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Epidemiology of invasive Haemophilus influenzae serotype b disease following implementation of a booster vaccine dose in South Africa

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2024

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UNIVERSITY OF WITWATERSRAND, JOHANNESBURG FACULTY OF HEALTH SCIENCES

SCHOOL OF PATHOLOGY



Epidemiology of invasive *Haemophilus influenzae* serotype b disease following implementation of a booster vaccine dose in South Africa

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1 DECLARATION

I, James Tumusiime, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science (Medicine) in Vaccinology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



8th day of_October_2024 in University of Witwatersrand.

2 ABSTRACT

In 2000, before the introduction of the *Haemophilus influenzae* serotype b (*Hib)* vaccine, *Hib* was among the most commonly occurring invasive bacterial infections responsible for serious infections and deaths among children <5 years worldwide. After the introduction of the *Haemophilus influenzae* serotype b conjugate vaccine (*HibCV*), significant drops in the incidence of invasive *Hib* disease were seen globally as well as in South Africa. However, a resurgence in *Hib* disease prompted the introduction of the *Hib* vaccine booster (*Hib_VB)* in South Africa's Expanded Programme on Immunization (EPI) schedule in 2009. Given that no study had been done yet to assess the impact of this *Hib_VB*, this secondary data analysis aimed to assess the trends in invasive *Hib* disease post introduction of the *Hib_VB* in South Africa.

This was a cross-sectional study which used retrospective observational surveillance data of invasive *Hib* disease. A pre- and post-*Hib_VB* analysis, to look at the trends of invasive *Hib* disease incidence among children <5 years following the introduction of the *Hib_VB*, was done. A risk factor analysis was also carried out to assess the characteristics of children <5 years with invasive *Hib* versus non-typeable *Haemophilus influenzae* (NT *Hi*) disease.

Based on the observations of this study, the pre- and post-*Hib_VB* analysis showed that there was a significant reduction in the incidence of invasive *Hib* disease from the pre- *Hib_VB* years 2006-2008 to each of the post-*Hib_VB* years 2013, 2014, 2015, 2016, 2017, 2018, and 2019. The reduction ranged from 55.1% (95% CI: 30.1-72.0) in 2013 to 75.9% (95% CI:58.1-87.8) in 2018 compared to 2006-2008 ($p<0.001$). It was also observed that there was a reduction in the incidence of *Hib* among infants too young to receive any *Hib* vaccine (<6 weeks).

In conclusion, the *Hib_VB* was effective in further reducing the incidence of invasive *Hib* disease among children <5 years in South Africa. It is recommended that all children receive *Hib* vaccine doses on time to ensure protection of all vulnerable children.

3 ACKNOWLEDGEMENTS

I would like to acknowledge the GERMS-SA surveillance team, the staff at the National Institute for Communicable Diseases, as well as all the clinicians and laboratory staff at the various hospitals in South Africa. GERMS-SA have for many years, been collecting and collating episodes of invasive *Haemophilus influenzae* in South Africa, and were very willing to share their data used for this study.

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6 ABBREVIATIONS

ALA	Aminolaevulinic acid
AORs	Adjusted Odds Ratios
CDC	Centre for Disease Control and Prevention
CI	Confidence Interval
CPS	Capsular Polysaccharide
CSF	Cerebrospinal fluid
CSV	Comma Separated Values
DTaP-IPV/*Hib*	Diphtheria, Tetanus, Pertussis and Inactivated Polio /*Hib* Vaccine
EPI	Expanded Programme on Immunization
ESS	Enhanced Surveillance Sites
GERMS-SA	Group for Enteric Respiratory and Meningeal Diseases in South Africa
Hi/ *H. influenzae*	*Haemophilus influenzae*
Hib	*Haemophilus influenzae* serotype b
HibCV	*Haemophilus influenzae* serotype b Conjugate Vaccine
Hib/MenC	*Haemophilus influenzae* serotype b and meningococcal serogroup C
Hib_VB	*Haemophilus influenzae* serotype b Vaccine Booster
NHLS	National Health Laboratory Services
NICD	National Institute for Communicable Diseases
NS	Non-serotype
NT *Hi*	Non-typeable *Haemophilus influenzae*
PCR	Polymerase Chain Reaction
PEM	Protein Energy Malnutrition
PREM	Premature Birth
PRP	Polyribosyl Ribitol Phosphate
StatsSA	Statistics South Africa
UNAIDS	The Joint United Nations Program on HIV/AIDS
UK	United Kingdom
WHO	World Health Organization

7 BACKGROUND

7.1 The *Haemophilus influenzae* pathogen

Haemophilus influenzae, a Gram-negative coccobacillus is not only fastidious but also pleomorphic and grows under aerobic conditions, however, it can also grow under anaerobic conditions. It is noteworthy that the disease-causing strain of *H. influenzae* has a polyribosyl ribitol phosphate (PRP) capsule which is a major virulence factor (1). The PRP capsule is used by the pathogen as a protection barrier from phagocytosis (1). This protective barrier is more protective in the absence of anti-capsular antibodies, and it also facilitates penetration into the blood stream and the cerebrospinal fluid (1). *H. influenzae* has 6 capsular serotypes among which *H. influenzae* serotype b (*Hib*) is one. Among the 6 known *H. influenzae* serotypes (a-f), serotype b contributed approximately 95% to the overall incidence of invasive *H. influenzae* diseases before the widespread introduction of the *Hib* vaccine (2,3). Meningitis, pneumonia, epiglottitis, osteomyelitis, septic arthritis, septicaemia, cellulitis, and pericarditis are the most common systemic clinical syndromes attributed to *Hib* (4,5). Invasive *Hib* mortality is mostly attributed to meningitis and pneumonia (5).

7.2 Burden of invasive *Hib* in the pre-vaccine era

Pre-*Haemophilus influenzae* serotype b (pre-*Hib*) vaccine introduction globally, *Hib* was among the most common invasive infections which occurred among children <5 years. In 2000, *Hib* accounted for 8.13 million (95% CI: 7.3m – 13.2m) serious infections and 371,000 (95% CI: 247,000 – 527,000) estimated deaths among children 1-59 months worldwide, of which 8,100 (95% CI: 5,600-10,000) of those deaths occurred in children living with HIV (5,6). Among the unvaccinated individuals, the incidence of *Hib* peaked between 6 and 7 months in developing countries and among older children in developed countries (5). Neurological sequelae following *H. influenzae* meningitis was observed in similar proportions across both

high- and low-income countries. These included mental seizure disorder (6.1%), intellectual disability (6.1%), partial hearing loss (10.2%), complete hearing loss (6.7%) and spasticity/paresis (5.1%)(1,7). Furthermore, a global study, done among 4000 patients with invasive *Hib* disease found that 90% presented with one of six invasive *Hib* disease clinical syndromes namely, meningitis, bacteremia, epiglottitis, pneumonia, arthritis, and cellulitis. Meningitis was reported to occur in 52% of those *Hib* patients (5,8).

Before the introduction of routine immunization with *Hib* conjugate vaccine (*HibCV*), *Hib* was reported to be the most important cause of bacterial meningitis in England and Wales between 1990 and 1992. Among the 483 *Hib* cases that were reported among children under the age of 2 years, 65% (314) of these were diagnosed with meningitis. Other clinical syndromes that were observed among children under 2 years of age in England and Wales included cellulitis (10%), epiglottitis (7%), bacteremia (6%), septic arthritis (5%), pneumonia (3%), and osteomyelitis (1%) (9). These proportions varied across regions with approximately 50%, 40%, and 55% of *Hib* meningitis cases occurring in <12 months children in the World Health Organization (WHO) American, European, and Western Pacific Regions, respectively. Furthermore, 80% of *Hib* meningitis cases among children <12 months occurred in regions with high mortality (an overall case fatality rate from *Hib* of ≥17.3%), which included Africa and Asia (9,10).

In other studies, *Hib* was reported to be a major cause of pneumonia globally, causing an estimated 1.76 million episodes of severe pneumonia, which accounts for at least 25% of severe pneumonia occurring in children <5 years (8,11). In the United States (US), pre-*Hib* vaccine introduction, 1 in 200 children developed *Hib* prior to their 5th birthday. This was coupled with an overall incidence of 19-69 per 100,000 per annum among children < 5 years, and an overall mortality of 3% to 6% in patients with *H. influenzae* meningitis (1,12,13). In the United Kingdom, in the pre-vaccination era, *Hib* contributed the highest number of cases of invasive

H. influenzae affecting mostly children and only 10% occurring in adults (14). A study done in Cape Town, South Africa during the pre-*Hib* vaccine era reported an invasive *Hib* incidence rate of 169 and 47 per 100,000 among children less than 1 year and less than 5 years respectively (15). Unfortunately, the national laboratory surveillance system for *Hib* in South Africa was only established at the same time that the *Hib* vaccine was introduced in 1999 (5), therefore no national data from South Africa are available for the pre-*Hib* vaccine era.

7.3 Introduction of the *Hib* conjugate vaccine (*HibCV*)

The high global burden of *Hib* in children necessitated the development and introduction of a vaccine aimed at reducing mortality and morbidity rates due to invasive *Hib*, especially among children <5 years old. The first vaccine, in the US, was introduced in 1985 and this was a pure capsular polysaccharide (CPS) vaccine with the aim to elicit antibody response by activating B-cells independent of T-cell help (16). This vaccine had low efficacy against invasive *Hib* disease in children ≤18 months(17,18), leading to the development of a conjugate *Hib* vaccine (*Hib*CV) two years later.

The conjugate vaccine showed success by conferring immune responses that gave a longer and more robust immunity among children ≤18 months, compared to the CPS vaccine. Children were further protected from invasive *Hib* disease prompting the US to exclusively use the conjugate vaccine among this age group (<5 years) (1). There was a 99% reduction in invasive *Hib* disease among children <5 years between the 1980s-1990s in the United States (19). It was further reported to reduce the incidence of epiglottitis, a syndrome that had been observed to frequently occur among children with invasive *Hib* (20). The impact of *Hib*CV introduction was assessed in Kenya among 40,482 children under 13 years who were admitted to hospital over a 14-year period. A 92% reduction in the incidence of invasive disease from 62.6 (95% CI: 46.0-83.3) per 100,000 in 2000 to 4.5 (95% CI: 2.5-7.5) per 100,000 in 2014 was observed

(21). Similar significant reductions in the incidence of invasive *Hib* incidence were observed among GAVI-funded countries like Senegal (90%), Malawi (89%), Rwanda (91%), and Uganda (88%) (1), following the introduction of the *Hib*CV.

7.4 Introduction of the *Hib* conjugate vaccine (*HibCV*) in South Africa

South Africa introduced the *Hib*CV as a 3-dose schedule in the Expanded Programme on Immunization (EPI) in 1999 and this was given at 6, 10, and 14 weeks of age (5). The country's 3 dosage *HibCV* coverage was observed to be between 80-92% between 1999 and 2004 (5,20). However, it is recommended by the Center for Disease Control and Prevention (CDC) that all children under 5 years are vaccinated against *Hib* and as such there is still a need for efforts that ensure a 100% *Hi* vaccine coverage is achieved within the target group (2,3). In the first year, after the introduction of the vaccine, the National Health Laboratory Services (NHLS) reported an incidence of invasive *Hib* of 6.2 and 0.9 per 100,000 among children < 1 year and 1 to 4 years old, respectively (22). From the year 1999 to 2004, a 65% (from 6.2 to 2 per 100,000) and 79% (from 0.9 to 0.2 cases per 100,000) decrease in the burden of invasive *Hib* disease was observed among those < 1 year and 1 to 4 years old, respectively (22).

7.5 Resurgence of invasive *Hib* disease

A follow-up analysis in 2010, to assess the trends of the invasive *Hib* disease 10 years after the introduction of the *Hib*CV within the South African population, was done. This study observed a resurgence in the incidence of invasive *Hib* disease among children <5 years from approximately 0.7 cases per 100,000 in 2003/4 to 1.3 per 100,000 in 2009 ($p<0.001$) (23). This was a surprising observation given that the vaccination coverage of the *Hib*CV was approximately 80% (23).

The overall prevalence of HIV in South Africa was approximately 10.6% in 2008 (**APPENDIX A)**, which translated into 5.4 million people living with HIV (24). Whilst the under 5 years

prevalence of HIV is not well reported, the Joint United Nations Program on HIV/AIDS (UNAIDS) reported that there were over 160 000 (120 000 - 290 000) children under 14 years living with HIV in 2023, which was also reported by the Statistics South Africa (StatsSA) to be an HIV prevalence in children <15 years of 1.1% in South Africa (25). This HIV prevalence could have been one of the contributors to the reduced efficacy of the *Hib*CV among children who got invasive *Hib* despite being vaccinated with *Hib*CV (26). These would thus be children with a lower level of immunity after vaccination (26). However, another study noted that of 51% (135) of the children who had been classified as vaccine failures (breakthrough infections of invasive *Hib* disease among children that have received the full vaccine dosage), 53% were not HIV-infected (1,23). This showed that the child's HIV status may not have been the only factor contributing to the resurgence of *Hib* among children <18 months. In addition, among the children that were HIV-uninfected many of them were likely HIV-exposed which might have affected their immune function. The high HIV prevalence in the mothers, which is around 30% in South Africa (25), would have impacted on the amount of protective antibodies shared between infant and mother in the final stages of pregnancy.

