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Impact of Pneumococcal Conjugate Vaccine Thirteen Valent on the Reduction of Invasive Pneumococcal Disease

Aissata Coulibaly
Walden University

Walden University

College of Health Sciences

This is to certify that the doctoral dissertation by

Aissata Coulibaly

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Dr. John Nemecek, Committee Chairperson, Public Health Faculty
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Chief Academic Officer
Eric Riedel, Ph.D.

Walden University
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Abstract

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Aissata Coulibaly

MPH, Emory University, 2009

DDS, University of Montpellier, 1992

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Many children under the age of 5 die each year of invasive pneumococcal disease. Childhood vaccination against this disease reduces morbidity and mortality. Despite the introduction of a pneumococcal conjugate vaccine (PCV13) in a central African country in 2011, all provinces have not yet been vaccinated. The purpose of this quantitative quasi-experimental study was to determine whether there was an association between the introduction of PCV13 and new cases of pneumococcal disease in 2 provinces in central Africa. The sample size for the study was 380. The theoretical framework for this study was the epidemic model supported by the concept of herd immunity. Key research questions examined the incidence of pneumococcal disease in children by age, gender, and province. The independent variables were age, gender, province, and introduction of PCV13. The dependent variable was incidence of invasive pneumococcal disease. The research questions were evaluated using chi-square test of independence and logistic regression. The results of the study indicated that vaccination with PCV13 significantly reduced incident cases of invasive pneumococcal diseases (aOR 0.333, 95% CI 0.628-0.177, $p = 0.001$). However, this association was not significant for age (aOR 0.574, 95% CI 1.186-0.278, $p = .134$), and there were no significant gender differences (aOR 1.047, 95% CI 1.929-0.569, $p = 0.882$). Positive social change may result by enabling the protection of more children in the central Africa country provinces that have not yet adopted using PCV13 and by introducing the vaccine in other African countries.

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Dedication

This dissertation is dedicated in loving memory to my sister, Alimata Coulibaly, who supported my pursuit of higher education up to her sudden passing and encouraged me to always push myself. I would also like to dedicate this study to my loving husband, Patrick Diaha, for his support and understanding.

Acknowledgments

I would like to thank the DRC Ministry of health and the Expended Program of Immunization for allowing me to use the data collected as a part of the surveillance activities; my chairperson, Dr. John Nemecek, for his guidance throughout this dissertation process. Your patience and encouragement are very much appreciated. Finally, I am grateful to my committee members for their mentorship during the completion of this research.

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Chapter 1: Introduction to the Study

Introduction

The gram-positive bacterium that causes invasive pneumococcal infections (such as pneumonia, septicemia, and meningitis) especially in children is the streptococcus pneumoniae (S. Pneum) or streptococcus; this bacterium is a normal inhabitant of the upper respiratory track flora (Grall et al., 2011). According to the Centers for Disease Control and Prevention (CDC, 2011), in 2008, about 1.6 million children less than 5 years of age die because of pneumococcal diseases worldwide each year, and over 95 % of them of these deaths occur in the developing world. This shows that the disease is a public health concern for younger children with a higher burden for the under developed world.

Pneumococcal infection starts with the bacteria colonizing in the nasopharynx of healthy children, where it grows and establishes a carriage. At this stage, the pneumococcus can either remain asymptomatic or can take three different paths: potentially causing otitis media (ear ache) by migrating through the eustachian tube, pneumonia by descending down the respiratory tract, or meningitis by invading the bloodstream through the respiratory epithelium (Dube, Kaba, Whittaker, Zar, & Nicol, 2013). Forty six serogroups and at least 93 serotypes of streptococcus pneumoniae have been identified (Coskun-Ari1, Guldemir, & Durmaz, 2012). So far, only a small number of the 93 serotypes have been detected from patients with invasive pneumococcal disease worldwide; that number was distributed according to age, sex, and geography (Dashti, Abdinia, & Karimi, 2012). Pneumococcal infection is treated with antibiotics, but more pneumococci are becoming resistant to antibiotics; therefore, attention needs to be placed

on the prevention of the disease in order to reduce morbidity and mortality (Liňares, Ardanuy, Pallares, & Fenol, 2010).

The most cost effective prevention of pneumococcal disease in children is through vaccination with pneumococcal conjugate vaccine (PCV) (Pittet, & Posfay-Barbe, 2012). The protection is achieved by the induction of a protective antibody response against the bacterial polysaccharide capsule. PCV vaccine available to date only includes antibodies against 13 out of the 93 serotypes (Weil-Olivier, van der Linden, de Schutter, Dagan, and Mantovani, 2012). Three different vaccines have been developed; starting with the seven valents (PCV7) containing the seven most diseases causing serotypes that are 4, 6B, 9V, 14, 18C, 19F, and 23F; followed by the 10 valents (PCV10) containing three additional serotypes (1, 5, 7F), and the PCV 13 containing six additional serotypes 1, 3, 5, 6A, 7F, and 19A (Weil-Olivier et al., 2012). Even though PCV 7 has reduced the incidence of the disease, pneumococcal disease was caused by the non vaccine serotype in some cases (Weil-Olivier et al., 2012); therefore, a vaccine covering more serotypes was needed, resulting in the development of PCV10 and PCV13.

According to the Democratic Republic of Congo (DRC's) Ministry of health, beginning in April 2011, the vaccine began to be introduced in DRC by province to eventually cover the entire country. Therefore, it is important to study the impact of the vaccine in the reduction of the burden of the disease in order to cover the entire country in DRC and/or other African countries. The PCV13 shields 13 serotypes, which is highly effective; however, more research is needed for the development of vaccines with greater coverage in the future. To achieve this, it will be crucial to monitor the circulating serotypes in a given geographical area to evaluate the effectiveness of the vaccine

available in that setting, and then compare the circulating strains and the ones included in the vaccine (Sakai, Talekar, Klugman, & Vidal, 2013). An effective vaccine has the potential to eliminate many sick children and unnecessary deaths due to pneumococcal infections.

The chapter begins with the background of the problem, problem statement, and significance of the study. The chapter includes the research questions that guided the study, as well as a short definition of main terms. The theoretical framework for the study is also presented, with further discussion provided in the literature review. In these sections, I establish the goals for the study and illustrate the need for continued pneumococcal vaccine research in the field of health.

Background of the Study

Pneumococcal disease is caused by infection with streptococcus pneumoniae bacteria. These bacteria can spread from one person to another person through close contact (CDC, 2013). Pneumococcal disease can lead to severe health problems, including pneumonia, blood infections, and meningitis (CDC, 2013). Pneumococcal infection is generally preceded by a colonization of germs in the nasopharynx, which is usually asymptomatic (without symptoms) in most of the cases and does not turn into the disease (Dube et al., 2013). When the colonization transitions to the disease phase, it can be severe, affecting a child's quality of life, and sometimes death occurs (Rodewald, Maes, Stevenson, Lyons, Stokley, & Szilagyi, 1999). The asymptomatic carrier state is mostly seen in children attending daycare centers; therefore, those children constitute the reservoir (disease carrier) for the pneumococci bacteria (Rodewald et al., 1999).

