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UNIVERSITY OF WITWATERSRAND,

FACULTY OF HEALTH SCIENCES

SCHOOL OF PATHOLOGY

Hospitalizations for Influenza after introduction of Pneumococcal Conjugate Vaccines at Chris Hani Baragwanath Academic Hospital in South Africa, 2009-2018

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A research report submitted to the Faculty of Heath Sciences, University of Witwatersrand, Johannesburg in partial fulfilment of the requirements of Master of Science in Medicine in the field of Vaccinology



WITS

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DECLARATION

I, Farisai Kuonza (880911) am submitting my research report in partial fulfilment of the requirements of Master of Science in Medicine in the field of Vaccinology at the school of Pathology, University of Witwatersrand. I declare that materials displayed in this research report have not been submitted before for any degree at any University and they are my own work. I have appropriately accredited materials from other sources using standard referencing,



25 February 2021

Signature Date

DEDICATION

I dedicate this reach report to my parents for always encouraging and supporting me to achieve more in life.

ABSTRACT

Background

Pneumococcal diseases are of public health importance among children under 5 years of age due to the high burden of morbidity and mortality. Disease and mortality due to *Streptococcus pneumoniae* can be prevented by using suitable vaccines. Pneumococcal conjugate vaccines (PCVs) have been introduced into the childhood vaccination programs globally, what has resulted in significant decreases in pneumococcal disease in both vaccinated and unvaccinated children due to indirect effects. Secondary respiratory infection by *Streptococcus pneumoniae* following influenza infection is a common and challenging clinical problem. PCV-7 was introduced in the South African Expanded Program on Immunization in April 2009. The current research aimed to describe hospitalization and mortality due to influenza after introduction of pneumococcal vaccines in South Africa. Data from the Chris Hani Baragwanath Academic Hospital (CHBAH) was used.

Methods

This study used secondary data obtained from the Severe Acute Respiratory Illness Surveillance (2009 to 2013) and the Respiratory and Meningeal Pathogens Unit surveillance (2015 to 2018) studies done at CHBAH, in Soweto, South Africa among children <5 years old. Adjusted incidence rates of influenza associated hospitalizations and deaths were calculated by month, year, and age group. Poisson regression was used to describe the trend in incidence of influenza associated hospitalizations and deaths among children by year and age group. The proportion of hospitalized children infected with influenza virus among the pneumonia cases was determined by year, age group, and HIV exposure.

Results

There were 14 941 children <5 years of age enrolled into the surveillance studies at CHBAH between 2009 to 2013 and 2015to2018, 894 (6.0%) were PCR positive for influenza and 7 389 (49.5%) had disease coded as pneumonia. There were 63 influenza-associated in-hospital deaths during the study period. The incidence estimates of influenza associated hospitalization varied by month, year, and the seasonality varied from year to year. There was a decreasing trend in influenza

associated hospitalization from 2010 up to 2017 and an increase in the incidence of influenza associated death from 2009 to 2017. The overall incidence of influenza associated hospitalizations and deaths varied between 67-272 per 100 000 population and 6-24 per 100 000 population in all age categories, respectively. Influenza associated hospitalization incidence was highest in children 4 months to <1 year [372 (95% CI: 347-398)] and in 2009 [378 (95% CI: 344-413)] per 100 000 population. The incidence of influenza associated death was elevated in 2017 [24 (95% CI: 15-33)] per 100 000 population and in children aged 4 months to <1 year [24 (95% CI: 17-31) per 100 000 population]. Compared to children hospitalized in 2009, children admitted from 2010 to 2018 were less likely to be hospitalized for influenza associated illness and the relative risk for all age groups ranged from 0.09 (95% CI: 0.03-0.19) to 0.73 (95% CI: 0.38-0.95). Overall, 12% (95% CI: 11%-13%) of all the children hospitalized for influenza associated illness had pneumonia.

Conclusion

There was a decreasing trend in influenza associated hospitalizations incidence from 2010 to 2017 and an increasing trend of influenza associated deaths from 2009 to 2017. The incidence estimates of influenza-associated hospitalization and deaths varied by month, year, season, and age with high estimates being recorded in children aged 4 months to <1 year and in 2009. Despite the introduction of PCV, extra interventions are still required to further reduce influenza associated hospitalizations and deaths in children <5 years of age.

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LIST OF ABBREVIATIONS

AIDS-Human Immunodeficiency Virus

ALRI-Acute Lower Respiratory Infection

CDC-Centre for Disease Control

CHBAH-Chris Hani Baragwanath Academic Hospital

CI-Confidence Intervals

EPI-Expanded Program on Immunisation

HIV-Human Immunodeficiency Virus

IIV-Inactivated influenza vaccine

IPD-Invasive Pneumococcal Disease

LAIV-Live attenuated influenza vaccine

NICD-National Institute for Communicable Diseases

PCV-Pneumococcal Conjugate Vaccine

SARI-Severe Acute Respiratory Illness

UNICEF-United Nations Children's Fund

VDP-Vaccine preventable disease

WHO-World Health Organisation

CHAPTER 1: INTRODUCTION

The chapter covers the pathogenesis of pneumococcal diseases, the estimated global burden, and the different disease-causing serotypes affecting different age groups. The role of immunisation in diminishing incidence of pneumococcal disease is highlighted as a major intervention that contributed to the reduction of morbidity and mortality. The relationship between pneumococcal and influenza diseases is explained in detail. Critical review of the available literature on pneumococcal and influenza disease follows thereafter. The chapter ends with the study justification, aim, and objectives.

1.1 Background

Pneumococcal diseases are diseases caused by the bacterium *Streptococcus pneumoniae,* (or pneumococcus) (1). Globally, pneumococcal diseases are of great public health importance due to the high morbidity and mortality specially among children <5 years, and are responsible for 8-12% of all deaths in children in low and medium-income countries (2). Disease incidence and death rates due to *S. pneumoniae* are elevated in developing than in developed countries, with most deaths occurring in Asia and Africa. *S. pneumoniae*, commonly colonizes the nasopharynx, is carried by many people without causing disease as a commensal of the respiratory tract and horizontal transmission is predominantly through respiratory droplets. Roughly, 20-50% of healthy children have at least one serotype of *S. pneumoniae* in their nasopharynx at any given time and children act as reservoirs of the bacterium. Pooled prevalence estimates of *S. pneumoniae* carriage in children <5 years of age are elevated in low income countries than in middle income countries (3). Nasopharyngeal colonization with a homologous strain is a prerequisite for pneumococcal disease to occur (3).

S. pneumoniae may infect different organ systems resulting in several clinical manifestations, including serious illnesses such as pneumonia, meningitis and bacteraemia and less severe diseases such as otitis media, bronchitis, and sinusitis. Pneumonia is a syndrome that causes inflammation of the air sacs in lungs and other than being caused by bacteria, it can also be caused by fungi and viruses. Pneumonia ranges in severity from mild disease to deadly disease. It is extremely severe in new-borns, young children, the elderly who are above 65 years, and the immunocompromised. The clinical signs and symptoms of pneumonia depend on the nature of disease-causing pathogen, age, and health status of an individual. Signs and symptoms of pneumonia may include chest pain cough, fever, and shortness of breath. When *S. pneumoniae* is found in normally sterile sites such as the blood stream or cerebrospinal fluid, the condition is called Invasive Pneumococcal Disease (IPD) (4). Children below 5 years and especially those <2 years of age are at greatest risk of developing and dying from IPD. In developing countries, the case fatality rates in children are up to 20% for pneumonia, and 50% for meningitis (5).

Based on the composition of the bacterial polysaccharide outer capsule, pneumococci are classified into more than 90 serotypes (6). The distribution of the different disease-causing serotypes varies by geographic region and time. Disease condition and severity, presence of antimicrobial resistant genes and age are also associated with different serotypes. Disease-causing serotypes found in children are different from those found in adults. Of all the *S. pneumoniae* serotypes described to date only a few are normally recovered from disease cases (7).

The high burden of disease and mortality linked to *S. pneumoniae* can be prevented by using suitable vaccines. Consequently, pneumococcal conjugate vaccines (PCV) have been added into the childhood vaccination programs in most countries. The serotypes included in conjugate vaccines target the main disease-causing serotypes in children. PCV-10 and PCV-13 comprise of serotypes which cause more than 70% of serious pneumococcal disease in children worldwide (8). The introduction of pneumococcal vaccines in children resulted in substantial decreases in pneumococcal disease in the vaccinated and unvaccinated children. Vaccines against *S. pneumoniae* do not only protect the vaccinated population, but also decrease disease in

unvaccinated persons in the population through herd protection or indirect effects (9). There is decreased disease incidence and transmission in communities if young children are vaccinated and the unvaccinated children also benefit from protection. Immunisation health benefits may extend to unvaccinated populations and may protect the vaccinated against other pathogens that they were not vaccinated against. Currently, the available pneumococcal vaccines given to children are the 10- and 13-valent PCV (PCV-10, and PCV-13). The numerical value indicates the number of serotypes included in the vaccine. Pneumococcal conjugate vaccines have decreased IPD and hospitalization for pneumonia in children.

Secondary respiratory infections by *S. pneumoniae* following influenza viral infection are a common and challenging clinical problem. Influenza is a viral infection which affects the lower respiratory tract. It is contagious and can cause moderate to serious symptoms. There are three types of influenza viruses which are type A, B and C. Influenza type A and type B are responsible for annual influenza outbreaks whilst influenza type C infections cause mild disease. Influenza type A viruses are classified into subtypes based on hemagglutinin and neuraminidase proteins on the exterior of the virus. The main subtypes of influenza type A viruses that currently affect humans are A(H1N1) and A(H3N2) (10). Influenza type B viruses are normally more contagious. Type B influenza viruses are classified into two lineages which are B/Victoria and B/Yamagata (11). High-risk persons for severe influenza infection include children who are healthy and are of the age group 6 to <24 months, individuals aged 2 years or older with underlying chronic diseases, adults ≥ 65 years, and pregnant women who are past first trimester during influenza season. These populations are at risk of hospitalization after developing severe influenza which may result in death (12).

After infection with influenza, the host may become more susceptible to bacterial infections by *S. pneumoniae* . The causes for this polymicrobial synergy between influenza and *S. pneumoniae* are still not very well understood. It is believed that cell damage by the influenza virus allows bacterial invasiveness and infection (13). A malfunctioning innate immune defence following influenza has also been implicated as the primary trigger for increased vulnerability to secondary bacterial

infections. The influenza/ *S. pneumoniae* synergism has been demonstrated in mice models where it was established that a *S. pneumoniae* challenge after influenza infection led to 100% mortality. The result was peculiar for viral infection preceding bacterial infection. The reverse in the order of administration (*S. pneumoniae* infection first then challenge with influenza) resulted in protection from influenza and increased survival (14).

The current research aimed to describe the hospitalization and mortality associated with influenza infection after introduction of pneumococcal vaccines into the Expanded Program on Immunization (EPI) in South Africa based on the premise that pneumococcal vaccination is protective for influenza hospitalization.

1.2 Literature review

1.2.1 Pneumococcal diseases

Pneumococcal diseases remain the most important infectious cause of morbidity and mortality in children in low- and medium-income countries. There has been a significant decrease in the frequency of pneumococcal disease and deaths, but more action is required globally to accelerate this reduction. Currently, the burden of disease due to pneumococcal infections in children <5 years is still high. Zar et al (2013) estimated that globally there were 120 million episodes of pneumonia in 2011 of which 14 million of these pneumonia cases progressed to severe episodes and 1.3 million episodes resulted in death. A high percentage of these deaths occurred in the first 2 years of life, depicting the severity of pneumonia in young children (15). It is of utmost importance to prioritize pneumococcal disease interventions to children because of high mortality rates.