A similar pattern of resurgence in *Hib* was observed in the United Kingdom (UK). A 10-year analysis (1990-2001) was carried out by Vaccine Institute of the UK and Department of Child Health and a significant drop of 87% in invasive *Hib* disease from 855 cases to 37 cases in children <5 years of age was reported. This was during the first 3-4 years post vaccine introduction (27). This was following the introduction of *Hib*CV scheduled for children at 8 weeks, 12 weeks, and 16 weeks. However, the efficacy of the *HibCV* was proven to offer peak protection only until 2 years of age among children in the UK. In developing countries, it was demonstrated to offer peak protection up to 1 year of age after vaccination. (28). This drop in efficacy was reported to lead to an increase in disease during the years that followed after the peak protection period (2 years and over). It was thus documented that 55% of *Hib* vaccine

failures in the UK occurred in children at a median age of 23 months (29). Additionally, 61% of these children presented with meningitis, and 44% presented with a clinical risk factor (prematurity, malignancy) or a deficiency in immunity (29). Among children <5 years, there was an increase in the number of cases of invasive *Hib* disease among children who had been fully vaccinated with a primary series, from 0.65 cases per 100,000 children in 1998 to 4.6 cases per 100,000 in 2002 (28).

7.6 Introduction of the *Hib* Vaccine booster (*Hib_VB*)

Premised on the observations shown above, the UK introduced the *Hib* Vaccine Booster (*Hib_VB*) in 2003 in response to presumed waning immunity, low levels of anti-PRP concentrations, and persistence of *Hib* nasopharyngeal carriage among vaccinees (30). This booster dose formulation (*Hib*MenC) was given to children aged 12-13 months which resulted in an 82% decline in incidence of invasive *Hib* within 2 years, from 4.6 per 100,000 to 1.1 per 100,000 among children <5 years (30). At the time of that observation, the booster coverage was 71.8% and 63.2% for the 6 to 12 months and 13 to 48 months age groups, respectively. It had been previously reported that the immunity offered by the 3-dose series could only provide immunity to the children in their first 2 years of life and when the booster dose was assessed against this observation among under <5 years, it had significantly reduced the number of invasive *Hib* cases in that age group by 51% (30). This booster was further observed to have had an indirect effect on children older than 5 years and adults, having reduced the incidence of invasive *Hib* disease among adults by 49% over a period of 3 years after *Hib_VB* introduction campaign (30).

In 2009, South Africa introduced an 18-month *Hib_VB*. This was a multivalent dose that contained *Hib* and the antigens of diphtheria, tetanus, pertussis, and inactivated polio vaccine (DTaP-IPV/*Hib*) (21). This dose was primarily introduced for poliomyelitis prevention but also

with hopes that it would reduce *Hib*CV vaccine failures among South African children (21). Globally, the reason that a booster dose was recommended was due to the resurgence of the *Hib* among various countries as shown earlier. These populations within which it was introduced would achieve sustained control of disease (21). This was demonstrated in the UK, before the introduction of the booster vaccine, the laboratory reports on *Hib* in England, included 50 laboratory reports of *Hib* among children <5 years. By 2009 these case reports had dropped to less than 10 laboratory reports, and this remained the trend through 2012 (Figure 5.1). The University of Oxford website reported on vaccine impact, specifically about the *Hib*/MenC vaccine (*Hib* booster vaccine in the UK) quoting the Public Health England's website that by 2012 (over 8 years post-*Hib_VB* introduction), there were only 2 cases of *Hib* among children <5 years in England (31).

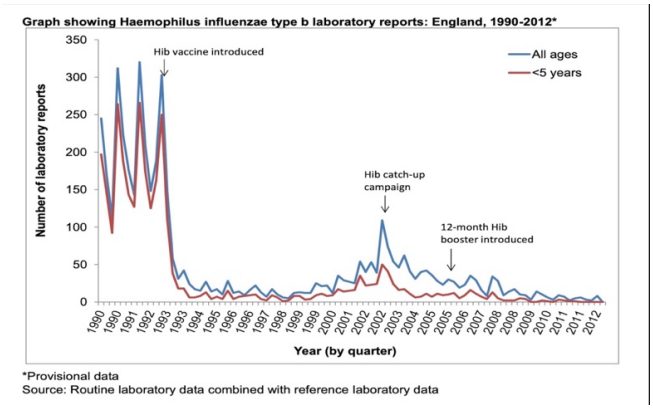


Figure 7.1 ***Haemophilus influenzae serotype b lab reports of people in England that were collected by the English Public Health Organization from 1990 to 2012*** (31)**.**

Based on the observations made in the UK, the booster vaccine that was introduced in South Africa would also show that there would be a reduction in the incidence of *Hib* disease among children < 5 years as well as other age groups as was the case in the UK post-introduction of the *Hib_VB*.

7.7 Vaccination uptake in South Africa

Vaccine coverage is one of the factors that determines the effectiveness of a vaccine introduced in the EPI schedule of a given country. The higher the coverage, the higher the chances of both a direct and indirect vaccine protective effect. The coverage of the first three doses of *Hib*CV formulation in South Africa, as per the estimates from previous coverage data was 70% in 2002 and in 2009 the World Health Organization (WHO) estimated it to be at 69% among 1-year-olds (23). In 2022, the global primary schedule (first 3 doses) coverage of *Hib* was estimated by the WHO to be at 76%. In 2020 a South African EPI coverage reported 83.9% (95% CI:82.9-84.9) of children had received all primary vaccinations and 76.8% (75.4-78.2) of children had received all age-appropriate vaccines from birth until 18 months (32).

8 RATIONALE

The most recent study assessing the impact of the *Hib*CV in South Africa was published in 2011 with data specific to pre-booster trends in invasive *Hib* disease (23). Observations were concerning about there being an increase in the incidence of invasive *Hib* disease in children < 5 years of age in South Africa and a *Hib* vaccine booster was introduced. However, there had not yet been any evaluation that was done to assess the trends in *Hib* invasive disease post-introduction of this booster vaccine. As such this study was done to assess whether there was a decrease in the incidence of invasive *Hib* disease since the introduction of the booster vaccine, and further assess age-specific incidence of *Hib* invasive disease.

9 RESEARCH QUESTION, AIMS AND OBJECTIVES

Research Question: What impact has the *H. influenza*e serotype b conjugate booster vaccine had on reducing the incidence of invasive *Hib* infections in South Africa from pre-booster years (2006-2008) to post-booster years (2013-2019) among children aged <18 months, 18-23 months, 2 to <5 years, 5-18 years, and adults (>18 years)?

9.1 Aims

This study aimed to evaluate the trends in the incidence of invasive *Hi* disease pre-and post the introduction of a booster dose of *Hib* conjugate vaccine at 18 months of age (2006-2019), among children under 18 months, 18-23 months, 2 to <5 years, 5-18 years, and adults (>18 years). In addition, the study evaluated risk factors for invasive *Hib* versus the non-typeable serotype of invasive *H. influenzae* infections in South Africa following the introduction of the booster dose.

9.1.1 Objectives

1. To describe the trends in the incidence of invasive *Hib* disease among children under 18 months, 18-23 months, 2 to <5 years, 5-18 years, and adults (>18 years) from 2006 to 2019.
2. To determine the impact of a booster dose of *Hib* vaccine on invasive *Hib* disease following its introduction in 2009 by comparing the incidence pre-*Hib_VB* (2006-2008) and post-*Hib_VB* (2013-2019).
3. To determine risk factors for invasive *Hib* versus non-typeable *Hi* infections in children <5 years in South Africa following booster introduction at 18 months of age between 2009 and 2019.

10 METHODS

10.1 Study design

This study was a cross-sectional study which used retrospective observational surveillance data to perform a secondary data pre- and post-analysis. This was done by looking at the incidence trends of invasive *Hib* prior to the introduction of a *Hib_VB* and comparing them with those after the introduction of the *Hib_VB*.

10.2 Population

The population that was under surveillance included all people living in South Africa between 2006 and 2019. These were used to examine the trends in the incidence rates of invasive *Hib* in age groups <18 months, 18-23 months, 2 to <5 years, 5-18 years, and over 18 years, from 2006 to 2019. These years included time frames pre- and post-introduction of the *Hib*CV booster vaccines. Population total estimates were obtained from the United Nations' Department of Economic and Social Affairs Population Division. These were cross-referenced with estimated population numbers in the StatsSA mid-year population totals data sets (33–36). The overall HIV prevalence in South Africa from 2009 to 2019 increased from 10.6% to 13.5% (34,37). Whilst the HIV prevalence among children <5 years was not specifically reported, that among children under 14 years was reported to be 1.1% (25).

10.3 Sources of data

The primary data were collected by the GERMS-SA (previously known as Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa) surveillance program, which carries out laboratory-based surveillance on pathogens of public health importance. GERMS-SA is housed within the National Institute for Communicable Diseases (NICD), a division of the National Health Laboratory Service (NHLS).

This surveillance project captures laboratory-confirmed cases of invasive *H. influenzae* from all South African clinical microbiology laboratories in both the public and private healthcare sectors, as well as military and mining sectors (35). Episodes of invasive *H. influenzae* were detected by culture or Polymerase Chain Reaction (PCR) from any sterile-site specimen (e.g., blood, cerebrospinal fluid (CSF), pleural fluid). These were reported to the NICD, and isolates/residual specimens were sent to the Centre for Respiratory Diseases and Meningitis, NICD for confirmation and further phenotypic and genotypic testing. Upon confirming the *H. influenzae* isolates using the gamma-aminolaevulinic acid (ALA)-porphyrin test, serotyping of *H. influenzae* was done by slide agglutination using antisera for types a–f (Murex Biotech Ltd., Dartford, Kent, UK) and confirmed using a real-time PCR assay (23). To identify serotype b-specific genes, a multiplex real-time PCR assay was utilized, and two additional multiplex real-time PCR assays were done to identify serotypes other than b namely a, c, d, e, and f. The serotypes that had lost the ability to produce serotype b capsules were still classified as serotype b in these data and isolates that were positive for *Iga1* and negative for *BexA* and serotype b-specific genes were classified as non-typeable *H. influenzae* (23). Isolates not sent to the NICD for further characterization were captured as audit cases through a comparison of GERMS-SA line lists with the National Health Laboratory Service laboratory information system.

At 26 selected hospitals sites (Enhanced Surveillance Sites (ESS)), trained surveillance officers collected clinical data on all laboratory-confirmed cases of *H. influenzae* occurring at their hospital. This was done through a structured patient interview, after obtaining informed consent from the patient or guardian, and/or through a medical record review. These enhanced surveillance data were then linked to the laboratory data from the matching isolate/specimen on a Microsoft Access database (35).

10.4 Inclusion and Exclusion criteria

The patient had to have had a normally sterile specimen (blood, CSF, pleural fluid, joint fluid) taken which, after being cultured, was positive for *H. influenzae*. The patient was excluded if any organism other than *H. influenzae* was detected.

10.4.1 Inclusion criteria

Objective 1 and 2

- Laboratory confirmed invasive *Hib* with a recorded Date of Birth (Age).

Laboratory confirmed invasive *Hi* cases recorded in the NHLS and NICD surveillance database collected from both Enhanced and Non-enhanced sites were used. These cases were further refined by including only those that had a recorded date of birth which was used to calculate the age of the patient.

Objective 3

- Cases who were under the age of 5 years
- Cases who had *Hi* serotype data available this episode
- Cases who presented at an enhanced surveillance site
- Cases who had hospital outcome data available

10.4.2 Exclusion criteria

Objective 1 and 2

- Cases without age, as calculated from their date of birth, were excluded.

Objective 3

  - All non-serotyped (NS) and those without clinical data were excluded.

- All cases that did not meet the inclusion criteria as stated under objective 3 were excluded.
- All cases that were 5 years or older were also excluded.

10.5 Data Analysis and management

10.5.1 Variables

Table 10.1: Demographic and other variables that were used in the *Haemophilus influenzae* trends and risk factor analyses carried out on invasive *H. influenzae* data collected in South Africa between 2006 and 2019.