Pneumococcal disease is prevented with available pneumococcal vaccines. As of 2012, the World Health Organization recommended using pneumococcal vaccines as a part of the routine childhood vaccination schedule; 86 countries have introduced the vaccine including 23 low-income member states. The 23 low-income countries had the assistance of the Global Alliance for Vaccines and Immunizations (GAVI) to finance the vaccine (WHO, 2012). The burden of pneumococcal disease caused by streptococcus pneumoniae in sub-Saharan Africa has prompted the GAVI Alliance to finance the introduction of the vaccine in several countries including the DRC (WHO, 2012). According to the WHO (2013), pneumonia was the leading cause of death in the DRC since the year 2000 as compared to all other causes of death in children less than 5 years of age. Research has been conducted to study the impact of the pneumococcal conjugate vaccine on the reduction of invasive pneumococcal diseases in different countries, but no studies have been conducted in the DRC. In this study, I address the gap in knowledge of the impact of the PCV13 on the circulating strains of streptococcus pneumoniae in the DRC.

Low-income countries face difficulty in affording and sustaining quality lifesaving vaccines; therefore, in order for their programs to generate the most desirable outcomes from a public health standpoint, alternative solutions need to be put in place. Due to the high cost of vaccines and the difficulties in sustainability, manufacturing appropriate vaccine products has proven to be difficult due to underinvestment. Peltola, Booy, and Schmitt (2004) claimed that the high cost of vaccines keeps many children from getting a highly effective vaccine against the pneumococcal diseases. There is a need to make the vaccine more accessible to the children most at risk. To remove some of

the market risks, a pilot initiative called the Advance Market Commitment (AMC) for pneumococcal vaccines was launched in 2009 (Cernuschi et al., 2011). These initiatives set predetermined terms that legally bind the purchasing of vaccines. To date, 14 countries have already introduced pneumococcal vaccines through the AMC with 39 countries expected to introduce before the end of 2013 (Cernuschi et al., 2011). This has helped protect more children through routine vaccination therefore reduce the burden of the disease.

Problem Statement

There is a high incidence of pneumococcal diseases among children worldwide. Pneumococcal disease is classified as the leading cause of mortality and morbidity in children worldwide (Cohen, Hyde, Verania, & Watkins, 2012). Prevention of the disease is important in reducing the morbidity and mortality of the disease and the best, most cost-effective prevention is immunization through childhood vaccination (CDC, 2012). Antao and Hausdorff, (2009) claimed that there is a high burden of pneumococcal diseases in children and stated that the disease can be prevented with an available vaccine. The bulk of pneumococcal research has focused on the burden and antibiotic treatment, without giving equal attention to the prevention of the disease with the available vaccines and the effectiveness of the vaccine. This discrepancy led scholars to examine the pneumococcal conjugate vaccine, which may help reduce the morbidity and mortality of the invasive form of the disease.

Although the vaccine has been shown to have an impact in some African countries as well as some South and North American and Europeans countries, there was a need to determine the effects of the vaccine on the circulating serotypes in the DRC.

Starting in April 2011, according to the DRC's Ministry of health, the pneumococcal conjugate vaccine (PCV13) began gradually being introduced into the DRC's expanded program of immunization to eventually cover the whole country; thus far, it has reached five of the country's 11 provinces: The first two provinces (Kinshasa and Bas Congo) introduced the vaccine in April 2011, followed by two other provinces (Nord Kivu and South Kivu) in July 2011 and the province of Bandundu in October 2011. A total of 677,308 children were targeted in the five provinces, and as of July 2013 the coverage with PCV13 was 88.8% as reported by the DRC's immunization authority. Evaluation of the effectiveness of the vaccine was a key step in continuing with the introduction of the vaccine to the entire country; therefore, there was a need to evaluate the provinces that have immunized thus far.

Purpose of the Study

The purpose of this quantitative secondary data analysis was to determine if a relationship existed between two DRC provinces where PCV13 had been introduced/not introduced and determine if the covariates (age and gender) had an impact on that relationship. The intent of this study was to examine the relationship between DRC provinces' childhood immunization rates for pneumococcal vaccine and the incidence of invasive pneumococcal disease. The independent variable was province (Kinshasa, Katanga). The dependent variable was the number of incident cases (observed, not observed).

An association between the pneumococcal vaccination rates of children who have routinely been vaccinated against the disease and the prevention of the disease might create a reason for other DRC cities and provinces to mandate the routine use of the

vaccine for all young children. Health care personnel in the DRC might be more motivated to routinely recommend and use the vaccine if they understand through evidentiary data that children's lives will be improved by eliminating this disease from their lives.

Research Questions and Hypotheses

RQ1: What is the difference in the number of incident cases of invasive pneumococcal disease in children between the Kinshasa province following the introduction of PCV13 and a comparison group in the Katanga province where the vaccine was not introduced?

Directional Hypothesis 1:

$H_0$1: There is no difference in the number of incident cases of invasive pneumococcal disease in children between the Kinshasa province following the introduction of PCV 13 and the Katanga province where the vaccine was not introduced.

H_a1: Children in Kinshasa province where the PCV 13 was introduced showed a decrease in the number of incident cases of invasive pneumococcal disease as compared to the children of the same age in the Katanga province where the vaccine was not introduced.

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: province type: (Kinshasa, Katanga)
- Statistical analysis: Chi-square test of independence

RQ2: Is there an association between age and incident cases of invasive pneumococcal disease in children among the Kinshasa province (PCV13) and Katanga province (control)?

Directional Hypothesis 2:

$H_0$2: There is no association between age and incident cases of invasive pneumococcal disease in children controlling for province (intervention vs. control)

H_a2: Older children (2-5 years) were more likely to contract invasive pneumococcal disease in the control province compared to the PCV13 intervention province

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: Province type: (Kinshasa, Katanga)
- Covariate: Age
- Statistical analysis: Logistic regression

RQ3: Is there an association between gender and incident cases of invasive pneumococcal disease in children among the Kinshasa province (PCV13) and Katanga province (control)?

Directional Hypothesis 3:

$H_0$3: There is no association between gender and incident cases of invasive pneumococcal disease in children controlling for province (intervention vs. control)

H_a3: Males were more likely to contract invasive pneumococcal disease in the control province compared to the PCV13 intervention province.

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: Province type: (Kinshasa, Katanga)
- Covariate: Gender
- Statistical analysis: Logistic regression

The objective of this study was to determine whether vaccinating young children against pneumococcal disease protected one community better than those communities that have not yet adopted routine vaccination with pneumococcal vaccine. The pneumococcal vaccination of young children has been shown to prevent serious illness, hospitalizations, and even death (Rodewald et al., 1999). If vaccination of young children against pneumococcal disease had an additional benefit to protect communities, then there may be an additional reason to require health care personnel to use the available PCV vaccines.

