Africa. The purpose of the study was to determine the proportion of hospitalization due to VPDs at Chris Hani Baragwanath Academic Hospital and quantify in-hospital mortality for less than 15 years children hospitalised with a VPD from January 2014 to December 2018. We also determined factors associated with under < 15 years children Vaccine-preventable diseases (VPD)-related hospitalisations at CHBAH.

**Methods**

Children < 15 years of age who were hospitalized in CHBAH starting from January 2014 to December 2018 were included in the study. Paediatric and neonatal patients were retrospectively searched from the hospital discharge summaries database by using the ICD-10 codes for the first, second and third diagnosis. From the discharge summaries the following variables were included: patient date of birth, age, gender, date of admission, date of outcome/discharge, outcome (discharged to home, death, and transfer), primary, secondary and tertiary discharge diagnosis and HIV-infection. The proportion of hospitalization and in-hospital mortality with 95% CI were computed for each of VPDs and pooled outcome variables: EPI-VPDs; if a patient is diagnosed for at least one of the following VPDs; Tetanus, Polio, Diphtheria, TB, Hepatitis B, Hemophilus influenza type (Hib), Pertussis, Pneumococcal and Measles, non-EPI VPDs; if a diagnosis was for at least one of VPDs; Varicella, Rubella, Mumps, Hepatitis A and Meningococcal and overall VPDs; is a sum of the EPI_VPDs and the non-EPI-VPDs, by using the total number of admission as the denominator. Changes in hospitalisation and in-hospital death due to VPDs were assessed by using trend analyses. Logistic regression was used to determine factors associated with the pooled proportion of hospitalization due to VPDs outcome variables.

**Results**

A total of 83,031 under 15 years children were hospitalized and included in the hospital discharge summary database from January 2014 to December 2018, among them, 13,113 have no ICD-10 discharge diagnosis and excluded for further analysis. There were 69,918 paediatric and neonate participants in this study with a median age of 6.44 months, with an interquartile range of 0.46 to 29.34 months over the five years. The majority of the participants (65.7%) were aged 18 months and below. The overall hospitalization due to VPDs were observed in 2,361 (3.38% (95%CI: 3.24-3.51%)) participants. There were 2,147 (3.07%) who had EPI-VPDs. There were 221 (0.32%) had Non-EPI VDPs admissions in this study.

None of the participants had hospitalized due to Tetanus, Polio, and Diphtheria in this study. The most occurring cause of admission for the EPI-VPDs was TB which was observed in 1,936 (2.77% (95%CI: 2.65-2.89%)) participants followed by Pneumococcal disease (n=125; 0.18% (95%CI: 0.15-0.21%)), pertussis (n=69; 0.10% (95%CI: 0.8- 0.12%)), Hib (n=20; 0.03%(95%CI: 0.02- 0.044%)), measles (n=11; 0.02% (95%CI: 0.1-0.3%)) and lastly Hepatitis B (n=5; 0.01% (95%CI: 0.00-0.02%)).

The most occurring cause of admission for the Non-EPI-VPDs was Varicella which was observed in 116 (0.17% (95%CI: 0.14-0.20)) participants followed by Hepatitis A (n=69; 0.10% (95%CI: 0.08-0.12)), Meningococcal and Rubella with equal estimates (n=13; 0.02% (95%CI: 0.01-0.03%)) and lastly Mumps (n=10; 0.01% (95%CI: 0.00-0.02%)

There were 4,111 deaths outcomes (5.88%; 95%CI: 5.71-6.06%) which were observed among the study participants. Of these deaths, 142 (3.45%) were due to VPDs. Out of 2361 patients hospitalised due to VPDs, 142 (6.01%) died; of the 142, 134 were from EPI-VPDs.

There was a gradual increase in the number of patients admitted with non-EPI-VPDs from 2014 to 2016, which then decreased onwards; however, the increase was not statistically significant,

p-value>0.05. The EPI-VPDs increase swiftly from 2014 to 2015 in which it peaked before decreasing in the subsequent years. The overall VPDs which is the sum of EPI and non-EPI followed a similar pattern with the EPI-VPDs, which was predominant in this study. The EPI-VPDs showed a general decrease in the number of in-hospital mortality over time; however, there were significant oscillations in the trend. The Non-EPI-VPDs showed a gradual increase in in-hospital mortality which peaked in 2016 and decreased after that.

The participant's age was associated with high odds of being hospitalized due to EPI-VPDs, non-EPI and overall VPDs. Those who were HIV positive had increased odds to have EPI, non-EPI and overall EPI VPDs when compared to those who were HIV negative.

**Conclusion**

The results show that vaccine-preventable diseases are contributing 3.38% of < 15 years children hospitalization in CHBAH from 2014 to 2018. From admissions due to VPDs, EPI-VPDs share was significant especially hospitalization due to Tuberculosis was the most common cause. From non-EPI-VPDs, the highest proportion was due to varicella, followed by Hepatitis A. Strengthening the national immunization system and reaching eligible children for vaccination is important for the prevention of hospitalization and death of VPDs. The Department of health should start looking for additional evidence for the inclusion of selected non-EPI VPDs in the national EPI system.

## Acknowledgement

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## ABBREVIATIONS

| | |
|---|---|
| BCG | Bacillus Calmette-Guérin |
| CHBAH | Chris Hani Baragwaneth Academic Hospital |
| CRS | Congenital Rubella syndrome |
| DTP | Diphtheria, Tetanus and Pertussis |
| EPI | Expanded Programme on Immunization |
| hep B | Hepatitis B |
| Hib | Haemophilus influenza type b |
| HPV | Human papillomavirus |
| MCV | Measles containing vaccine |
| MMR | Measles, Mumps and Rubella |
| NICD | National Institute of Communicable Diseases |
| NDoH | National Department of Health |
| PCV | Pneumococcal conjugated Vaccine |
| RMPRU | Respiratory and Meningeal Pathogens Research Unit |
| RV | Rota Virus |
| TB | Tuberculosis |
| Td | Tetanus and reduced strength of Diphtheria Vaccine |
| UNICEF | United Nations Children's Fund |
| VPD | Vaccine-preventable diseases |
| VZV | Varicella Zoster virus |
| WHO | World Health Organization |

# 1. CHAPTER ONE: INTRODUCTION

This chapter contains the background and review of the literature for the study.

## 1.1 BACKGROUND

Vaccinations are one of the most efficient and cost-effective public health interventions, resulting in significant reductions in global child morbidity and mortality over the past five decades (1–5). According to the 2018 World Health Organization and United Nations Children's Fund global immunization estimation, coverage rates for the third dose of diphtheria, tetanus and pertussis vaccine (DTP3) reached 86 per cent, up from 72% in 2000 and 20% in 1980 and it is estimated that two to three million child deaths are averted each year due to vaccination(6,7). Despite these improvements in global immunization coverage, the burden of vaccine-preventable diseases (VPDs) remains high and responsible for 1.5 million annual deaths in children under the age of five globally, of these deaths more than 500,000 were from Africa(6,8,9).

In May 1974, the 27th World Health Assembly resolved to build on the success of the smallpox eradication programme and established the Expanded Programme on Immunization (EPI) to ensure that all children, in all countries, benefited from the life-saving vaccines. The continued discovery, research and development of new and improved vaccines has made immunization even more effective in combating major causes of childhood illness and death(10).

Most countries of the world have incorporated an increasingly broad immunization agenda in their public health interventions and expanding the target groups and the number of vaccine-preventable diseases. When countries planning to add vaccines to their EPI system, several factors need to be taken into consideration. These include disease burden; vaccine safety and effectiveness; vaccine cost and impact on the health sector(11,12). The immunisation service expansion does not only focus on the EPI system in public health facilities but also private health facilities are providing

vaccination for vaccine-preventable diseases that are not included in the national immunization system (13–15).

In South Africa, the immunization program has come a long way since it was launched in 1974 when there were only six vaccines in the schedule: diphtheria, pertussis, and tetanus (DPT), measles, polio and Bacillus Calmette-Guérin (BCG) for protection against tuberculosis(16). In 1995 the country introduced the hepatitis B (hep B) vaccine and in 1999 *Haemophilus influenzae type b* (Hib) vaccine. Since 2008, two additional booster doses of Tetanus and a reduced concentration of diphtheria toxoid were recommended at 6 and 12 years of age(17,18). Additionally, in 2009, both the pneumococcal conjugate vaccine (PCV) and rotavirus vaccine (RV) were introduced into the EPI schedule, and more recently, Human Papillomavirus (HPV) vaccine was introduced in 2014 for nine years pre-teenage girls for the prevention of cervical cancer(19–22).

The SA-EPI programme is routinely assessed and surveillance of VPD conducted to assess the efficacy of the EPI programme; in May 2011 PCV 7 valent, which contains seven strains of pneumococcal bacteria was changed to PCV13 by including six additional strains(23,24).

The measles vaccination product and schedule in South Africa has been updated since 01 December 2015. A product called MeasBio® (Biovac) replaces the previous product Rouvax® (Sanofi Pasteur) due to the manufacturer discontinuing the previous product. MeasBio® has been in use in other countries for over 30 year. MeasBio® will be administered at the age of 6 months and 12 months, requiring two additional visits in the Expanded Programme on Immunisation schedule. The reasons for the change in schedule are twofold. Firstly, the manufacturer indicted MeasBio® should be given alone in all vaccination visits because of limited evidences on co-administration. The schedule change allows measles vaccine to be given as the only vaccine at the scheduled visit.

Secondly, it has been recommended to vaccinate against measles as early as 6 months of age to prevent the high morbidity and mortality associated with the disease in young infants. A 6-month dose as part of the routine schedule should prevent serious measles complications in young infants. (24–27).

In 2015, the pentavalent vaccine containing Diphtheria, Pertussis, Tetanus, Haemophilus influenzae type b (Hib) and Hepatitis B was phased out and replaced by the hexavalent vaccines against Diphtheria, Pertussis, Tetanus, Haemophilus influenzae type b (Hib), Hepatitis B and polio) (19,20,28).Currently, in addition to Expanded Programme on Immunization (EPI), private health facilities in South Africa are providing vaccination for vaccine-preventable diseases like; Meningococcal, Rubella, Mumps, Varicella and Hepatitis A are provided in private health facilities as depicted in Table one(20,28,29).

Table 1.1 Comparison of EPI and private vaccination schedules in South Africa(29)

| Vaccines | Target VPD | Age of child | |
|---|---|---|---|
| | | EPI schedule | Private /Non-EPI / schedule |
| BCG (Bacille Calmette Guerin vaccine) | Tuberculosis | At birth | At birth |
| OPV (Oral polio vaccine) | Polio | OPV0 at birth and OPV 1 at 10 weeks | OPV0 at birth and OPV 1 at 10 weeks |
| DTaP-IPV-HB- Hib (Hexavalent) Diphtheria, Tetanus, Acellular Pertussis, Inactivated Polio Vaccine and Haemophilus Influenzae Type B and Hepatitis B Combined | Polio | 6 ,10 ,14 and 18 weeks | 6 ,10 ,14 and 18 weeks |
| | Diphtheria | 6 ,10 ,14 and 18 weeks | 6 ,10 ,14 and 18 weeks |
| | Tetanus | 6 ,10 ,14 and 18 weeks | 6 ,10 ,14 and 18 weeks |
| | Pertussis | 6 ,10 ,14 and 18 weeks | 6 ,10 ,14 and 18 weeks |
| | Hemophilus type b | 6 ,10 ,14 and 18 weeks | 6 ,10 ,14 and 18 weeks |
| | Hepatitis B Virus | 6 ,10 ,14 and 18 weeks | 6 ,10 ,14 and 18 weeks |
| Rotavirus (Rotarix) | Rotavirus | 6 weeks and 14 weeks | 6 weeks and 14 weeks or 6,10 and 14 weeks |
| PCV (pneumococcal conjugate Vaccine) | Streptococcus pneumonia | 6weeks,14 weeks and 9 months | 6weeks,10 weeks, 14 weeks and at 12-15 months |
| MCV (Measles containing vaccine) | Measles | MCV1 at 6month and MCV2 at12-15 months | Not applicable |
| HPV ( human papillomavirus vaccine) | Human papilloma Virus | 9 years | |
| Td vaccine Tetanus and reduced strength of Diphtheria Vaccine | Tetanus and Diphtheria | 6 years and 12 years | 12 years |
| HPV | Human Papilloma Virus | 9 months | 9 months |
| Meningococcal conjugate | Meningococcal | Not applicable | 9 months and 15 months |
| Varicella vaccine | Variceal | Not applicable | 15 month and 6 year |
| Hepatitis A vaccine | Hepatitis A | Not applicable | 12 and 18 months |
| MMR | Rubella | Not applicable | 12 month and six-year |
| | Mumps | Not applicable | 12 month and six-year |
| | Measles | Not applicable | 12 month and six-year |
| Influenza | | Not applicable | |

## 1.2 LITERATURE REVIEW

According to South Africa's National Institute for Communicable Diseases (NICD), the last confirmed case of wild poliovirus was in 1989. The burden of Haemophilus influenza type b (Hib) and diphtheria cases reduced significantly and also, maternal and neonatal tetanus has been eliminated(30,31). Based on the report of South African Diphtheria event-based surveillance, from 1980 to 2014, a total of 412 cases were reported. Three quarters (75%) of cases were under the age of 18 years and not fully immunized for diphtheria(32). National surveillance program in 2017 identified 313 cases of invasive H. influenza (HI) disease and the majority of children <15 years of age with Hib had not been fully vaccinated(33).