Variable Name	***Categories/ Options***	***Explanation***	***Objectives (Action taken)***			***Available for ESS only or all episodes***
			1	***2***	***3***	
Sex	*M (Male)* *F (Female)* *U (Unknown)*	*Biological sex ascribed at birth. Those whose sex at birth was not known, fell in the "unknown" category.*	*All sex based data were used*			*All episodes*
Age groups	*<18 months* *18-23 months* *2- to <5 years* *5-18 years* *>18 years*	*This variable divided cases by specified age based categories.*	*All age-related data were used*	*Only 3 age categories were used namely, <18 months, 18-23 months and 2- to <5 years*		*All episodes*
	< 5 years *>5 years*	*This variable divided cases by greater than and less than 5 years age.*	*All age-related data were used*	*Cases <5 years were used in these objectives*		*All episodes*
Provinces	*Eastern Cape* *Free State* *Gauteng* *Kwazulu Natal* *Limpopo* *Mpumalanga*	*This variable showed what province the Hi cases were from.*	*All province-related data were used*			*All episodes*

	Northern Cape *Northwest* *Western Cape*				
Vaccination Status	*- Unvaccinated* *- Partial Primary* *- Complete Primary* *- Primary Complete + Booster*	*This variable determined what vaccination status the cases belonged to premised on how many dosages they had received in their lifetime.*	*All vaccinate-related data were used*		*ESS*
Serotyped	*Y (Yes)* *N (No)*	*This was whether the patient's Hi isolate was categorized into the various Hi serotypes or not.*	*Both serotyped & non serotyped data were used used*	*NS data were dropped.*	*All episodes*
Hi Serotypes	*- Hib (Hi serotype b)* *- a to f (Hi types a to f, excluding serotype b)* *-NT (Hi non-typeables)*	*This entailed the Hi serotype that was classified from the analysis of their Hi disease.*	*All Hi serotyped data were used in the first trends graph (figure 11.4)and then only Hib serotyped data were used afterward.*	*Hib and non-typeable Hi (NT Hi) serotype data were used*	*All episodes*
Enhanced Sites	*- Y (Yes)* *- N (No)*	*This entails whether the Hi case was reported from an Enhanced site or not*	*Data from both enhanced and non-enhanced sites were used.*	*All data not from enhanced sites were dropped*	*N/A*
HIV Status	*- P (Positive)* *- N (Negative)* *- U (Unknown)*	*This was the patient's HIV status at the time of their admission*		*All HIV-infected cases/data were used.*	*ESS*

HIV Exposure in <5	*- Y (Yes)* *- N (No)*	*.All Children <5 years whose mothers were HIV-infected during their pregnancy were considered HIV-exposed. This category also included those children who were HIV positive (Y). Children of HIV-uninfected mothers were considered HIV-unexposed (N).*		*All HIV-exposure data used.*	*ESS*
Tuberculosis treatment (TBRX)	*Y (Yes)* *N (No)* *U (Unknown)*	*This variable consisted of patients who were reported to have received TB treatment in the previous 3 months*		*All Hib and NT cases with in the TBRX category were included*	*ESS*
Medical disease risk (MDR)	*- Y (Yes)* *- N (No)*	*This was a variable that assessed whether a patient had any medical risk factors as described in further detail below.*		*All Hib and NT cases with in the MDR category were included.*	*ESS*
Disease outcome	*- D (Death)* *- R (Recovered)* *- Unknown*	*This is the outcome at the end of the hospital admission. The patient was classified as either dead (D) or discharged resulting from recovery (R),*		*All Hib and NT cases with a disease outcome were included except those with an unknown outcome*	*ESS*
Clinical Data Collected	*- Y (Yes)* *- N (No)*	*This variable was created and it consisted of a*		*All Hib and NT cases with clinical*	*ESS*

		patient who met all the criteria below. 1)had disease outcome known, 2)had data collected from enhanced sites 3)had source data consisting of medical records or interview records categorized under the "Yes" option.		*data were included in and those without clinical data were excluded.*	

The basic demographic details of all *Hi* cases were available. Some of the isolates were submitted to NICD for determination of the serotype. However, for objective 3, the clinical data that were used were only available for a selected subset of the main dataset, i.e., cases that were identified at the 26 enhanced surveillance sites.

10.5.2 Case definitions

Invasive *H. influenzae* disease: A confirmed case was one from which *Haemophilus influenzae* had been isolated from a specimen obtained from a sterile body site (e.g., cerebrospinal fluid (CSF), blood, joint fluid, pleural fluid, pericardial fluid), through culture or using a validated polymerase chain reaction (PCR) assay. The following *Hi* groupings were used for the study: *Hib,* a, c-f, non-typeables.

Hib: A positive case of invasive *Hib* was defined if an individual whose sterile site specimen, after being cultured or identified via PCR, was identified specifically as *H. influenzae* serotype b.

Non-typeable: A positive case of *Hi* which, after being cultured or identified via PCR, was identified specifically as non-typeable.

10.5.3 *Hib* vaccination status definitions for *Hib* cases who met the objective 3 inclusion criteria above.

Vaccine history was documented from either seeing the child's Road to Health Card (RTHC), telephonic consultation from the vaccination clinic, or documented vaccination history in the child's medical records.

Primary Series: These are the three *Hib* vaccination doses that were given to children at 6, 10, and 14 weeks.

Booster dose: was given at 18 months, introduced in 2009.

- **Unvaccinated**: cases who had a vaccination history but were recorded to not have received any *Hib* vaccine in their lifetime.
- **Partial Primary:** cases of *Hi* who had received at least one primary dose of the *Hib* vaccine and thus had not completed the primary dose series.
- **Complete Primary:** cases who had received all three doses from the primary series vaccination schedule but had not received the *Hib* booster vaccine dose.
- **Complete primary + booster:** cases who had received all three doses from the primary series vaccination schedule plus the *Hib* booster vaccine dose.
- **Vaccine failure in children ≥18 months:** a child who has received 3 +1 doses of *Hib* vaccine but still got invasive *Hib* disease 2 or more weeks post the last *Hib* vaccine dose. Pre-booster vaccine failure occurred among children <18 months who received 3 doses of *Hib* vaccine and still developed invasive *Hib* disease 2 or more weeks post the last vaccine dose.

10.5.4 Data management

Data were collected from both enhanced and non-enhanced hospital sites and were protected and managed by data protection policies governed by the NICD. These data, before being sent

through for analysis, were deidentified to ensure that no participants could be traced back to personal identifying information. Deidentified data were provided by the NICD, in a Comma Separated Values (CSV) Excel sheet format and this was imported into Stata 17 (StataCorp Inc., College Station, Texas, USA) for data cleaning and analysis. Data were cleaned by dropping the data that did not meet the inclusion criteria.

New variables such as age-categorical variables, clinical outcome variables, and medical risk variables were created to further assist in the classification of data that were used in the analysis **(Table 10.1)**. These new variables along with existing variables were used in the data analysis. Data were dropped in a step-wise approach in accordance with what was shown in the flow diagram **(Figure 11.1),** for each of the analyses. The data set was kept on password secured laptops that were only accessible to the student and the supervisors.

10.5.5 Missing data

An assessment of all the episodes that were collected and characterized as *H. influenzae* isolates, showed that almost all of them had the basic demographic data namely, age (which was derived from the Date of Birth (DOB), except for 200 episodes (4.1%), sex, and province. Given that *H. influenzae* is a fastidious organism and not all laboratories sent all isolates to the reference laboratory, this meant that not all isolates were available for serotyping. Furthermore, additional clinical information was only collected from patients that presented with *H. influenzae* at a subset of 26 ESS hospitals. This additional clinical information is what was used in objective 3 in the multivariable model and the rest of the episode data without additional clinical data were dropped. However, before these data were dropped, a comparison of data between the episodes gathered from enhanced vs non-enhanced sites, and serotyped vs NS data were done to demonstrate any significant differences which may have introduced bias in the interpretation of the results.

10.6 Statistical analysis

10.6.1 Objectives 1 and 2

The annual population totals in South Africa from 2006 to 2019 were obtained from the United Nations Department of Economic and Social Affairs, Population Division website (36), and transferred to a Microsoft Excel spread sheet where the incidence rate was calculated. Incidence was calculated in Microsoft Excel (Microsoft Corporation Inc., Washington, USA), by dividing the number of cases each year by the total mid-year population for that same year **(APPENDIX B)**. The under 18 months population totals for each year were calculated by adding the mid-year population total among the under 1 years plus 50% of the population among the under 2 years of a given year.

Incidence was calculated separately for different age categories and for the different serotypes. The confidence interval for the incidences calculated was computed using Stata 17. This was done using the code "*cii means x y, poisson*" whereby "x" would be the total population that was specific to that number of cases within that given category and "y" would be the number of cases of a given *Hi* serotype. For example, an *Hib* case count of 44 in a given year with a mid-year population total of 56,422,274 would have an incidence of 0.078 per 100,000 population and a Confidence Interval (CI) of 95%: 0.06 – 0.11 as output by the Stata 17 using the above mentioned formula "*cii means 56 422 274 44, poisson".*

These incidence rates in each of the four *H. influenzae* categories above were plotted on a line graph across the years of surveillance from 2006 to 2019. Afterward, NS cases were dropped from the data set after noting the proportions of patients that were in each age-based category.

The impact of dropping NS data on the results was assessed by comparing whether there was a difference between serotyped and NS data types and a p-value of less than 0.05 was considered a significant difference when using a chi-squared test in Stata 17.

A pre- and post *Hib_VB* introduction analysis was carried out by comparing the *Hib* incidence rates in pre- *Hib_VB* years to those in post-*Hib_VB*. The years that were focused on in the pre-*Hib_VB* were 2006-2008. The mean incidence of those three years (2006-2008) was used as the reference incidence rate compared to the incidence in post- *Hib_VB* years (2013-2019). This was calculated in excel using the formular "*=AVERAGE (incidence in 2006: incidence in 2007: incidence in 2008)*".

Percentage changes between the reference incidence rate and the post- *Hib_VB* years (2013-2019), were calculated along with their 95% confidence intervals. Percentage differences that had a p-value <0.05 were considered significant. These were calculated in Stata 17 using the code "*iri a b a-total b-total*" whereby "*a*" was the case count of the reference year (mean case count in 2006-2008) whereas "*b*" was the given comparative year. "*a-total*" was the average total population in that reference year(s) (2006-2008) and "*b-total*" was the total population in a given comparative year. The same calculations were done for the a.c-f and the NT Hi incidence tables as per the pre- and post *Hib_VB* introduction analysis in the *Hib* table, as explained above.

10.6.2 Objective 3

The risk factor analysis was restricted to children who were less than 5 years of age, with serotyped data available from enhanced surveillance sites and with clinical data available.

A logistic regression model was used to carry out the risk analysis on the acquisition of invasive *Hib* disease vs non-typeable *Hi* disease. The outcome variables (dependent) were the *Hib* and NT *Hi* and the independent variables were a range of characteristics including but not limited to demographic characteristics as listed out in Table 10.1 above. The variables that were significant at <0.05 in the univariate analysis using a logistic test were then analyzed in a multi-variable regression model collectively. This output consisted of an adjusted odds ratio (AOR)

and a p-value as well as a confidence interval at 95%. It should be noted that some variables that were not significant at the univariate analysis level were included *apriori* in the multi-variable regression model based on existing literature that had reported associations between these variables with the outcomes being assessed. These variables included HIV status, age category and *Hib* vaccination status, medical disease risk, and disease outcome.

10.7 Consent from participants

Hib has been a notifiable medical condition to the Department of Health in South Africa since 1999 (22), and all laboratory confirmed cases of invasive *H. influenzae* disease were reported to the NICD. For the clinical data collected from the enhanced surveillance sites, trained surveillance officers obtained written informed consent from patients/guardians prior to interviewing the participants.

11 RESULTS SECTION

11.1 Study Participants

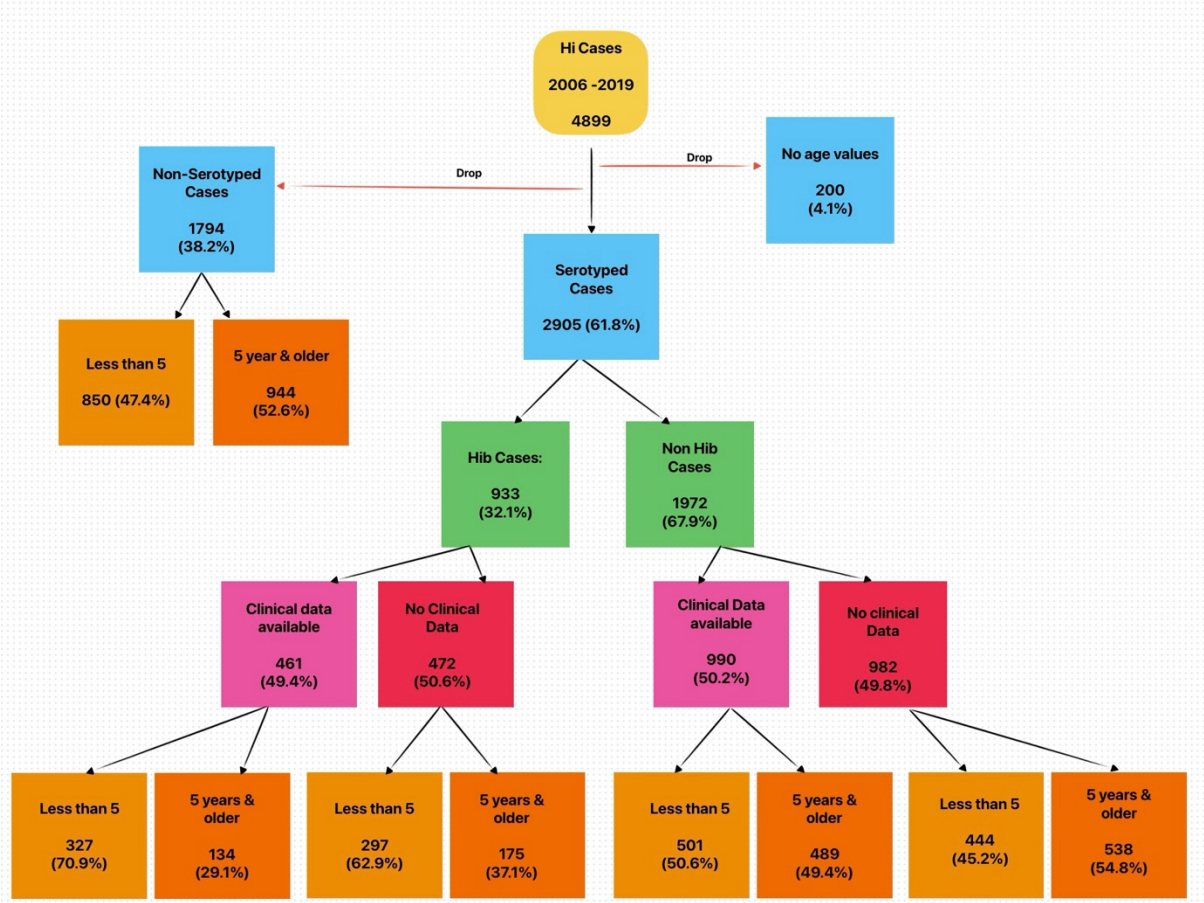


Figure 11.1 Flow chart showing the breakdown of invasive *Haemophilus influenzae* episodes among persons <5 and ≥5 years age groups in South Africa from 2006 to 2019.