Streptococcus pneumoniae is the principal etiological agent of vaccine-preventable severe pneumonia and it contributes 18.3% of all pneumonia illnesses. Childhood pneumonia is a clinically serious disease that results from multifaceted collaboration of environmental and host factors. In young children there are several risk factors for developing pneumonia and specifically pneumococcal pneumonia. According to epidemiological investigations of childhood pneumonia, risk factors for developing the disease include zinc deficiency, suboptimum breastfeeding, and undernutrition (16). Lack of exclusive breastfeeding in early months of life and low birth weight are some of the risk factors for pneumonia in low to medium income countries (17).

PCVs have been effective for prevention of clinical and radiological pneumonia and other pneumococcal diseases; therefore, incomplete vaccination (missed doses) is a major avoidable risk factor for the diseases. Inadequate clean air circulation in closed spaces due to household

overcrowding resulting in indoor air pollution is also a risk factor for pneumococcal diseases (18). Indoor air pollution caused by using of biomass or solid fuels intensifies risk of developing pneumonia. The risk of developing pneumococcal disease is also high in children with previous influenza infection as viral infections predisposes bacterial infections, especially *S. pneumoniae* . Chronic diseases such as heart disease, diabetes, lung disease, kidney disease, sickle cell anaemia, asplenia are also risk factors for pneumococcal disease (19).

HIV infection is the single strongest risk factor for the development of pneumococcal disease and is particularly prevalent in children in low income countries. HIV-exposed uninfected children have additional risk of pneumococcal diseases in comparison to HIV-unexposed children, however the reason is not clearly understood (20). HIV infected children are at danger of secondary vaccine-preventable bacterial and viral infections (21). The bacterial- and viral infections cause substantial morbidity and mortality in this population. The effect of vaccine- preventable diseases in HIV infected children does not only relate to the high numbers of deaths in this population but from the high frequency of these illnesses having effects on short and long-term mortality and morbidity due to compromised immunity.

1.2.2 Pneumococcal disease in the pre PCV period

Pneumococcal carriage is a requirement for pneumococcal disease. Verani et al (2018) established the baseline pneumococcal carriage and prevalent serotypes in young children in a study conducted in Mozambique between October 2012 and March 2013 in children immediately before PCV-10 introduction. They noted that there was a non-significant difference in carriage rate between HIV-infected and HIV-uninfected children. Pneumococcal carriage was common among the children with little variation by age and geographic region (22). Annual surveys are recommended to inform change in carriage of PCV serotype specific pneumococci after the introduction and uptake of pneumococcal vaccines in such communities.

In South Africa, before PCV introduction between 2003 and 2008 in the childhood immunisation programme, the risk of IPD was 21 times higher in HIV infected children in comparison to HIV uninfected in the <12 months and 12-36months old age groups (23). Surveillance of pneumococcal diseases before the introduction PCV-7 in South Africa indicated that 70% of IPD in infants was due to serotypes included in PCV-7. In children <5 years, most of all IPD (65%) was related to HIV infection (24). Moreover, HIV-infected children in South Africa had a 40 times higher risk of hospitalization for IPD (25). This depicted the rationale for introduction of PCV in the South African vaccination program.

1.2.3 Pneumococcal vaccines and vaccination schedule

PCV-10 and PCV-13 are the two polysaccharide-protein conjugate vaccines presently available since 2009. Formerly, PCV-7 was available but is progressively being removed from the market. Currently about 9 other PCVs comprising 10–20 serotypes are undergoing clinical trials in humans (26). PCV-10 comprises purified capsular polysaccharides from 10 serotypes: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. PCV-13 is made up of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (27). PCV-7, PCV-10 and PCV-13 are licensed for use in children from six weeks to 5 years of age against IPD, acute otitis media and pneumonia caused by serotypes of *S. pneumoniae* included in the vaccine.

The USA Center for Disease Control (CDC) recommends vaccination with PCV-13 for all children <2 years of age on a schedule of four doses at eight weeks, 16 weeks, 24 weeks, and 12 through to 15 months. The World Health Organisation (WHO) recommends three doses (administered at six-, ten- and fourteen weeks or two-, four- and six months) or alternatively, two doses in the first 4 months of life coupled with a booster given anytime from the age of nine to fifteen months. In South Africa, the PCV-13 dosing schedule consists of three doses administered at six, 14 weeks

and nine months of age. This schedule was implemented to extend the period of protection against IPD in children infected with HIV, who accounted for two-thirds of cases at the time of implementation of vaccine. The District Health Information Software (DHIS) estimates for vaccine coverage of last dose of PCV administered at nine months of age rose from 10.4% in 2009 of the PCV to 64.3% in 2010 and 99% in 2012 (unpublished data - DHIS, extracted May 2020).

In 2007, WHO gave recommendation that countries with a high prevalence of HIV, mortality rates of >50 per 1 000 live births in children <5 years or with risk factors for pneumococcal disease, prioritize the initiation of PCV-7 in their national immunisation programs (28). South Africa introduced PCV-7 into its' routine EPI in April 2009. The PCV-13, which was projected to be more protective against IPD, replaced PCV-7 in May 2011. PCV-13 was projected to give an additional 20% protection against IPD (29).

1.2.4 PCV vaccination in the HIV infected children

HIV infection has become a manageable chronic illness with the advent of antiretroviral therapy (ART). Vaccination is an important strategy in preventing vaccine preventable diseases among the HIV infected individuals. However, there is increased waning immunity after vaccination resulting in reduced duration of seroprotection among the HIV infected compared to uninfected children (30). In South Africa there are no guidelines and procedures for using vaccines for HIV infected children. Vaccinating HIV infected children with CD4+ count more than 200 cells/µL and a viral load under 50 copies/mL is generally considered safe (31).

Severely immunocompromised children infected with HIV, having a CD4 count <200 cells/µL may be vaccinated with non-live vaccines which are possibly safe, though their effectiveness may be low. The use of pneumococcal vaccines in HIV infected children has prevented pneumococcal pneumonia and recurrent IPD (32). Vaccination against pneumococcal disease has been proposed

as an approach to lower the elevated burden of pneumococcal disease in HIV infected children. Globally, recommendations for vaccination against *S. pneumoniae* differ with age group, schedule, and country (29).

1.2.5 Influenza infection

Influenza is a viral infectious disease affecting the respiratory system caused by influenza viruses and it is a major public health problem. Symptoms of influenza comprise cough, sore throat, fever, headache, muscles, and joints pain. The spectrum of the disease varies in severity ranging from mild symptoms to pneumonia and death. Nearly all the symptoms of influenza are self-limiting and resolve within a week of initial infection, though some symptoms, such as cough, can be serious may take long time to resolve. Influenza may be fatal in vulnerable populations like the children, elderly and individuals with comorbidities for instance HIV, diabetes, and other chronic infections. Influenza infection in the paediatric population causes a considerable burden each year worldwide. Children with chronic illnesses and healthy children can fall victim to complications to the virus itself or secondary bacterial infections like pneumonia. Complications and hospitalizations due to influenza disease are more frequent in young children (33).

The global disease burden of influenza disease is high. A systematic review by Nair et al (2011) estimated that in 2008, globally there were 90 million new cases of influenza (data from nine studies) in children <5 years of age. Of these, 20 million cases of influenza-associated acute lower respiratory infections (ALRI) occurred in children <5 years of age (33). The authors estimated that in 2008, there were nearly 111 500 deaths in children <5 years of age which were caused by influenza associated ALRI. Most of the deaths (99%) occurred in developing countries. This underscores that more interventions are still needed to curb influenza transmission and infection in developing countries. The incidence of influenza and mortality due to influenza differed considerably in the different countries included in the systematic review (33). The utmost

important and widespread complication of influenza is pneumonia. Primary pneumonia occurs as a continuation of influenza disease caused by the influenza virus and secondary pneumonia occurs as combined bacterial and viral infection a few days apart (34). There is also increased severe influenza disease admissions during winter months.

A retrospective study from Spain conducted across six influenza seasons (2010 - 2011 to 2015 - 2016) established that the most common subtype of influenza virus circulating was A/H1N1. The study noted that more than 50% of the influenza cases were <2 years of age. Of the influenza cases, 62.2% of them had pneumonia and 11.7% had bacterial pneumonia indicating the polymicrobial synergy that exists between influenza and pneumonia (35). Different influenza strains affect different geographic areas every year and the severity of the influenza strain depends on the vulnerable population with or without pre-existing chronic diseases in the areas. In South Africa, influenza circulates mostly during the winter months. The season usually begins first week of June; though, it could begin as premature as April or as late as July. The winter season lasts about 12 weeks and it varies between seven weeks and 25 weeks.

1.2.6 Disease incidence, hospitalization, and mortality for influenza in South Africa

South Africa is a middle-income country, but socioeconomic status varies within the country with regions that are comparable to low-income countries. Some communities within the country therefore have excessively elevated levels of exposure to risk factors for infectious illnesses. Influenza-associated mean annual hospitalization rate for 2007-2012 in South Africa was projected to be 75 per 100 000 person-years in the influenza season (36). Murray et al (2015) reported incidence of influenza ranging from 7–17% among the SARI patients for the period 2009-2011 which was dependent on age, year, province, and HIV status (37). The high prevalence of HIV infection in South Africa possibly results in elevated statistics of serious influenza related sickness resulting in additional admissions.

Influenza disease accounts for 6 000-11 000 deaths in South Africa every year, with nearly 50% of influenza deaths occurring in old people, and approximately 30% in people infected with HIV (38). In 2018, approximately 13.1% of South Africans were HIV infected (39). This population of HIV infected individuals is particularly vulnerable to influenza infection.(40). In the absence of anti-retroviral therapy, people living with HIV are at risk of being hospitalized for influenza, having prolonged influenza disease and experience higher death rates in comparison to the general uninfected population (35,36). HIV-infected individuals have higher likelihood of hospitalization due to influenza-associated pneumonia. When hospitalized with influenza-associated ALRT infection, people living with HIV-infected individuals are more likely to die than those with no HIV infection because of bacterial coinfections which are highly prevalent in the HIV infected people (41). A study done in South Africa on influenza related mortality reported high case-fatality of 5% among individuals with HIV infection compared to 2% reported in those with no HIV infection (42).

Hospitalization rates are also high among the elderly and in children <5 years. During the influenza season in South Africa, about 14% of patients admitted in hospital for pneumonia and 25% of patients presenting with influenza symptoms test positive for the disease. Persons with chronic diseases including diabetes, pregnant women, lung, and heart disease have high risk of hospitalization and dying from influenza. Nearly 10% of cases of pneumonia hospitalized in South Africa are due to influenza. Furthermore, in South Africa influenza inflicts a significant economic burden in the form of healthcare costs and lost productivity due to hospitalizations (43).

Several risk factors have been described for influenza-associated SARI hospitalization. Abadom et al (2016) in a study done in South Africa established that factors related to hospitalization comprised previous smoking history, HIV infection, tuberculosis and being <5 years of age. Completion of PCV schedule in children below 5 years of age was related to decreased risk of influenza hospitalization. (44). The high-risk groups for severe influenza should be given priority

for vaccination against influenza in South Africa and other comparable settings. The annual influenza vaccination prevents the significant financial and health burden especially for high risk groups.

1.2.7 Complications of influenza infection

Most people infected with influenza recover in a few days, but some people develop severe complications which result in death. Sinusitis, bronchitis, and otitis media are moderate complications of influenza. The most common severe complications associated with influenza are primary influenza pneumonia, pneumonia due to unusual pathogens, exacerbations of chronic pulmonary diseases and secondary bacterial pneumonia (45). Pneumonia can result as a complication of influenza and can cause death in high risk populations. Other severe complications caused by influenza include myocarditis, encephalitis, and multi-organ failure (46). Encephalitis is a condition occurring after influenza virus infects the brain tissue causing irritation and inflammation. The nerve cells can be destroyed and leads to bleeding and brain damage (47). Influenza virus infection can activate excessive inflammatory responses leading to sepsis. Influenza can also worsen chronic medical conditions.