Over the years South Africa has had several measles outbreaks: between 2003 and 2005 there were 1,676 cases reported(34), and from 2009 to 2011 there were more than 18,000 laboratory-confirmed measles case-patients reported(35). Recently in 2017, there were 210 measles cases in an outbreak in communities that were unvaccinated or had low vaccination coverage(25). After the introduction of the pneumococcal conjugate vaccine, the incidence of invasive pneumococcal disease reduced by 79% in children younger than five years, from 30 per 100 000 population in 2005 to 6 per 100 000 per population in 2017(32). According to the child health care Problem Identification Programme (Child PIP), Rotavirus vaccine introduction has led to a significant reduction of the incidence of dehydration due to diarrhoea from 2008 to 2009 compared with later years, including a 44% reduction by 2012(36).

According to a retrospective descriptive hospital-based study done on pertussis in Bloemfontein, South Africa, children <18weeks of age were most hospitalized age group. This indicates infants were not yet received the complete primary series of pertussis vaccine(37). Hepatitis B is a VPD and notifiable in South Africa but there is no active national surveillance system for hepatitis B(38).

According to a WHO, Hepatitis A level of endemicity are classified as (39): High endemicity if seroprevalence is 90% by 10 years of age, intermediate if seroprevalence is <90% by 10 years but 50% by 15 years of age, low if seroprevalence is <50% by 15 years but 50% by 30 years of age, and very low if seroprevalence is <50% by 30 years of age. A study done in Sarah Baartman districts, Eastern Cape, South Africa shows, 138 (71%) cases were 16 years old or younger and children from six to 12 years old children were the most affected group(40). Another study was done in Western Cape Province (WCP), South Africa indicated a Hepatitis A seroprevalence up to age 10 years was <90%, this shows intermediate endemicity(41). Meningococcal disease is endemic in South Africa with sporadic cases occurring throughout the year, usually increasing from May to October(42,43). The average incidence in the population over the past decade is 1 per 100 000 people, with a peak of 8 per 100 000 people in infants and approximately 17% of people with meningococcal disease have died, with case fatality ratios increasing with age(44,45). Most of the available data on Varicella-Zoster Virus (VZV) epidemiology are from industrialised countries that cannot be used to guide decisions on the immunization policy against VZV in Africa(46). Studies indicate Varicella can lead to serious complications and prolonged hospitalization of children(47,48).

WHO annual disease review report and research was done in 28 sentinel site of congenital rubella syndrome (CRS) in South Africa reported that 95 laboratory-confirmed CRS cases from 2010 to 2017(49,50). No data exist regarding the epidemiology of mumps infection in South Africa, however, it is known to be a common infection in childhood(51)

## 1.3 PROBLEM STATEMENT

According to the South Africa National Department of Health (NDoH) service report, immunization coverage at the national level was fluctuating for the lasts five years: In 2015 the national immunisation coverage of under 1 year was above 80% and decreased to 78.5% in 2016. In 2017 there was a major drop to 71.2%. In 2018, the immunisation coverage of under 1 year improved to 77.0%, but the coverage was still 10 percentage points below the national target of 87% for 2018 (52,53). Administrative report is based on aggregated administrative reports from health service providers on the number of vaccinations administered during a given period (numerator data) and reported target population data (denominator data). Such data may be biased by inaccurate numerator and/or denominator data.

Additionally, there has been disagreement about how well the schedule has been implemented on the ground and the NDoH has disputed low WHO/UNICEF immunization coverage estimations like MCV2 was 50% but the national department of health report was 82% for the year 2018 (22,52,54–56). Due to suboptimal vaccination coverage, it is likely to cause vaccine-preventable diseases outbreak.

There is conflicting information in South Africa between the nationally reported morbidity related to vaccine-preventable diseases. A comparative study done on three diseases (Measles, Meningococcal meningitis and Typhoid) notification in South Africa indicates, reported cases were significantly lower than cases that were diagnosed in lab and health facilities(57).

Incidence of vaccine preventable diseases depends on direct and indirect protection of vaccination program. Direct protection occurs by lowering the probability of vaccine recipients to become infected. Vaccine efficacy measures these protective effects of vaccination which is different from vaccine to vaccine and child age. Even though the child is fully immunized, not mean that the child is totally protected from VPDs. Indirect protection arises by reducing transmission within the population, thereby lowering the transmission rate for both vaccinated and unvaccinated

individuals this is described as “herd immunity” , it has a particular threshold proportion of immune individuals that should lead to a decline in incidence of Vaccine preventable diseases.

Table 1.2 Herd immunity Threshold for selected VPDs

| **Herd immunity threshold** | | |
|---|---|---|
| **VPDs** | **Reproduction number ($R_0$)** | **Vaccine coverage needed** |
| Diphtheria | 6-7 | 85% |
| Measles | 12-18 | 92-94% |
| Mumps | 4-7 | 75-86% |
| Pertussis (whooping cough) | 12-17 | 92-94% |
| Polio | 2-15 | 50-93 |
| Rubella | 6-7 | 83-85% |
| Smallpox | 5-7 | 80-85% |

Hospital admissions and mortality represent the most serious disease presentation and people who have access to the hospital and it is an indirect reflection of problems with access to effective primary health care. Avoiding hospital admission is important in decreasing the burden of managing severe cases and as well as enhancing patients' quality of life (58–60). Moreover, severe morbidity that leads to hospitalization due to vaccine-preventable diseases is avoidable if all children were properly vaccinated. Evaluation of VPD hospitalisations provides an estimate of preventable mortality and resources that could be reallocated where needed Thus, hospitalizations due to VPDs should be evaluated. This study aims to determine the proportion of hospitalization due to VPDs and mortality thereof at Chris Hani Baragwanath Academic Hospital (CHBAH) for 5 years (January 2014 and December 2018).

## 1.4 JUSTIFICATION

Many VPDs can be prevented by the administration of vaccines currently included in the EPI or by providing licenced vaccines at private health facilities. Hospitalisation and death are very important events, which can be used to determine the incidence of severe disease caused by VPDs. These results can be used to evaluate the EPI program (for diseases already included in EPI), and to prioritise the development or introduction of vaccines not included in EPI yet. Understanding the number of hospitalisations that are due to VPDs, through studies, will allow us to identify the specific burden of Vaccine-preventable disease and to organize health services and controlling mechanism in response to the studied group

## 1.5 Study aim and Objectives

### 1.5.1 Aim

This study aims to determine the proportion of hospitalization due to VPDs at Chris Hani Baragwanath Academic Hospital and quantify in-hospital mortality for less than 15 years children hospitalised with a VPD from January 2014 to December 2018. We also determined factors associated with under < 15 years children Vaccine-preventable diseases (VPD)-related hospitalisations at CHBAH.

### 1.5.2 Objectives

1. To determine the proportion of hospitalization due to VPD at Chris Hani Baragwanath Academic Hospital between January 2014 and December 2018

2. To determine the proportion of in-hospital mortality due to VPD Chris Hani Baragwanath Academic Hospital between January 2014 and December 2018

3. To analyse changes in VPD hospitalisation and mortality at Chris Hani Baragwanath Academic Hospital

4. To determine factors associated with VPD hospitalisation at CHBAH

# 2. CHAPTER TWO: METHODS

## 2.1 Study design

A retrospective analytic study using hospital discharge summaries at CHBAH from January 2014 to December 2018

## 2.2 Study area

This study was conducted at Chris Hani Baragwanath Academic Hospital which is the largest hospital in the southern hemisphere. It is a public hospital in the South African township of Soweto, which is a low-income area of the city of Johannesburg, in Gauteng province. Paediatric department of the hospital provide a service for < 15 years children and the department has ambulatory Paediatric service, Inpatient service, Paediatric Haematology and Oncology and neonatal unit with total of 408 paediatric beds (61). Vaccine and Infectious Diseases Analytics Research Unit (VIDA) is based in the Chris Hani Baragwanath Academic Hospital. The unit undertakes epidemiological, translational and laboratory research in the prevention of major infectious diseases causing death in young children. There is existing surveillance or data collection system in the RMPRU from paediatric and neonatal discharge summaries of CHBA hospital.

## 2.3 Study population

Children aged less than 15 years hospitalised at CHBAH from January 2014 to December 2018 were included in the study.

## 2.4 Inclusion /Exclusion criteria

All Children < 15 year of age admitted to CHBAH between January 2014 and December 2018 and diagnosis and lab-confirmed as due to a VPD and non-Vaccine preventable as per ICD-10 were included.

## 2.5 Key definitions of variables

**Vaccine-preventable diseases;** are a type of diseases that have a vaccine for prevention and there is an existing licensed vaccine in the Republic of South Africa. The following 14 diseases are considered as vaccine-preventable in this study; Tuberculosis, Polio, Hepatitis B, Diphtheria Pertussis, Tetanus, Haemophilus influenzae type b (Hib), Pneumococcal, Measles, Meningococcal, Rubella, Mumps, Varicella and Hepatitis A

**Pooled VPDs; Is a** composite of having been admitted for at least one of the VPDS namely; Tuberculosis, Polio, Hepatitis B, Diphtheria Pertussis, Tetanus, Haemophilus influenzae type b (Hib), Pneumococcal, Measles, Meningococcal, Rubella, Mumps, Varicella and Hepatitis A

**EPI Vaccine-preventable diseases;** Vaccine-preventable diseases which are included in the South African national Expanded Program on Immunization. Expected to be provided free of charge in public health facilities. Nine VPDs (Tuberculosis, Polio, Hepatitis B, Diphtheria Pertussis, Tetanus, Haemophilus influenzae type b (Hib), Pneumococcal, Measles) are included in the national immunization system.

**Non-EPI vaccine-preventable diseases;** VPDs which are not included in the national immunization system and their vaccination program is only in the private health facilities. The following VPDs are included in this study; Meningococcal, Rubella, Mumps, Varicella and Hepatitis A.

**Hospitalization due to EPI VPDs;** patients considered to be hospitalized due to EPI-VPDs if they had admissions due to at least one of the following VPDs and their ICD codes; Tuberculosis (A15, A15.0, A17, A17.0, A18, A18.0, A18.1, A18.2, A18.3, A18.4, A18.5, A19, P37.0, U50.0 and U50.2), Polio ( A80.30), Hepatitis B ( B16), Diphtheria (A36), Pertussis (A37, A37.0 and A37.1), Tetanus (A 33, A34 and A35), Haemophilus influenzae type b (G00.0, J14, A41.3), Pneumococcal (J13, G00.1, A40.3) and Measles (B05, B05.0, B05.1, B05.2).

**In-Hospital mortality due to EPI VPDs**; Patients outcome considered to be in-hospital death due to EPI-VPDs if they had admitted and died in the hospital with the diagnosis of at least one of the following VPDs and their ICD codes; Tuberculosis (A15, A15.0, A17, A17.0, A18, A18.0, A18.1, A18.2, A18.3, A18.4, A18.5, A19, P37.0, U50.0 and U50.2), Polio ( A80.30), Hepatitis B ( B16), Diphtheria (A36), Pertussis (A37, A37.0 and A37.1), Tetanus (A 33, A34 and A35), Haemophilus influenzae type b (G00.0, J14, A41.3), Pneumococcal (J13, G00.1, A40.3) and Measles (B05, B05.0, B05.1, B05.2)

**Hospitalization due to non-EPI- VPDs;** patients considered to be hospitalized due to non-EPI-VPDs if they had admissions due to at least one of the following VPDs and their ICD coding; Meningococcal (A39.0), Rubella (B06, P35.0), Mumps (B26, B26.2, B26.3), Varicella (B01, B01.0, B01.1, B01.2, B02) and Hepatitis A (B15)

**In-hospital mortality due to non –EPI VPDs;** Patients outcome considered to be in-hospital death due to non-EPI-VPDs if they had admitted and died in the hospital with the diagnosis of at least one of the following VPDs and their ICD codes; Meningococcal (A39.0), Rubella (B06, P35.0), Mumps (B26, B26.2, B26.3), Varicella (B01, B01.0, B01.1, B01.2, B02) and Hepatitis A (B15)

## 2.6 Data collection and management

Paediatric and neonatal discharge summaries from the hospital (Annex B) were used to identify patients admitted with the diagnosis of vaccine-preventable diseases from January 1$^{st}$, 2014 to December 31, 2018. The database relies on the international classification of diseases 10$^{th}$ revision (ICD-10) that is currently used in the hospital. All patients that have ICD code were included in the study. We have searched for EPI and non-EPI vaccine-preventable diseases in the paediatric and neonatal discharge summary by using the ICD-10 codes depicted in Annex C.

For each of the VPDs, a variable contains the "Yes/No" option was created and coded based on their ICD codes. And also additional combined outcome variables like; EPI-VPDs, non-EPI VPDs and overall VPDs were created.EPI -VPDs were coded as "Yes" if a patient is diagnosed for at least one of the following VPDs; Tetanus, Polio, Diphtheria, TB, Hepatitis B, Hemophilus influenza type (Hib), Pertussis, Pneumococcal and Measles. Non-EPI-VPDs were coded as "Yes" if a diagnosis was for at least one of VPDs; Varicella, Rubella, Mumps, Hepatitis A and Meningococcal. The overall VPDs, which is a sum of the EPI_VPDs and the non-EPI-VPDs was created to show overall hospitalization and death due to VPD.