Theoretical Framework

The theoretical framework for this study was the epidemic model, supported by the concept of herd immunity. An epidemic model is based on the following assumptions: (a) infectious disease is transmitted by person-to-person contact only; (b) persons susceptible to the disease will develop the disease after contact with an infected person, thereby acquiring immunity to the illness; (c) there is a fixed probability of coming in contact with an infectious person; (d) the population has no contact with anyone outside the community; and (e) the conditions remain constant throughout the epidemic (Fine, 1977). Herd immunity or threshold protects susceptible individuals in a community from disease assuming there is a minimum vaccination threshold (Libster & Edwards, 2011, p. 163; Piedra et al., 2005). Herd immunity applies to infectious disease that can be transmitted from person to person.

Nature of the Study

A quantitative, quasi-experimental research design was used to test the hypotheses. I used this design because I wished to examine the effect of the vaccination

and age and gender and looking prospectively at who got the disease and who did not. I evaluated an intervention site with another site not receiving the intervention. The data were collected during routine surveillance of the invasive pneumococcal diseases. A quantitative approach was appropriate because the hypotheses derive from the theoretical framework.

The study was guided by three research questions about whether or not there was a difference in the number of incident cases of invasive pneumococcal disease between the children in Kinshasa province following the introduction of PCV13 and a comparison group in the Katanga province where the vaccine was not introduced. The dependent variable for H1-H3 was number of incident cases of the disease. The independent variables were province type (Kinshasa or Katanga), gender (male, female) and age groups.

Archival data on the entire population that were extracted from the surveillance system data were used. Archival data represented the best method because it was not only less time consuming than collecting the data on my own, but they were readily available. The data were originally collected as part of the normal surveillance system of the DRC ministry of health (Frankfort-Nachmias & Nachmias, 2008). Permission was received from the government of the DRC for use of the archival data in the study (Appendix B). The data were originally collected after administration of a questionnaire (Appendix C) to each visiting patient.

The population for this study was children who lived in the DRC, and who had been immunized with PCV13 starting in April 2011 as recorded in an official regional immunization record in the Kinshasa province; a comparison group of the same age

group in the Katanga province was used where the vaccine was not introduced. The sample was taken from the sentinels surveillance data of pneumococcal disease in the municipalities of Kalembelembe, Kingasani of the Kinshasa province and the hospital of Sendwe in the Katanga Province in DRC. There were an estimated 67.51 million people in the DRC including 3 400 000 children in the year 2012 (WHO, 2013). According to the DRC's immunization authority, as of July 2013, 958 809 (54.4%) children less than 1-year-old received the first dose of PCV13 against 675977 (38.4%) who received the third dose. In 2009 the pneumococcal disease incidence was ≥ 3000 per 100,000 children less than 5 years of age; the mortality rate was between 300 and 500 per 100,000 children less than 5 years of age (Wang, 2009). In the same year, DRC was among the 10 countries with the greatest pneumococcal deaths in the world all of which are in Africa and Asia (Wang, 2009).

Definitions

The following definitions are commonly used in public health to describe pneumococcal vaccination as it relates to health care:

Antibodies: Proteins generally found in the blood that detect and destroy invaders, like bacteria and viruses. Part of the immune system, antibodies come in different types, called isotypes. Mammals carry five isotypes. Each performs a different role in the body (Jewett-Tennant, 2013).

Bacteria: Any of a large group of single-celled microorganisms that display a wide range of metabolic types, geometric shapes, and environmental habitats and niches of occurrence. Normally only several micrometers in length, bacteria assume the form of spheres, rods, spirals, and other shapes (Vidyasagar, 2015).

Eustachian tube: A passage from the tympanum of the ear to the pharynx (Merriam Co, 1913).

Gram positive Bacteria: A bacterium that retains the violet stain used in Gram's method. In gram positive bacteria, about 90% of the cell wall is made up of peptidoglycan and small amounts of teichoic acid (Amils, 2011).

Herd immunity: Herd immunity is a public health prevention strategy to reduce ongoing transmission of vaccine-preventable diseases (Plans-Rubió, 2012). When a sufficient number of individuals are immune to a disease, the disease cannot continue to be transmitted person-to-person (Plans-Rubió, 2012). Herd immunity works to reduce risk of infection in the susceptible person by surrounding them with people who are immune to the disease.

Infection: An invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms (Thomson & Smith, 1994).

Nasopharynx: The area of the upper throat that lies behind the nose (Moss, 1989)

Meningitis: According to CDC (2014), meningitis is defined as the inflammation of the membranes of the brain or spinal cord.

Otitis media: An acute or chronic inflammation of the middle ear. An acute inflammation, especially in infants or young children, that is caused by a virus or bacterium; usually occurs as a complication of an upper respiratory infection; and is marked by earache, fever, hearing loss, and sometimes rupture of the tympanic membrane (Berman, 1995).

Pneumonia: The inflammation of one or both lungs, with dense areas of lung inflammation. It is a lower respiratory tract infection associated with typical inflammation clinical sign such as fever, and problem breathing. (Gereige & Laufer, 2013)

Respiratory epithelium: The tissue lining the mouth, nose, throat, and trachea. This lining acts as a barrier between the air coming into the body and the inner tissues of the respiratory mechanism, and it also serves to warm, clean, and moisten the air in preparation for its arrival in the lungs (McDowell, Barrett, Glavin, Harris, & Trump, 1978).

Septicemia: A term referring to the presence of pathogenic organisms in the bloodstream, leading to sepsis (Stibich, 2014).

Serotype: A category into which material, usually a bacterium, is placed based on its serological activity, in terms of the antigens it contains or the antibodies produced against it (CDC, 2014).

Vaccine: A preparation of killed microorganisms, living attenuated organisms, or a living fully virulent organism that is administered to produce or artificially increase immunity to a particular disease. Vaccines are made of a microorganism that resembles the disease causing one. (WHO, 2014).

Assumptions

The following assumptions were made about this study:

1. The study sample was children who have visited one of the three sentinel surveillance sites in the municipalities of Kalembelembe, Kingasani in

Kinshasa; province of Kinshasa; and the hospital of Sendwe in the town of Lubumbashi, Province of Katanga.

2. It was assumed that children visiting the sentinel surveillance sites had not biased the study, and that the archival data used were of a good quality.
3. It was presumed that the instruments used were the appropriate means for measuring the variables chosen.
4. The generalizability of this study may have been good for similar populations of provinces having introduced the vaccine and those having not introduced.
5. The study was enhanced by measuring the immunization status of the study participants.
6. The vaccination status with the number of doses may have reflected the immunization responses.
7. Objective immunization status measures may have helped identify those at risk for pneumococcal invasive diseases after demonstrating the impact of the vaccine.