1.2.8 Benefits of pneumococcal vaccines on pneumococcal diseases

In vaccinated HIV infected children, PCV is effective against the vaccine serotype pneumococcal disease. The HIV infected population has an elevated burden of pneumococcal disease, therefore there is a need for complementary plans to avoid pneumococcal disease in adults infected by HIV. PCV is linked to 69% reduced odds of vaccine-serotype IPD hospitalization and 46% decreased likelihood of hospitalization for IPD caused by any serotype in children older than 16 weeks of age without HIV infection in South Africa (48).

Childhood PCV immunization decreases probability of the nasopharynx acquiring serotypes incorporated in the vaccine in children and simultaneously decreases transmission of the disease to persons who are not vaccinated. Nzenze et al (2015) established that from 2009 to 2011, in children <2 years, there was a decline in *S. pneumoniae* colonization from 74.9% to 67.0% after the introduction of PCV (49). On comparison of the period before PCV (2007-2009) and the period after introduction of PCV-13 (2012), they noted decreases in IPD and vaccine serotype colonization attributable to PCV-7 and PCV-13 serotypes in children.

In South Africa, there was decrease in IPD resistant to antibiotics and a decrease in incidence of vaccine serotype in HIV uninfected children after PCV-7 was introduced. Among HIV uninfected children, the incidence estimates of IPD due to serotypes in PCV-7 declined by 85% (95% CI: 79 to 89) (50). After switching to PCV-13, in South Africa, national laboratory-based surveillance observed a decrease in overall cases of IPD from 54·8 to 17·0 per 100 000 person-years for children below 2 years of age (51). Part of this decrease has been credited to improvements in the care of HIV infected individuals. In South Africa, a study done during the 2010 to 2012 period showed an overall vaccine efficacy of 75.8% (95% CI, 54.1–87.2) for ≥1 doses of PCV-13 in averting vaccine serotype IPD (52) .

Surveillance programmes on pneumococcal disease in other settings reveal that IPD due to serotypes included in the vaccine declined following vaccine introduction (8,53). Likewise, Waight et al (2015) noted a decrease in IPD incidence by more than 50% after using PCV for 8 years in England and Wales and continuous herd protection was induced among the unvaccinated population. However, they observed an increase in IPD due to serotypes which are not included in PCV-13 in children below 5 years of age (54). Hospitalizations may be prevented using PCV due to the contribution of *S. pneumoniae* in the complicated influenza disease.

Introduction of PCV-10 in Kenya caused a significant decrease in PCV-10 serotype IPD in young children below 5 years of age. A yearly IPD incidence reduction in young children in 2011 following vaccine introduction of 60.8 cases per 100 000 in the pre-vaccine era vs 3.2 per 100 000 in the post vaccine era was observed (55). PCVs disrupt nasopharyngeal carriage of *S. pneumoniae* and its transmission. PCV-10 was included in the EPI in Sindh, Pakistan in February 2013. After PCV introduction, vaccine-type IPD in children was nearly eliminated and there was substantial decrease in adult IPD highlighting the significance of indirect protection in attaining general population impact (56).

Gentile et al (2018) established a significant reduction in consolidated pneumonia and pneumococcal pneumonia in hospitalized children <5 years of age when comparing hospitalization rates before the PCV-13 was introduced in Argentina (2007-2011) to a period after vaccine introduction (2012-2014). They noted a substantial decline in prevalence of consolidated and pneumococcal pneumonia mostly in children aged 1 year to <2 years of age and a decrease in disease incidence triggered by serotypes in the vaccine (57).

In a randomized clinical trial conducted in South Africa, Klugman et al (2003) established that in HIV uninfected children, PCV-9 lowered the occurrence of the first bout of IPD caused by serotypes in the vaccine by 83% and they reported a vaccine efficacy of 65% in HIV-infected children (58). Similarly, an ecological study from Portugal which evaluated the impact of PCV-7 and PCV-13 on pneumococcal pneumonia hospitalizations in adults ≥65 years established that vaccination resulted in the reduction of pneumococcal pneumonia hospitalization (59). There has been consistent evidence of decline in pneumococcal disease in children that received PCV and in additional groups not selected by vaccination programs (60). The reduction may be ascribed to herd immunity through declining of serotypes in the vaccine and consequent decrease in the transmission of disease in non-vaccinated groups (61). Herd effect has been highlighted to protect more vulnerable groups like the elderly population (62).

1.2.9 Benefits of pneumococcal vaccines on influenza hospitalization

The effect of PCV-9 on influenza hospitalizations has been described in a randomised trial in Soweto, South Africa in 1998 to 2001. A decline in influenza-associated hospitalizations was observed among children vaccinated with PCV-9 compared to controls. Recipients of PCV-9 had a 45% reduction in hospitalization related with influenza infection (63). In another study done in South Africa, that was carried out during the H1N1 2009 pandemic season and the 2012 influenza season, Abadom and colleagues established that in children <5 years of age, completing the PCV-7 schedule was related to a 26% decrease in hospital admission for influenza-related ALRI (44). In addition to PCV immunisation protecting children from influenza-associated hospitalizations, lives of adults may be spared by herd protection.

Annual decreases of between 39% and 50% in influenza-associated hospitalizations in children <2 years were experienced in the USA from 2000 to 2004 after the roll out of PCV-7 (64). More so, a matched case-control, multicentre study was conducted to evaluate PCV in averting hospital admissions due to influenza in children <5 years of age during the influenza pandemic (2009 to 2010) and the 2010 to 2011 influenza outbreak in Spain. PCV reduced influenza hospitalizations by 48% during the 2009 to 2010 influenza pandemic wave in fully vaccinated children. In contrary, in the 2010 to 2011 epidemic, there was no observed reductions in influenza-associated hospitalizations (65). Likewise, Yang et al (2019) in their study in adults ≥65 years of age, established a decrease in the burden of influenza infection in the elderly in Hong Kong when vaccine coverage of pneumococcal and influenza increased, in comparison to the population in Brisbane where vaccination rates were constant (66).

1.3.0 Influenza vaccines

The seasonal influenza vaccine administered annually protects against the influenza viruses that research shows will be most widespread during the approaching season. The WHO is responsible for monitoring the circulating strains of influenza viruses because they mutate and change their genetic composition. The WHO then recommends the serotypes to be incorporated in to the influenza vaccine for the subsequent influenza season. (67). There are many influenza vaccine products licensed and recommended for use worldwide. The two kinds of influenza vaccines mostly utilized are the inactivated (IIV), and the live attenuated vaccine (LAIV). LAIV is approved for use in people 2 to 49 years old with no underlying medical conditions whilst IIV is approved for use in people 6 months or older including pregnant women and those with chronic medical conditions. Influenza vaccines are also available as trivalent (three-component) and quadrivalent (four-component) containing three or four virus strains. The trivalent vaccines (IIV3) target H1N1 virus, H3N2 virus, and B virus, while the quadrivalent ones (IIV4) target influenza A viruses, and influenza B viruses (68).

IIV3 are available in three different formulations which are subunit vaccines, whole-virus vaccines, and split-virus vaccines. There are two IIV4 vaccines that have been developed which are the split inactivated vaccine and the subunit vaccine (69). The different vaccines are licenced for use in different age groups with the trivalent influenza made with adjuvant licensed for people ≥65 years. The inactivated influenza vaccine has a low efficacy on preventing infection, but has been reported to decrease hospitalizations, pneumonia, and mortality. According to South African guidelines, persons who are 6 months and older should receive influenza vaccine every year before the beginning of influenza season. Seasonal vaccination with influenza in Portugal prevented 21% of hospitalizations and 19.5% of deaths in the high-risk population for influenza infection (70).

Because of limited resources in South Africa, certain groups of individuals are given priority for influenza vaccine by the government. The groups that are prioritised for the targeted vaccination include healthcare workers, pregnant women, elderly people ≥65 years, individuals with cardiovascular illnesses and HIV infected persons (30). Other groups that would benefit from

influenza vaccination are individuals ≥6 months with high likelihood for complicated influenza infection because of coexisting infections.

1.3.1 Other factors affecting hospitalizations and mortality for influenza in South Africa

PCV introduction into the childhood EPI in South Africa occurred simultaneously with introduction of ART in the public health system. ART has improved quality of life and lifespan among the HIV infected individuals. Before introduction of ART, the burden of influenza was high among the HIV infected resulting in hospitalization due to severity of the infection or even death (25). Incidence of influenza among the HIV infected has reduced**.** Currently South Africa faces a further problem in understanding the impact of the introduction of PCV as this took place at the same time with changes in parent to child transmission of HIV programs within the country, additionally to more effective management of HIV infected children. Current decrease in hospitalizations in the HIV infected population cannot therefore be attributed to PCV only but also to the contribution of ART.

Influenza vaccinations have also reduced occurrence of influenza infection and hospital admission in children <5 years of age. Vaccination of pregnant women may be protective of influenza disease to the women and the infants. WHO recommends that all pregnant women be vaccinated against influenza using the inactivated vaccine. Studies have shown that influenza vaccination in pregnancy improves birth outcomes, reduces probability of hospitalization due to influenza for both mother and may protect infant from influenza infection during the first months of life when they are most vulnerable (71,72). Protection against influenza infection may reduce incidence of influenza hospitalization among infants. Children ≥ 6 months of age may be vaccinated against influenza. Since the study population for this research includes this age group, the influenza vaccine may be protective of influenza associated hospitalization and death. Temporal trends in influenza associated hospitalization and mortality data should consequently be interpreted with

caution taking into consideration of these changes and interventions, which independently may influence the incidence of influenza and pneumonia in addition to hospitalization and mortality.

1.4 Justification for the study

Influenza disease is a public health burden responsible for serious disease in approximately 3–5 million people and causes 290 000–650 000 deaths globally every year (73), and it is a vital cause of financial loss worldwide (74). The study aims to describe influenza-associated hospitalizations and deaths in children after PCV introduction into the vaccination program in South Africa. PCV might prevent hospitalizations and deaths due to influenza in children because of the contribution by *S. pneumoniae* in complicating influenza disease. Laboratory-based surveillance studies have shown continued decreases in IPD in children after PCV was introduced into childhood vaccination programs. The impact of PCV introduction into the EPI in South Africa on the trends in hospital admissions and mortality related to influenza virus infection has not been explored. Estimations of seasonal influenza associated hospitalization and death burden are beneficial to ascertain groups with high risk in South Africa. Furthermore, baseline estimates of influenza associated hospitalization and deaths, permit evaluation of the effect of unexpected events, such as the occurrence of future novel influenza pandemics.

The results from this research will guide future research so that knowledge gained expands public health decision making in the prevention and control of influenza. It will also assist policy makers in making decisions based on evidence on influenza prevention programmes, for instance influenza vaccination. This results in more effective resource allocation in South Africa and other low to middle income countries. The anticipated reduction in hospitalizations due to influenza could translate to reduced cost on the overburdened health system. This study will investigate the temporal associations of PCV-7 and PCV-13 use on influenza related hospitalizations and deaths in children in South Africa admitted at CHBAH. PCV-10 was not targeted in the current study because it was not introduced in the South African EPI program.

1.5 Study aim and objectives

1.5.1 Study aim

To describe the incidence of influenza disease hospitalizations at CHBAH after the introduction of PCVs among South African children <5 years.

1.5.2 Study objectives

1. To estimate the incidence of influenza associated hospitalizations at CHBAH among children <5 years of age between 2009 and 2018 by month and age group.
2. To describe the trend in incidence of influenza associated hospitalizations and influenza associated deaths among children <5 years of age between 2009 and 2018 by year and age group
3. To estimate the incidence of influenza associated deaths among children <5 years of age between 2009 and 2018 by year and age group.
4. To determine the proportion of hospitalized children <5 years of age infected with influenza virus among the pneumonia cases by year, age group and HIV exposure status.