From vaccine-preventable diseases, we excluded the rotavirus, Human papillomavirus and Influenza. The reason for exclusion was HPV is not a common disease among children and rota and Influenza were not properly diagnosed and classified in the source database. Eligible paediatric and neonatal patients were retrospectively searched from the hospital discharge summaries database using the ICD-10 codes **(Annex C)** for the first, second and third diagnosis. From the discharge summaries the following variables were included: patient date of birth, age, gender, date of admission, date of outcome/discharge, Outcome (discharged to home, death, transfer), primary, secondary and tertiary discharge Diagnosis and HIV-infection (Annex C). Also, duration of hospital stay and Age (month and year) created as a composite variable.

## 2.7 Data Analysis

### Descriptive analysis

Statistical analysis was performed by using Stata 14 (StataCorp, CollegeStation, TX). Descriptive statistics were summarized by using absolute frequencies for the baseline demographic characteristics.

**Objective 1 data analysis**

The proportion of the combined outcome variables; hospitalisation due to EPI-VPD, Non-EPI-VPD and Overall VPDs were computed with 95% CI by using a total number of admissions as the denominator. In addition to combined outcome variables, the proportion of hospitalization due to each of the 14 VPDs was calculated with 95% CI by using total admissions as the denominator.

Chi-square test was used to assess the association between the outcome variables; hospitalization due to each of 14 VPDs, combined EPI-VPDs, combined non-EPI VPDS and combined overall VPDs and independent variables such as age, gender, HIV status and length of hospital stay.

**Objective two data analysis**

For the outcome variables; death due to each of 14 VPDs, EPI-VPDs and non-EPI VPDs proportions were calculated with their 95% CI by using the number of patients hospitalized due to their specific diagnosis as the denominator. To compute the outcome variable, the proportion of death due to overall VPDs, all death numbers were used as the denominator.

**Objective three trend analysis**

Annual Changes in hospitalisation and death were assessed by using trend analyses and 95 % CI for trends were computed. Outcome variables included for trend analyses were;

a. The proportion of hospitalisation due to combined EPI-VPDs
b) The proportion of hospitalization due to combined non-EPI-VPDs
c) The proportion of hospitalization due to overall VPDs
d) The proportion of hospitalisations resulting in death due to EPI-VPDs
e) The proportion of hospitalization resulting in death due to non-EPI VPDs
f) The proportion of hospitalization resulting in death due to overall VPDs

**Objective four**

Logistic regression was used to determine factors associated with the combined proportion of hospitalization due to VPDs outcome variables. Univariate and adjusted models were used to assess the association between independent variables such as age, gender, HIV status and length of hospital stay and outcome combined variables; hospitalization due to EPI-VPDs, non-EPI-VPDs and overall VPDS.

## 2.8 Ethical Considerations

The study received ethical clearance from the Faculty of Health Sciences Human Research Ethics Committee (HREC) of the University of Witwatersrand (Ethical Clearance number: (Appendix F) and permission letter also obtained from CHBAH( Appendix E). As a means of maintaining confidentiality, the data for the study was password-protected and was only be available to the two supervisors and the Investigator.

# 3. CHAPTER THREE: RESULTS

## 3.1 Baseline characteristics of paediatric and neonatal admissions

There were 69,918 paediatric and neonate participants in this study with a median age of 6.44 months, with an interquartile range of 0.46 to 29.34 months. Majority of the participants (65.7%) were aged 18 months and below. There were 33.75% (n=23 588) participants aged between 28 days and 18 months while those aged above 5 years were the least with a proportion of 13.03% (n=9 110) as shown in Table 3.1. Majority of the participants were males (47.68%, n=33,336).

Table 3.1: Study participants demographic description

| **Variable name** | **Category** | **Frequency (Percentage)** |
|---|---|---|
| Age | Neonates | 22 332 (31.94%) |
| | 28 days ≤18 months | 23 588 (33.74%) |
| | 19 months ≤ 60 months | 14 888 (21.29%) |
| | Above 5 years | 9 110 (13.03%) |
| Gender | Male | 33 336 (47.68%) |
| | Female | 24 756 (35.41%) |
| | Missing | 11 826 (16.91%) |
| HIV status | Positive | 1 561 (2.23%) |
| | Negative | 12 501 (17.88%) |
| | Unknown | 55 856 (79.89%) |
| Hospital length of stay (days) | Median time<br>IQR | 3 days<br>1 to 7 days |

A total of 1,561 (2.23%) of the study participants were HIV positive cases; however, approximately 80% had an unknown HIV status in this study. The days of hospital stay after admission ranged from 0 days to 739 days, of which approximately 95% of the participants stayed in the hospital for at most one month. The median hospital stay was 3 days with an interquartile range of 1 to 7 days in this study.

### 3.2 The proportion of hospitalisation due to combined EPI-VPD, Non-EPI-VPD and Overall VPDs at Chris Hani Baragwanath Academic Hospital

The EPI-VPDs outcome was a composite of having been admitted for at least one of the VPDS namely Tetanus, Polio, Diphtheria, TB, Hepatitis B, Hemophilus influenza type (Hib), Pertussis, Pneumococcal and Measles. However, none of the participants had Tetanus, Polio, and Diphtheria in this study, Table 3.2. There were 2,147 (3.07%) had EPI-VPDs (at least one of the conditions specified) in this study of which 19 (0.88%) of them had coinfections (at most two VPDs). All these coinfections were mainly TB-Pneumococcal coinfections which accounted for 63% (n=12) of the total coinfections observed. A pictorial view of these coinfections is shown in Figure 3.1 below.

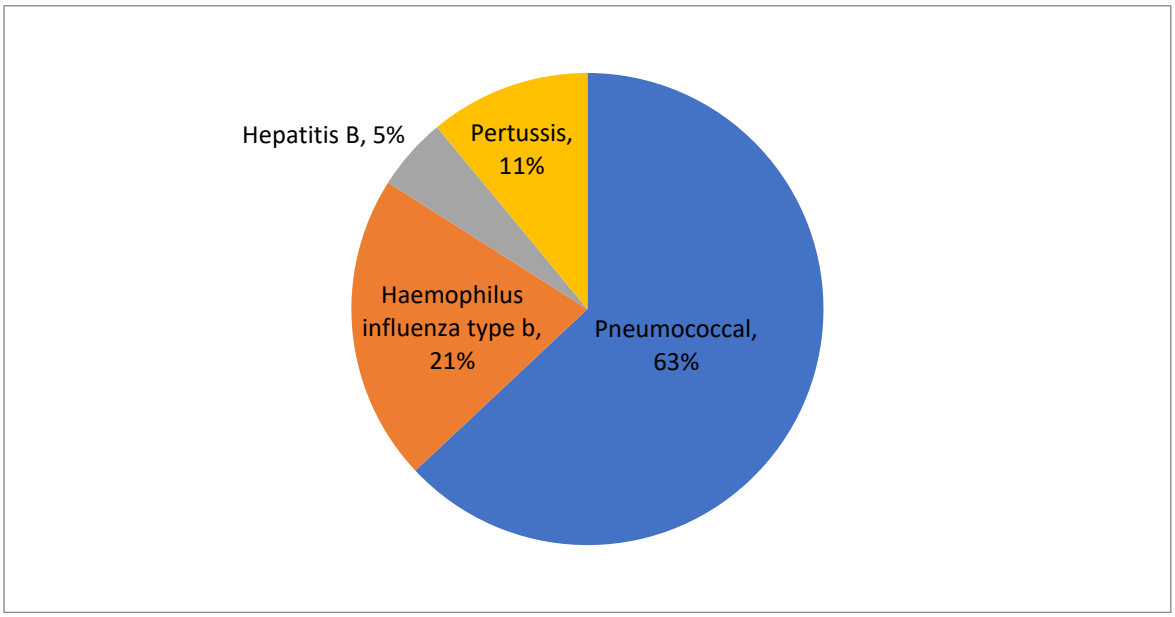


Figure 3.1: The TB-coinfection conditions for the EPI VPDs

The Non-EPI-VPDs were considered to be Varicella, Rubella, Mumps, Hepatitis A and Meningococcal, Table3.2. There were 221 (0.32%) had Non-EPI VDPs admissions in this study, and none of these was a coinfection. The overall VPDs, which is a sum of the EPI_VPDs and the non-EPI-VPDs were observed in 2,361 (3.38% (95%CI: 3.24-3.51%)) participants, Table 3.2.

All the three outcome proportions were significantly different between age, gender and HIV status as shown by the significant Chi-square P-values below 5%. The median hospital length of stay for the group defined by the three outcomes was also significantly different, $p<0.005$. Among the neonates' group, 0.11% (n=24), of them had non-EPI-VPDs which were predominant with among those aged 28 days to 18 months, 19 months to 60 months and above 5 years had EPI-VPDs predominantly, that is, n=1 188(5.04%), n=549(3.69%) and n=395 (4.34%) respectively. The 28 days to 18 months and the above 5 years age groups had the highest proportion of the overall VDPs of 5.29% and 5.06% respectively. Among the males and female participants, the EPI-VPDs were predominant at approximately 4% each. However, the overall VDPs proportion was higher in the female stratum. Among the HIV positive group, those who had EPI-VPDs were 31.07% (n=485) which also contributed to the highest overall VDPs proportion in the HIV status strata. The hospital length of stay was highest among those with EPI-VPDs (7 (IQR: 4-13) days) as compared to those with non-VPDs (5 (2-8) days) in this study.

Table 3.2: The proportion of hospitalisation due to combined EPI-VPD, Non-EPI-VPD and Overall VPD,s at Chris Hani Baragwanath Academic Hospital

| Variable | Categories | EPI-VPDs (No) n (Row %) | EPI-VPDs (Yes) n (Row %) | Non-EPI-VPDs (No) n(Row %) | Non-EPI-VPDs (Yes) n(Row %) | Overall VPD (No) n(Row %) | Overall VPD (Yes) n(Row %) | Row Totals |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | Neonates | 22 317 (99.93) | 15 (0.07) | 22 308 (99.89) | 24 (0.11) | 22 293 (99.83) | 39(0.18) | 22 332 |
| | 28 days ≤18 months | 22 400 (94.96) | 1 188(5.04) | 23 528 (99.75) | 60(0.25) | 22 341 (94.71) | 1 247(5.29) | 23 588 |
| | 19 months ≤ 60 months | 14 339 (96.31) | 549(3.69) | 14 819 (99.54) | 69(0.46) | 14 274 (95.88) | 614(4.12) | 14 888 |
| | Above 5 years | 8 715 (95.66) | 395 (4.34) | 9 042 (99.25) | 68(0.75) | 8 649 (94.94) | 461(5.06) | 9 110 |
| | Chi2 P-value | **<0.001** | | **<0.001** | | **<0.001** | | |
| **Gender** | Male | 32 148 (96.44) | 1,188 (3.56) | 33 222 (99.66) | 114(0.34) | 32 038 (96.11) | 1,298(3.89) | 33 336 |
| | Female | 23 799 (96.13) | 957(3.87) | 24 656 (99.6) | 100(0.40) | 23 702 (95.74) | 1,054(4.26) | 24 756 |
| | Unknown | 11 824 (99.98) | 2(0.02) | 11 819 (99.94) | 7(0.06) | 11 817 (99.92) | 9(0.08) | 11 826 |
| | Chi2 P-value | **<0.001** | | **<0.001** | | **<0.001** | | |
| **HIV status** | Positive | 1 076 (68.93) | 485(31.07) | 1 545 (98.98) | 16(1.02) | 1062 (68.03) | 499(31.97) | 1 561 |
| | Negative | 12 045 (96.35) | 456(3.65) | 12 475 (99.79) | 26(0.21) | 12 019 (96.14) | 482(3.86) | 12 501 |
| | Unknown | 54 650 (97.84) | 1,206(2.16) | 55 677 (99.68) | 179(0.32) | 54 476 (97.53) | 1,380(2.47) | 55 856 |
| | Chi2 P-vale | **<0.001** | | **<0.001** | | **<0.001** | | |
| **Hospital length of stay (days)** | Median (IQR) | 3 (1-7) | 7(4-13) | 3 (1-7) | 5(2-8) | 3 (1-7) | 7(4-12) | 3 (1-7) |
| | Mann-Whitney P-value | **<0.001** | | **<0.001** | | **<0.001** | | |
| **Total cases**<br>**Total proportion (n)**<br>**Proportion 95%CI** | | | n=2,147<br>3.07<br>(2.94-3.20) | | n=221<br>0.32<br>(0.28-0.36) | | n=2,361<br>3.38<br>(3.24-3.51) | |

### 3.3 The proportion of hospitalisation due to EPI-VPD at Chris Hani Baragwanath Academic Hospital between January 2014 and December 2018

The EPI-VPDs were considered to be Tetanus, Polio, Diphtheria, TB, Hepatitis B, Hemophilus influenza type (Hib), Pertussis, Pneumococcal and Measles. However, none of the participants had Tetanus, Polio, and Diphtheria in this study. The summary of the remaining EPI-VPDs are shown in Table 3.3 and 3.4 stratified by age in months, HIV status and gender to determine any association between these variables and the EPI-VPDs. The median differences between the lengths of hospital stay were also determined for each EPI-VPD outcome assessed.