Scope and Delimitations

The scope of the study was the pneumococcal vaccination of young children in the province of Kinshasa in the DRC and whether or not children were better protected from pneumococcal disease when compared to other DRC cities and provinces that have not yet routinely adopted pneumococcal vaccine. The time period was 2009 to July 2013. The delimitations of this study were the following:

1. The study was delimited to an archival, quantitative, correlational, quasi-experimental design.
2. The study was delimited to the years 2009-July 2013 when pneumococcal vaccination data for Kinshasa were collected and made publically available.
3. The study was delimited to the data abstracted from the sentinel surveillance data on pneumococcal illness.
4. The study was delimited to data collected and provided by the ministry of health of the Democratic Republic of Congo.

Any provision, condition, variable, or subject not specified was considered beyond the scope of this study.

Limitations

The following limitations were recognized in this study:

1. Not all cities/provinces in the DRC reported the percentage of pneumococcal vaccinated children.
2. This study used archival data provided by the ministry of health of the DRC from 2009 to July 2013 for pneumococcal disease.
3. This is a quasi-experimental study that provided information in a limited time frame and may not have predicted future vaccination rates.
4. A weighted average of pneumococcal vaccination rates for children was used to estimate the percentage of children where there was more than one service area providing information for a city/province.

5. Variations in pneumococcal vaccine effectiveness within different disease seasons, if appropriate, were taken into account.
6. Data on the vaccination status and number of doses received were not collected; therefore, the epidemiology principle of "dose-response" could not be assessed.

Significance

This study was significant because it had the potential to demonstrate the effectiveness of controlling a vaccine preventable disease in a part of the world where the disease is still problematic with a highly effective vaccine for children 5 years of age or under. The vaccine has the potential to eliminate many sick children and unnecessary deaths due to pneumococcal infections, thus creating positive social change. This research study might play a part in the decision-making process relative to pneumococcal disease burden in the DRC and may assist with the decision to replicate the program in other provinces in the DRC and/or other African countries (Levine et al., 2006). It might also help to know the impact of the PCV 13 on the different pneumococcal circulating serotypes in DRC. The outcome of this study might help improve the quality of the program because the information obtained can help researchers in developing new vaccines.

Summary and Transition

Researchers have established vaccination as an essential ingredient for preventing vaccine preventable diseases. Vaccines induce protection by producing antibodies to fight against the germs that enter the body, therefore helping reduce morbidity and mortality (Pittet, & Posfay-Barbe, 2012). Vaccination has been described as one of the 10 greatest

public health achievements in the 20th century (CDC, 2013). There are many infectious diseases that are vaccine-preventable, and invasive pneumococcal disease is one of them. A child who is completely vaccinated acquires immunity against vaccine preventable diseases (CDC, 2013).

PCV13 protects against the most disease-causing serotypes of streptococcus pneumoniae. Introducing the vaccine into the routine childhood vaccination schedule throughout the entire DRC might help reduce the burden of pneumococcal diseases among the country's children and promote a healthy population.

In Chapter 2. I present a review of the existing literature and how new research is suggesting an association between the use of the PCV13 vaccine in the childhood immunization schedule and the reduction in the incidence of invasive pneumococcal diseases.

Chapter 2: Literature Review

Introduction

Invasive pneumococcal diseases are deadly diseases that could be prevented with available vaccines. The WHO, (2013) estimated that 800,000 children under the age of 5 die each year of invasive pneumococcal disease. Childhood vaccination against this disease reduces morbidity and mortality (CDC, 2012). According to the immunization authority, pneumococcal conjugate vaccine (PCV13) was introduced in the DRC in 2011; however, all provinces have not yet been vaccinated. The vaccine introduction was completed in only 5 of the 11 provinces of the country. There was the need to know the impact of the vaccine in order to confidently continue with the introduction in the remaining provinces.

The purpose of this study was to determine whether there was an association between the introduction of PCV13 and new cases of pneumococcal disease in two provinces in central Africa. In the literature review, I establish the need for continued research concerning the value of the pneumococcal conjugate vaccine that helps the individual fight off the invading bacteria, thereby protecting him or her from harmful invasive pneumococcal diseases. The impact of the vaccine on the circulating serotypes in a geographical area is a relatively new field of research being conducted because the available vaccines only contain 13 of the 93 serotypes existent. Scholars have examined the cost effectiveness of the pneumococcal conjugate vaccine, its impact in the reduction of mortality and morbidity, as well as the importance of prevention through vaccination as evidenced by the antibiotic's resistance recently observed.

The number of doses of vaccine is important for the development of immunity to the disease. The development of immunity through antibody creation is instrumental in the recipient's ability to resist infection, thereby staying healthy and exempting him or her from deadly vaccine preventable diseases. Vaccination with the three doses of pneumococcal conjugate vaccine at 2, 4, and 6 months of age is followed up with a booster dose when the antibody concentration declines (Käyhty, and Eskola, 1996). The decision to give a booster vaccination is based on the rate of decline and persistence or not of immunologic memory (Akinsola et al., 2012).

This chapter provides a review of the evolution of the antibody theory, specifically the inherent importance of the development of immunity after receiving the appropriate vaccine inoculation. In addition, pneumococcal conjugate vaccine impacts research relating to the questions addressed in this study. Research on the diseases caused by the streptococcus pneumonia, the different disease causing serotypes of the bacteria, the serotypes covered by the available vaccines, and their role in the development of invasive pneumococcal diseases were incorporated into this chapter. In order to have an objective discussion of the literature, this chapter includes a discussion of research that challenges some of the outcomes of research in these areas. The chapter culminates with an explanation of how past research influenced this study.

Literature Search Strategy

A search of literature was conducted digitally through electronic medical databases such as Pub Med (NCBI and MeSH databases), Walden library databases (Academic Search Complete and ScienceDirect), and Google scholar. The list of search terms used to conduct the literature search included *pneumococcal diseases,*

streptococcus pneumonia serotypes, *burden of pneumococcal diseases*, *pneumococcal conjugate vaccines,* and *impact of the vaccines on circulating pneumococcal strains*. Full text peer-reviewed articles spanning from 1990 to the last 5 years were obtained digitally and reviewed for this study.

Theoretical Foundation

The theoretical framework for this study was the epidemic model supported by the concept of herd immunity. An epidemic model is based on the following assumptions: (a) infectious disease is transmitted by person-to-person contact only; (b) persons susceptible to the disease will develop the disease after contact with an infected person, thereby acquiring immunity to the illness; (c) there is a fixed probability of coming in contact with an infectious person; (d) the population has no contact with anyone outside the community; and (e) the conditions remain constant throughout the epidemic (Fine, 1977). Herd immunity or threshold protects susceptible individuals in a community from disease assuming there is a minimum vaccination threshold (Libster & Edwards, 2011, p. 163; Piedra et al., 2005). Herd immunity applies to infectious disease that can be transmitted from person to person.