CHAPTER 2: METHODS

This chapter presents the study design, setting and study population. Definitions of study variables and eligibility criteria are described in depth. The data collection for Severe Acute Respiratory Illness (SARI) and Respiratory and Meningeal Pathogens Research Unit (RPMRU) datasets used for analysis are also outlined and so are the measures taken to ensure data quality. Data analysis methods and ethical considerations are described.

2.1 Study design

This research project is a secondary analysis of observational data obtained from the SARI surveillance study (2009 to 2013) and the RMPRU surveillance study (2015 to 2018) done at CHBAH, in Soweto, South Africa.

2.2 Study setting

The SARI study was implemented in February 2009 in three provinces of South Africa. The sites used in the program were CHBAH in Soweto, an urban area of Gauteng Province, Matikwana and Mapulaneng Hospitals in Mpumalanga Province and Edendale Hospital in KwaZulu-Natal Province. Additionally, another site; Klerksdorp Hospital (Northwest Province) was launched in 2010. For the current project we only used data collected for the national SARI surveillance by the National Institute for Communicable Diseases from children admitted at CHBAH from 2009 to 2013. From 2015 through to 2018, the RMPRU took over the surveillance at CHBAH under RMPRU Surveillance study.

CHBAH is Africa's largest tertiary hospital. The hospital is a public sector hospital serving the population of Soweto. Soweto is a township in the southern part of the Gauteng province and is a low-income area of the city of Johannesburg (Figure 1). In Soweto, nearly 53% of adults are unemployed and about 40% of families have a daily income below two United States dollars (75). In 2018, the population of Soweto included approximately 220 000 children <5 years of age out of a total of about 1.5 million mainly black South Africans. Approximately 90% of individuals in Soweto who require hospitalization are admitted at CHBAH (76). All health care including hospitalization and inpatient care of children at CHBAH is provided free-of-charge by the State.

In April 2009, PCV-7 (Prevnar®; Pfizer) was introduced into the South African Expanded Program on Immunisation (EPI). It was given to infants beginning their routine childhood vaccinations only, with no catch-up campaign for older children. The vaccine was offered to children aged six and 14 weeks, and 9 months. PCV-13 (Prevnar13®; Pfizer) replaced PCV-7 in May 2011 and it was administered in the same schedule. Children aged 18 to 36 months were offered a single dose of PCV during the transition period from PCV-7 to PCV-13 in 2011.

2.3 SARI surveillance study

The SARI study was a prospective hospital-based sentinel syndromic surveillance. It aimed to assess the burden of pneumonia associated hospitalization and to evaluate trends of important respiratory pathogens related to pneumonia. It also sought to assess and describe respiratory syncytial virus seasonality, influenza and other pathogens that infect the respiratory system and to describe how coinfections relate to patient morbidity and outcome among its several other objectives. The study enrolled hospitalized patients of all ages using age specific case definitions for eligibility (77).

***Figure 1**: Map of Soweto and surrounding area*



2.4 RMPRU surveillance study

The RMPRU study was a prospective hospital-based sentinel syndromic surveillance and aimed to provide pathogen-specific estimates of children <5 years hospitalized with pneumonia and gastro-enteritis after the introduction of PCV and rotavirus vaccines into the EPI, as well as clinical course and outcome of children admitted with pneumonia or diarrhoea. It enrolled hospitalized children <5 years of age using age specific case definitions.

2.5 Study population and sample size

The study population for this research comprised of all children <5 years of age that were hospitalized between 2009-2013 and 2015-2018 at CHBAH, Soweto in South Africa and enrolled into the surveillance studies. 2014 was excluded from the analysis because it was a transition period from SARI surveillance to RMPRU surveillance. No sampling was done for the current analysis as such all the children hospitalized at CHBAH that met the inclusion criteria were included in this analysis. Overall, 14 941 children were included in the study. Assuming an incidence of 9.3% (77) for influenza, we estimated the true yearly incidence within ~1% with 95% confidence.

Margin of error =1.96* estimated incidence rate/ sqrt (N)

= 1.96 * 0.093/ sqrt (14,941)

= 0.00149 (approximately equal to 1%)

2.6 Inclusion criteria

The study SARI and RMPRU participants met the following criteria for inclusion in the study,

a) children <5 years of age at time of admission.
b) children hospitalized at CHBAH from 2009 to 2013, and 2015 to 2018.
c) children enrolled into the SARI and RMPRU surveillance studies who had a PCR test for influenza.

Influenza associated death was defined as any death in a child with PCR positive result for influenza type A or B.

2.7 Exclusion criteria

1. Children transferred to intensive care unit from other hospitals and not passing through the admission ward
2. New-borns who were not discharged following delivery

2.8 Laboratory diagnosis of influenza and HIV

After recruitment of children into the study, nasopharyngeal aspirates or nasopharyngeal swabs were collected and sent for laboratory testing. From 2009 to 2013, nasopharyngeal aspirates were sent to the National Institute for Communicable Diseases (NICD) in transport medium at 4^0C-8^0C for influenza testing. From 2014 to 2018 testing was done at RMPRU. Reverse-transcription polymerase chain reaction (PCR) test was used to analyse samples for influenza A and B viruses. HIV exposure status was recorded based on the information available from the Road to Health card for RMPRU and SARI Surveillance.

2.9 Data collection method

Surveillance staff reviewed the admission diagnoses of children <5 years of age admitted at CHBAH. Hospitalized children with an admission diagnosis of neonatal sepsis and lower respiratory tract infection (LRTI) including pneumonia were identified as possible participants. Parents or legal guardians of identified cases were approached and informed about the surveillance study and for those willing for child to partake in the study, written informed consent was obtained. A questionnaire was completed by interview on clinical data and medical history. The paediatric discharge summary database is a database of all paediatric admissions at CHBAH which captures

the discharge diagnosis and outcome of each hospitalized child. Discharge diagnosis and discharge outcome were extracted from this database. The research utilized the SARI and RMPRU databases to obtain all laboratory confirmed influenza hospitalizations during the study period.

2.10 Definition of variables

Age at admission -calculated from date of birth as reported on the Road to health card

Outcome-the outcome of the child as reported in the Paediatric Discharge summary database (discharged or died) and in the SARI data

HIV exposure status-as indicated on the Road to health card

Influenza- indicated in the laboratory results

PCV vaccination-as reported on the Road to health card

Pneumonia diagnosis-extracted from the discharge summary based on the International Classification of Diseases, Tenth Revision codes as defined by; B05.2, B20.6, B25.0, B59, J12.1, J13, J12.9, J13/J91, J14, J15.1, J15.0, J15.2, J15.3, J15.4, J15.8, J15.9, J16.8, J18.0, J18.1, J18.1/J91, J18.9, J22, J15.5, J10.0, J12.2, J12.8, J85.1

PCV 1-first dose of pneumococcal vaccine administered at 6 weeks

PCV 2-second dose of pneumococcal vaccine administered at 14 weeks

PCV 3-third dose of pneumococcal vaccine administered at 9 months

2.11 Data analysis

Analyses were done using STATA version 15.0. For descriptive analysis, frequencies were summary measures applied to categorical variables. Age was categorised into age groups of ≤3 months, 4 months to <1 year, 1 to <2 years and 2 to <5 years. The age categories were selected in line with the time of PCV vaccinations and age at which maternal derived antibodies are protective against diseases. Children <5 years of age have higher risk of hospitalization and difficulties due to influenza than those >5 years of age, mostly if they have coexisting infections and, moreover the children >5 years have elevated death rates (78). No continuous variables were utilised in the analysis so there was no need to display means, medians, and standard deviations. The frequencies were calculated by the diseases of interest which were influenza and pneumonia.

Estimates of population denominator data for Johannesburg metropolitan area region D (Soweto) were used to calculate incidence estimates (Table 1). Population estimates from 2009-2016 were available from Statistics South Africa (79). A linear regression model was used to extrapolate the estimates for 2017 and 2018. Incidence of influenza-associated hospitalization and deaths was calculated per 100 000 children using the number of influenza PCR positive cases, adjusting for days when enrolments did not occur and non-enrolment due to refusal, in the numerator and divided by the midyear total population for the age category for Soweto, multiplied by 100 000. Incidence calculations were calculated for the period 2009-2013, 2015-2018 (2014 was not included as it was the transition period between SARI to RMPRU Surveillance). Incidence rates were calculated by month and age group for influenza associated hospitalization and by year and age group for influenza associated deaths.

Confidence intervals for incidence rates and proportions were calculated using Wald method. Influenza associated hospitalization and influenza associated death trends were described by age group and year using Poisson regression. The outcome variable was the number of influenza associated hospitalizations and deaths. An offset variable which was the population estimate which was a derived weight variable was included in the model to modify each observation so that the count outcome was weighted on population size. Effect of maternal antibodies were not controlled for in the analysis because data on maternal immunisation status was incomplete. Proportion of

hospitalized children <5 years of age infected with influenza virus among the pneumonia cases was calculated by the number influenza PCR positive cases by age group, HIV exposure status and year, divided by number of pneumonia cases of the same category. We considered P values <0.05 as significant.

Table 1: *Population estimates for Soweto (Johannesburg region D)*

	Population estimates								
Year	**2009**	**2010**	**2011**	**2012**	**2013**	**2015**	**2016**	**2017**	**2018**
≤3 months	21 657	22 660	23 777	24 083	24 347	24 521	24 433	25 419	25 792
4 months to <1 year	21 657	22 660	23 777	24 083	24 347	24 521	24 433	25 419	25 792
1 to <2 years	22 794	23 352	24 009	24 113	24 358	24 415	24 415	24 923	25 136
2 to <5 years	72 358	72 431	72 878	72 568	72 549	72 846	73 111	73 039	73 120
Total	116 809	118 433	120 664	120 764	121 154	121 782	121 959	123 381	124 048

2.12 Ethical considerations

The study is a secondary data analysis of anonymized data from the SARI and RMPRU surveillance. Written permission to use the data was requested and obtained from NICD and RMPRU. The research did not involve any human being participation rather was dependent on secondary data subsequently there were no issues related to physical or social harm to the participants. Ethics clearance certificate was obtained from the Faculty of Health Sciences Research Ethics Committee of the University of Witwatersrand. The HREC number for SARI is M081042, for RMPRU surveillance is 131109 and for the current study is M191044. The data were password protected to maintain confidentiality and were accessible to the investigator and the supervisors.

CHAPTER 3: RESULTS

3.0 Introduction

This section provides results of the analyses carried out to achieve the objectives of the study. The chapter begins with a description of the characteristics of the hospitalized children. This is followed by the presentation of the incidence of influenza associated hospitalization and deaths by year and age group. The proportions of influenza cases among pneumonia cases are presented at the end of the chapter.

3.1 Description of overall cohort

A total of 14 941 children <5 years of age were hospitalized at CHBAH between 1 January 2009 to 31 December 2018 and enrolled into the surveillance studies (2014 was excluded from the analysis because it was a transition period from SARI surveillance to RMPRU surveillance). Table 2 shows the baseline characteristics of the enrolled children. Among the hospitalized children, 894 (6.0%) of them tested positive for influenza infection and 7 389 (49.5%) had a pneumonia diagnosis of different causes. 5 768 (38.6%) of the children were between 4 months to <1 year of age at admission.

Children who were 4 months to 1 year of age had the highest prevalence of influenza infections which was 40.6% and the same age group had most pneumonia cases (41.2%). Of the 14 941 children, 8 615 (57.7%) were male, 10 824 (72.4%) were of the black race and 2 748 (18.4%) were HIV-exposed. Out of the 14 941 children hospitalized and enrolled into the study, 909 (6.1%) children <5 years of age died in hospital and of these 63 (6.9%) of these died from influenza related

illness. Table 3 shows the characteristics of children infected with influenza virus stratified by age group and HIV exposure status. A third (n=44) of the HIV-exposed influenza cases were 4 months to <1 year old.