In descending order, the most occurring cause of admission for the EPI-VPDs was TB which was observed in 1,936 (2.77% (95%CI: 2.65-2.89%)) participants followed by Pneumococcal (n=125; 0.18% (95%CI: 0.15-0.21%)), pertussis (n=69; 0.10% (95%CI: 0.8- 0.12%)), Hib (n=20; 0.03%(95%CI: 0.02- 0.044%)), measles (n=11; 0.02% (95%CI: 0.1-0.3%)) and lastly Hepatitis B (n=5; 0.01% (95%CI: 0.00-0.02%)).Age categories proportions were significantly different for the TB outcome. The TB outcome was predominant among those aged between 28 days and 18 months, 4.38% (n=1032), among the females, n=864 (3.49%) and the HIV positive group (n=464; 29.72%), Table 3.3. The Hepatitis B and Hib outcomes were nearly negligible among all baseline strata considered. The pertussis outcome was predominant in those age 28 days and 18 months, n=66, 0.28%, among females (n=32(0.13%)) and the HIV negative group, n=28(0.22%), Table 3. 4.The Pneumococcal and measles outcomes were nearly negligible among all the baseline categories considered. The median hospital stay was significantly different between TB, Hib, Pertussis, Hepatitis B and Pneumococcal groups, p-value<0.005, with those reported to have Hib outcome staying longest compared to the rest of the other EPI-VPDs outcomes, 11( IQR 3.5-16) days.

Table 3.3: The proportion of hospitalisation due to EPI-VPD at Chris Hani Baragwanath Academic Hospital

| Variable | Categories | TB (No) n (Row%) | TB (Yes) n (Row%) | Hepatitis B (No) n(Row%) | Hepatitis B (Yes) n(Row%) | Hib (No) n(Row%) | Hib (Yes) n(Row%) | Row Total |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | Neonates | 22 342 (99.96) | 8(0.04) | 22 332 (100) | 0 | 22 332 (100.0) | 0 | 22 332 |
| | 28 days ≤18 months | 22 556(95.62) | 1 032 (4.38) | 23 586 (99.99) | 2 (0.01) | 23 575 (99.94) | 13 (0.06) | 23 588 |
| | 19 months ≤ 60 months | 14 363 (96.47) | 525 (3.53) | 14 886 (99.99) | 2 (0.01) | 14 886 (99.99) | 2 (0.01) | 14 888 |
| | Above 5 years | 8 739 (95.93) | 1 936(2.77) | 9 109 (99.99) | 1 (0.01) | 9 105 (99.95) | 5(0.05) | 9 110 |
| | Chi2 (Fisher exact) P-value | **<0.001** | | **(**0.497**)** | | **0.001** | | |
| **Gender** | Male | 32 266 (96.79) | 1,070 (3.21) | 33 335 (100.0) | 1 (0.00) | 33 325 (99.97) | 11 (0.03) | 33 336 |
| | Female | 23 892 (96.51) | 864 (3.49) | 24 752 (99.98) | 4(0.02) | 24 747 (99.96) | 9(0.04) | 24 756 |
| | Unknown | 11 824 (99.98) | 2(0.02) | 11 826 (100.0) | 0(0.00) | 11 826 (100.0) | 0(0.00) | 11 826 |
| | Chi2 (Fisher exact) P-value | **<0.001** | | (0.162) | | 0.127 | | |
| **HIV status** | Positive | 1 097 (70.28) | 464 (29.72) | 1 561 (100.0) | 0(0.00) | 1 555 (99.62) | 6(0.38) | 1 561 |
| | Negative | 12 111(96.88) | 390 (3.12) | 12 501 (100.0) | 0(0.00) | 12 497 (99.97) | 4(0.03) | 12 501 |
| | Unknown | 54 774 (98.06) | 1,082(1.94) | 55 851 (99.99) | 5(0.01) | 55 846 (99.98) | 10(0.02) | 55 856 |
| | Chi2 (Fisher exact) P-value | **<0.001** | | (0.636) | | **<0.001** | | |
| **Hospital length of stay (days)** | Median (IQR) | 3 (1-7) | 7(4-12) | 3 (1-7) | 8(4-28) | 3 (1-7) | 11(3.5-16) | 3 (1-7) |
| | Mann-Whitney P-value | **<0.001** | | **0.0409** | | **0.0032** | | |
| **Total cases** | | | n=1,936 | | n=5 | | n=20 | |
| **Total proportion (n)** | | | 2.77 | | 0.01 | | 0.03 | |
| **Proportion 95%CI** | | | ( 2.65-2.89) | | ( 0.00-0.02) | | (0.02- 0.044) | |

*Reported row percentages, column values are only for those who had the VPD outcome, IQR=inter-quartile range, boldfaced values significant at 5%

Table 3.4: The proportion of hospitalization due to EPI-VPD at Chris Hani Baragwanath Academic Hospital

| Variable | Categories | Pertussis (No) n(%) | Pertussis (Yes) n(%) | Pneumo (No) n(%) | Pneumo (Yes) n(%) | Measles (No) n(%) | Measles (Yes) n(%) | Row Total n(%) |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | Neonates | 22 329 (99.99) | 3(0.01) | 22 328 (99.98) | 4(0.02) | 22 332 (100.0) | 1(0.00) | 22 332 |
| | 28 days ≤18 months | 23 522 (99.72) | 66(0.28) | 23 510 (99.67) | 78(0.33) | 23 583 (99.98) | 5(0.02) | 23 588 |
| | 19 months ≤ 60 months | 14 888 (100) | 0(0.00) | 14 864 (99.84) | 24(0.16) | 14 886 (99.99) | 2(0.01) | 14 888 |
| | Above 5 years | 9 110 (100.0) | 0(0.00) | 9 091 (99.79) | 19(0.21) | 9 106 (99.96) | 4(0.04) | 9 110 |
| | Chi2 (Fisher exact) P-value | **<0.001** | | (0.815) | | **0.002** | | |
| **Gender** | Male | 33 299 (99.89) | 37(0.11) | 33 262 (99.78) | 74(0.22) | 33 332 (99.99) | 4(0.01) | 33 336 |
| | Female | 24 724 (99.87) | 32(0.13) | 24 705 (99.79) | 51(0.21) | 24 749 (99.97) | 7(0.03) | 24 756 |
| | Unknown | 11 826 (100.0) | 0(0.00) | 11 826 (100.0) | 0(0.00) | 11 826 100.0) | 0(0.00) | 11 826 |
| | Chi2 (Fisher exact) P-value | **0.001** | | **<0.001** | | (0.116) | | |
| **HIV status** | Positive | 1 559 (99.87) | 2(0.13) | 1 538 (98.53) | 23(1.47) | 1 561 (100.0) | 0(0.00) | 1 561 |
| | Negative | 12 473 (99.78) | 28(0.22) | 12 466 (99.72) | 35(0.28) | 12 499 (99.98) | 2(0.02) | 12 501 |
| | Unknown | 55 817 (99.93) | 39(0.07) | 55 789 (99.88) | 67(0.12) | 55 847 (99.98) | 9(0.02) | 55 856 |
| | Chi2 (Fisher exact) P-value | **<0.001** | | **<0.001** | | (1.000) | | |
| **Hospital length of stay (days)** | Median (IQR) | 3 (1-7) | 8(5-16) | 3 (1-7) | 7(3-15) | 3 (1-7) | 2(1-6) | 3 (1-7) |
| | Mann-Whitney P-value | **<0.001** | | **<0.001** | | 0.4836 | | |
| **Total cases**<br>**Total proportion (n)**<br>**Proportion 95%CI** | | | n=69<br>0.10<br>( 0.8- 0.12) | | n=125<br>0.18<br>(0.15-0.21) | | n=11<br>0.02<br>(0.1-0.3) | |

### 3.4 The proportion of hospitalisation due to non- EPI-VPD at Chris Hani Baragwanath Academic Hospital between January 2014 and December 2018

The Non-EPI-VPDs were considered to be Varicella, Rubella, Mumps, Hepatitis A and Meningococcal those summary results are shown in Table 5 and 6. In descending order, the most occurring cause of admission for the Non-EPI-VPDs was Varicella which was observed in 116 (0.17% (95%CI: 0.14-0.20)) participants followed by Hepatitis A (n=69; 0.10% (95%CI: 0.08-0.12)), Meningococcal and Rubella with equal estimates (n=13; 0.02% (95%CI: 0.01-0.03%)) and lastly Mumps (n=10; 0.01% (95%CI: 0.00-0.02%).

Among those aged above 5 years, the proportion with Varicella was 0.32%, n=29. For the other non-EPI VPDs, the occurrence of the outcomes was negligible across all the baseline strata considered. Those who had Rubella stayed for a longer time in hospital followed by those who had Meningococcal condition, (9 (IQR 6-21) days and (8 (6-11) days) respectively.

Table 3.5: The proportion of hospitalisation due to Non-EPI-VPD at Chris Hani Baragwanath Academic Hospital

| Variable | Categories | Varicella (No) n (%) | Varicella (Yes) n (%) | Rubella (No) n(%) | Rubella (Yes) n(%) | Mumps (No) n(%) | Mumps (Yes) n(%) | Row totals n(%) |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | Neonates | 22 316 (99.93) | 16 (0.07) | 22 324 (99.96) | 8(0.04) | 22 332 (100.0) | 0(0.00) | 22 332 |
| | 28 days ≤18 months | 23 542 (99.80) | 46 (0.2) | 23 583 (99.98) | 5(0.02) | 23 587 (100.0) | 1(0.00) | 23 588 |
| | 19 months ≤ 60 months | 14 863 (99.83) | 25(0.17) | 14 888 (100.0) | 0(0.00) | 14 883 (99.97) | 5(0.03) | 14 888 |
| | Above 5 years | 9 081 (99.68) | 29(0.32) | 9 110 (100.0) | 0(0.00) | 9 106 (99.96) | 4(0.04) | 9 110 |
| | Chi2 (Fisher exact) P-value | **0.002** | | (0.407) | | **(0.003)** | | |
| **Gender** | Male | 33 272 (99.81) | 64 (0.19) | 33 334 (99.99) | 2(0.01) | 33 331(99.99) | 5(0.01) | 33 336 |
| | Female | 24 704 (99.79) | 52(0.21) | 24 752 (99.98) | 4(0.02) | 24 751 (99.99) | 5(0.02) | 24 756 |
| | Unknown | 11 826 (100.0) | 0(0.00) | 11 819 (99.94) | 7(0.06) | 11 826 (100.0) | 0(0.00) | 11 826 |
| | Chi2 (Fisher exact) P-value | **<0.001** | | **(0.003)** | | (0.333) | | |
| **HIV status** | Positive | 1 547 (99.10) | 14 (0.90) | 1 560 (99.94) | 1(0.06) | 1 561 (100.0) | 0(0.00) | 1 561 |
| | Negative | 12 486 (99.88) | 15(0.12) | 12 500 (99.99) | 1(0.01) | 12 500 (99.99) | 1(0.01) | 12 501 |
| | Unknown | 55 769 (99.84) | 87(0.16) | 55 845 (99.98) | 11(0.02) | 55 847 (99.98) | 9(0.02) | 55 856 |
| | Chi2(Fisher exact ) P-value | **<0.001** | | (0.243) | | (0.761) | | |
| **Hospital length of stay (days)** | Median (IQR) | 3 (1-7) | 5(2-7.5) | 3 (1-7) | 9(6-21) | 3 (1-7) | 2(1-5) | 3 (1-7) |
| | Mann-Whitney P-value | **0.0008** | | **0.0006** | | 0.4812 | | |
| **Total cases** | | | 116 | | 13 | | 10 | |
| **Total proportion (n)** | | | 0.17 | | 0.02 | | 0.01 | |
| **Proportion 95%CI** | | | (0.14-0.20) | | (0.01-0.03) | | (0.00-0.02) | |

*Reported row percentages, column values are only for those who had the VPD outcome, IQR=inter-quartile range, boldfaced values significant at 5%

Table 3.6: The proportion of hospitalisation due to Non-EPI-VPD at Chris Hani Baragwanath Academic Hospital

| Variable | Categories | HEPA (No) n(%) | HEPA (Yes) n(%) | Meningo (No) n(%) | Meningo (Yes) n(%) | Row total n(%) |
|---|---|---|---|---|---|---|
| **Age (years)** | Neonates | 22 332 (100.0) | 0(0.00) | 22 332 (100.0) | 0(0.02) | 22 332 |
| | 28 days ≤18 months | 23 587 (100.0) | 1(0.00) | 23 581 (99.97) | 7(0.03) | 23 588 |
| | 19 months ≤ 60 months | 14 853 (99.76) | 35(0.24) | 14 884 (99.97) | 4(0.03) | 14 888 |
| | Above 5 years | 9 077 (99.64) | 33(0.36) | 9 108 (99.98) | 2(0.02) | 9 110 |
| | Chi2 (Fisher exact) P-value | **<0.001** | | (0.677) | | |
| **Gender** | Male | 33 301 (99.9) | 35 (0.10) | 33 328 (99.98) | 8(0.02) | 33 336 |
| | Female | 24 722 (99.86) | 34(0.14) | 24 751 (99.98) | 5(0.02) | 24 756 |
| | Unknown | 11 826 (100.0) | 0(0.00) | 11 826 (100.0) | 0(0.00) | 11 826 |
| | Chi2 (Fisher exact) P-value | **<0.001** | | (0.252) | | |
| **HIV status** | Positive | 1 560 (99.94) | 1(0.06) | 1 561 (100.0) | 0(0.00) | 1 561 |
| | Negative | 12 494 (99.94) | 7(0.06) | 12 499 (99.98) | 2(0.02) | 12 501 |
| | Unknown | 55 795 (99.89) | 61(0.10) | 55 845 (99.98) | 11(0.02) | 55 856 |
| | Chi2 (Fisher exact) P-value | (0.209) | | (0.830) | | |
| **Hospital length of stay (days)** | Median (IQR) | 3 (1-7) | 4(2-7) | 3 (1-7) | 8(6-11) | 3 (1-7) |
| | Mann-Whitney P-value | 0.090 | | **0.0019** | | |
| **Total cases** | | | 69 | | 13 | |
| **Total proportion (n)** | | | 0.10 | | 0.02 | |
| **Proportion 95%CI** | | | (0.08-0.12) | | (0.01-0.03) | |

*Reported row percentages, column values are only for those who had the VPD outcome, IQR=inter-quartile range, boldfaced values significant at 5%

### 3.5 The proportion of death due to VPDs at Chris Hani Baragwanath Academic Hospital between January 2014 and December 2018

The survival outcomes of participants with VPDs were assessed. The results of the death outcomes are summarised in Table 3.7. There were 4,111 deaths outcomes (5.88%; 95%CI: 5.71-6.06%) which were observed among the study participants. Of these deaths, 142 (3.45%) were due to VPDs. Out of 2361 patients hospitalised due to VPDs, 142 (6.01%) died; of the 142, 134 were from EPI-VPDs.