The dataset used consisted of cases of laboratory confirmed invasive *H. influenzae* disease diagnosed in South Africa between 2006 and 2019. In this data set, there was a total of 4899 cases. 200 (4.1%), which had no age available and were dropped **(Figure 11.1)**. Of those with age available (n=4699), there were 2905 (61.8%) *H. influenzae* serotyped **(Figure 11.1)**.

Table 11.1: Demographic-based differences between invasive *Haemophilus influenzae* non-serotyped (NS) and serotyped cases in South Africa between 2006 and 2019.

Variable	**Non-Serotyped** ***N=1,794 (38.2%)***	**Serotyped** ***N=2,905 (61.8%)***	**Chi-squared test p-values**
Age (<5 years)	850 (35.1%)	1,569 (64.9%)	Reference
5 years and over	944 (41.4%)	1,336 (58.6%)	<0.001
Sex (Female)	824 (35.6%)	1,488 (51.9%)	Reference
Male	933 (40.4%)	1,377 (59.6%)	0.001
Province: (EC)	254 (57.9%)	185 (42.1%)	Reference
FS	89 (38.0%)	145 (62.0%)	<0.001
GA	675 (38.3%)	1,087 (61.7%)	<0.001
KZ	271 (44.0%)	345 (56.0%)	<0.001
LP	32 (46.4%)	37 (53.6%)	0.076
MP	94 (49.0%)	98 (51.0%)	0.039
NC	24 (30.0%)	56 (70.0%)	<0.001
NW	52 (58.4%)	37 (41.6%)	0.921
WC	303 (24.9%)	915 (75.1%)	<0.001
Clinical Data (Yes)	598 (29.2%)	1,451 (70.8%)	Reference
No	1,196 (45.1%)	1,454 (54.9%)	<0.001

Among the 2905 serotyped cases, 933 (32.1%) were classified as *Hib* cases whereas 1972 (67.9%) cases were classified as non-*Hib* cases. The non-*Hib* serotyped cases included 505 (25.6%) cases that were classified as types a.c-f and 1,467 (74.4%) cases were classified as non-typeables **(Figure 11.1)**. Among the 933 *Hib* cases, 461 (49.4%) were from Enhanced Surveillance Sites (ESS) and had clinical data available whereas 472 (50.6%) did not have clinical data **(Figure 11.1).**

Table 11.2 Demographic-based differences between invasive *Haemophilus influenzae* cases with clinical outcomes data and those without clinical outcomes data reported in South Africa between 2006 and 2019.

Variable	**Clinical Data N= 1,451 (49.9%)**	**No Clinical Data N= 1,454 (50.1%)**	**P-value**
Age (<5 years)	828 (52.8%)	741 (47.2%)	Reference
5 year and over	623 (46.6%)	713 (53.4%)	<0.001
Sex (Female)	730 (49.1%)	758 (50.9%)	Reference
Male	721 (52.4%)	656 (47.6%)	<0.001

Among *Hib* cases with clinical data 327 (70.9%) were less than 5 years old whereas 134 (29.1%) *Hib* cases were 5 years and older and in *Hib* cases without clinical data, 297 (62.9%) were less than 5 years old whereas 175 (37.1%) *Hib* cases were 5 years and older **(Figure 11.1).** Additionally, of the 1972 non-*Hib* cases, 990 (50.2%) had clinical data available whereas 982 (48.9%) did not have clinical data.

Among non-*Hib* cases with clinical data, 501 (50.6%) were less than 5 years old whereas 489 (49.4%) non-*Hib* cases were 5 years and older, and in non-*Hib* cases without clinical data, 444 (49.4%) were less than 5 years old whereas 538 (54.8%) *Hib* cases were 5 years and older **(Figure 11.1)**. Among the non-*Hib* cases with clinical data, 734 (74.1%) were NT *Hi* whereas 256 (25.9%) were a.c-f serotypes, and in non-*Hib* without clinical data, 733 (74.6%) were NT *Hi* whereas 249 (25.4%) were a.c-f serotyped. Of the 734 NT cases with clinical data, 354 (48.2%) were less than 5 years and among the 256 a.c-f cases with clinical data, 147 (57.4%) were less than 5 years old. Of the 733 NT cases with clinical data, 302 (41.2%) were less than 5 years and among the 256 a.c-f cases with clinical data, 142 (57.3%) were less than 5 years old.

As shown in the Table 11.1, serotyped vs NS data differed by age distribution and sex and across all provinces except, Limpopo and Northwest. Additionally, the comparison of between clinical and non-clinical data also showed that they differed in age distribution but not sex**.** It should be noted that the NHLS/NICD group predefined which hospitals sent clinical data prior to the study, therefore the differences pertaining to clinical data availability were not examined at provincial level.

11.2 Objective One

On average, the overall incidence of invasive *Hi* disease between the years 2006 and 2019 in South Africa was 0.65 *(95% CI: 0.63-0.67)* per 100,000 population. In 2006, the incidence specific to each of the invasive *Hi* serotypes were 0.14 *(95% CI: 0.11-0.18)*, 0.20 *(95% CI: 0.16-0.24)*, 0.07 *(95% CI: 0.05-0.10)* and 0.36 *(95% CI: 0.31-0.41)* among the *Hib*, NT *Hi*, a.c-f, and NS case categories, respectively **(Figure 11.2)**. By 2019, incidence, specific to each of the invasive *Hi* serotypes, was 0.07 (95% CI: 0.05-0.09), 0.14 *(95% CI: 0.11-0.18)*, 0.04 *(95% CI: 0.03-0.07)* and 0.19 *(95% CI: 0.12-0.23)* among the *Hib*, NT *Hi*, a.c-f, and NS case categories, respectively **(Figure 11.2)**.

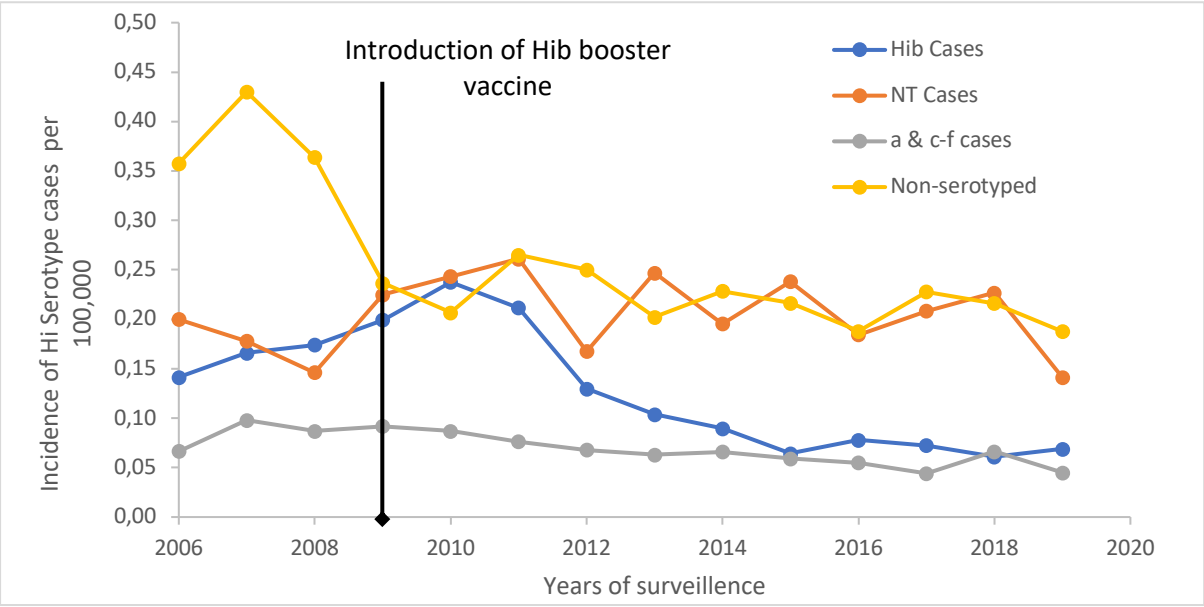


Figure 11.2 Incidence of invasive *Haemophilus influenzae* episodes by serotype and year, South Africa, 2006 to 2019 (N=4899)

The trends of these cases indicate an increase in the incidence of invasive *Hib* cases from 2006 to 2010 from 0.14 *(95% CI: 0.11-0.18)* to 0.24 *(95% CI: 0.20-0.28)* per 100,000 respectively **(Figure 11.2)**. Thereafter, the incidence reduced significantly (p<0.001) by 72.9% *(95% CI: 60.39-81.83)*, from 0.24 *(95% CI: 0.20-0.28)* per 100,000 in 2010 to 0.06 *(95% CI: 0.05-0.09)* per 100,000 in 2015. From 2015 onwards, the incidence of *Hib* cases remained constant until 2019, ranging from 0.06-0.08 per 100,000 **(Figure 11.2)**.

For almost all the years, NT disease had the highest incidence of serotyped *Hi* disease, except in 2008 when *Hib* incidence was higher. The trends in NT cases were observed to fluctuate within the range of 0.14-0.27 per 100,000 population across the observed duration of the study from 2006 to 2019. **(Figure 11.2)**. However, when comparing the incidence of NT in 2010 to that in 2019, there was a significant decrease (p<0.001) in the incidence of NT by 41.9% *(95% CI: 22.77-56.61)* from 0.24 *(95% CI: 0.20-0.28)* in 2010 to 0.14 *(95% CI: 0.11-0.18)* per 100,000 population in 2019.

The a, c-f *Hi* serotype groups were observed with the lowest overall *Hi* incidence within the range of 0.04-0.10 per 100,000 from 2006 to 2019 **(Figure 11.2)**. However, when comparing the incidence of a, c-f in 2010 to that in 2019, there was a significant decrease (p<0.001) in the incidence of a, c-f by 51.27% *(95% CI: 19.68-71.03)* from 0.09 *(95% CI: 0.08-0.12)* in 2010 to 0.04 *(95% CI: 0.03-0.07)* per 100,000 population in 2019.

11.2.1 *Hi* incidence in the pre-*Hib*_VB (2006-2008) years compared to the post-*Hib*_VB years (2013-2019) among children <5 years

The following tables below show the various changes in *Hi* incidence across three serotype groups namely, *Hib*, a, c-f and NT *Hi*. These changes were obtained by comparing mean

incidence across the three pre-*Hib_VB* years (2006-2008) to the incidence post-*Hib_VB* years, 2013-2019, for each serotype of *Hi*.

Table 11.3: Percentage change in the incidence of invasive *Haemophilus influenzae* serotype b (*Hib*) disease, comparing the mean incidence pre-*Haemophilus influenzae* serotype b Vaccine booster introduction (pre-*Hib_VB*) years (2006-2008) to post-*Hib_VB* years (2013-2019), per 100,000 among children <5 years (N=393).

Year	*Hib* Case count	*Hib* incidence	Percentage change (95 % Confidence Interval)	p-value
2006	48	0.84	---	---
2007	60	1.03	---	---
2008	61	1.01	---	---
Mean (2006-2008)	56	0.96	ref	ref
2013	31	0.46	-55.4 (-30.05 ; -72.04)	<0.001
2014	31	0.45	-55.7 (-30.56 ; -72.25)	<0.001
2015	17	0.25	-75.8 (-58.03 ; -86.78)	<0.001
2016	26	0.38	-63.1 (-40.59 ; -77.64)	<0.001
2017	24	0.35	-65.8 (-44.28 ; -79.64)	<0.001
2018	17	0.25	-75.9 (-58.06 ; -87.79)	<0.001
2019	22	0.32	-68.9 (-48.59 ; -81.85)	<0.001

Table 11.4: Percentage changes in the incidence of invasive a, c-f *Haemophilus influenzae*, comparing the mean incidence pre-*Haemophilus influenzae* serotype b Vaccine booster introduction (pre-Hib_VB) years (2006-2008) to post-*Hib_VB* years (2013-2019) per 100,000 among children <5 years (n=223).