Literature Review

Antibody Theory

According to the antibody theory, health is the multidimensional product of constant interactions between biological mechanisms, psychological processes, and the immune system. The antibody theory, as developed by Brein, Haurowitz, Mudd, Alexander, and Pauling, based on the antigen-template theory assumes that antibodies can be produced only by cells in which the antigen is present. The specific affinity of an

antibody molecule toward the antigen is due to a complementarity in structure derived from the folding of a part of the polypeptide chain of a globulin molecule in direct contact with a determinant or haptenic region of the antigen. The antigen serves as a template in the final stage of formation of a globulin molecule. According to the antibody theory, there is a similarity between antibody formation and adaptive enzyme formation which allows for the continued production of antibody after the antigen has disappeared from the body (Jerne, 1955). A renewed contact with the antigen stimulates the replication of these enzymic units. Circulating antibody molecules are partial replicas of the modified enzymic units, carrying specificity but lacking enzymatic action (Jerne, 1955).

Vaccines provide protection through immune receptors called antibody in the presence of a pathogen. The antibodies are produced by the B lymphocytes that can bind to a pathogen (Siegrist, nd). The T lymphocytes play a role in limiting the spread of the infection by recognizing and killing infected cells or secreting specific antiviral cytokines. Most vaccines involve both B and T cells responses (Siegrist, 2008).

In the DRC, the clinical and laboratory diagnostic of pneumococcal diseases are made based on the WHO's Algorithm represented in Tables1and 2.

Table 1

WHO Coordinated Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) Surveillance Network. Tier 1: Meningitis Surveillance

Case type	Definition	Reference
Suspected meningitis	Any child aged 0-59 months admitted to a sentinel hospital conducting surveillance with sudden onset of fever (> 38.5 °C rectal or 38.0 °C axillary) and one of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal sign Or Every patient less than 5 years of age hospitalized with a clinical diagnosis of meningitis.	WHO-*recommended standards for surveillance of selected vaccine-preventable diseases, 2003*
Probable bacterial meningitis	A suspected meningitis case (as defined above) with CSF examination showing at least one of the following: • Turbid appearance; • Leukocytosis (> 100 cells/mm^3); • Leukocytosis (10-100 cells/ mm^3) AND either an elevated protein (>100 mg/dl) or decreased glucose (< 40 mg/dl) Note: if protein and glucose results are not available, diagnose using the first two conditions (i.e. turbid appearance or leukocytosis > 100 cells/mm^3)	WHO-*recommended standards for surveillance of selected vaccine-preventable diseases, 2003*
Confirmed meningitis	A suspected meningitis case that is laboratory-confirmed by growing (i.e. culturing) or identifying (i.e. by Gram stain, antigen detection, immunochromotography, PCR or other methods) a bacterial pathogen (Hib, pneumococcus or meningococcus) in the CSF or from the blood in a child with a clinical syndrome consistent with bacterial meningitis	WHO-*recommended standards for surveillance of selected vaccine-preventable diseases, 2003*

Table 2

WHO Coordinated Invasive Bacterial Vaccine Preventable Diseases (IB-VPD) Surveillance Network. Tier 2: Meningitis-Pneumonia-Sepsis Surveillance

Case type	Definition	Reference
Pneumonia	Any child aged 0-59 months admitted to a sentinel hospital conducting surveillance, demonstrating a cough or difficulty breathing and displaying fast breathing when calm (as defined by age): Age 0 to <2 months: 60 breaths/minute or more Age 2 to < 12 months: 50 breaths/minute or more Age 12 to <59 months: 40 breaths/minute or more	*WHO/UNICEF Integrated Management of Childhood Illness Chart Booklet - Standard, 2008*
Severe pneumonia	Any child aged 0-59 months admitted to a sentinel hospital conducting surveillance, demonstrating a cough or difficulty breathing and displaying one or more of the following: Inability to drink or breastfeed Vomiting everything Convulsions Prostration/lethargy Chest in-drawing Stridor when calm	*WHO/UNICEF Integrated Management of Childhood Illness Chart Booklet - Standard, 2008*
WHO-defined endpoint pneumonia	Pneumonia in a patient with a chest radiograph showing an infiltrate consistent with pneumonia, i.e., dense, fluffy alveolar consolidation and/or pleural effusion [79].	*Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of pediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ. 2005 May; 83(5):353-9.*
Sepsis	Any child aged 0-59 months admitted to a sentinel hospital conducting surveillance with the presence of at least 2 of the following danger signs and without meningitis nor pneumonia clinical syndrome: Inability to drink or breastfeed Vomiting everything Convulsions (except in malaria endemic areas) Prostration/lethargy (abnormally sleepy or difficult to wake) Severe malnutrition Hypothermia (≤36oC)	*EMRO Surveillance for invasive Hib, Pneumococcal and Meningococcal Diseases. Standard Operating Procedures for Clinical and Laboratory Staff, 2007.*

Note. WHO, 2012. Invasive Bacterial Vaccine Preventable Diseases Surveillance Case Definition

Pneumococcal Infections

Streptococcus pneumonia, the bacteria responsible for the pneumococcal infections, colonize the nasopharynx before either infecting the mucosa causing otitis, pneumonia, or the blood stream causing invasive pneumococcal diseases (Nurhonen, Cheng, & Auranen, 2013). Pneumococcal diseases cause severe clinical manifestations in children such as pneumonia, meningitis, sepsis, and bone and joint infections. The bacterium is responsible for most severe cause of bacterial meningitis in children less than 5 years of age (Knoll et al., 2009). Infection with the bacteria can lead to extreme illness and cause loss of life in most cases.

Pneumococcal diseases are classified into two groups: the invasive pneumococcal diseases (IPDs) and the noninvasive pneumococcal diseases (Ercan, Severge, Topkaya, Ercan, & Altınkaya, 2011). The case is classified as IPD when the bacteria are isolated from the blood, cerebro spinal fluid, or pleural fluid and manifesting into meningitis, sepsis, or bacteremia pneumonia (Adalata, & Riordanb, 2007). The noninvasive disease is manifested into otitis media, sinusitis, and bronchitis (Ansaldi et al., 2008).

Meningitis

Less common but severe forms of pneumococcal disease are often deadly or leave the child with a permanent disability. Meningitis or inflammation of the meninges is an infectious disease affecting the brain membrane and spinal cord that is caused by either neisseria meningitides or streptococcus pneumonia in most of the cases (Uiterwijk & Koehler, 2012). The disease is characterized by fever, headache, stiff neck, nausea, vomiting, photophobia, and altered consciousness. The diagnostic is done by analyzing a sample of the cerebrospinal fluid after lumbar puncture and detecting the serotype of the

bacteria (Uiterwijk & Koehler, 2012). Meningitis can be treated with antibiotics (Uiterwijk & Koehler, 2012).

Pneumonia

The most common severe form of pneumococcal diseases occurs when the bacteria enters the blood stream and subsequently invades other sites of the body such as the cerebrospinal fluid (CDC, 2014). Pneumonia is an infection of the lungs caused by viruses, bacteria, and fungi (CDC, 2014). The most common pneumonia is caused by the bacteria streptococcus pneumonia (CDC, 2014). Children are most at risk for pneumonia. The disease is the leading cause of death in children less than 5 years of age worldwide (CDC, 2014).