Table 3.7: The proportion of death due to VPD at Chris Hani Baragwanath Academic Hospital between January 2014 and December 2018 with reference to the positive VPDs and overall participant outcome at the end of follow-up.

| **VPD name** | **Sample size considered (Positive VPD)** | **Absolute frequency dead** | **Proportion dead (95%CI)** |
|---|---|---|---|
| TB | 1,936 | 81 | 4.18 (3.33-5.17) |
| HepB | 5 | 0 | 0 |
| Pertussis | 69 | 2 | 2.90(0.4-10.08) |
| Hib | 20 | 5 | 25.00 (8.66-49.10 |
| Pneumo | 125 | 46 | 36.80(28.35-45.89 |
| Measles | 11 | 0 | 0 |
| **EPI-VPDs** | **2,147** | **134** | **6.24(5.26-7.35)** |
| Meningo | 13 | 1 | 7.69(0.19-36.03 |
| Varicella | 116 | 1 | 0.86(0.00-4.71) |
| Rubella | 12 | 3 | 23.08 (5.04-53.81) |
| Mumps | 10 | 0 | 0 |
| HepA | 69 | 3 | 4.35 (0.91-12.12) |
| **Non-EPI VPD** | **221** | **8** | **3.62 (1.58-7.01)** |
| **Overall VPD** | **2,361** | **142** | **6.01(5.09-7.05)** |
| **Overall study Outcome** | | | |
| Discharged | 69,918 | 64,538 | 92.31 (92.11-92.51) |
| Referred | | 1,269 | 1.81 (1.72-1.92) |
| Died | | 4,111 | 5.88 (5.71-6.06) |

### 3.6 The annual changes in VPD hospitalisation and death at Chris Hani Baragwanath Academic Hospital over 5 years

The annual trends of the VPDs summaries are shown in Table 3.8, and the corresponding graphical presentations are displayed in Figure 3.2 and 3.3 for both the VPD hospitalisation and VPDs-related deaths outcomes.

Table 3.8: The annual changes in VPD hospitalisation and death at Chris Hani Baragwanath Academic Hospital over 5 years

| **Year** | **VDP type** | **Admissions Proportions(95%CI)** | **Deaths Proportions(95%CI)** |
|---|---|---|---|
| 2014 | EPI_VPDS | 3.84(3.51-4.51) | 0.31(0.22-0.43) |
| | Non_EPI VPDS | 0.31 (0.21-0.47) | 0 |
| | Overall VPDs | 4.12(3.77-4.48) | 0.31(0.22-0.43) |
| 2015 | EPI_VPDS | 4.18 (3.85-4.52) | 0.20(0.13-0.28) |
| | Non_EPI VPDS | 0.36(0.26-0.47) | 0.007(0.0002-0.04) |
| | Overall VPDs | 4.53(4.18-4.89) | 0.20(0.13-0.29) |
| 2016 | EPI_VPDS | 3.14(2.86-3.44) | 0.18(0.11-0.26) |
| | Non_EPI VPDS | 0.40(0.31-0.52) | 0.04(0.01-0.08) |
| | Overall VPDs | 3.54(3.23-3.86) | 0.21(0.14-0.31) |
| 2017 | EPI_VPDS | 2.33(2.09-2.59) | 0.12(0.07-0.20) |
| | Non_EPI VPDS | 0.22(0.15-0.31) | 0.007(0.0002-0.04) |
| | Overall VPDs | 2.55(2.30-2.81) | 0.13(0.08-0.21) |
| 2018 | EPI_VPDS | 2.07(1.85-2.31) | 0.17(0.11-0.24) |
| | Non_EPI VPDS | 0.29(0.22-0.40) | 0.007(0.0002-0.04) |
| | Overall VPDs | 2.36(2.12-2.61) | 0.17(0.11-0.25) |

With regards to Figure 3.2, there was a gradual increase in the number of patients admitted with non-EPI-VPDs from 2014 to 2016, which then decreased onwards; however, the increase was not statistically significant at 5%, p-value>0.05. The EPI-VPDs increase swiftly from 2014 to 2015 in which it peaked before decreasing in the subsequent years. The overall VPDs followed a similar pattern with the EPI-VPDs, which was predominant in this study.

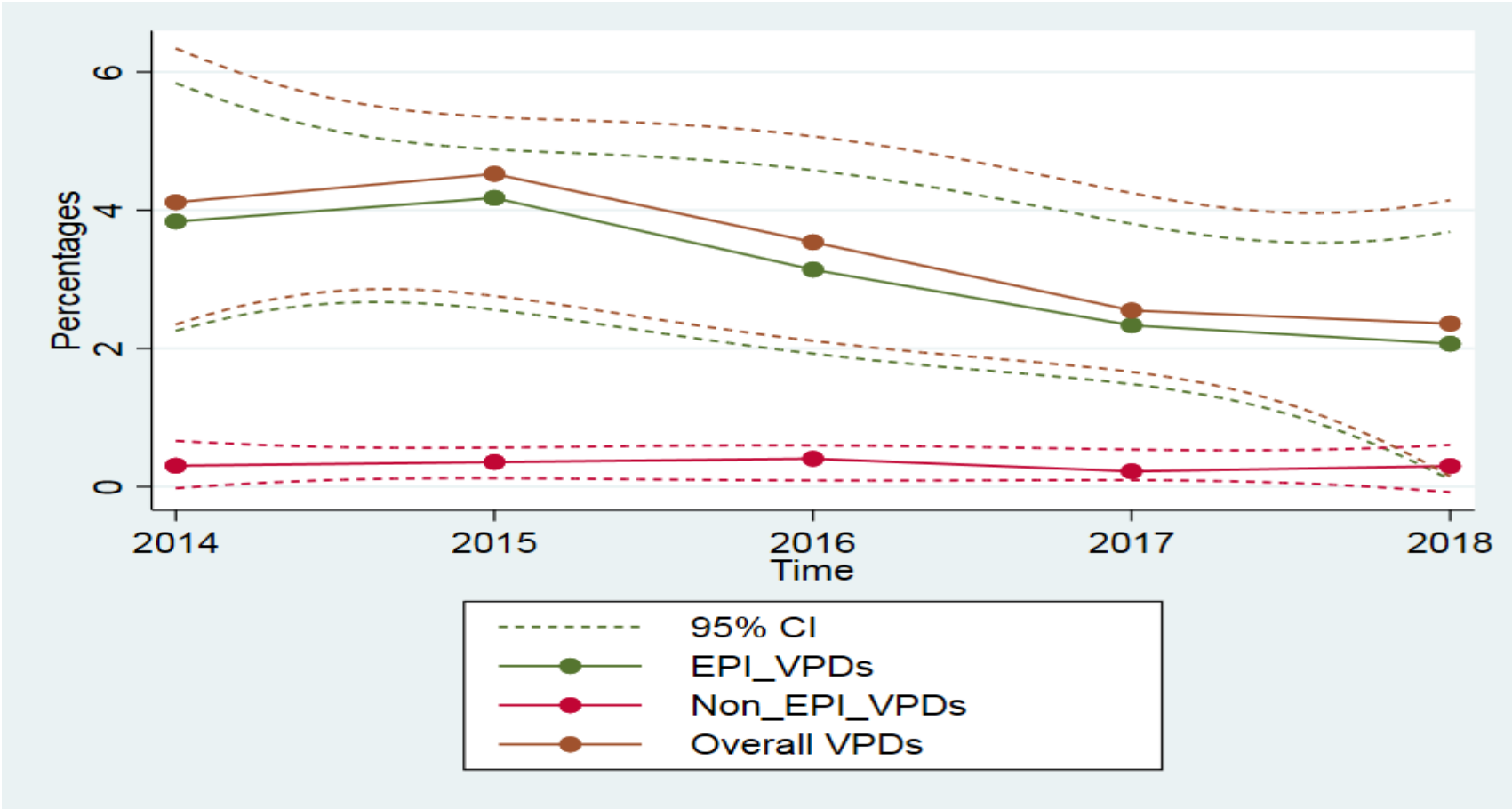


Figure 3.2: The annual admission trend of the VPDs as percentages based on admissions for the observed values, fitted values and the corresponding 95% confidence interval.

The annual deaths trends for the three main outcomes are shown in Figure 3.3 below. The EPI-VPDs showed a general decrease in the number of deaths over time; however, there were significant oscillations in the trend. The Non-EPI-VPDs showed a gradual increase in death which peaked in 2016 and decreased after that.

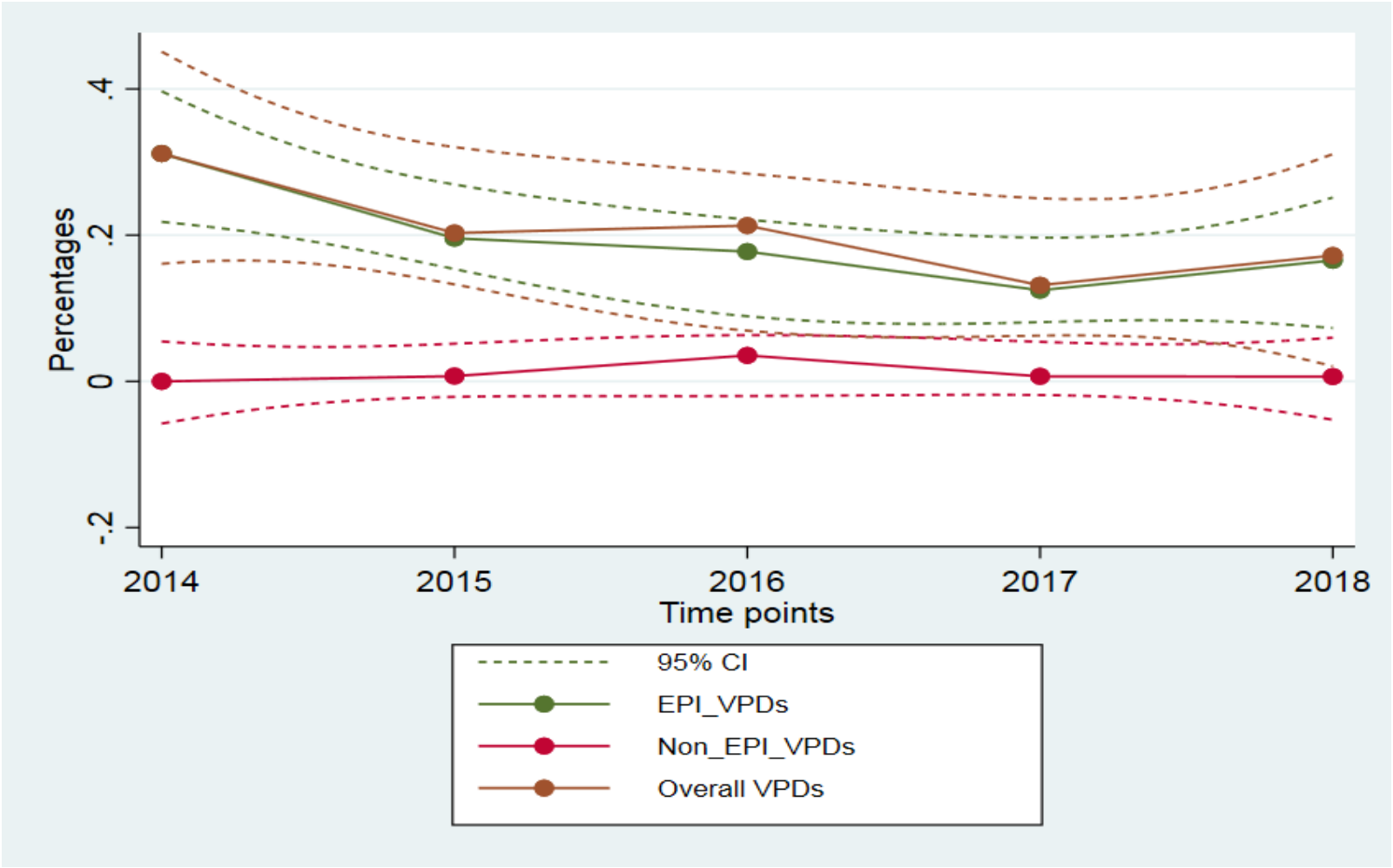


Figure 3.3: Annual death trend of VPD related outcomes as percentages for the observed values, fitted values and the corresponding 95% confidence interval.