***Table 2**: Characteristics of children <5 years of age enrolled for surveillance*

Characteristic	**Total N (%)**	**Influenza positive cases N (%)**	**All cause Pneumonia N (%)**	**Without Pneumonia N (%)**
Total	14 941	894(6.0)	7 389(49.5)	7 552(50.5)
Age category				
≤3 months	5 118(34.3)	119(13.3)	1 824(24.7)	3 294(43.6)
4 months to <1 year	5 768(38.6)	363(40.6)	3 045(41.2)	2 723(36.1)
1 to <2 years	2 328(15.6)	219(24.5)	1 398(18.9)	930(12.3)
2 to <5 years	1 727(11.6)	193(21.6)	1 122(15.2)	605(8.0)
Sex				
Male	8 615(57.7)	509(56.9)	4 183(56.6)	4 432(58.7)
Female	6 326(42.3)	385(43.1)	3 206(43.4)	3 120(41.3)
Race				
Black	10 824(72.4)	633(70.8)	5 971(80.8)	4 853(64.3)
Asian	24(0.2)	0(0.0)	15(0.2)	9(0.1)
Coloured	256(1.7)	16(1.8)	119(1.6)	137(1.8)
White	4(0.03)	0(0.0)	3(0.04)	1(0.01)
Unknown	3 833(25.7)	245(27.4)	1281(17.3)	2 552(33.8)
HIV Exposure Status				
HIV-unexposed	12 193(81.6)	762(85.2)	6 322(85.6)	5 871(77.7))
HIV-exposed	2 748(18.4)	132(14.8)	1 067(14.4)	2 748(22.3)
Outcome				
Discharged	14 032(93.9)	831(93.0)	7 028(95.1)	7 004(92.7)
Died	909(6.1)	63(7.1)	361(4.9)	548(7.3)

The least number of HIV-exposed children among influenza cases were in the ≤3 months age category.

***Table 3**: Characteristics of hospitalized children <5 years of age infected with influenza*

	HIV Status	
	HIV-exposed N(%)	**HIV-Unexposed N(%)**
Age category		
≤3 months	7(5.3)	112(14.7)
4 months to <1 year	44(33.3)	319(41.9)
1 to <2 years	39(30.0)	180(23.6)
2 to <5 years	42(31.8)	151(19.8)

3.2 PCV vaccination

Table 4 displays the number of children who received PCV. The children were vaccinated elsewhere prior to hospitalization. Among children who were less than 3 months of age, 1 607 (31.4 %) and 1 700 (29.5%) received first (6 weeks) and second doses (14 weeks) of PCV, respectively. Among children who were 4 months to <1 year of age, 2 227 (38.6 %), 981 (35.5%) and 542 (9.4%) received first, second and third doses of PCV, respectively. 546 (31.6%), 462 (26.8%) and 316 (18.3%) of children aged 2 to <5 years received the 3 PCV doses, respectively.

***Table 4**: PCV vaccination by age group*

	Vaccination Status			
	Vaccinated N(%)	**Not Vaccinated N(%)**	**Unknown N(%)**	**Total N**
Age group	**PCV1 (6 weeks)**			
≤3 months	1 607(31.4)	2 977(58.2)	534(10.4)	5 118
4 months to <1 year	2 227(38.6)	2 802(48.6)	739(12.8)	5 768
1 to <2 years	920(39.5)	966(41.5)	442(19.0)	2 328
2 to <5 years	546(31.6)	782(45.3)	399(23.1)	1 727
	PCV2 (14 weeks)			
≤3 months	1 700(29.5)	3 329(57.7)	739(12.8)	5 118
4 months to <1 year	981(33.5)	339(11.6)	1 610(55.0)	5 768
1 to <2 years	783(33.6)	1 103(47.4)	442(19.0)	2 328
2 to <5 years	462(26.8)	866(50.1)	399(23.1)	1 727
	PCV3 (9 months)			
≤3 months	0(0.0)	4 584(89.6)	534(10.4)	5 118
4 months to <1 year	542(9.4)	4 486(77.8)	740(12.8)	5 768
1 to <2 years	530(33.7)	1 356(58.3)	442(19.0)	2 328
2 to <5 years	316(18.3)	1 012(58.6)	399(23.1)	1 727

3.3 Incidence of influenza hospitalization by month

Figure 2 shows the monthly incidence of influenza associated hospitalization from January 2009 to December 2013 and January 2015 to December 2018. The highest monthly incidence of influenza associated hospitalization per 100 000 population was recorded in the winter season of 2018 followed by winter season of 2009. The lowest incidence of hospitalization was recorded in

2013. The seasonality of the influenza infection is shown by the cyclic trend of the influenza associated hospitalization incidence with the peaks being observed in winter (May to September) seasons and minimum incidence in summer. There is a general decreasing trend in influenza hospitalization from 2009 to 2017. In 2018 there was an increase in the incidence of influenza associated hospitalizations.

3.4 Incidence of influenza associated hospitalization by age group and year

The overall incidence of influenza-associated hospitalization during the period 2009 to 2018 in children was highest among children aged 4 months to <1-year age group and it was 372 (95% CI: 347-398) per 100 000 population (Table 5). The highest influenza associated hospitalization incidence in all the years was recorded in 2009 and it was 378 (95% CI: 344-413). It was followed by 2018 which was 339 (95% CI: 301-370). Children aged 4 months to <1-year age had the highest incidences of influenza associated hospitalizations from 2009 to 2018. Their incidences ranged from 131 (95% CI: 85-177) in 2013 to 702 (95% CI; 591-813) in 2009. Children in the 2 to <5 years age group had the lowest incidences ranging from 12 (95% CI: 4-21) in 2013 to 173 (95% CI: 142-203) in 2009 compared to children of other age groups.

3.5 Description of influenza associated hospitalizations and deaths by Poisson Regression

Table 6 shows the relative risks of influenza associated hospitalizations stratified by age category and year. Compared to children hospitalized for influenza in 2009, children of all age groups and in all the consecutive years (2010-2018) were less likely to be hospitalized for influenza. The relative risks were statistically significant except those of children that were 4 months to <1 year, 1 to <2 years and 2 to <5 years in 2018. Children with influenza infection in 2017 were 14 times more likely to die from influenza associated illness compared to children of influenza associated illness in 2009 [14.23(95% CI: 3.35-59.38; p-value<0.001; Table 7)]. Children with influenza in

2018 were 9 times more likely to die compared to children of influenza associated illness in 2009 [9.37(95% CI: 2.21-40.28; p-value 0.002)].

3.6 Incidence of influenza deaths by age group and year

Table 8 shows the incidence of influenza associated deaths by year and age group per 100 000 population. The overall incidence of influenza-associated deaths during the period 2009 to 2018 in children was elevated among children aged 4 months to <1-year age group (24 per 100 000 population; 95% CI: 17-31). There was a gradual increase in influenza associated deaths incidence from 2009 to 2017. Overall incidence of influenza associated deaths in all children was elevated in 2017 (24; 95% CI: 15-33; Table 8). Children in the 4 months to <1-year age group had the highest incidence of death in 2017 (31; 95% CI: 10-53) and 2018 (38; 95% CI: 15-63).

3.7 Proportion of influenza cases among children diagnosed with pneumonia

The overall proportion of influenza infection among children <5 years with pneumonia was 0.12 (95% CI: 0.11-0.13) (Table 9). In all age categories the proportion of influenza cases varied from 0.06 (95% CI: 0.05-0.08) to 0.17 (95% CI: 0.15-0.19). The children aged 2 to <5 years had the highest proportion of influenza infection. The highest proportion of influenza infection among children with pneumonia occurred in 2018 and it was 0.29 (95% CI: 0.25-0.32). The lowest proportion occurred in 2012 and it was 0.06 (95% CI: 0.04-0.08). HIV-unexposed children and HIV-exposed children had similar proportion of influenza infection among pneumonia cases which was 0.17 (95% CI: 0.14-0.20) and 0.17 (95% CI: 0.16-0.18).

***Figure 2**: Incidence of observed influenza associated hospitalization per 100 000 among children <5 years of age at CHBAH, Soweto, South Africa (2009-2018)*

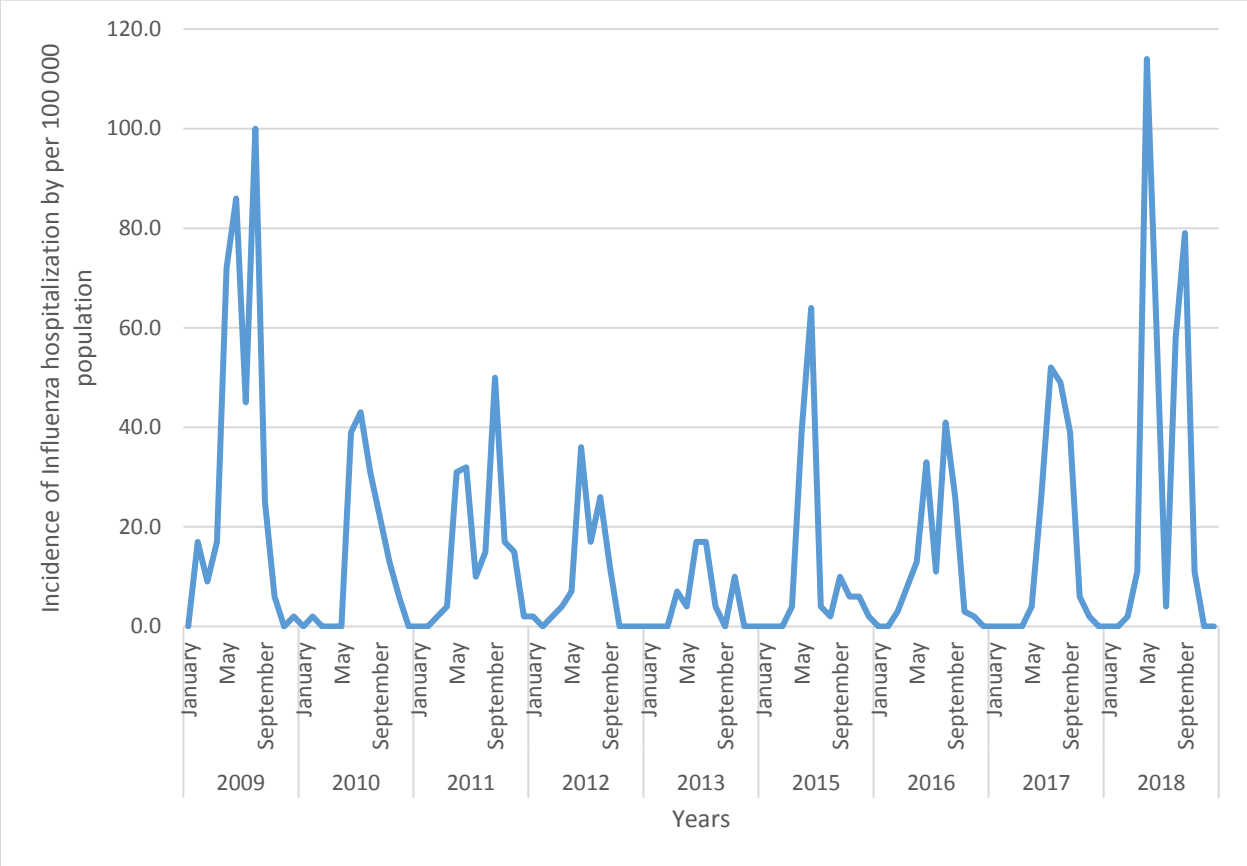


Table 5: *Incidence of influenza associated hospitalizations per 100 000 by age group and year in children <5years at CHBAH, Soweto, South Africa, 2009–2018*