Otitis Media

Otitis media is an inflammatory infection of the middle ear caused by streptococcus pneumonia and is characterized by a collection of fluid (Stephen, 1995). It is one of the noninvasive forms of pneumococcal diseases (Stephen, 1995).

Serotypes of the Streptococcus pneumonia

Immunochemistry is used with the differentiation of streptococcus pneumonia into over 93 serotypes grouped into about 48 serogroups. Of those 93-plus serotypes, only about 15 cause most of the invasive diseases in the world (Onwubiko, Shires, Quin, Swiatlo, & McDaniel, 2007). Currently the conjugate vaccines available only contain 13 serotypes; there is a need for more vaccine research, but developing a vaccine that will cover the most frequent serotypes found in invasive diseases is difficult because serotype distribution is function to age, geographic location, and time (Pai, Gertz, & Beall, 2006).

Surveillance with the identification of serotypes in countries is important to determine the vaccine impact after introduction (Hinds et al., nd).

Pneumococcal vaccines

Pneumococcal disease prevention is becoming important as more serotypes are becoming resistant to antibiotics (Ochoa et al., 2010). Two types of vaccines are currently available for pneumococcal diseases prevention: the pneumococcal polysaccharide vaccines and the pneumococcal conjugate vaccines, the latter being the subject of this study.

Although polysaccharides have been available since the mid-1980s, they are not recommended for use in children < 2 years probably due to their immature immune system. In addition, the immune response after vaccination with the polysaccharide is B-cell-dependent with release of IGM as opposed to conjugates vaccines which elicits mucosal immune response by induction of IgA antibodies (Pletz et al., 2008). Success in the vaccination of young children came with the development of pneumococcal conjugate vaccines starting with the seven valents which included the seven most pediatric disease causing serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). Compared to polysaccharides covering 23 serotypes, conjugates vaccines have a low coverage of pneumococcal serotypes with only 50% protection for infections in adults; although they are effective in infant against invasive pneumococcal diseases (Pletz et al., 2008).

The pneumococcal polysaccharides vaccine (PPV) contains 23 of the over 90 serotypes of the streptococcus pneumoniae bacteria which were responsible for about 90% of most invasive diseases in the United States and constitute the most antibiotics resistant strains. There are some drawbacks with the PPV23 even though it is highly

effective and inexpensive, because of the need to revaccinate in older adults in whom the effectiveness is only 50 to 70% due to a decline in antibody over time; and its ineffectiveness in children less than 2 years of age because of the immaturity of their B cells (Artz, Ershler, & Longo, 2003).

To respond to this problem, alternate vaccines called pneumococcal conjugate vaccines are being developed by linking the polysaccharide antigens with immunogenic carrier proteins, activating a response from the T cells and improving the antibody quality (Chiu, & Mclntyre, 2013). This vaccine not only provides coverage for younger children, but also longer and durable protection against the strains included in it (Chiu, & Mclntyre, 2013). The first PCV was licensed in the year 2000 after scholars showed a decrease in invasive pneumococcal diseases in general and somewhat of otitis media in children (Chiu, & Mclntyre, 2013). Beside the conjugation of PPV, studies are underway to develop another vaccine called pneumococcal protein vaccine that will eventually cover all serotypes of the bacteria with the potential to stimulate immunologic memory (Artz et al., 2003). Licensing of the PCV vaccines began with the seven valent one (PCV7) in the year 2000 for the United States and in 2001 or later for Europe and the rest of the world. This vaccine covered about 80% of the most invasive disease causing pneumococcal pneumoniae strains in children in the United States and the majority of the disease causing around the world (Weil-Olivier, van der Linden, de Schutter, Dagan, & Mantovani, 2012.

The pneumococcal conjugate vaccine is one of the greatest public health successes in the past decade. In light of the success of the vaccine in drastically reducing the incidence of invasive disease in infants and children, more research was undertaken to

include more serotypes leading to the development and licensing of PCV10 and PCV13 respectively from 2008 and 2010 and later in countries. PCV13 recommended use is as follows (Paradiso, 2011):

1. For all children as a 4-dose series at 2, 4, 6, and 12–15 months of age.
2. Children, 24 months of age who have received >1 dose of PCV7 should complete the immunization series with PCV13.
3. Children 14–59 months who are fully vaccinated with PCV7 should receive a single dose of PCV13.
4. Children with underlying medical conditions increasing susceptibility to pneumococcal infection who are fully vaccinated with PCV7 should receive a single dose of PCV13.

Impact of Vaccines on the Circulating Strains

PPV was shown to have reduced the disease incidence in adults 65 years or older and children 2 years and older with certain conditions such as heart disease. According to the Centers for Disease Control and Prevention (2012), healthy adults who get the PPV vaccine develop protection within 2 to 3 weeks (Dagan, 2009). PCV has been shown in studies to be effective against invasive and non-invasive pneumococcal diseases. It was shown in the literature that PCV reduced the burden of antibiotic resistant streptococcus pneumoniae serotypes (Dagan, 2009). Particularly vaccination with PVC 7 has been demonstrated to cause a reduction of the nasopharyngeal carriage types of the penicillin resistant serotypes of streptococcus (Dagan, 2009).

In a 2009 publication the impact of PCV 7 vaccine on the strains of streptococcus pneumonia in the United States of America was studied. Data of 1999-2000 and 2004-

2005 were compared regarding the circulating strains and the antibiotic resistant of them as well as the impact of the PCV7 on them. The results showed an increased prevalence of isolates with intermediate penicillin resistance and erythromycin resistance respectively from 12.7% to 17.9% and from 25.7% to 29.1% and a decreased prevalence of penicillin resistant isolates from 21.5% to 14.6% between the two respiratory illness seasons; the prevalence of multidrug resistance did not change. The study also showed that there was a change in the Streptococcus Pneumoniae population between the two seasons with an increase of the serotypes 19A (14.5%), 3 (11.2%), 6A (7.1%), 19F (7%) and 11A (6%) for the period 2004-2005 of whom only 16.3% are included in the PCV 7 vaccine; and a decrease in the prevalence of most of the vaccine containing serotypes.

In conclusion PCV7 has been found to have an impact on the vaccine containing serotypes (Richter et al, 2009). A study conducted by CDC (2012) in the US have showed that PCV7 vaccines are highly effective (90%) in younger healthy children helping disease incidence decrease by 99% for the vaccine serotypes and an increase in the incidence of invasive pneumococcal diseases due to the serotypes not included in the vaccine.

Implications of Past Research on Present Research

The impact of pneumococcal vaccines is well documented within the fields of immunization and vaccine preventable diseases. Vaccination and immunization are intertwined with disease prevention. The antibody theory has broadened our understanding of the influence of vaccines on disease prevention (Siegrist, 2008). The physiological response to an infection and the ability to prevent it depend upon the ability of the body to produce antibodies in order to react to the infectious agent (Siegrist, 2008).