### 3.7 Factors associated with VPD hospitalisation

This study assessed for the factors associated with composite EPI-VPDs, non-EPI-VPDs and overall VPDS outcomes. Univariate and adjusted models were assessed, as shown in Table 3.9. In the adjusted models, gender was not associated with any of the VPD outcomes, while the total hospital stays were not slightly associated with increased odds; however, the odds contribution was negligible. The participant's age was strongly associated with high odds of being diagnosed with EPI-VPDs. With reference to the neonates' age group and adjusting for other factors, participants aged 28 days to 18 months, 19 months to 60 months and above 5 years had odds of 61.17 (95%CI: 36.72-101.9), OR=53.05(31.73-88.69) and OR=58.31(34.75-97.85) times more likely to have EPI-VPDs respectively. Those who were HIV positive had an increased odd of 8.59 (95%CI: 7.43-9.94) times to have EPI-VPDs compared to those who were HIV negative adjusting for other factors.

Table 3.9: Factors associated with VPD hospitalisation at CHBAH

| **Variable** | **Categories** | **EPI-VPDs OR (95%CI) [p-value]** | | **Non-EPI-EPDs OR (95%CI) [p-value]** | | **Overall VPD OR (95%CI) [p-value]** | |
|---|---|---|---|---|---|---|---|
| | | Univariate | Adjusted | Univariate | Adjusted | Univariate | Adjusted |
| **Age category** | Neonates | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | 28 days ≤18 months | 78.91 (47.41-131.35) [<0.001] | 61.17(36.72-101.9) **[<0.001]** | 2.37(1.48-3.81) [<0.001] | 2.278(1.415-3.664) [0.001] | 31.91(23.19-43.91) [<0.001] | 25.12(18.24-34.61) **[<0.001]** |
| | 19 months ≤ 60 months | 56.96(34.09-95.18) [<0.001] | 53.05(31.73-88.69) **[<0.001]** | 4.327(2.719-6.889) [<0.001] | 4.152(2.605-6.616) **[<0.001**] | 24.59(17.78-34.01) [<0.001] | 23.01(16.62-31.85) **[<0.001]** |
| | Above 5 years | 67.43(40.24-112.99) [<0.001] | 58.31(34.75-97.85) **[<0.001]** | 6.99(4.386-11.14) [<0.001] | 6.488(4.057-10.384) **[<0.001**] | 30.47(21.95-42.29 [<0.001] | 26.67(19.18-37.09) **[<0.001]** |
| **Age (months)** | | 1.006(1.005-1.007) [0.123] | -------- | 1.011(1.001-1.013) [<0.001] | | 1.080(1.068-1.092) [<0.001] | -------- |
| **Gender** | Male | 1 (reference) | -------- | 1 (reference) | -------- | 1 (reference) | -------- |
| | Female | 1.09(0.998-1.187) [0.056] | -------- | 1.182(0.903-1.547) [0.223] | -------- | 1.097(1.011-1.193) [0.028] | -------- |
| | Unknown | 0.005(0.001-0.018) [<0.001] | -------- | 0.173(0.080-0.371) [<0.001] | -------- | 0.019(0.009-0.036) [<0.001] | -------- |
| **HIV status** | Negative | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| | Positive | 11.91(10.33-13.73) [<0.001] | 8.59(7.43-9.94) **[<0.001]** | 4.969(2.659-9.283) [<0.001] | 3.359(1.787-6.314) **[<0.001]** | 11.716(10.186-13.477) [<0.001] | 8.41(7.28-9.69) **[<0.001]** |
| | Unknown | 0.583(0.522-0.661) [<0.001] | 0.584(0.521-0.653) **[<0.001]** | 1.543(1.022-2.329) [<0.001] | 1.23(0.812-1.876) **[0.325]** | 0.632(0.568-0.702) [<0.001] | 0.024(0.012-0.047) **[<0.001]** |
| **Hospital length of stay (days)** | | 1.009(1.007-1.010) [<0.001] | 1.005(1.004-1.007) **[<0.001]** | 0.998(0.988-1.008) [0.696] | -------- | 1.008(1.006-1.009) [<0.001] | 1.005(1.003-1.007) **[<0.001]** |

The participant's age was strongly associated with high odds of being diagnosed with non-EPI-VPDs. With reference to the neonates' age group and adjusting for other factors, participants aged 28 days to 18 months, 19 months to 60 months and above 5 years had odds of 2.37 (95%CI: 1.48-3.81), OR=4.32(2.72-6.89) and OR=6.99(4.39-11.14) times more likely to have non-EPI-VPDs. Those who were HIV positive had an increased odds of 3.36 (95%CI: 1.79-6.31) times to have non-EPI-VPDs compared to those who were HIV negative adjusting for other factors.

The overall VPDs outcome was also associated with age and HIV status in this study after adjusting for other factors. With reference to the neonates' age group and adjusting for other factors, participants aged 28 days to 18 months, 19 months to 60 months and above 5 years had odds of 25.12 (95%CI: 18.24-34.61), OR=23.01 (16.62-31.85) and OR=26.67 (19.18-37.09) times more likely to have overall VPDs. Those who were HIV positive had an increased odds of 8.41 (95%CI: 7.28-9.69) times to have overall VPDs compared to those who were HIV negative adjusting for other factors.

# 4. CHAPTER FOUR: DISCUSSION

Vaccines are the most effective public health intervention that protect human being against infectious diseases. Thanks to immunization, the morbidity and mortality of many diseases have significantly decreased at the global level (62,63). However, if an optimal level of immunization coverage is not maintained, diseases that have been temporarily eliminated may reappear because infectious agents continue to circulate worldwide. For this context, it is important to quantify vaccination effects on VPDs to inform the community about the advantages of vaccination, to improve coverage and to take additional public health interventions. Even though there are different assumptions and criteria are required to include VPDs to EPI or routine immunization, the outcome of hospitalization and death due to non- EPI VPDs will give additional information on the burden of non-EPI VPDs. Therefore, we reconstructed the 5 years proportion and trend of 14 VPDs at CHBAH in South Africa.

The trend of overall vaccine-preventable diseases was decreasing in the subsequent years except for increases swiftly from 2014 to 2015 in which it peaked before decreasing. This is possible maybe because of vaccination coverage reduction in 2014/2015, due to a shortage of EPI vaccines locally and BCG shortage globally(64) and redaction of factors like HIV infections. The proportion of hospitalization due to VPDs over five years period was (3.4%) (2361/69,918), the proportion of VPDs among neonates is 0.5 %( 123/27,000) and 5% (2238/42913) were children age between one month and 15 years. This preventable amount of admissions was observed in a single hospital in a specified period.

## 4.1 EPI Vaccine-preventable diseases hospitalization and outcome

The EPI-VPDs were considered to be Tetanus, Polio, Diphtheria, TB, Hepatitis B, Hemophilus influenza type (Hib), Pertussis, Pneumococcal and Measles expected to be provided for free in public health facilities of South Africa (29). From the overall 2,361 VPDs, EPI-VPDs account 3.07% (2,147/69,918) of < 15 years child hospitalization. From admitted 123 neonates due to VPDs, 65% are due to EPI-VPDs. This finding shows there was a large number of children were hospitalized due to EPI-Vaccine preventable diseases when

compared with the same age group study done in Latvia children's clinical university hospital from 2005 to 2016 which is only 201 EPI-VPD cases were observed(65).

From admitted 2,147 EPI-VPDs, 6.24% (134/2147) were discharged with death outcome. The proportion of hospital mortality due to EPI-VPDs was 12% (10/80) and 6% (124/2067) among neonates and post neonate period respectively. The trend of EPI-VPDs shows a general decrease in the number of deaths over time; however, there were significant fluctuations in the trend. The death outcome indicates the health service gaps both in immunization coverage and case management after hospitalization.

No cases of tetanus, polio and diphtheria were observed in the study period at CHBAH, this is a consistent finding with WHO- VPDs monitoring database and South African NICD disease surveillance reports(30,31,50).

Tuberculosis was the most common causes of admissions from other vaccine-preventable diseases in the hospital which is 2.8% (1,936/69,918 ). From all type of TB cases Miliary tuberculosis and TB of nervous system accounts 11% (219/1,936) and 5% (99/1936) respectively. Age was significantly associated with tuberculosis admissions, in which less than 4 years children are the most hospitalized age group. This is possible may be due to BCG vaccine efficacy which does not prevent all type of Tuberculosis(66). According to WHO estimation South African BCG coverage dropped from 93 % in 2014 to 75 % in 2018 estimation, so low coverage also will be the possible reason for the high proportion of hospitalization due to all type tuberculosis infection among < 4 years children(50), this is also consistent with the study that show the impact of global shortages of BCG vaccine on tuberculous meningitis in children (67). In addition to the age of patients, gender and HIV status were also significantly associated with Tuberculosis hospitalization. This is consistent with findings that show TB infections are common among immunocompromised patients specifically due to HIV(68,69). From children (one month to 15 years) admitted with the diagnosis of TB 4.15% (79/1902) have died, 34

neonates admitted with TB diagnosis and 5.9% have died. These show TB is not only caused severe diseases among < 15 years children but also contribute a significant amount to hospital death. Relatively the death amount was low when compared with a hospital-based study done in a large tertiary hospital in Nigeria; from admitted children with TB diagnosis 28 % of children were died(70)

The proportion of hospitalization due to Pneumococcal infection was 0.18% (125/69,918), which is the largest hospitalization from EPI-VPDs next to TB. The result does not show a variation with other studies done in South Africa(32). Of 125 admitted children due to pneumococcal infection 46 of them were died in the hospital, this is the largest proportion of death when compared with other VPDs (46/125) 36.80 %, out of 46 deaths, 65% were due Pneumococcal meningitis. This large proportion of death may due to poor case management. Among known more than 90 serotypes, PCV13 contains the following serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F that not classified in the source document.

The proportion of hospitalization due to diagnosis of pertussis was 0.10% (69/69,918). All independent variables (age, gender, HIV status and hospital stay) were significantly associated with the proportion of hospitalization. All hospitalized children were < 1 year old and the median age is two months. This finding is consistent with the study done in Bloemfontein; South Africa infants were also the most affected group. The same study indicated those most of under 1 year hospitalized children due to pertussis were not vaccinated(37). According to this study the median age is 2 months, which is not covered by primary vaccination schedule, due to this fact South African government should think about additional strategies like maternal immunization.

Hospitalization due Hemophilus influenza type b (Hib) were only 0.03% (20/69,918) ,consistent with other studies and reports(31,32). HIV status and gender were significantly associated with hospitalization due to Hib. From patients admitted due to Hib 25% (5/20) of them were died at CHBAH from 2014 to 2018, most of

Hib deaths are due to septicaemia 80% (4/5). According to the South Africa NICD 2017 public health surveillance bulletin, half ( 54%) of reported Hib cases were not vaccinated(30).

The proportion of hospitalization due to measles was 0.02% (11/69,918). Age was significantly associated with measles admission in the hospital, 55% (6/11) of them were between 2 to 4 years. There was no death observed due to measles infection during the five years study period . The measles vaccine is less effective in infants less than one year old, the South African age shift for the first dose form nine months to six month might affect the efficacy of vaccine. But in this study, hospitalization due to Measles infection among infants is low 9% (1/11) , this may be due to limitations like using hospitalization data and lack of all important factors. It is known that most measles-related deaths are caused by complications associated with the disease, which indicates Bara hospital was good in preventing complications and death(71).

According to the South African NICD report from 2012 to 2016 annual confirmed measles cases were very low, only 17 cases were reported in 2016. the same report shows an increased number of confirmed cases, which was 186 in 2017, out of these 96 cases were from Gauteng. At the same time, evidence shows most of the reported were not vaccinated. And also there was a 15% difference in the national MCV2 2018 coverage estimate among the government and UNICEF/WHO. All this evidence shows the need for intensive work on measles coverage to reach a herd immunity threshold that is 95%(25,50).

The proportion of hospitalization due to Hepatitis B 0.01% (5/69,918) The only hospital stay was significantly associated with hospitalization due to HBV which is the median day of hospital stay was 8 with an IQR of 4 to 28 days. No death was observed due to Hepatis's B infections during the study period. Research is showing the prevalence of HBV is decreasing in South Africa starting from the introduction of vaccine(72,73). Hepatitis B is a vaccine-preventable disease and is notifiable in South Africa. There is no active national surveillance for hepatitis B to fully understand the burden of disease(74).

### 4.2 Non-EPI Vaccine-preventable diseases hospitalization and outcome

In South Africa, non-EPI-VPDs were considered to be Varicella, Rubella, Mumps, Hepatitis A and Meningococcal which are expected to be provided in the private health facilities(29). From overall VPDs

2,361 (3.38%), non- EPI VPDs accounts 221 (0.32%) . this shows the contribution of non- EPI VPDs was low when compared with EPI-VPDs. From children hospitalized due to non-EPI VPDs 3% were discharged with death outcome, this also lower than EPI-VPDs. There was a gradual increase in the number of patients admitted with non-EPI-VPDs from 2014 to 2016 which then decreased onwards. The Non-EPI-VPDs death showed a gradual increase in which peaked in 2016 and decreased thereafter. The hospitalization and death due to the non-EPI-VPDs trend indicate there was a gradual change. This evidence is not enough to include non- EPI VPDs to EPI, so further diseases surveillance is required.

The most occurring cause of admission for the Non-EPI-VPDs was Varicella-zoster virus (VZV) which was observed in 116 (0.17% ). Age was significantly associated with varicella hospitalization. Children under 4 years were highly affected especially infants were the most hospitalized age group due to varicella. Based on the proportion of hospitalization, VZV infection was the third largest cause of hospitalization next to Tuberculosis and pneumococcal but in terms of death, its share was lower than other EPI-VPDs. The finding is consistent with other reported literature(47,48,75). South Africa is providing VZV vaccine in private health facilities and the status of coverage is not well known. Research mostly done in high income developed countries reported that the introduction of the vaccine to their national EPI system decreased hospitalization and complications due to VZV(75–77). Additional assessments of the epidemiological and economic impact of immunisation against varicella are required before recommending to include with national EPI system.