Year	a.c-f *Hi* Case count	a.c-f incidence	Percentage change (Confidence Interval)	p-value
2006	23	0.40	---	---
2007	29	0.50	---	---
2008	28	0.46	---	---
Mean (2006-2008)	27	0.45	ref	ref

2013	19	0.28	-39.23 (-13.42; -68.06)	0.097
2014	18	0.26	-42.85 (7.64; -70.35)	0.066
2015	22	0.32	-30.50 (26.71; -62.28)	0.208
2016	17	0.25	-46.35 (2.07; -72.56)	0.043
2017	12	0.18	-62.02 (-22.48; -82.47)	0.004
2018	20	0.29	-36.86 (16.84; -66.43)	0.120
2019	8	0.12	-74.89 (-43.17; -90.14)	<0.001

Table 11.5: Percentage changes in the incidence of invasive non-typeable *Haemophilus influenzae* incidence, comparing the mean incidence pre-*Haemophilus influenzae* serotype b Vaccine booster introduction (pre-*Hib_VB*) years (2006-2008) to post-*Hib_VB* years (2013-2019) per 100,000 children <5 years (n=478).

Year	NT *Hi* Case count	NT *Hi* incidence	Percentage change (Confidence Interval)	p-value
2006	56	0.98	---	---
2007	52	0.89	---	---
2008	32	0.53	---	---
Mean (2006-2008)	47	0.80	ref	ref
2013	57	0.84	4.52 (42.99; -36.52)	0.971
2014	47	0.69	-14.28 (31.26; -44.02)	0.457
2015	44	0.64	-20.15 (23.10; -48.29)	0.285
2016	36	0.52	-34.74 (2.91; -58.93)	0.054
2017	37	0.54	-32.73 (5.73; -57.49)	0.071
2018	48	0.70	-12.95 (-33.02;43.01)	0.500
2019	22	0.32	-60.33(-32.85; -77.23)	<0.001

There was a significant *(p<0.001)* downward trend in the number of invasive *Hib* cases from the pre-*Hib_VB* years 2006-08 to 2015. The significant downward trend continued through to 2019 **(Table 11.3)**. The reduction was more than 50% with the lowest being 55.1% (95% CI: 30.1-72.0) in 2013 and the highest being recorded in 2018 at 75.9% (95% CI:58.1-87.8) All these percentage reduction in the incidence of *Hib* were significant **(Table 11.3)**. In the non-*Hib* categories the percentage differences in the incidence of a, c-f *Hi* were not significant from the pre-*Hib_VB* years 2006-08 to 2015. However, there were significant percentage reductions

in the incidence of a.c-f *Hi* in the years 2016-2019 when compared to the mean incidence in the pre- *Hib_VB* years 2006-08 **(Table 11.4)**. The NT *Hi* group, on the other hand, had only one significant difference in incidence of NT *Hi* observed in, 2019 (-60.33% 95% CI: -32.85 to -77.23, p<0.01). All the other post-*Hib_VB* years had no significant percentage differences in the incidence of NT *Hi* **(Table 11.5).**

11.3 Objective Two

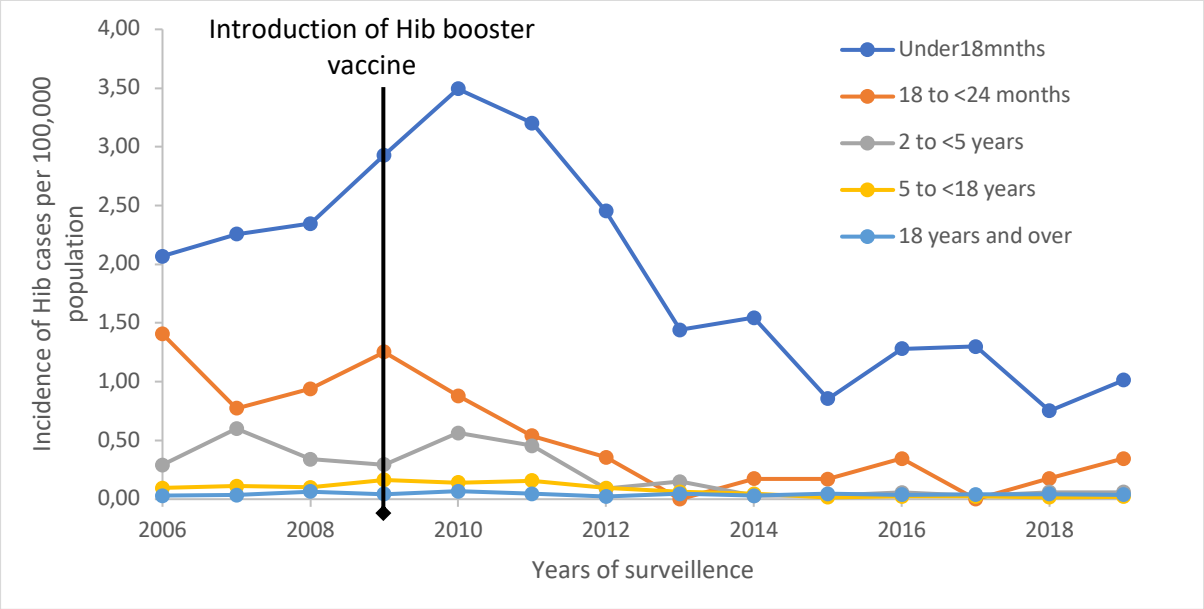


Figure 11.3: Incidence of invasive *Haemophilus influenzae* serotype b (*Hib*) episodes by age groups and year, South Africa, 2006 to 2019 (N=933).

11.3.1 Summary of Incidence of invasive Haemophilus influenzae serotype b (Hib) episodes in children <5 years, in age groups, 2006 - 2019

The highest overall incidence of *Hib,* from 2006 to 2019, was in the <18 months age group**.** Before the introduction of the *Hib_VB* through to one year after, the incidence of *Hib* among the under 18 months age group increased from 2.07 *(95% CI: 1.41-2.92)* per 100,000 population in 2006 to 3.49 *(95% CI: 2.66-4.50)* per 100,000 population in 2010. Thereafter, there was a significant decrease in the *Hib* incidence by 72.87% *(95% CI: 60.39- 81.8,*

p<0.001) from 3.*49 (95% CI: 2.66-4.50)* per 100,000 population in 2010 to 0.86 *(95% CI: 0.48-1.41)* per 100,000 population in 2015. Between 2015 and 2019, the trend in *Hib* incidence continued to fluctuate within the range of 0.75-1.30 per 100,000 population **(Figure 11.3).**

The age group of 18 to <24 months had the second highest overall incidence. A decrease was first observed in the 18 to <24 months age group, from 1.41 *(95% CI: 0.57-2.90)* per 100,000 population in 2006 to 0.77 *(95% CI: 0.35-0.96)* per 100,000 population in 2007 **(Figure 11.3)**. Thereafter, from 2007 to 2009, the incidence of *Hib* increased from 0.77 *(95% CI: 0.21-1.98)* per 100,000 to 1.25 *(95% CI: 0.50-2.58)* per 100,000 population **(Figure 11.3)**. Between, 2006-2015, post the introduction of the *Hib_VB,* the incidence of *Hib* significantly reduced by 87.81% *(95% CI: 5.16-99.73, p=0.023)* from 1.41 *(95% CI: 0.57-2.90)* in 2006 to 0.17 *(95% CI: 0.04-0.96)* per 100,000 population in 2015. Thereafter, from 2015-2019, there was a non-significant increase in the incidence of *Hib* by 50.30% *(95% CI: -8.54-99.16, p=0.622)* to 0.34 *(95% CI: 0.04-1.25)* per 100,000 population.

The age group 2 to <5 years had the 3rd highest overall *Hib* incidence. The incidence within this group also reduced significantly by 86.06% *(95% CI: 37.40-98.49, p=0.002)* from an average incidence of 0.41 *(95% CI: 0.27-0.83)* per 100,000 between 2006-2008 to 0.03 *(95% CI: 0.07-0.21)* per 100,000 in 2014.

In the age groups 5 to <18 years, the incidence of invasive *Hib* was a steady and consistent averaging 0.12 *(95% CI: 0.07-0.20)* cases per 100,000 between 2006 and 2012. This incidence dropped by 48.66% *(95% CI:-27.1:80.9, p=0.122)* to 0.06 *(95% CI: 0.02-0.13)* cases per 100,000 in 2013 (a time when the first group of 1-year-olds that were eligible for the booster in 2009 became 5 years of age). It continued with a non-significant drop by 65.28% *(95% CI: -44.61–94.06, p=0.114)* to an incidence of 0.02 *(95% CI: 0.004-0.06)* per 100,000 in 2019. There were no significant differences in the change in incidence of *Hib* observed in the age

group 18 years and over. The incidence of invasive *Hib* disease was low pre-VB and remained low in the post-VB years.

There was an observed decrease in the incidence of invasive *Hi* cases among children that were considered ineligible for vaccination (<6 weeks) as shown in an age trends graph in the appendix **(APPENDIX D).**

11.3.2 Impact of the *Hib_VB* dose among children <5 years of age in South Africa

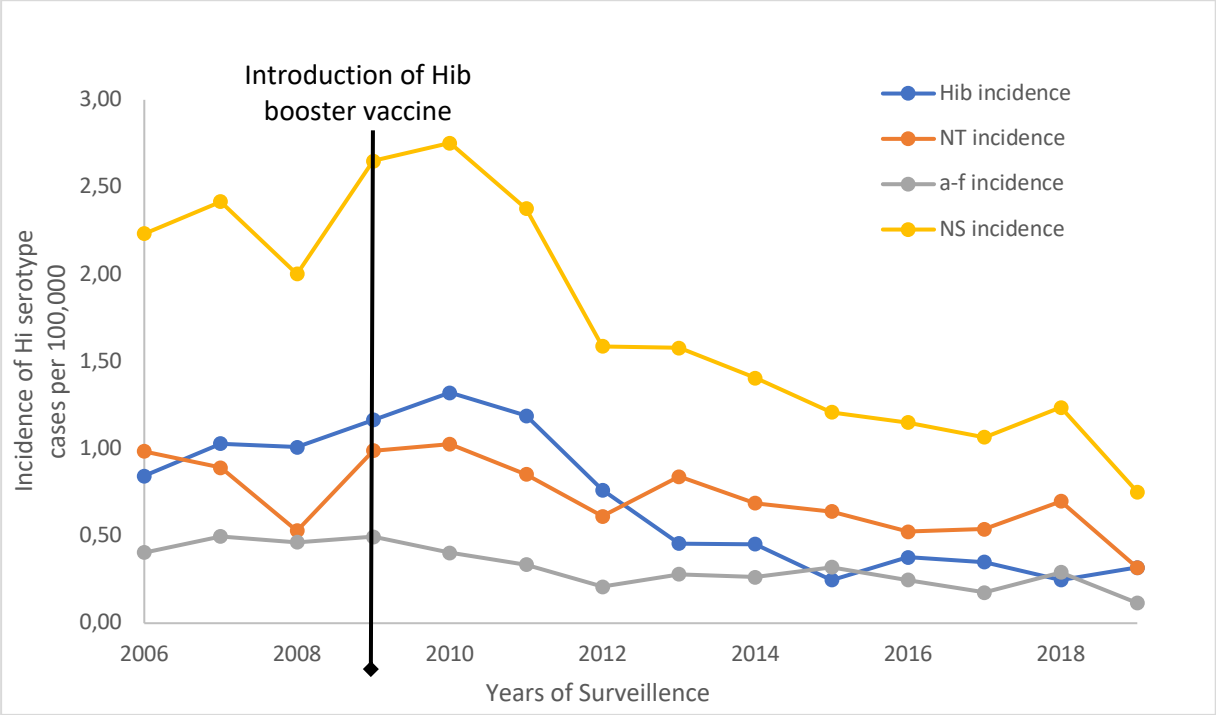


Figure 11.4: Invasive *Haemophilus influenzae* incidence from 2006 to 2019 by *H. influenzae* serotype episodes among children <5 years in South Africa from 2006-2019.

Children <5 years of age had the highest incidence of *Hi* disease, throughout the years of surveillance, from 2006 to 2019. The incidence of NS *Hi* had an upward trend from 2006 which peaked in 2010, and this was followed by a downward trend until 2019 **(Figure 11.4)**.

11.3.3 Vaccine status among children with clinical outcomes data

Of the 2,905 *H. influenzae* serotyped cases, there were 1,451 (50.0%) with clinical data and among these 1,451 cases, 828 (57.1%) were under the age of 5 years (327 *Hib* and 501 non-*Hib*) **(Figure 11.1)**. Among these 828 cases, there were 384 (46.4%) cases that had a documented vaccination history (131 *Hib* and 253 non-*Hib*) leaving 444 (53.6%) without a known vaccination history. Among those <5 years with invasive *Hib* disease and a documented vaccine history, 23 (17.6%), 49 (37.4%), 51 (38.9%), and 8 (6.1%) were unvaccinated, had partially completed their primary doses, had completed their primary doses, and had completed primary + booster doses, respectively. Among the *non-Hib* vaccine outcomes, 47 (18.6%), 59 (23.3%), 119 (47.0%) and 28 (11.1%) were unvaccinated, partial primary, complete primary and complete primary + booster categories, respectively. The table below shows the breakdown of these 131 cases of *H. influenzae* with known vaccination history by their vaccination status from 2009 to 2019.

Table 11.6: Frequency of invasive *Haemophilus influenzae* serotype b (*Hib*) cases among 4 different vaccination categories in the <5 year age group in South Africa from 2009-2019 (N=131).