In an attempt to better understand the physiological response to infection, researchers studied the human immune system. Studies began to conclude a direct connection between the immune system and the protection against diseases in the presence of infectious agents (Granoff, Gupta, Belshe, & Anderson, 1998). The presence of an infectious agent stimulates a physiological chain of events that begins with early-induced responses to eliminate the infection or hold it in check until specific, acquired immune responses have time to develop (Granoff, Gupta, Belshe, & Anderson, 1998). The immune response appears to act like a signaling substance on the nervous system; engaging the areas of the brain that direct the induction of immunologic memory could be an important second mechanism of protection (Granoff, Gupta, Belshe, & Anderson, 1998).

The cost effectiveness of vaccination against infections in general and pneumococcal diseases in particular has been demonstrated in several studies. In a study conducted in Sweden in 2008 to determine if vaccination with the 7 valents pneumococcal conjugate vaccine is a cost-effective intervention taking into account herd immunity has showed that protection of children can be achieved at low and moderate cost when herd immunity is taken into account. Using a Markov model developed by Wisloff et al in 2006, the authors have compared a pneumococcal vaccination program and a no vaccination program of a hypothetical Swedish birth cohort of 95,000 infants (Bergman et al, 2008).

O'Brien, et al. (2009) in a study attempted to determine if the burden of invasive pneumococcal diseases was higher in children younger than five years of age compared to other age groups. The burden was measured using archival data of countries or

neighboring countries whenever available, results showed that Pneumococcal disease caused about 826 000 deaths in children aged 1–59 months around 11% of the overall mortality in children less than 5 years of age.

Zangeneh, Baracco, & Al-Tawfiq, (2011) provided insight on the approved new vaccine containing emerging pneumococcal serotypes in addition to the septivalent and its potential to protect against most disease causing ones. Ayieko et al in their Assessment of Health Benefits and Cost-Effectiveness of 10-Valent and 13-Valent Pneumococcal Conjugate vaccination in Kenyan Children found that by investing annually $14million in the vaccine, 43% of infection with the disease could be avoided; this could help save $1.97 million in treatment cost and a 6.1 % reduction in child mortality. Therefore introducing the pneumococcal conjugate vaccine is highly cost effective (Ayieko et al., 2013).

Literature Relating to Differing Methodologies

The majority of studies in the arena of the impact of the PCV13 have been correlational in nature due to the difficulty in measuring the vaccine effectiveness. The relationship between PCV vaccination and prevention against invasive pneumococcal diseases in children less than 5 years of age has been relatively unexplored, although the literature suggests a possible connection.

Whitney et al, (2003) provided evidence that the pneumococcal conjugate vaccine seven valent (PCV7) induced a decline in the invasive disease in children especially the less than 2 years of age and may also reduce the burden of disease in adults. They have examined surveillance data from the active bacterial core surveillance of the CDC for the years 1998-2001 to evaluate the burden of the invasive disease before and after the

introduction of the PCV-7 vaccine. Sixteen million persons were under surveillance in 2000, of those 433,591 were less than two years of age and 652,551 were between the ages of two and four. The results showed a drop in the rate of invasive disease after the introduction of the PCV7 vaccine from an average of 24.3 cases per 100,000 persons in 1998 and 1999 to 17.3 per 100,000 persons in 2001 with the largest decline in the less than 2 years group.

After comparing the incidence of invasive pneumococcal diseases in children less than 2 years of age before and after vaccination with PCV7 in a study, the authors observed a significant decrease of at least 60%. They have concluded that the conjugate vaccine is effective on children too young to receive the pneumococcal polypeptide. In this prospective population-based study using laboratory surveillance data, infants aged 0 to 90 days residing in 8 US states were examined for invasive streptococcus pneumoniae infection during the period of July 1st 1997- June 30 2004. One hundred and forty-six cases of invasive Pneumococcal Diseases were identified of which 89 before the introduction of the vaccine and 57 after the introduction (Poehling et al., 2006).

Using a retrospective study of children admitted in a hospital in Alberta, Canada for complicated pneumonia over a 10 year period (1997-2007); the authors came to the conclusion that there was an increase in the incidence of complicated pneumonia after vaccination with PCV 7 with 67% of the cases accounting for the non-vaccine serotypes prompting the need for new vaccines covering more serotypes. It should be noted that the data used was 5 years before and 5 years after introduction of the PCV7. Data collected in the charts of inpatient children up to 17 years of age suffering from complicated pneumonia (N=228) was examined and have revealed that streptococcus pneumoniae was

a predominant microorganism identified with non-vaccine serotypes (Chibuk, Robinson, & Hartfield, 2010).

In a case control study, Ercan, Severge, Topkaya, Ercan, & Altınkaya, (2011) examined 138 children completely vaccinated with pneumococcal vaccine and 109 unvaccinated control subjects aged 12–59 months. Data from October 2007 and April 2008 was analyzed to determine the effect of the pneumococcal conjugate vaccine on the pneumococcal carriage in Turkish children. The results did not show a significant difference in pneumococcal carriage rate between the two groups (10.1% vs 16.5%) but there was long term protection against the serotypes included in the vaccine.

Another study using a randomized controlled trial analyzed the indirect effect of 7-valent pneumococcal conjugate vaccine on pneumococcal carriage in newborns in rural Gambia. Twenty villages with infants aged 2-30 months vaccinated with PCV 7 were compared with ten villages as controls were sampled using nasopharyngeal swabs. The other villages received meningococcal conjugate vaccine; it was concluded that PCV-7 induced a significant reduction of the vaccine type pneumococcal carriage in the unvaccinated infant population; the likely reduction probably came from the herd immunity provided by the children and adults vaccinated population (Egere et al, 2012).

Afonso et al, (2013) used an interrupted time-series to analyze 5 cities in Brazil that had good data quality and high PCV10 vaccination coverage. They used the data from the national hospitalization information system from January 2005 to August 2011 to assess the PCV10 effectiveness in children 2-24 months after introduction of the vaccine in the national immunization program. The results showed that hospitalization of children for pneumonia was reduced one year after the introduction of the vaccine.

A study conducted in Uruguay to determine the impact of vaccination with the pneumococcal conjugate vaccine concluded that the vaccine caused a reduction in the incidence of pneumonia in hospitalized children in Uruguay five year after the introduction of the vaccines (PCV7 and PCV13). Also it was concluded that the disease incidence reduction was higher for PCV13 compared to PCV7. In the study secondary surveillance data for the years 2009-2012 was used to compare incidence rate pre- PCV introduction and post-both PCV7 and PCV13 (Hortal, Estevan, Meny, Iraola, & Laurani, 2014).