Hepatitis A contribute for 0.10%(69/69,918) < 15 years children hospitalization. Age was significantly associated with hospitalization due to Hepatitis A, specifically the age ranges from year 2 to 9 were highly affected. This showed that young children who are exposed to the virus usually have no symptoms of the disease and consistent with other reported studies(39)(75). In this study from 69 admitted children due to Hepatitis A, 4.35% have died. Older children often experience several weeks of hospitalizations and are at risk of acute liver failure and death. Because of the nature of a disease recommending vaccine only to prevent mortality and morbidity is not advisable(78,79). WHO recommends vaccination against HAV be integrated into the national immunization schedule for children aged ≥1 year if indicated based on the incidence of acute

hepatitis A, change in the endemicity from high to intermediate, and consideration of cost-effectiveness(39,80). South Africa is providing HAV vaccine in private health facilities. The government should collect and review the information needed to estimate their national burden of hepatitis A before including the national EPI system.

Meningococcal infection causes only 0.02% of hospitalization (n=13/69,918). One patient death was observed from admitted 13 children with the diagnosis of meningococcal infection. The result showed a small proportion of death when compared with other literature which is up to 17% of cases have died even with access to the best medical care (44,81). This may be indicating that CHBAH was providing timely and proper case management for admitted meningococcal cases. Length of hospital stay was significantly associated with hospitalization due to meningococcal. The median days of hospital stay were 8 days with an IQR of 6 to 11 days. Infants are the most affected groups 54% (7/13) which consistent with the NICD report(44,82). Meningococcal disease is a category 1 notifiable medical condition (NMC) in South Africa, surveillance has been ongoing since 2003 through the GERMS-SA surveillance programme of the National Institute for Communicable Diseases. Under-notification after laboratory confirmation is the key factor in South Africa and other countries particularly in Africa incomplete or lacking surveillance data makes it difficult to estimate reliable global burden(43,81).This study not included detail serogroups of meningococcal that is one of limitation of the study. So that we can't say all 13 cases of meningococcal were vaccine-preventable since there is no vaccine for some of the serogroups. Although the vaccine is recommended for certain high-risk groups, the meningococcal vaccine is not part of South Africa EPI system(29).

Rubella causes 0.02% of hospitalization in CHAH from 2014 to 2018. Length of hospital stay was significantly associated with hospitalization due to rubella. The median days of hospital stay were 9 days with an IQR of 6 to 21 days. Among admitted children with rubella diagnosis, 23 % (3/13) were discharged with death outcome. WHO annual review and research have done in 28 sentinel site of congenital rubella syndrome in South Africa reported that 95 laboratory-confirmed CRS cases from 2010 to 2017(49,50), when we compared with our finding, that was 13 CRS cases in one hospital (CHBAH) with a shorter period

indicates Bara hospital share from national CRS was not small. In 2015, South Africa a sentinel site surveillance programme was set up to establish baseline data on the burden of CRS in South Africa. The omission of rubella vaccine from EPI was based on the understanding that natural rubella infection in childhood should render most women of childbearing age immune and therefore prevent CRS. Besides, under conditions of imperfect vaccine coverage, the addition of a rubella-containing vaccine (RCV) could increase the susceptibility of adult women by slowing, but not interrupting, rubella transmission. For this reason, the introduction of an RCV into the EPI should be carefully considered(25,83).

Mumps contribution to child hospitalization was the lowest one from non-EPI VPDs which is 0.01% (10/69,918). No death was observed due to mumps infection and the median of hospital stay was also lower than other VPDs. Private health facilities are providing a combination of live attenuated (weakened) measles, mumps and rubella viruses vaccine. It is not part of the Expanded Program for Immunization (EPI) for South Africa(29). No data exist regarding the epidemiology of mumps infection in South Africa, however, it is known to be a common infection of childhood(50,51).

### 4.3 Factors affecting VPD hospitalization

The overall VPDs outcome was also associated with age and HIV status in this study after adjusting for other factors. As the age increased, the risk of having a VPD increased as well; hence, a dose-response pattern was observed. This result shows further analysis and checking the participant immunization status is required. But we can assume the reason behind this association may be poor immunization coverage and waning immunity. HIV positive were 9 folds more likely to have overall VPDs compared to those who were HIV negative (OR=9.297(95%CI: 0.052-10.735)).

### 4.4 Limitations of the study

Secondary data analyses have inherent limitations in that the variables collected are already pre-determined and might exclude some required information, for example in the discharge summaries used, the following desired variables were missing; vaccination status of the child and mother, another underlying disease status. So, Utilizing the Hospital discharge summary and a retrospective study

design limit the degree of analysis that can be performed. Specific research questions, such as risk factors for Hospitalization due to VPDs only be addressed very crudely (HIV status, age, hospital stay and gender ) and detail that may be of interest, such as Vaccination status, were not available on this dataset. The change in disease diagnostic mechanisms, laboratory procedures and ICD-code occurred over 5 years that may cause a random error and leads to wrong disease classifications. study. Even though the available BCG vaccine is not protecting all type of Tuberculosis infections, we included all types of Tuberculosis cases in the study, due to the challenging nature of Tuberculosis infection diagnosis and classification in children. We also used all pneumococcal and meningococcal hospitalization as vaccine-preventable diseases due to lack of serotype based diagnosis in the source database and it was difficult to differentiate serotypes that have vaccines.

# 5. CHAPTER FIVE: CONCLUSION AND RECOMMENDATION

## 5.1 CONCLUSION

The results have shown that still, vaccine-preventable diseases are contributing < 15 years in children hospitalization in CHBAH from 2014 to 2018. From admissions due to VPDs, EPI-VPDs share was very large especially hospitalization due to Tuberculosis was predominant. From non-EPI-VPDs, the most causes of admission were due to varicella, followed by Hepatitis A.

There was a gradual increase in the number of patients hospitalized due to non-EPI-VPDs from 2014 to 2016, which then decreased onwards; however, the increase was not statistically significant. The EPI-VPDs increase swiftly from 2014 to 2015 in which it peaked before decreasing in the subsequent years. The overall VPDs followed a similar pattern with the EPI-VPDs, which was predominant in this study. The participant's age was associated with high odds of being hospitalized due to EPI-VPDs, non-EPI and overall VPDs. Those who were HIV positive had an increased odd to have EPI, non-EPI and overall EPI VPDs when compared to those who were HIV negative.

From all hospitalized <15 years children in five years, 5.88% (4,111) study participants were discharged with death outcome. Of these deaths, 142 (3.45%) were due to VPDs. Out of 2361 patients hospitalised due to VPDs, 142 (6.01%) died; of the 142, 134 were from EPI-VPDs. Most of the deaths due to vaccine-preventable were patients admitted with the diagnosis of Tuberculosis and pneumococcal. The EPI-VPDs showed a general decrease in the number of deaths over time. The Non-EPI-VPDs showed a gradual increase in death which peaked in 2016 and decreased after that.

**5.2 Recommendation**

The following recommendations arise from the study and may be of relevance as relevant for the South African Health Department and CHBAH plan.

1. Strengthening the national immunization system and reaching eligible children for vaccination is important for the prevention of hospitalization and death of VPDs.
2. The Department of health should start looking for additional evidence for the inclusion of selected non-EPI VPDs in the national EPI system. Strengthen surveillance system, vaccine cost-effectiveness studies and estimating the burden of diseases are recommended for VPDs especially diseases like Varicella and Hepatitis A.
3. CHBAH should take possible actions that prevent hospital death after admissions due to VPDs.
4. Comprehensive HIV prevention is also important among < 15 years children to prevent hospitalization due to VPDs.

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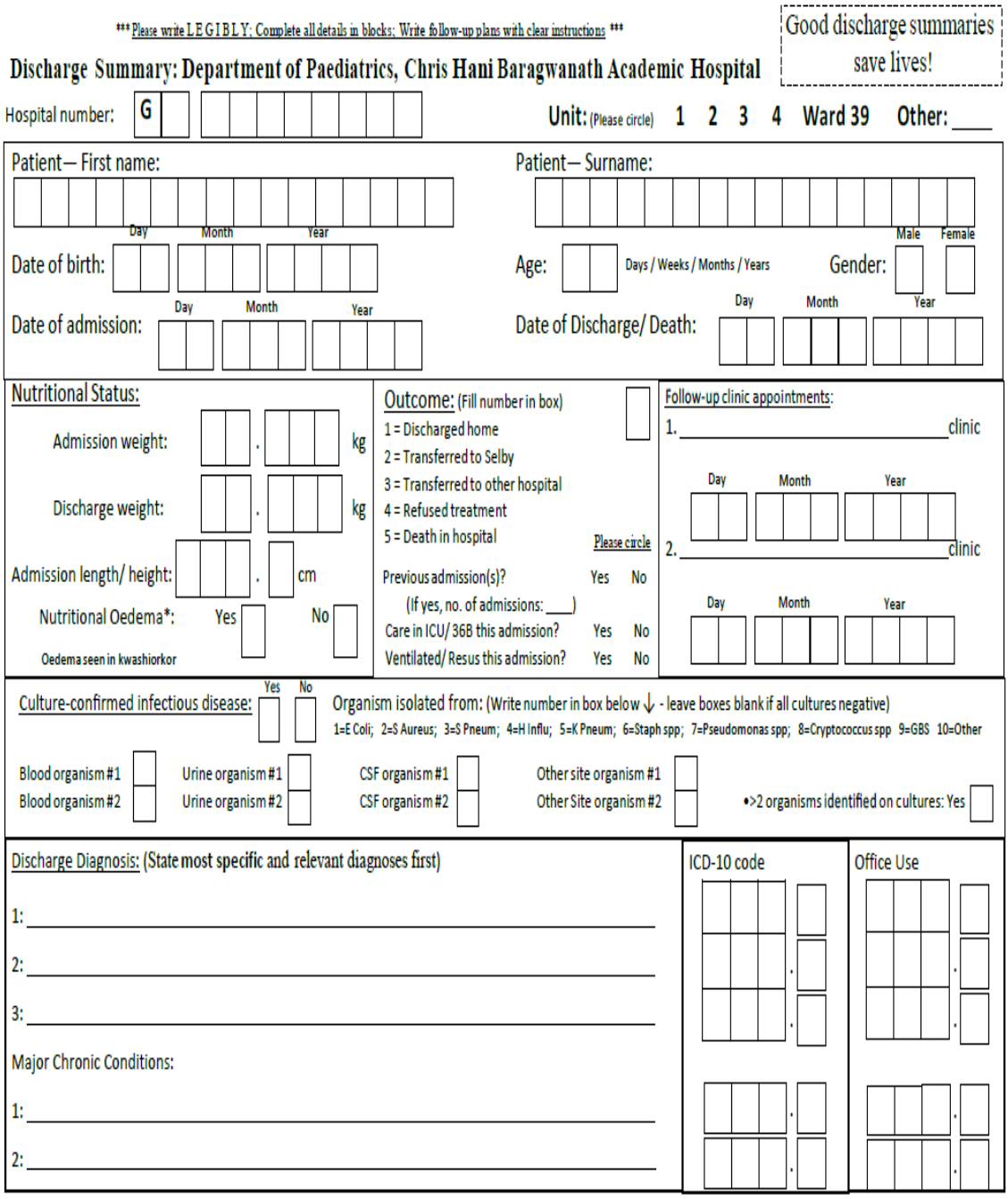
Appendices

APPENDIX A- Vaccine Schedules for South Africa

| Age of child | EPI schedule (6-10-14 wks) | Private (6-10-14 wks) |
|---|---|---|
| At birth | OPV(0)[1] | OPV (0)[1] |
| | BCG | BCG |
| 6 weeks | OPV(1)[1] | OPV(1)[1] |
| | RV (1) | RV (1) |
| | PCV(1) | PCV (1) |
| | DTaP-IPV-Hib-HBV (1) | DTaP-IPV-Hib-HBV (1) |
| 10 weeks | | RV[2] (2) |
| | | PCV (2) |
| | DTaP-IPV-Hib-HBV (2) | DTaP-IPV-Hib-HBV (2) |
| 14 weeks | RV (2) | RV[2] (2 or 3) |
| | PCV(2) | PCV[3] (3) |
| | DTaP-IPV-Hib-HBV (3) | DTaP-IPV-Hib-HBV (3) |
| 6 months | Measles[4] (1) | |
| 9 months | PCV(3) | Measles or MMR[5] (1) |
| | | MCV (1) |
| 12-15 months | Measles (2)[4] at 12 months | PCV (4)[6] |
| | | MMR (1 or 2) |
| | | Varicella[7] (1) |
| | | Hepatitis A (repeat 6 months later) |
| | | MCV (2) |
| 18 months | DTaP-IPV-Hib-HBV (4) | DTaP-IPV-Hib-HBV (4) |
| 5-6 years | Td vaccine (6 years) | DTaP or Tdap-IPV |
| | | MMR (2 or 3) |
| | | Varicella (2) |
| 9 years | HPV[8] | HPV[9] (from 9 years) |
| 12 years | Td vaccine | Tdap-IPV[10] |

# APPENDIX B Paediatric discharge Summary



*** Please write LEGIBLY; Complete all details in blocks; Write follow-up plans with clear instructions ***

Good discharge summaries save lives!