	Incidence of influenza associated hospitalizations among children <5 years at CHBAH, Soweto, South Africa, 2009–2018									
		2009	**2010**	**2011**	**2012**	**2013**	**2015**	**2016**	**2017**	**2018**
Overall	**All**	378 (344-413)	156 (134-179)	177 (153-201)	107 (88-125)	59 (45-72)	137 (117-159)	141 (120-162)	176 (154-201)	339 (301-370)
Age Category										
≤3 months	122 (108-137)	305 (231-378)	154 (103-206)	176 (123-230)	79 (43-114)	86 (49-123)	94 (55-132)	90 (52-128)	69 (37-101)	74 (41-107)
4 months to <1 year	372 (347-398)	702 (591-813)	340 (264-416)	319 (248-391)	203 (147-260)	131 (85-177).	440 (358-523)	360 (285-435)	243 (183-302)	679 (578-779)
1 to <2 years	228 (209-249)	434 (349-520)	180 (126-234)	308 (238-378)	116 (73-159)	37 (13-61)	102 (62-143)	205 (148-261)	212 (156-268)	450 (367-532)
2 to <5 years	67 (61-73)	173 (142-203)	43 (28-58)	32 (19-44)	48 (32-64)	12 (4-21)	16 (7-26)	16 (7-26)	111 (87-135)	154 (126-183)

***Table 6**: Relative Risks of influenza associated hospitalization by age group and year using Poisson regression analyses*

	Relative risks of influenza associated hospitalization ***Relative risk (95% CI; p-value)***			
Year	≤3 months	4 months to <1 year	1 to <2 years	2 to <5 years
2009	*Reference group*			
2010	0.51(0.32-0.92; 0.002)	0.51(0.32-0.74; <0.001)	0.41(0.24-0.65; <0.001)	0.21(0.14-0.44; 0.030)
2011	0.52(0.31-0.91; <0.001)	0.43(0.34-0.65; <0.001)	0.73(0.38-0.95; 0.002)	0.18(0.09-0.34; <0.001)
2012	0.21(0.12-0.53; <0.001)	0.34(0.21-0.44; <0.001)	0.29(0.12-0.48; <0.001)	0.34(0.12-0.53; <0.001)
2013	0.32(0.14-0.61; <0.001)	0.19(0.10-0.34; <0.001)	0.11(0.03-0.23; <0.001)	0.12(0.04-0.22; <0.001)
2015	0.31(0.11-0.64; <0.001)	0.59(0.42-0.91; <0.001)	0.22(0.10-0.39; 0.003)	0.09(0.03-0.19; 0.002)
2016	0.34(0.23-0.63;<0.001)	0.63(0.39-0.78; <0.001)	0.47(0.28-0.76; <0.001)	0.10(0.04-0.21; <0.001)
2017	0.25(0.12-0.55; <0.001)	0.29(0.21-0.45; <0.001)	0.54(0.33-0.81; <0.001)	0.55(0.37-0.87; <0.001)
2018	0.19(0.10-0.52, <0.001)	0.86(0.55-1.24 ; 0.697)	0.96(0.64-1.45; 0.587)	0.76(0.58-1.15; 0.284)

Table 7: *Relative Risks of influenza associated deaths by year using Poisson regression analyses*

Variable	Relative risk	P-Value
Year by influenza associated deaths		
2009	*Reference group*	
2010	2.41(0.45-12.67)	0.281
2011	1.83(0.14-10.57)	0.446
2012	0.54(0.09-5.32)	0.553
2013	0.49(0.12-5.33)	0.551
2017	14.23(3.35-59.38)	<0.001
2018	9.37(2.21-40.28)	0.002

***Table 8**: Incidence of observed influenza associated deaths per 100 000 children <5 years at CHBAH, Soweto, South Africa, 2009 to 2018*

Incidence of observed influenza associated deaths among children <5years of age at CHBAH, Soweto, South Africa,								
	Overall Incidence (95% CI)	**2009**	**2010**	**2011**	**2012**	**2013**	**2017**	**2018**
Overall		2(0-4)	4(0.5-8)	3(0-7)	3(0-7)	8(0-24)	24(15-33)	16(0-25)
Age category								
≤3 months	7(4-11)	5(0-13)	4(0-13)	8(0-20)	0	0	8(0-19)	4(0-11)
4 months to <1 year	24(17-31)	5(0-13)	4(0-13)	4(0-12)	4(0-13)	4(0-12)	31(10-53)	38(15-63)
1 to <2 years	17(12-23)	0	9(0-20)	4(0-12)	0	0	28(7-49)	24(5-13)
2 to <5 years	6(4-8)	0	1(0-4)	0	0	0	18(8-27)	4(0-9)

***Table 9**: Proportions (ratios) of influenza infection among pneumonia cases*

Characteristic	Proportion of influenza infection among the pneumonia cases (95% CI)
Overall Proportion	0.12(0.11-0.13)
Age category	
≤3 months	0.06(0.05-0.08)
4 months to <1 year	0.12(0.11-0.13)
1 to <2 years	0.10(0.11-0.13)
2 to <5 years	0.17(0.15-0.19)
Year	
2009	0.14(0.12-0.16)
2010	0.07(0.06-0.09)
2011	0.10(0.08-0.12)
2012	0.06(0.04-0.08)
2013	0.08(0.05-0.11)
2015	0.10(0.08-0.13)
2016	0.13(0.11-0.16)
2017	0.14(0.11-0.16)
2018	0.29(0.25-0.32)
HIV Exposure Status	
HIV-exposed	0.17(0.14-0.20)
HIV-unexposed	0.17(0.16-0.18)

CHAPTER 4: DISCUSSION

4.0 Introduction

The chapter reflects on the results from the analysis and ends with the study limitations.

4.1 Influenza associated hospitalizations and deaths

This research aimed to describe the influenza associated hospitalizations and deaths among hospitalized children after introduction of pneumococcal conjugate vaccines into the Expanded Program on Immunization in South Africa. We have shown a decreasing trend in influenza associated hospitalizations from 2010 to 2017 whilst influenza associated death incidence increased gradually from 2009 to 2017. The decreasing trend might be due to the introduction of PCV in South Africa in 2009. Other factors that might explain a decreasing trend in hospitalization include improved public health care system due to widespread introduction of ART and Prevention of Mother to Child Transmissions (PMTCT) which took place concurrently when PCV vaccine was introduced. Maternal and child influenza vaccination may also have contributed to the decreasing trend in hospitalization.

Our incidence estimates for influenza associated hospitalization varied by month and by year as well. Incidences within winter seasons varied from year to year. There were seasonal variations in incidences of influenza associated hospitalization and the epidemiologic trend was in agreement with observations in similar settings and also expected for South Africa (74,79). Yearly and monthly variations in intensity of the influenza virus burden, variable treatment seeking behaviour and availability of accessible health care could explain the difference in incidences by month.

The differences in hospitalization pattern may be due to variations in demographic attributes of the children infected with influenza for the different years. Similarly, indicators of health such as elevated burden of malnourishment, which is a risk cause for pneumonia and other coexisting infections and illnesses could also affect the hospitalization pattern. Coexisting comorbidities may increase susceptibility to influenza infection due to their effect on the immune system. Differences in influenza associated hospitalization incidences among the lower respiratory tract infection South African surveillance cases with other countries may be due to differences in the case definitions for surveillance, differences in study-population characteristics, and variations in the methodology of the investigation. Influenza is an important public health problem for South Africa.

The burden of hospitalizations and deaths due to influenza varied greatly from year to year due to different transmission dynamics and virulence attributes of the circulating strains. High number of influenza associated hospitalizations occurred in 2009 followed by 2018 as shown by the monthly incidences. Elevated influenza associated hospitalizations in 2018 could have been because of a combination of factors including the circulating influenza strains, spectrum of coexisting infections and previous immunity in the population. Similarly, in Sozhou, China, rates of influenza and influenza-associated excess hospitalizations peaked in the 2009 to 2010 pandemic season (80). In South Africa, influenza is usually responsible for annual isolated outbreaks in winter season between May and September. Influenza infections usually peak with more cases above the numbers normally expected when there is an outbreak in a defined geographical area. The 2009 pandemic influenza A(H1N1) virus which was first isolated in 2009 caused a global influenza pandemic, could have contributed to the large numbers of hospitalizations recorded in the same year in South Africa.

Our findings are comparable to those reported by McMorrow et al (2019) who established that annual hospitalization rates due to influenza infection were elevated in young children aged 6 to 11 months and it was [545 (95% CI, 409-703] which was higher than what we reported for the same age category (81). They established that HIV-exposure was associated with elevated incidence of hospitalization due to influenza in all age groups. However, our results contrasts with

results from a study done in England which reported that healthy children <5years of age had the highest influenza admission rate compared to those with comorbidities (82).

Whilst HIV infection and exposure does not meaningfully increase predisposition to influenza, individuals with AIDS are susceptible to influenza associated sickness and death because of immunosuppression (40). Bacterial coinfections may have contributed to some of the influenza-related lower respiratory tract infection hospitalizations in the HIV-exposed group. It has been documented that HIV-infected people are at high risk of hospitalization for IPD and a synergistic relationship occurs between influenza and *S. pneumoniae* (63). These outcomes highlight the necessity to focus on HIV-infected persons for influenza immunisation as HIV prevalence is still high in low to middle income countries.

The overall proportion of influenza cases among pneumonia cases was 0.12 (95% CI: 0.11-0.13) depicting that more than 10% of all of children enolled into the surveillance had influenza and pneumonia. Influenza has been documented as one of the factors that predisposes children to pneumonia. A study that investigated influenza coinfection and outcomes in children with complicated pneumonia reported that influenza occurred in 3.1% of young children with pneumonia (83). They reported a proportion of children with influenza infection among pneumonia cases which is lower than what we reported. Young children with pneumonia and influenza simultaneously have severe clinical outcomes in comparison to children with pneumonia without coexisting influenza infection.

We found that HIV-exposed and unexposed children had a similar proportion of influenza infection among the pneumonia cases. HIV-exposed children are susceptible to ALRI from respiratory viruses due to their malfunctioning immune systems. As risk of HIV transmission from parent to child declines and availability of ART rises, the epidemiology of most opportunistic illnesses is changing in the HIV infected people. However, HIV infected children still get infected with these diseases. More so, HIV infected individuals are liable to both influenza and pneumonia

simultaneously; and may result in their deaths. These findings suggest that HIV infected individuals carry an excess burden for serious ailments associated with influenza and therefore should be given priority for influenza vaccination.

Dananche et al (2018) reported a lower proportion of influenza infection among those with pneumonia than our findings (84). They reported an average proportion of influenza virus infection of 9.7% (95% CI: 7.9–11.8%) in 888 children with pneumonia. Influenza associated pneumonia is common in children <5 years old in developing countries. The differences in our estimates could be because of differences in demographics and socioeconomic status of the populations investigated. Our study took place in a low resource setting where poverty is high, and malnutrition is endemic in children. Influenza is a predisposing factor for pneumococcal associated pneumonia and a regular causative pathogen accountable for pneumonia in most populations.

Our overall hospitalization incidence rate in children ≤3 months of age was lower than those of children in the 4 months to <1-year age. Circulating maternal antibodies for influenza and PCV dose administered at 6 weeks could be accountable for this finding. Protection by circulating maternal antibodies against influenza may slowly wane beginning from the third month of life onwards (85). We reported higher incidence of hospitalization in children below 2 years of age in comparison to those of the age group 2 to <5 years. It is not understood why young children who are <2 years of age, irrespective of their HIV status are at a high risk of influenza related hospitalization. Nevertheless, the poor innate immune response to influenza virus for the duration of childhood could be responsible for influenza virus causing serious disease requiring hospitalization in otherwise healthy children. The immature immune system mechanisms which are responsible for identifying influenza and triggering cytokine response to curb replication of the virus, may account for the higher hospitalization rates noted in young children.