Year	**Unvaccinated N = 23** (%)	**Partial primary N = 49** (%)	**Complete primary N = 51**(%)	**Complete primary + booster N = 8** (%)	**Total N=131**
2009	2 (20.0%)	4 (40.0%)	3 (30.0%)	1 (10.0%)	10
2010	0 (0.0%)	5 (33.3%)	10 (66.7%)	0 (0.0%)	15
2011	5 (17.9%)	10 (35.7%)	12 (42.7%)	1 (3.6%)	28
2012	3 (15.0%)	11 (55.0%)	6 (30.0%)	0 (0.0%)	20
2013	0 (0.0%)	4 (40.0%)	5 (50.0%)	1 (10.0%	10
2014	0 (0.0%)	5 (62.5.9%)	3 (37.5%)	0 (0.0%)	8
2015	2 (22.2%)	4 (44.4%)	2 (22.2%)	1 (11.1%)	9
2016	6 (50.0%)	2 (16.7%)	3 (25.0%)	1 (8.3%)	12

2017	3 (37.5%)	2 (25.0%)	2 (25.0%)	1 (12.5%)	8
2018	0 (0.0%)	1 (20.0%)	3 (60.0%)	1 (20.0%)	5
2019	2 (33.3%)	1 (37.4%)	2 (33.3%)	1 (16.7.8%)	6

In the unvaccinated group, 9 (39.1%) of the *Hib* cases were too young to be vaccinated (below 6 weeks old) and 14 (60.9%) of these *Hib* cases missed all of the doses that they were eligible for (2 (14.3%), 9 (64.3%), 3 (21.4%) in the 10-14 weeks, 14 weeks to 18 months and 18 months to <5 years categories, respectively). In the partial primary category, 25 (51.0%) of the *Hib* cases were younger than 14 (+2) weeks and thus ineligible for the completion of their primary series whereas 24 (48.9%) of the *Hib* cases, missed the primary series doses they were eligible for. In the complete primary, there were 35 (68.6%) *Hib* cases that were ineligible to receive their booster vaccine (<18 months) and 16 (31.3%) *Hib* cases that missed their booster vaccine (>18 months).

Among the 16 *Hib* cases who had received their full primary doses, 8 (50%) of them had at least one medical condition in the medical risk category and these included lung disease (2), head injury (1), protein energy malnutrition (PEM)(7), prematurity (3) and anaemia (1). In children with a complete primary + booster (vaccine failures), there were 8 *Hib* cases and among these, 5 (62.5%) of them had at least one medical condition in the medical risk category namely Protein Energy Malnutrition (PEM) (1), prematurity (1), and others namely lung disease, malignancy, head injury and anaemia (3). The 8 vaccine failures were from 3 provinces namely Gauteng (3, 37.5%), Kwazulu Natal (1, 12.5%) and Western Cape (4, 50.0%).

Of the 131 *Hib* cases with a known vaccination history, 88 (67.2%) cases were exposed to HIV, and 17 (13.0%) of these *Hib* cases were HIV positive. Furthermore, it was observed that 16 (31.2%) and 7 (87.5%) of the *Hib* cases in the primary complete and primary complete + booster (vaccine failures) categories, respectively, were exposed to HIV. Additionally, 7

(43.7%) of the *Hib* cases in the primary complete and 2 (28.6%) cases in the primary complete + booster (vaccine failures) were among HIV-positive children.

11.4 Objective Three

11.4.1 Factors that increased the risk of acquiring *Hib* versus NT *Hi* disease in children <5 years in South Africa.

There was a total of 828 (16.9%) out of 4899 *H. influenzae* cases, that were used in the risk factor analysis (Table 8). Of the 828 *H. influenzae* cases, 327 were *Hib* cases and 501 were *non-Hib* cases, of which 354 were NT *Hi* **(Table 11.1)**.

Table 11.7: Comparison of risk factors for invasive *Haemophilus influenzae* serotype b (*Hib*) disease and non-typeable *Haemophilus influenzae* (NT *Hi*) disease among children <5 years of age with clinical data available, from 2009 – 2019.

		Disease serotype			Univariate analysis			Multivariable analysis	
	Total n/N(%)	Hib N=327 n/N (%)	NT Hi N=354 n/N (%)	Odds Ratio	95% confidence intervals	p-value	Adjusted Odds Ratio	95% confidence intervals	p-value
Sex									
Female	336 / 681(49)	163/ 327 (50)	173/ 354(49)	reference					
Male	345 / 681(51)	164/ 327 (50)	181/ 354(51)	0.96	0.71-1.30	0.799	0.99	0.65-1.48	0.943
Province Category									
Gauteng	234/681(34)	100/ 327 (31)	134/ 354(38)	reference					
Eastern Cape	15/681(2)	9/ 327 (3)	6/ 354(2)	2.01	0.69-5.83	0.199	0.76	0.14-4.02	0.748
Free State	43/681(6)	27/ 327 (8)	16/ 354(5)	2.26	1.16-4.42	0.017	2.36	0.98-5.68	0.056
Kwazulu Natal	120/681(18)	59/ 327 (18)	61/ 354(17)	1.30	0.83-2.02	0.250	1.36	0.76-2.44	0.306
Limpopo	13/681(2)	11/ 327 (3)	2/ 354(1)	7.37	1.60-34.00	0.010	6.40	1.02-40.19	0.048
Mpumalanga	10/681(1)	8/ 327 (2)	2/ 354(1)	5.36	1.11-25.79	0.036	5.70	0.85-38.10	0.072
Northern Cape	27/681(4)	23/ 327 (7)	4/ 354(1)	7.71	2.58-22.98	<0.001	5.49	1.49-20.25	0.010
Northwest	8/681(1)	7/ 327 (2)	1/ 354(0.3)	9.38	0.14-77.46	0.038	18.36	1.58- 213.71	0.020
Western Cape	211/681(31)	83/ 327 (25)	128/ 354(36)	0.87	0.60-1.27	0.467	1.73	1.01- 2.94	0.042
Age category									
< 18 months	525/681(77)	247/ 327 (76)	278/ 354 (79)	reference					
18 to <24 months	43/681(6)	19/ 327 (6)	24/ 354 (7)	0.89	0.48-1.67	0.718	1.12	0.49-2.58	0.788
2 to <5 years	113/681(17)	61/ 327 (19)	52/ 354 (15)	1.32	0.89-1.98	0.182	1.80	0.99-3.29	0.052
Hib Vaccination Status									
Unvaccinated	60/681(9)	23/ 327 (7)	37/ 354(9)	reference					
Partial Primary	90/681(13)	49/ 327 (15)	41/ 354(12)	1.92	0.98-3.74	0.054	1.05	0.42-2.61	0.915
Complete Primary	126/681(19)	51/ 327 (16)	75/ 354(24)	1.09	0.58-2.05	0.780	0.58	0.24-1.36	0.209
Complete Primary +booster	32/681(5)	8/ 327 (2)	24/ 354(6)	0.54	0.21-1.39	0.201	0.24	0.07-0.88	0.031
Unknown	373/681(55)	8/ 327 (60)	177/ 354(50)	1.78	1.01-3.11	0.043	1.02	0.47-2.25	0.942
HIV status									
Negative	354/681(52)	183/ 327 (56)	171/ 354(48)	reference					
Positive	157/681(23)	70/ 327 (21)	87/ 354(25)	0.75	0.52-1.09	0.139	0.90	0.54-1.50	0.683
Unknown	170/681(25)	74/ 327 (23)	96/ 354(27)	0.72	0.50-1.04	0.081	0.99	0.58-1.70	0.975
HIV exposure									

No	*236/558(42)*	*119/ 259(46)*	*117/ 299 (39)*	*reference*					
Yes	*322/558(58)*	*140 / 259(54)*	*182/ 299 (61)*	*0.75*	*0.54-1.06*	*0.104*			
Tuberculosis infection									
No	*540/616(88)*	*266/ 306 (87)*	*274/ 310 (88)*	*reference*					
Yes	*76/616(12)*	*40/ 306 (13)*	*36/ 310 (12)*	*1.14*	*0.71-1.85*	*0.582*			
Medical disease risk									
No	*360/ 606(59)*	*205/ 299 (69)*	*155/ 307(50)*	*reference*					
Yes	*246/606(41)*	*94/ 299 (31)*	*152/ 307(50)*	*0.47*	*0.34-0.65*	*0.000*	*0.65*	*0.42-1.01*	*0.055*
Specimen type									
CSF	*201/681(30)*	*179/ 327 (55)*	*22/ 354(7)*	*reference*					
Blood	*417 /681(61)*	*136/ 327 (42)*	*281/ 354(79)*	*0.05*	*0.03-0.10*	*0.000*	*0.06*	*0.03-0.10*	*0.000*
Other	*63/681(9)*	*12/ 327 (4)*	*51/ 354(14)*	*0.03*	*0.01-0.06*	*0.000*	*0.05*	*0.02-0.13*	*0.000*
Disease Outcome									
Death	*160/678(24)*	*42/ 325(13)*	*118/ 353(33)*	*reference*					
Recovered	*518/678(76)*	*283/ 325(87)*	*235/ 353(67)*	*3.38*	*2.29-5.01*	*0.000*	*3.29*	*1.87- 5.77*	*0.000*

Table 11.7 summarizes the univariate and multivariate logistic regression results for the variables included in the preceding bivariate analysis. Each of the multivariate logistic regression is based on one independent variable among children < 5 years in South Africa and how it influences that likelihood of these children either being *Hib* or NT *Hi* infected. In the univariate analysis, Table 11.7 indicated that children did not have any significant odds of getting *Hib* ($p<0.05$), based on their sex, age, HIV status, HIV exposure or tuberculosis infection **(Table 11.7)**.

However, children had higher significant odds of being diagnosed with *Hib* compared to NT *Hi,* if they were from some provinces namely, Free State (OR = 2.26 *(95% CI:1.15 – 4.42, p=0.017)*, Limpopo (OR = 7.37 *(95% CI:1.60 – 33.99, p=0.010)*, Mpumalanga (OR = 5.36 *(95% CI:1.11 – 25.79, p=0.036)*, Northern Cape (OR = 7.71 *(95% CI:2.58 – 22.98, p<0.001)*, and Northwest (OR = 9.38 *(95% CI:1.16 – 77.46, p=0.038)* compared to the reference province Gauteng; if they were with an unknown vaccination status (OR = 1.73 *(95% CI:1.02 – 3.11, p=0.043)* and if they had recovered from *Hi* disease (OR = 3.38 *(95% CI:2.29 – 5.01, p<0.001)*. Children had significantly lower odds of being diagnosed with *Hib* compared to NT *Hi* if their specimen types drawn were blood (OR = 0.06 *(95% CI:0.04 – 0.10, p<0.001)* or other types (OR = 0.03 *(95% CI:0.01 – 0.06, p<0.001)* besides CSF.

Additionally, children who had at least one medical risk also had a reduced risk of being diagnosed with *Hib* as compared to NT *Hi* (OR = 0.47 *(95% CI:0.01 – 0.06, p<0.001)* **(Table 11.7)**. In the multivariate analysis, after controlling for factors like sex, age and HIV status, children were more likely to get *Hib* as compared to NT *Hi* if they were from Limpopo (aOR:6.40; 95% CI:1.02-40.19; p=0.048), Northern Cape (aOR:5.49; 95% CI:1.49-20.25; p=0.010), Northwest (aOR:18.36; 95% CI:1.58-213.71; p=0.020), Western Cape (aOR:1.73; 95% CI:1.0-2.94; p=0.042) provinces and had recovered from the invasive *Hi* disease

(aOR:3.29; 95% CI:1.87-5.77; p=0.000). Children were less likely to get *Hib* as compared to NT *Hi* if they had completed their primary *Hib* vaccine series along with a booster shot (aOR:0.24; 95% CI:0.07-0.88; p=0.031), and their specimen type was blood (aOR:0.06; 95% CI:0.03-0.10; p=0.000) or other types (aOR:0.05; 95% CI:0.02-0.13; p=0.000) besides CSF **(Table 11.7)**.

12 DISCUSSION

Due to the high incidence of invasive *Hib* both globally and in South Africa, many countries introduced the conjugate *Hib* vaccine into their EPI schedule. South Africa introduced the vaccine in 2000 in its EPI schedule given at 6, 10, and 14 weeks and this reportedly reduced the incidence of *Hib* (22). However, a resurgence in *Hib* in South Africa led to the introduction of a booster vaccine dosage in 2009 that is given at 18 months of age as part of a pentavalent vaccine (Pentaxim®) (5). Since the introduction of this booster vaccine in South Africa's EPI schedule, there has not yet been any published data concerning the trends in *Hib* post-*Hib_VB* years. As such this research essay sought to examine the impact of the *Hib* booster vaccine dosage 10 years since its introduction in the South African EPI schedule. Various findings in each of the objectives are discussed below.

12.1 Key Findings

12.1.1 Overall Findings in South Africa

A resurgence in the incidence of invasive *Hib* disease had been observed during the pre-*Hib_VB* introduction years however, an overall decrease was observed in *Hib* during the post-*Hib_VB* introduction years. There were significant decreases in serotype a-f, NT, and b from 2010 to 2019 for all ages and again in the <5 years. However, the decreasing trend in incidence for each year past 2013 was only observed for serotype b in the <5 years **(Figure 11.2, Table**

11.3) whereas the other serotypes fluctuated year on year, with both significant and non-significant decreases from 2013 (table 11.4 and 11.5). The incidence of invasive *Hib* disease reduced significantly during the post-*Hib_VB* introduction years compared to pre booster years. NS *Hi* episodes had the highest overall cases of *Hi* and this was observed to be increasing from the 2006 and peaked in 2010, after which it started decreasing and continued to do from 2010 through to 2019. The NS *Hi* cases also had the largest decrease in the number of cases.