**Discharge Summary: Department of Paediatrics, Chris Hani Baragwanath Academic Hospital**

Hospital number: G

Unit: (Please circle) 1 2 3 4 Ward 39 Other: ____

Patient— First name:

Patient— Surname:

Date of birth: Day Month Year

Age: Days / Weeks / Months / Years

Gender: Male Female

Date of admission: Day Month Year

Date of Discharge/ Death: Day Month Year

**Nutritional Status:**

Admission weight: . kg

Discharge weight: . kg

Admission length/ height: . cm

Nutritional Oedema*: Yes No

Oedema seen in kwashiorkor

**Outcome:** (Fill number in box)

1 = Discharged home
2 = Transferred to Selby
3 = Transferred to other hospital
4 = Refused treatment
5 = Death in hospital

Please circle

Previous admission(s)? Yes No

(If yes, no. of admissions: ___)

Care in ICU/ 36B this admission? Yes No

Ventilated/ Resus this admission? Yes No

**Follow-up clinic appointments:**

1. _____ clinic

Day Month Year

2. _____ clinic

Day Month Year

**Culture-confirmed infectious disease:** Yes No

Organism isolated from: (Write number in box below ↓ - leave boxes blank if all cultures negative)

1=E Coli; 2=S Aureus; 3=S Pneum; 4=H Influ; 5=K Pneum; 6=Staph spp; 7=Pseudomonas spp; 8=Cryptococcus spp 9=GBS 10=Other

Blood organism #1
Blood organism #2

Urine organism #1
Urine organism #2

CSF organism #1
CSF organism #2

Other site organism #1
Other Site organism #2

•>2 organisms identified on cultures: Yes

**Discharge Diagnosis:** (State most specific and relevant diagnoses first)

1: _____

2: _____

3: _____

Major Chronic Conditions:

1: _____

2: _____

ICD-10 code

Office Use

**Clinical notes:** Summary of presenting illness:

Main clinical findings:

Progress in ward:

Procedures/ Investigations (List test e.g. CXR, Echo, U/S, CT scan; date done & main findings):

**Lab tests:**

FBC (adm):

UE (adm):

Bili (T/D): ___/___ T Prot/Alb: ___/___ ALP/ GGT: ___/___ ALT/AST: ___/___

Pending results (State lab ref no.):

**HIV status and TB status:** (Please circle)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| • Mom PMTCT: | Yes | No | Unk | • Child PMTCT: | Yes | No | Unk |
| • HIV Exposure: | Yes | No | Unk | • Current ARV Rx: | Yes | No | Unk |
| • HIV Elisa: | Pos | Neg | Unk | • Current TB Rx: | Yes | No | Unk |
| • HIV PCR: | Pos | Neg | Unk | • Previous TB Rx: | Yes | No | Unk |
| • Defaulted ARV: | Yes | No | Unk | • Defaulted TB Rx: | Yes | No | Unk |

CD4+ (Abs count/%): ____/____ (%) Date:

HIV Viral load: Date:

**Medication given to patient during hospitalisation** (List most important drugs first):

1. 4. 7.
2. 5. 8.
3. 6. 9.

**TTO medication** (List drugs without doses; if >6 drugs state most important drugs first. All drugs with doses to be written in OPD file):

1. 3. 5.
2. 4. 6.

**Follow-up instructions** (Be specific please!):

**Caregiver/ Parent name:** **Contact no.:**

Doctor's name: Please print name legibly Signature Date

Sponsored by RMPRU (Respiratory and Meningeal Pathogens Research Unit) - Your partner in improving health through robust data collection

## APPENDIX C Vaccine preventable diseases , ICD-10 codes and diagnostic criteria

| Serial. No | Disease (VPDs) | ICD-10 codes | Operational definitions of ICD cods and diagnostic criteria |
|---|---|---|---|
| 1 | Tuberculosis | A15, A15.0, A17, A17.0, A18, A18.0, A18.1, A18.2, A18.3, A18.4, A18.5, A19, P37.0, U50.0, U50.2 | All form of TB |
| | | | Clinical diagnosis, With or without bacteriological or histological confirmation and radiological |
| 2 | Polio | A80.30 | virological testing, |
| 3 | Hepatitis B | B16 | Acute hepatitis B |
| | | | detect HBsAg antibody by using quality-assured serological in vitro diagnostic test (IVD)for Acute hepatitis B |
| 4 | Diphtheria | A36 | A positive culture with toxin producing C. diphtheria |
| 5 | Pertussis | A37, A37.0, A37.1 | Whooping cough due to B. Pertussis |
| | | | confirmed by Culture, PCR and Serological diagnosis |
| 6 | Tetanus | A 33, A34 and A35 | Diagnosis based on clinical features |
| 7 | Haemophilus influenzae type b (Hib) | G00.0, J14, A41.3 | Septicaemia due to Hib, Pneumonia due to Hib and Haemophilus meningitis |
| | | | Diagnosis is isolating Hib from cerebrospinal fluid (CSF); a positive latex agglutination or PCRtest for Hib from CSF; finding purulent CSF with a gram stain showing gram negative coccobacilli; or by growth of Hib from blood cultures. |
| 8 | Pneumococcal | J13, G00.1, A40.3 | Pneumonia due to Streptococcus pneumoniae, Pneumococcal meningitis, Septicaemia due to Streptococcus pneumoniae |
| | | | PCR,Culture |

| | | | |
|---|---|---|---|
| 9 | Measles | B05, B05.0, B05.1, B05.2 | Measles, Measles complicated by pneumonia |
| | | | detection of anti-measles virus IgM antibodies by enzyme-linked immunosorbent assay (ELISA), or the detection of measles virus RNA by reverse transcriptase polymerase chain reaction (RT-PCR) |
| **Non EPI VPDs** | | | |
| 10 | Meningococcal disease | A39.0 | Meningococcal meningitis |
| | | | Culture and PCR |
| 11 | Varicella (chickenpox) | B01,B01.0,B01.1,B01.2 ,B02 | Varicella (Chickenpox) |
| | | | Clinically and PCR |
| 12 | Rubella | B06, P35.0 | Congenital Rubella syndrome,Rubella |
| | | | Serological testing, ELISA and RT-PCR |
| 13 | Mumps | B26,B26.2, B26.3 | Mumps |
| | | | Serological |
| 14 | Hepatitis A | B15 | Hepatitis A |
| | | | Serological testing (IgM anti-HAV) |

APPENDIX D Permission to use data set

*DST/NRF:Vaccine Preventable Diseases*
*Respiratory and Meningeal Pathogens Research Unit*
*11th Floor, Central West wing, Nurses Residence*
*Chris Hani Baragwanath Hospital*
*Tel (011) 983 4283*
*Fax 086 646 4208*

VPD
Vaccine Preventable Diseases
RMPRU
Respiratory & Meningeal Pathogens Research Unit

Tuesday, 24 March 2020

The Human Research Ethics Committee (HREC), Faculty of Health sciences,
University of the Witwatersrand.

**Re: Provisional Approval to access Respiratory and Meningeal Pathogens Research Unit (RMPRU) data**

Dear Sir/ Madam,

This serves to confirm that permission is hereby granted to **Mr Zinabu Temesgen Melsebo**, student number 2292818 to conduct his study at RMPRU. He is an MSc (Med) student in the field of Vaccinology. His project tittle is **Contribution of Vaccine-preventable diseases (VPDs) to children Hospitalization in Chris Hani Baragwanath Academic Hospital, Soweto, Gauteng from 2014 to 2018**, using data routinely collected by RMPRU from pediatric and neonatal discharge summaries.

He will only be given access to the data once he has provided full Ethics committee clearance certificate to RMPRU.

Yours faithfully

Portia Mutevedzi

**Dr Portia Mutevedzi (MSc, PhD) Senior Epidemiologist**

VPD
Vaccine Preventable Diseases
RMPRU
Respiratory & Meningeal Pathogens Research Unit

|DST/NRF:Vaccine Preventable Diseases|Respiratory and Meningeal Pathogens Research Unit|

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Appendix E Clearance certificate from Medical Advisory Committee, CHBAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

**PERMISSION TO CONDUCT RESEARCH**

Date: 20th May 2020

**TITLE OF PROJECT:**

Contribution of vaccine-preventable diseases (VPDs) to hospitalization in Chris Hani Baragwanth Academic Hospital, Soweto, Gauteng.

**UNIVERSITY:** Witswatersrand

**Principal Investigator**: Dr ZT Melsebo

**Department:** Pathology/Paediatrics

**Supervisor** : Prof P Mutevedzi

**Permission Head Department** (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
Date: 20/05/2020

.....
Approved/~~Not Approved~~
Hospital Management
Date: 22/05/2020

# Appendix F Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

**Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)**

**TO:** Mr ZT Melsebo
School of Pathology
Dept of Clinical Microbiology and Infectious Diseases
Respiratory and Meningeal Pathogens Research Unit
Chris Hani Baragwanath Academic Hospital

E-mail: zinabumelsebo77@gmail.com

**CC:** Supervisor: Drs P Mutevedzi and C Cutland <mutevedzip@rmpru.co.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

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

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

**DATE:** 2020/06/17

**REF:** *R14/49*

**PROTOCOL NO:** **M191039** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

**PROJECT TITLE:** *Contribution of vaccine-preventable diseases to hospitalization in Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa*

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 the Government funding of the University.

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UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Mr ZT Melsebo

# HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
## CLEARANCE CERTIFICATE NO. M191039

| | |
|---|---|
| **NAME:** (Principal Investigator) | Mr ZT Melsebo |
| **DEPARTMENT:** | School of Pathology<br>Dept of Clinical Microbiology and Infectious Diseases<br>Respiratory and Meningeal Pathogens Research Unit<br>Chris Hani Baragwanath Academic Hospital |
| **PROJECT TITLE:** | Contribution of vaccine-preventable diseases to hospitalization in Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa |
| **DATE CONSIDERED:** | 2019/10/25 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Drs P Mutevedzi and C Cutland |
| **APPROVED BY:** | Dr CB Penny, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 2020/06/17 |

**This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.**

### DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary 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 **October** and will therefore reports and re-certification will be due early in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

June 17,2020
Date

Appendix G Approval from the Department of Paediatrics, CHBAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Department of Paediatrics and Child Health
Metabolic Unit
Chris Hani Baragwanath Academic Hospital
P. O. Bertsham
2013

11 February 2020

**The Research Protocol Review Committee**
**Chris Hani Baragwanath Academic Hospital**
**Soweto**
**Johannesburg**
**South Africa**

Dear Madam/ Sir

I would like to inform you that **Zinabu Temesgen Melsebo** has been given a permission to conduct his research study in the Department of Paediatrics at Chris Hani Baragwanath Academic Hospital. The title of his study is: **"Contribution of vaccine-preventable diseases (VPDs) to the hospitalization in Chris Hani Baragwanath Academic Hospital, Soweto, Gauteng."**

While he has been given permission to conduct this study, he cannot start with data collection until he has provided the Department with Ethics Committee Clearance Certificate.

Yours Sincerely

Professor SC Velaphi
Head of Department of Paediatrics

# Appendix H title approval letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

06 January 2021
Person No: 2292818
PAG

Mr ZT Melsebo
Hawassa
2179
Ethiopia

Dear Mr Zinabu Melsebo

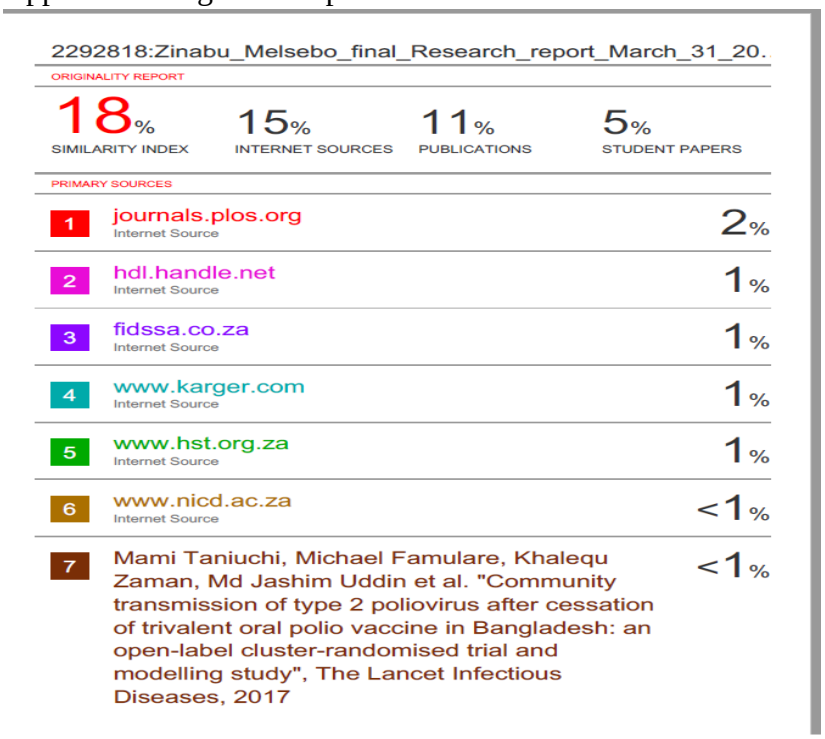
**Master of Science in Medicine: Approval of Title**

We have pleasure in advising that your proposal entitled *Contribution of Vaccine-preventable diseases (VPDs) to the hospitalization in Chris Hani Baragwanath Academic Hospital, Johanneburg, South Africa* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix I Plagiarism report



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