Our incidence estimates for hospitalization are comparable to those recorded in Uganda in a study which reported an incidence of influenza associated hospitalizations of 116 (95% CI 78–165) per

100 000 persons in children less <5 years of age (86). Our findings are comparable to those by Silvennoinen et al (2011) who reported annual average incidence of influenza-associated hospitalizations being elevated in children younger than 6 months [276 (95% CI: 220–336) per 100 000] and in children 6 to 11 months [173 (95% CI: 129–220) per 100 000 children] (87). The elevated incidence of influenza associated hospitalization amongst infants <6 months of age highlights the importance of finding efficient preventive measures for influenza disease in children younger than 6 months age group, for which there are no licenced influenza vaccines currently. It is imperative to identify key age groups that experience influenza disease to implement public health policies that are effective to curb the disease.

The influenza burden is unequally dispersed in populations with severe disease in young children below the age of 5 years than older children and adults. The low proportion of influenza cases in young infants <3 months with pneumonia among the children enrolled into the surveillance study, in comparison with young children aged 4 months through 1 year, may show variations in the probability of hospital admission with influenza. Infants younger than 6 months of age may well be protected against influenza infection by naturally acquired circulating maternal antibodies or acquired by influenza vaccination in pregnancy. Development of pneumonia may also be decreased by the presence of maternal antibodies. IgA which is present in breast milk may protect breast-fed infants against influenza-associated pneumonia. Extra vaccination efforts for children <1 year of age may assist in lowering the effects of the disease in communities.

There is a substantial problem of influenza-associated acute respiratory outcomes in young children. Our study found that most children who tested positive for influenza were aged between 4 and 12 months. This is consistent with a study that found that young children aged 6–11 months had elevated incidences of PCR-confirmed influenza disease than those aged <6 months (88). Children <5 years of age have high incidences of influenza associated hospitalization and complications compared to those > 5years, mostly if the children have coexisting illnesses like HIV. The progression to highly severe influenza disease may be favoured by some coexisting

chronic conditions, nevertheless hospitalization to the intensive care unit and death may result in healthy children.

Influenza-associated paediatric deaths are relatively rare, but coexisting infections have been linked to higher incidence of influenza associated deaths. We showed that there was a gradual increasing trend in influenza associated deaths from 2009 to 2017. This might be attributed to pre-existing comorbidities in the children that died from influenza associated illness for instance HIV infection. A study done in SARI hospitalized patients in South Africa between 2009 and 2013 reported that the case fatality for influenza associated deaths differed by HIV status and was 2% (13/620) ($p = 0.006$) in the HIV-uninfected and 5% (22/419) in HIV-infected (42). The study also reported influenza associated death incidences in children < 1 year and those between 1 and <5 years of age that were comparable to what we have reported. Presence of underlying medical conditions and pneumococcal co-infection have been independently linked to influenza associated deaths. Our findings support more research and investigations to focus on and monitor interventions and preventive methods for instance vaccines against influenza and HIV prevention in resource poor countries with high HIV burden. In South Africa, it is estimated that influenza causes more than 2500 pneumonia episodes and influenza-associated deaths every year in persons of all ages.

The overall incidence of influenza associated deaths varied from 7 to 24 deaths per 100 000 children during the study period. The incidence of death varied across the age categories and across years. The influenza associated death incidence variation might be accounted by the differences in the virulence of circulating strains of influenza during the study period. Our results are comparable to a study that reported that young children aged <12 months had elevated death rates for influenza compared to children those aged 12 to 59 months of age (22 vs 5 per 100 000 Person Years) (89). Increasing vaccination coverage in children, pregnancy, and caregivers of children may lower paediatric deaths associated to influenza.

We found that in 2017 and 2018, children were more likely to die of influenza associated illness than in 2009. The relative risks recorded for 2017 and 2018 are consistent with the high incidence of influenza associated hospitalization that we established for the same year. The high incidence of influenza associated deaths and the increasing trend of influenza associated deaths could be explained by coexisting infections, missed doses of PCV or virulence of the circulating influenza strain. Our research showed a decline in influenza associated hospitalisations and deaths. The reductions differed more after the introduction of PCV-13 compared to the PCV-7 era. PCV-13 contains more *S. pneumoniae* serotypes compared to PCV-7. The decrease may also be explained by the introduction of ART which also took place concurrently during the study period.

4.2 Limitations

Our study had several limitations. Data was available between 2009-2013 and 2015-2018, therefore PCV vaccination and hospitalization data for 2014 was not included in the analysis. Data used was covering different periods, the populations included may have differed and this may have influenced both types of datasets. The research was restricted by the absence of complete data on influenza vaccination status for children 6 months to 5 years of age and on maternal influenza vaccination. Influenza vaccinations are also extremely low in that population. Thus, we were not able to evaluate the confounding effect of influenza vaccination on numbers of influenza associated hospitalizations and deaths. Maternal influenza antibodies transferred through the placenta may protect the infants up to six months of age from severe influenza disease before a child is eligible to receive influenza vaccine. Our findings may also have been confounded by the introduction of PMCTC and ART to HIV exposed children. ART has significantly reduced influenza associated hospitalization and deaths. During the study period there were only 63 influenza associated deaths. We had to narrow our influenza associated deaths analysis because most incidences were 0 and this explains why we reported wide confidence intervals on some of the relative risks of influenza associated deaths.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.0 Introduction

This chapter presents the conclusions of the study findings and recommendations.

5.1 Conclusion

There was a decreasing trend in influenza hospitalizations from 2010 to 2017 and increasing influenza associated death incidence from 2009-2017. Incidence of influenza associated hospitalization was highest in children who were 4 months to <1 year [372 (95% CI: 347-398)] and in 2009 [378 (95% CI: 344-413)] per 100 000 population. The incidence of influenza associated death was high in children 4 months to <1 year of age and in 2017. The overall proportion for influenza infection among the pneumonia cases was 0.12 (95% CI: 0.11-0.13).

Influenza is still a major clinical problem in paediatrics and prevention measures should target healthy children and children with chronic conditions. Despite the introduction of PCV, extra interventions are still required to reduce influenza associated hospitalizations and deaths. Our findings suggest that children <5 years may benefit from receiving influenza vaccine to further decrease the incidence and severity of influenza in paediatric populations.

5.2 Recommendations

We recommend that additional strategies on influenza prevention are required to further reduce the remaining influenza related morbidity and mortality in the high-risk children. Based on the data from hospitalizations and mortality at CHBAH, we recommend that the HIV infected and the

HIV exposed, and uninfected children be prioritised for receiving PCV booster doses to further reduce morbidity and mortality. Moreover, studies to assess the severity and attributes of influenza in children younger than 6 months and their response to maternal influenza vaccine should be carried out. This is crucial to approximate the potential advantage of vaccinating expecting women. It is also crucial to assess the methods of influenza vaccine administration for instance intradermal, subcutaneous, or intramuscular or intranasal spray to improve protection. Lastly, research among children with chronic or coexisting diseases is recommended for illnesses that have been found to be related to serious influenza disease but for which the influenza vaccine is not advised.

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International Classification of Disease codes used for pneumonia

B05.2-Measles complicated by Pneumonia

B20.6-HIV disease resulting in Pneumocystis carinii (jiroveci) Pneumonia

B25.0-Cytomegaloviral pneumonitis

B59-Pneumocystosis (Pneumonia due to Pneumocystis carinii)

J10.0- Influenza due to other identified influenza virus with pneumonia.

J12.1- Respiratory synctial virus pneumonia

J12.2-Parainfluenza virus pneumonia

J12.8- J12.8 Other viral pneumonia

J12.9-Viral Pneumonia, unspecified

J13-Pneumonia due to Streptococcus pneumoniae

J13/J91-Pneumonia due to Streptococcus pneumoniae with pleural effusion

J14-Pneumonia due to Haemophilus influenzae

J15.0-Pneumonia due to Klebsiella pneumoniae

J15.1-Pneumonia due to Pseudomonas

J15.2-Pneumonia due to Staphylococcus

J15.3-Pneumonia due to Streptococcus, Group

J15.4-Pneumonia due to other streptococci

J15.5-Pneumonia due to Escherichia Coli

J15.8-Other bacterial pneumonia (agent not listed)

J15.9-Bacterial pneumonia, unspecified

J16.8-Pneumonia due to other specified infectious organisms

J18.0-Bronchopneumonia, unspecified

J18.1-Lobar Pneumonia, unspecified

J18.1/J91-Lobar Pneumonia, unspecified with pleural effusion

J18.9-Pneumonia ,unspecified

J22-Unspecified acute lower respiratory infection

J85.1- Abscess of lung with pneumonia

Farisai Kuonza Research Report Final 20 September 2020

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R14/49 Farisai Susan Kuonza

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M191044

NAME: (**Principal Investigator**)	Farisai Susan Kuonza
DEPARTMENT:	Pathology Chris Hani Baragwanath Academic hospital
PROJECT TITLE:	Hospitalizations for influenza after introduction of pneumococcal conjugate vaccines at Chris Hani Baragwanath Academic Hospital in South Africa, 2009 - 2018
DATE CONSIDERED:	25/10/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Marta Nunes and Dr Clare Cutland
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/07/2020

This clearance certificate is valid for 5 years from 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 Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. I **agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore be due in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

04 March 2014

FAXED & COURIERED

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Chris Hani Baragwanath Hospital
P O Box 90753, Bertsham
2013

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Dear Prof Madhi,

PROTOCOL: PNEUMO & GASTRO PATHOGENS - SURVEILLANCE ON PATHOGEN-SPECIFIC CAUSES OF PNEUMONIA AND DIARRHOEA HOSPITALIZATION IN CHILDREN

ETHICS REFERENCE NO: 131109

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial was reviewed by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol Review Committee (PRC) on: 29 November 2013.

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

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* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

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* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :
  - Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).
  - Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

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* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

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* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

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* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

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2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

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3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the Medicines Control Council of SA and that reimbursement should be appropriate according to the situation.

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5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

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6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

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7. GOOD CLINICAL PRACTICE

The South African Department of Health, Medicines Control Council requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

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8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

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8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records (this is applicable with the initial Approval).

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8.2 Protocol Review Committee Approval Signature page signed by the Acting Chairperson of the PRC.

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8.3 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

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9. WE AWAIT YOUR RESPONSES AS REQUESTED: Ensure to have these documents forwarded at the earliest for the HREC records.

* MCC Approval letter and/or letter of Notification before the above study may commence / or where an Amendment may be implemented (IF MCC APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* Copy of Independent Ethics Declaration Approval Form signed by the Principal Investigator. (this is applicable with the initial Approval).