In the age-specific trends graph**,** the highest overall incidence rate of invasive *Hib* was in the <18 months age group, and this was also the age group with the highest drop in invasive *Hib* disease during the post-*Hib_VB* introduction years. There was also a significant reduction in invasive *Hib* in all other age groups during the post-*Hib_VB* introduction years except in the 18 year and above age group. It was also noteworthy that the age group 5 to <18 years initially had a stable incidence of invasive *Hib* from 2006 to 2012 and in 2013, an approximate 50% significant decrease was observed which further significantly ($p<0.01$) reduced by over 80% by 2019. These significant reductions were attributed to the 5-year-olds having received a booster vaccine shot at 18 months of age.

12.1.2 Findings in the <5 years

The overall *H. influenzae* trends by various invasive *Hi* serotypes were similar in the given <5 years age groups in South Africa. However, a greater decrease was observed in invasive *Hib* disease in the *Hi* trends specific to <5 years age categories as compared to all age group categories. There were significant percentage decreases in all the post-*Hib_VB* years (2013-2019) as compared to the pre-*Hib_VB* years (2006-2008) in the *Hib* subtype, which was not the case in a.c-f *Hi* and NT *Hi*. The pre- and post-trend analysis further demonstrated that there was a large impact of the *Hib* booster vaccine, most specifically among <5 years demonstrated

by the large significant ($p<0.001$) percentage reductions in invasive *Hib* disease in each of the post-*Hib_VB* years (2013-2019).

It was observed that, in the post-*Hib_VB* years (2009-2019), there were more cases of *Hib* within the unvaccinated cohort (64.2%) that were ineligible to be vaccinated (less than 6 weeks). Half of the cases that were considered pre-booster vaccine failures (primary complete) and over 60% of vaccine failures (primary complete + booster) had at least one medical risk condition. In the multivariate analysis, comparing the acquisition of Hib to NT *Hi,* children were more likely to get *Hib* as compared to NT *Hi* if they were from provinces namely, Limpopo ($p<0.05$), Northern Cape ($p<0.05$), and Northwest ($p<0.05$), Western Cape ($p<0.05$). Children were less likely to get *Hib* as compared to NT *Hi* if they completed their primary series along with a booster shot ($p<0.05$) or were among the cases that were not identified from CSFs **(Table 11.7)**.

12.1.3 Discussion of Key Findings

Shortly after the introduction of the *Hib_VB* booster vaccine, an increase in the incidence of *Hib* was still observed. This was likely due to the increasing trends in *Hib* disease during the pre-Hib_VB years as well as the limited coverage of the booster vaccine at that time. Subsequently, in the post-*Hib_VB* years, there was an observed reduction in *H. influenzae* trends which demonstrated that the desired aim of reversing the resurgence in *Hib* across all age groups was achieved. This confirmed the prediction that a booster dose would benefit the children who were unvaccinated or incompletely vaccinated against *Hib* by providing an additional opportunity for vaccination or boosting immunity in the second year of life (22). This is because children may not have achieved optimal immunity in their first year due to physiological immaturity of the immune system. This prediction is further demonstrated in the largest and the second largest reduction in invasive *Hib* disease being observed among the <18

months and the 18 to <24 months old children, respectively. The widespread use of the *HibCV* vaccine and eventual usage of the booster vaccine was further predicted to protect children that were too young and thus ineligible for vaccination (22). This was demonstrated in the observed reduction in the trends of invasive *Hib* disease among children <6 weeks old**,** who were not eligible for any of the *Hib* vaccines, and among children <18 months old who would not have been eligible for the booster vaccine**.** (1)

In the <5-year age group, 14 out of the 23 (60.9%) unvaccinated *Hib* cases were older than 6 weeks and thus eligible for vaccine. Had these children been vaccinated, some of the *Hib* cases <5 years could have been averted. Pertaining to the 9/23 (39.1%) who were ineligible, whilst it is not feasible to immunize children under 6 weeks against *Hib,* children's mothers can potentially be immunized during pregnancy to protect their children until they are eligible for vaccination. However, maternal Hib vaccination is not being considered as an intervention at this stage. Additionally, a *Hib* vaccination during pregnancy versus placebo trial that was carried out involving 213 women and 213 neonates did not find a clear difference between the treatment and control arm in improving maternal, neonatal and infant health outcomes (38). However, this trial was observed to have a high risk for bias due to the nature of randomization it had for both groups. As such more studies with a reduced risk of bias should be carried out to ensure that generalizable observations can be made (38). With this observation, further studies could be carried out looking to assess much more generalizable impact maternal *Hib* vaccination during pregnancy has on neonatal health outcomes specifically concerning *Hib*.

Some of the vaccine failures (over 60%) in children <5 years were among those with at least one medical condition, and this could have increased their risk of acquiring *Hib.* Whilst there is evidence to suggest that there is an increased risk of *Hib* among people with comorbidities (39,40), the evidence was gathered from adults who are presumed to be less susceptible to invasive *Hib* whereas the analysis in this study was focused on children under 5 years.

Nevertheless, these cases were observed among people who were previously vaccinated and some of the comorbidities that were identified included lung diseases, malignancy, renal suppression and other comorbidities (40). Given that these medical risk conditions were similar to those which were observed among children in South Africa, it is reasonable to suggest that these comorbidities could have contributed to the vaccine failures. However, further studies should be carried out to demonstrate the impact that comorbidities could have on vaccinated children <5 years to better examine how best they contribute to vaccine failures. The increased incidence in *Hi* among NS cases, peaking in 2010, followed by the eventual overall consistent largest reduction, post Hib_*VB* era**,** suggests that majority of the NS cases among <5 were *Hib* cases.

The significant higher odds that were observed in acquiring *Hib* vs NT *Hi* disease in the multivariate analysis based on one's province**,** could be explained by the differences in the vaccine coverage within these provinces. This is because most of the provinces namely, Limpopo (70.5%), Northwest (75.2%) and Western Cape (80.9%) which were with higher odds were also observed with a lower overall vaccine coverage. This was the case as compared to the reference province, Gauteng (81.4%), with the exception of Northern Cape (81.6%) which had a slightly (0.1%) higher vaccine coverage (32). Furthermore, these differences could also have resulted from the differences in the diagnostic possibilities available in various provinces as compared to the reference province Gauteng. Given that some of these provinces had less well supported microbiology labs, they likely processed proportionately more CSF than blood specimens as compared to the reference province (Gauteng) and as such *Hib* would more likely be diagnosed than NT *Hi* therein. Children who had completed their primary series and also received their booster *Hib* vaccine were less likely to be diagnosed with *Hib* as compared to NT *Hi.* This observation was expected given that the booster vaccine was aimed at reducing the resurgence in *Hib* among children < 5 years.

Previous studies have shown that HIV did not affect the risk of acquiring *Hib* disease among vaccine failures and this was observed when 53% of invasive *Hib* disease cases were not HIV infected as compared to the 47% who were HIV infected (1,23). Similarly, while this study had a smaller number of cases with known vaccination history, similar findings were observed whereby 48% of the cases which were considered vaccine failures were not HIV infected. However, 52% of the vaccine failures were either HIV infected or had unknown HIV status, and given that, this proportion is much higher than the population prevalence of HIV among children <5 years which is less than 2% (24), showed that HIV status' influence on the risk of acquiring Hib could not be completely ruled out.

The multivariate analysis further showed no significant odds of having *Hib* as compared to NT *Hi* based on one's HIV status. This observation could suggest that one's HIV status did not affect one's risk of vaccine failure among children <5 years. However, an analysis to compare HIV infected and uninfected persons will have to be done to assess the difference in risk in various *Hi* serotype categories. Nevertheless, it was demonstrated that a child's HIV status did not influence their odds of having *Hib* as compared to NT *Hi* disease among children <5 years.

13 STRENGTHS AND LIMITATIONS

13.1 Strengths

The surveillance system used to collect *Hib* data was stable since 2000 and this was long running before and after the introduction of the booster and as such the research was able to present generalizable findings from the pre- and post-*Hib_VB* analysis of *Hib* statistics within South Africa. Both the *Hib* data from the surveillance and the denominator mid-year population data was based on the nationally representative data. This ensured that all the measures and calculations pertaining to the incidence of *Hib* could be generalized to the general population in South Africa.

13.2 Limitations

The overall *Hi* data analyzed were collected via hospital or healthcare surveillance points. These data were mostly of people who had access to health care services. This implied that the incidence rates that were recorded could have been an underestimation of the actual incidence of *H. influenzae* in the target population. Not all the cases had clinical data and thus could not all be included in the risk factor analysis of Hib vs NT *Hi* to give a much more representative comparative.

Additionally, the differences pertaining to clinical data availability were not examined at provincial level. This is because the NHLS/NICD selected which hospitals contributed clinical data. Even prior to the study it was expected that certain provinces would have more hospitals collecting clinical data than others. Furthermore, 38% of the data that were analyzed did not have serotyping testing therefore it was unknown what proportion of these data were either *Hib* or NT *Hi* to give a much more representative analysis of the SA *Hi* data.

Visser and colleagues noted that invasive disease, as was used in this research, is not a great indicator of *Hib* disease overall. This was in addition to the lower number of cases that tend to have invasive *Hib* pneumonia that would be bacteremic (5). Non-bacteraemic *Hib* pneumonia was not included in the surveillance study and is also difficult to diagnose as sputum samples are seldom cultured in children. *Hi* has a fastidious nature and high sensitivity to confounding factors such as sampling after the introduction of antibiotic therapy, transport delays, and incubation conditions, that could have affected the samples and thus diagnosis of patients, leading to underestimation of invasive disease (5).

14 CONCLUSION

The overall observations demonstrated that in the years following the introduction of Hib_*VB* in the South African EPI schedule, the trends in overall *Hib* incidence showed that it was

reducing. This reduction was observed in all main age groups, <5 years and more specifically among both the children that were not eligible for any *Hib* vaccine shot (<6 weeks) as well as those that were not eligible for the *Hib_VB* (<18 months). As such, the introduction of *Hib_VB* was beneficial to the South African population in reducing the overall incidence of invasive *Hib* disease as well as among children <5 years.

15 RECOMMENDATIONS

The CDC recommends that all children <5 years should be vaccinated against *Hib* (2,3). As such, it is recommended in South Africa that childhood coverage of the *Hib_VB* vaccine is increased to ensure that more children are protected and that children receive their vaccines on time. Catch-up vaccination also needs to be accomplished optimally. The CDC does not recommend *Hib* vaccines for children >5 years except under special conditions namely, children at high risk of *Hib* due to asplenia or haemological malignancy, children who have undergone stem cell transplant and those with medical conditions like elective splenectomy, HIV infection and Ig deficiency (41). Therefore, these children at a high risk in South Africa should be offered an extra vaccine dose after five years of age. It is crucial that surveillance pertaining to the incidence of *Hib* disease as well as *Hi* serotypes such as NT *Hi* is continued. This ensures that important fluctuations in serotypes, antibiotic susceptibility, disease incidence, and clinical syndromes are monitored. Further studies could look at vaccinating pregnant women to assess whether immunity can be conferred to the foetus trans-placentally which could prevent children under 6 weeks from developing *Hib* disease. Given the poor collection of children's vaccination history, a more robust documentation of vaccine history should be considered. This could take the form of national electronic capturing of individual childhood vaccinations.

16 ETHICS APPROVAL

Ethics approval was granted for the GERMS-SA surveillance program by the University of the Witwatersrand's Human Research Ethics Committee (WHREC), Medical (Number M1809107). Ethics approval was granted by the WHREC to carry out this MSc research (M230434) **(APPENDIX F).**

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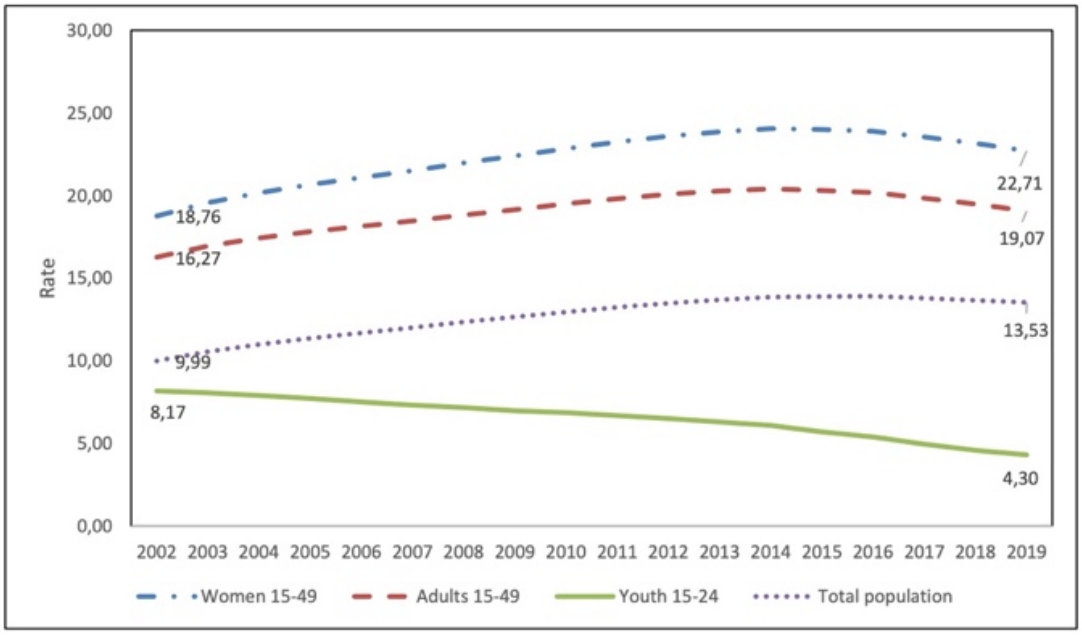
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18 APPENDICES

APPENDIX A: *Graph showing HIV prevalence from 2002 – 2019 in South Africa by age groups.*



(34,37).

Table: South Africa's population total by age categories.

(https://www.worldometers.info/world-population/south-africa-population/)

APPENDIX B: TABLE OF THE TOTAL POPULATION OF PEOPLE IN SOUTH AFRICA BY THE GIVEN AGE GROUPS FROM 2006 TO 2019 (VERTICALLY)

Total overall Population	Under 18mnths	Between 18 and 23months	Above 2 & and below 5 years	Between 4 and 18years	Above 18years	Total population of <5 years
49 491 773	1 547 352	497 695	2 741 994	13 666 549	31 038 183	5 685 609
49 996 095	1 595 497	517 263	2 830 500	13 348 186	31 704 650	5 834 138
50 565 812	1 663 017	531 938	2 950 051	13 069 142	32 351 665	6 044 499
51 170 779	1 706 975	559 218	3 063 495	12 850 936	32 990 156	6 266 385
51 784 922	1 689 399	569 051	3 190 310	12 701 014	33 635 148	6 429 672
52 443 326	1 686 445	557 046	3 299 203	12 622 552	34 278 080	6 564 285
53 145 033	1 711 931	562 401	3 354 175	12 595 003	34 921 524	6 681 564
53 873 616	1 733 945	572 233	3 363 470	12 641 102	35 562 867	6 779 309
54 729 551	1 748 750	578 082	3 371 255	12 737 893	36 293 571	6 829 698
55 876 504	1 753 177	583 579	3 417 536	12 880 089	37 242 124	6 864 561
56 422 274	1 719 452	580 748	3 452 004	13 015 737	37 654 333	6 871 663
56 641 210	1 694 720	564 279	3 457 210	13 161 305	37 763 696	6 851 891
57 339 635	1 728 053	562 634	3 432 242	13 393 676	38 223 031	6 869 080
58 087 055	1 776 551	580 135	3 397 460	13 656 903	38 676 007	6 908 444

**N: B The under 18 to 23 months population stats were generated by dividing the population total of the 2 years by half. As such the final total was half of the 2 years population totals and the other half was added onto the 1-year totals to have the total population stats of the under 18 months population group. (United Nations, Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022, Online Edition)*

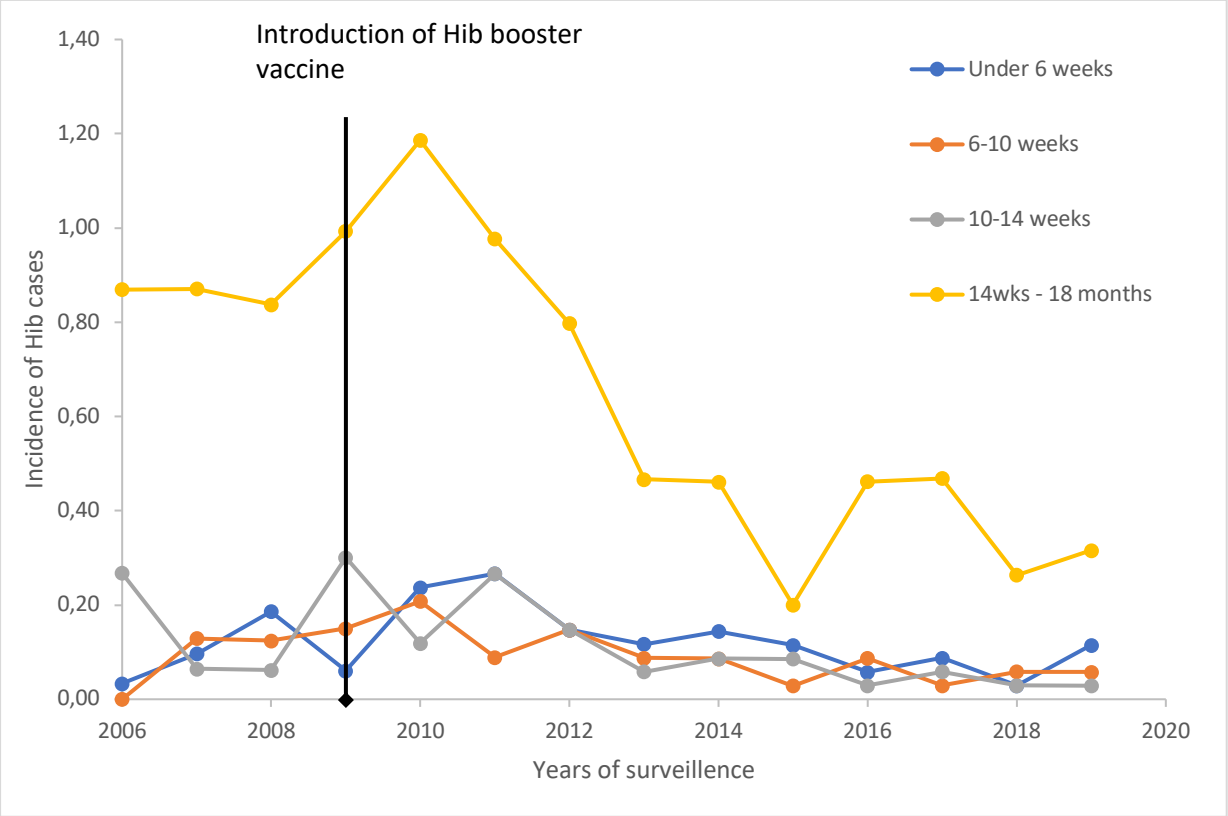
APPENDIX C: *HI* CASES COLLECTED FROM BOTH ENHANCED AND NON-ENHANCED SITES ACROSS ALL PROVINCES IN SOUTH AFRICA

	Non - Serotyped Cases; N=1,794 (38.1%)		**Serotyped Cases; N**=2,905 (61.8%)	
Variable	**Non-ES (%)**	**ES (%)**	**Non-ES (%)**	**ES (%)**
Sex: (Female)	482 (45.6%)	342 (46.5%)	688 (52.0%)	800 (50.7%)
Male	549 (51.9%)	384 (52.2%)	604 (45.6%)	773 (49.0%)
Unknown	27 (2.5%)	10 (1.7%)	34 (2.6%)	6 (0.1%)
Age: (< 5 years)	509 (48.1%)	341 (46.3%)	665 (50.2%)	904 (57.3%)
5 years and more	549 (51.9%)	395 (53.7%)	661 (49.9%)	675 (42.7%)
Province: (EC)	221 (20.9%)	33 (4.5%)	113 (8.7%)	72 (4.5%)
FS	43 (4.1%)	46 (6.3%)	59 (4.4%)	86 (5.3%)
GA	362 (34.2%)	313 (42.5%)	517 (39.4%)	570 (35.8%)
KZ	169 (16.0%)	102 (13.9%)	88 (7.0%)	257 (16.0%)
LP	17 (1.6%)	15 (2.0%)	18 (8.7%)	19 (1.2%)
MP	79 (7.5%)	15 (2.0%)	59 (4.5%)	39 (2.4%)
NC	3 (0.3%)	21 (2.9%)	8 (0.7%)	48 (3.0%)
NW	36 (3.4%)	16 (2.2%)	25 (8.7%)	12 (0.7%)
WC	128 (12.1%)	175 (24.7%)	439 (32.2%)	476 (31.0%)
South Africa (ES)	**1,058 (59.0%)**	**736 (41.0%)**	**1,326 (45.7%)**	**1,579 (54.4%)**

ES Enhanced surveillance hospital site: A hospital site where additional clinical data is collected from all patients with the disease under surveillance.

Non Enhanced surveillance site: All other hospitals in South Africa.

APPENDIX D: GRAPH SHOWING THE INCIDENCE OF INVASIVE *HIB* CASES AMONG CHILDREN UNDER 18 MONTHS OF AGE IN SOUTH AFRICA FROM 2006-2019



APPENDIX E: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Mr J Tumusiime
School of Pathology
Medical School
University

E-mail: 1687953@students.wits.ac.za

CC: Supervisor: Drs M Groome and S Meiring
<MichelleG@nicd.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

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

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

DATE: 2023/07/07

REF: R14/49

PROTOCOL NO: **M230434** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Epidemiology of invasive Haemophilus influenzae serotype b disease following implementation of a booster vaccine dose in 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 Government funding of the University.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Mr J Tumusiime

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230434

NAME: **(Principal Investigator)**	Mr J Tumusiime
DEPARTMENT:	School of Pathology Medical School University
PROJECT TITLE:	*Epidemiology of invasive Haemophilus influenzae serotype b disease following implementation of a booster vaccine dose in South Africa*
DATE CONSIDERED:	2023/05/05
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M18/09/107
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs M Groome and S Meiring
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/07/07 **EXPIRY DATE:** 2028/07/06

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

DECLARATION OF INVESTIGATORS

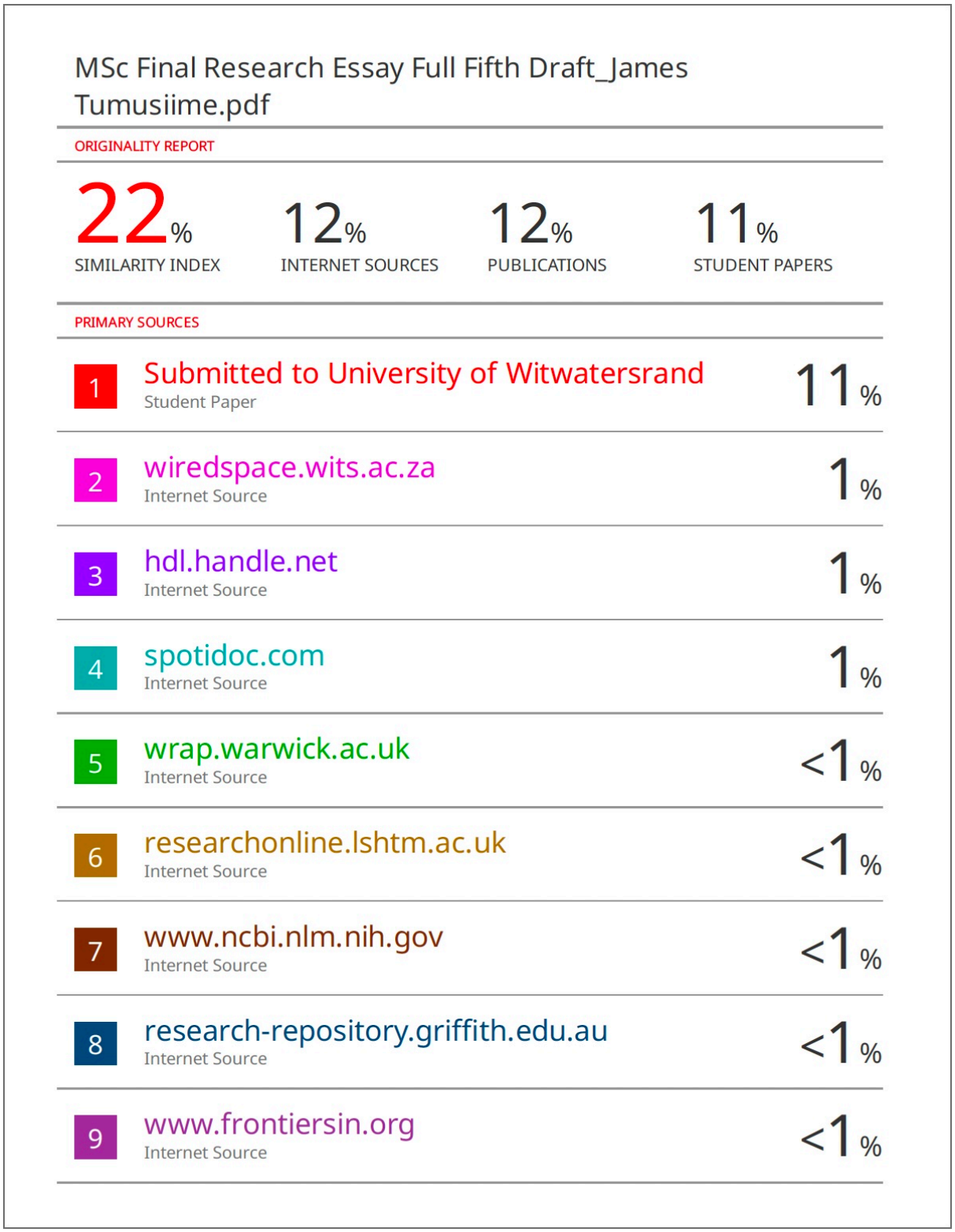
To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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

Signature of Principal Investigator

12/08/2023
Date

19 TURNITIN REPORT



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