* Kindly forward the above to the undersigned at fax: 011 274 9281 at your earliest convenience.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE

Regards,

PROF PETER CLEATON-JONES

For and on behalf of the Human Research Ethics Committee: (Medical)

INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

Ethics Reference No.	**131109**	**Date of Meeting**	**29 November 2013**
		Recertification Due	**28 November 2014 (If applicable)**
Principal Investigators:	Prof SA Madhi	**Investigators:**	Dr CL Cutland
			Dr MJ Groome
			Dr R Hassan-Moosa
			Dr Andrea Hugo
			Dr SA Jones
			Dr L Jose
			Dr AL Koen
			Dr SA Nzenze

Protocol Title:	Surveillance on pathogen-specific causes of pneumonia and diarrhoea hospitalization in children

DOCUMENTS REVIEWED				Tick As Appropriate Yes	No
Protocol Number	**Pneumo & Gastro Pathogens**	**Date:**	09 January 2014		
Protocol	PCV&gastro_pathogens, Protocol Version 1.1	**Date:**	09 January 2014	☑	☐
	PCV&gastro_pathogens, Protocol Version 1.0 - WITHDRAWN	**Date:**	05 November 2013	☑	☐
Investigator's Brochure	N/A - Version: N/A - Dated:			☑	☐
Subject Information/Consent Form	Information Leaflet and Informed Consent Form - Version: 1.1 - Dated: 10/Jan/2014			☑	☐
	Information Leaflet and Informed Consent Form for Transport, Storage and Future use of Samples - Version: 1.0 - Dated: 06/Nov/2013			☑	☐
Advertisements					
Questionnaires	Parent Interview Form - Version: 1.0 - Dated: 06/Nov/2013			☑	☐
Insurance/Compensation	N/A	Valid From	To:	☐	☑
Synopsis of Study/Trial Summary	Diarrhoea Hospitalization in Children			☑	☐
Other Documentation	Pn&gastro_pathogens, Protocol Summary Version 1.0 - Dated: 06/Nov/2013			☑	☐
	Letter from Bill & Melinda Gates Foundation, Re: Global Health Grant Number OPP1101764 - Dated: 28/Oct/2013			☑	☐
	Budget and Payment Schedule - Dated: 25/Sep/2013			☑	☐
	NHREC Trial Application ID#: 3600 - Dated: 06/Nov/2013			☑	☐
	HREC Application Form - Dated: 07/Nov/2013			☑	☐
	PRC Application Form - Dated: 07/Nov/2013			☑	☐
	Medical Advisory Committee: Chris Hani Baragwanath Hospital - Dated: 11/Nov/2013			☑	☐
Relevant Trial Hospital/(s)	Chris Hani Baragwanath Hospital			☑	☐
Syndicate and/or Research Unit	DST/NRF Vaccine Preventable Diseases - RMPRU			☑	☐

DETAILS OF COMMITTEE	
Name	University of the Witwatersrand Human Research Ethics Committee: (Medical)
Address	Division of the Deputy Registrar (Research), Department of Research, Senate House University of the Witwatersrand , 1 Jan Smuts Avenue, BRAAMFONTEIN, Johannesburg, 2000

DETAILS OF MEETING	Yes	No
Is the Investigator a member of the committee ?	☐	☑
If "Yes" did he/she vote ?	☐	☑
Is the Committee organised and operated according to applicable laws and regulations together with ?	☑	☐
Local GCP requirements ?	☑	☐
ICH GCP requirements ?	☑	☐
FDA GCP requirements ? FWA Registered No. IRB00001223	☑	☐
Progress reports required either in March and September or six monthly from start of study ?	☑	☐

DECISION ON APPROVAL : is approval given to conduct the trial ?	Tick As Appropriate
Yes - with no conditions	☑
Yes - with conditions	☐
Specify conditions :	
No	☐
Specify reasons	

INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

SIGNATURES		
I confirm that the details on this form are correct:		Date
Name: **Prof PE Cleaton-Jones** **Chair / Deputy Chair of Committee**	**Signature:**	**04 March 2014**

DECLARATION OF INVESTIGATOR/(S)

To be completed and ONE COPY returned to the Secretariat for the HREC at Wits Health Consortium, 8 Blackwood Avenue, Parktown, 2193
or Fax To: 011 274-9281

I/We fully understand the conditions under which I am/we are authorised to carry out and complete the above-mentioned research and I/we agree to ensure full compliance with these conditions. Should any amendment, alteration or departure be contemplated from the research procedure methodology or manner of execution, I/we will communicate with the Chairman of the Human Research Ethics Committee: (Medical) for approval prior to acting on any of the above mentioned proposed amendments, alterations or departures. I am/we are fully aware that any unauthosised amendment, alteration or departure as above will amount to misconduct and may lead to the institution of disciplinary procedures.

Any approval given by the HREC is conditional upon consent being obtained by the Investigator/s from the Superintendent (or equivalent official) of the Hospital, Clinic or Institution in which the research is, in part or full, to take place.

The Chairman may of course at his discretion place the matter before the full Committee.

DATE: 10/3/14 SIGNATURE: _____ NAME: SHABIR MAHDI

PROTOCOL NUMBER **Pneumo & Gastro Pathoge** ETHICS REF.: **131109**

Date Printe 04 March 2014

Wits Clinical Research

8 Blackwood Avenue, Parktown, 2193, South Africa
Tel. +27-11-274-9200, Fax: +27-11-274-9281
Postnet Suite 189, Private Bag x2600, Houghton, 2041

FAXED & COURIE

Prof SA Madhi,

Respiratory & Meningeal Pathogens Research Uni
11th Floor, West Wing, Nurses Residence
Chris Hani Baragwanath Hospital
P O Box 90753, Bertsham
2013

Fax: 086 646 4208

Dear Prof Madhi,

PROTOCOL NO: Pneumo & Gastro Pathogens

PROTOCOL TITLE: Surveillance on pathogen-specific causes of pneumonia and diarrhoea hospitalization in children

PRC REFERENCE NUMBER: 131109

****

Please be advised that your trial application was:

APPROVED

The Expert Reviewer /(s): Prof S Velaphi

Also reviewed by: Mrs J Palmer: Acting Chairperson Protocol Review Committee
Dr B Ikalafeng: Gauteng Department of Health
Medical Advisory Committee: Chris Hani Baragwanath Hospital

Yours sincerely

Palmer

Acting **MRS JENNIFER PALMER (BRYCE-BORTHWICK)**
Chairperson: Protocol Review Committee
04 March 2014

cc.

Respiratory & Meningeal Patho	Ms C Combrinck	**Tel** 011 983 4283 **Cell**	**Fax** 086 262 0626
Bill and Melinda Gates Foundat	Ms C Combrinck	**Tel** 011 983 4283 **Cell**	**Fax** 086 262 0626

HUMAN RESEARCH ETHICS COMMITTEE MEMBERS: (MEDICAL)
UNIVERSITY OF THE WITWATERSRAND

Attendance Register for the Ethics Meeting held on 29 November 2013 from 12:00 - 15:00

Venue: SCHOOL OF PHYSIOLOGY, Research Seminar Room, 6th Floor, Room 6Q16, Medical School, University of Witwatersrand, 7 York Road, Parktown

AFFILIATED TO THE UNIVERSITY OF THE WITWATERSRAND

Surname	Initials	Title	Discipline/s	Academic Qualifications	Gender	Present
Adam	Y	Dr	Obstetrics & Gynaecology	MB BCh; FCOG	F	Present
Cleaton-Jones	PE	Prof	Biomedical Ethics	BDS; MB BCh; PhD; DA (SA); DTM&H; DSc (Dent), FCD (SA) DPH; PhD Hon Causa, MASSAfr	M	Present
Conradie	FM	Dr	Infectious Diseases/HIV/TB	MB BCh; DTM&H; MSc; Dip HIV Man	F	Present
Cooper	PA	Prof	Paediatrics	MB BCh, PhD, DCH (SA), FCPaeds (SA)	M	Absent
Cubasch	H	Dr	Surgery	FCS (SA)	M	Absent
Dessein	PHMC	Prof	Rheumatology	MD, FCP (SA), FRCP, PhD	M	Present
Dhai	A	Prof	Biomedical Ethics	MB ChB; FCOG; LLM; PGDipIntResEthics	F	Present
Donde	B	Prof	Radiation Oncology	MB BCh, MMed Rad (T)	M	Present
Etheredge	H	Ms	Biomedical Ethics	MSc Med, BA	F	Present
Feldman	C	Prof	Pulmonology	MB BCh, PhD, DSc, FCP (SA), FRCP	M	Present
Gerrand	P	Ms	Social Work	MA (Social Work)	F	Absent
Langley	G	Prof	Nursing	MSc (Nursing), PhD	F	Present
Lownie	MA	Prof	Maxillo-Facial & Oral Surgery	BDS, BA (Hons), DipMFOS, FCMFOS(SA), MEd	F	Absent
Mokhachane	M	Dr	Paediatrics	MB BCh, FCP (Paeds) SA, MMed, Neonatology (SA)	F	Absent
Naidoo (Shan)	S	Prof	Public Health	MB BCh, DMTH, DHSM, DOH, MMED	M	Absent
Naran	NH	Dr	Chemical Pathology	PhD	M	Absent
Oettle	GJ	Prof	Surgery	BSc (Hons), MB BCh, FRCS	M	Absent
Paruk	F	Prof	Anaesthesia	MB ChB, FCOG(SA), Crit Care(SA), PhD	F	Absent
Penn	C	Prof	Speech Pathology	BA (Sp&HTh), PhD, CCC SL-P, OMS	F	Present
Penny	C	Dr	Internal Medicine	BSc Hons, PhD	M	Present
Ross	M	Prof	Public Health	MB ChB, FFCH(SA), MFamMed, MFPH	F	Absent
Sanne	IM	Prof	Infectious Diseases/HIV/TB	MB BCh, FCP (SA), DTM&H; MMed & PhD	M	Present
Smith, Cora	C	Prof	Psychiatry	BA, BA (Hons), M.A (Clin.Psych), PhD	F	Present
Stewart	A	Prof	Physiotherapy	BSc (Physio), MSc, PhD, DPE	F	Present
Szabo	CP	Prof	Psychiatry	MB BCh, MMed, MScMed, PhD; FCPsych(SA)	M	Present
Thom	RGM	Prof	Psychiatry	MB ChB, DCH, FCPsych, PhD	F	Present
Tsotsi	NM	Dr		BDS; MPH; MSc Med; PGDipInt ResEthics	F	Present
Van Gelderen	CJ	Prof	Obstetrics & Gynaecology	MB BCh, FRCOG, FCOG(SA)	M	Present
Velaphi	S	Prof	Paediatrics	MB BCh, FCPaeds, MMed	M	Present
Vorster	M	Prof	Psychiatry	BA, MB BCh; MMed, FCPsych(SA), PhD PGDipIntResEthics	F	Present
Wadee	A	Prof	Immunology	BSc, MSc, PhD	M	Absent
Willem	P	Dr	Human Genetics	MD, PhD	F	Present
Woodiwiss	AJ	Prof	Cardiovascular Pathophysiology	BSc Physiotherapy, BSc, MSc, PhD	F	Absent

NOT AFFILIATED TO THE UNIVERSITY OF THE WITWATERSRAND

Surname	Initials	Title	Discipline/s	Academic Qualifications	Gender	Present
Binkowska	BM	Dr	Clinical Medicine	MB ChB, MBL, MPA	F	Absent

Egan	A	Father	Theology	*BA (Hons), MA, MDiv, STL, PhD*	*M*	*Present*
Guidozzi	Y	Adv	Lawyer	BSc (Nurs), LLB, MBA	F	Absent
Ikalafeng	B	Dr	Governance	BSc (Hons)	F	Absent
Myburgh	C	Prof	Educationist	BSc (Hons), MCom, DEd, HED	M	Present
Poggenpoel	M	Prof	Psychiatric Nursing	RN; PhD	F	Present

Note 1: This committee has been in continuous operation since October 1966
Note 2: The large committee size is to ensure a good attendance at meetings
Note 3: A Quorum consists of 5 members, of which 1 non-affiliate and 1 non-medical member to be present
Note 4: The following members alternate: Prof C P Szabo and Prof R Thom
Prof P A Cooper and Dr S Velaphi
Dr I Sanne and Dr F Conradie

This is to certify that the Human Research Ethics Committee: (Medical) of the University of the Witwatersrand operates according to the following guidelines of good clinical practice:

1. **ICH Harmonised Tripartite Guideline for Good Clinical Practice.**
2. **SA National Department of Health 2006 Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2006).**
3. **Declaration of Helsinki 2008.**

The Committee's United States Federal Wide Assurance details are:

1. **Country code SF.**
2. **FWA Number: FWA00000715.**
3. **University of the Witwatersrand: IORG0000862.**
4. **Human Research Ethics Committee: (Medical): IRB00001223.**

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Cohen

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M081042**
PROJECT	Establishment of Sentinel Surveillance for Severe Acute Respiratory Infections (SARI) in South Africa
INVESTIGATORS	Dr C Cohen
DEPARTMENT	School of Public Health
DATE CONSIDERED	08.10.31
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.11.26 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor :

.....

.....

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

.....

2-DEC-2008 10:13 FROM:WITS-RESEARCH OFFICE 011 717 1265 TO:0011882997 P:1/1