Summary and Conclusions

The success of smallpox eradication in 1979 by the World Health Organization and its partners brought the optimism that other childhood vaccines preventable diseases could be controlled, eliminated or eradicated through vaccination (Gandon & Day, 2007). According to the literature, the use of vaccines has helped provide protection against a number of childhood infections (McLean, 1998). The impact of pneumococcal vaccines was well documented within the fields of immunization and vaccine preventable diseases. This study added to the existing literature by helping to know the impact of the PCV13 on different kinds of pneumococcal circulating serotypes in DRC.

Chapter 3 describes the methodology used to study the research questions. This chapter discusses the use of chi-square test of independence and logistic regression as valid means to analyze the possibility of a relationship between the introduction of the pneumococcal conjugate vaccine in the childhood immunization schedule and the reduction of the burden of the invasive pneumococcal diseases. The chapter includes a

description of the sample population, procedures, ethical considerations, measures, and analysis of the data.

Chapter 3: Research Method

Introduction

The purpose of this study was to determine whether there was an association between the introduction of PCV13 and new cases of pneumococcal disease in two provinces in central Africa. The pneumococcal conjugate vaccine was introduced to five provinces in the DRC. It was a gradual introduction that will eventually cover the whole country. No studies have been conducted to date that test the effectiveness of the PCV 13 vaccine in the DRC. This study was the first to attempt to evaluate the impact that this vaccine has made. The study may also provide insight as to whether or not the vaccine campaign should be widened to include not only the remaining provinces of the DRC, but also in the rest of the African countries.

Chapter 3 covers a description of the design, sampling and sample, instrumentation, data analysis, and ethical considerations. An overview of the study's design is given including a rationale for the choice of this particular research design. The sample characteristics and size, as well as a description of the sampling process, are presented. The data collection process and analysis are also described in this chapter.

Research Design and Rationale

This study employed a quasi-experimental design using chi-square and logistic regression analysis. I examined the effect of the vaccination and age and gender at the intervention site (Kinshasa province) versus the control site (Katanga province) to determine who got the disease and who did not. The instruments used for measurement of the variables allowed for the data to be analyzed through chi-square and logistic

regression. The research questions and the hypotheses reflect this type of analysis. The hypotheses, corresponding variables and statistical analysis are displayed in table 3.

Table 3

Hypotheses, Corresponding Variables, and Statistical Analysis

Hypothesis	**Independent variable**	**Dependent variable**	**Covariate**	**Statistical Analysis**
1	Province Type: (Kinshasa, Katanga)	Number of new cases (Observed, Not Observed)		Chi-square test of independence
2	Province Type: (Kinshasa, Katanga)	Number of new cases (Observed, Not Observed)	Age	Logistic Regression
3	Province Type: (Kinshasa, Katanga)	Number of new cases (Observed, Not Observed)	Gender	Logistic Regression

Methodology

In this quantitative secondary data analysis, I explored the relationship between the reduction in the number of incident cases of invasive pneumococcal disease and the introduction of PCV13 in the DRC. Disease incidence was compared in a province that introduced the vaccine, against another province that had not. The impact of the vaccine on circulating pneumococcal serotypes in the DRC was examined. Individuals considered for this study included children who lived in the DRC and who had been immunized with PCV13 starting in April 2011, as recorded in an official regional immunization record in the Kinshasa province, and a comparison group of the same age in the Katanga province where the vaccine was not introduced, as well as between sex (male, female). The data

abstracted were archival data, without personal identifying information as provided by the immunizing authority.

Population

The research population was obtained from the archival data collected in the three sentinel surveillance sites in the municipalities of Kalembelembe, Kingasani in Kinshasa, province of Kinshasa, and the hospital of Sendwe in the town of Lubumbashi, Province of Katanga from 2009 to July 2013. Each case was pneumococcal positive by one of the following tests: agglutination test, culture, or PCR. Serotyping is conducted for some of these cases at the Regional Reference Lab (RRL) of MRC in Gambia. Available archival data were used for analysis. Permission was received from the government of the DRC for use of the archival data in the study (Appendix B). Participants selected were (a) children included in the archival surveillance data of the sentinel surveillance sites, (b) children of an age where the disease is common, and (c) children presumed to have had the symptoms of an invasive pneumococcal disease.

Sampling and Sampling Procedures

Archival data from 2009 to July 2013 were extracted from the DRC's sentinel surveillance data set. This archived surveillance data set consisted of a representative sample of children who had visited surveillance sites complaining of signs and symptoms corresponding with the case definition of pneumococcal disease. The sample did not include children who had visited other hospitals in the provinces of Kinshasa and Katanga.

Power Analysis

Prior to conducting a power analysis, three statistical parameters were set to ensure appropriateness of sample size. These parameters included power, expected effect size, and critical alpha. Power was referred to as the probability of finding a statistical difference between groups provided one existed in the sample data set. For the social sciences, power is typically set at 80% (Cohen, 1992). This means that there is an 80% probability that, given the size of the sample collected, a significant difference will be found. The effect size was the degree of shared variance expected between the variables of interest. Cohen (1992) defined effect size in terms of Cohen's was .10 = small, .30 = medium, and .50 = large.

For this study, a medium expected effect size was adopted (i.e., .30). Critical alpha is the probability that a significant finding happened by chance. In the social sciences, critical alpha is usually set at .05 (Cohen, 1992). This means that there is only a 5% chance that the null hypothesis is rejected, when in fact it is true. Accordingly, a formal power analysis was conducted using the following parameters: (a) power = .80, (b) effect size = .30, and (c) alpha = .05. Thus, using G*Power 3.0.10 (a sample size power analysis program), a minimum of 88 participants was needed to produce an 80% probability of rejecting the null hypothesis (Faul, Erdfelder, Lang, & Buchner, 2007).

Procedure for Data Abstraction

Data were abstracted from the surveillance system; chosen children included in the DRC's three sentinels' sites data for pneumococcal surveillance and treatment (Kingasani and Kalembelebe in the province of Kinshasa and Sendwe in the province of Katanga). Children who visited other hospitals than the ones cited above for

pneumococcal infections in the three hospitals were not included in the study. The variables of interest to test the hypotheses were age, gender, location, and lab results. These archival data were originally collected using a case investigation form for pneumococcal disease designed by the DRC's ministry of health. The case investigation form used inquiries about some general information, clinical information, vaccination status, and outcome at discharge for each participant. The questionnaire also collected information about the national lab result, the regional lab result, and the antimicrobial sensibility test result. A copy of the case investigation form is provided in Appendix C. In some cases, some participants had antibiotic treatment before the collection of cerebro spinal fluid, possibly influencing the lab result. The data collected during the child's visit in one of the sentinel sites was part of the normal surveillance activity as prescribed by the immunization authority; therefore, no informed consent was necessary.

The questionnaire was scaled at the ordinal scale level. The data were provided with the identifiers stripped making all results anonymous. All data were extracted from the surveillance system and recorded using Microsoft Access and Excel. Statistical Package for the Social Sciences (SPSS) software program was used to analyze the data. Data analyses were conducted on the entire data set after screening for missing values and outliers.

Instrumentation

In the DRC, the surveillance system is operated by the ministry of health with the technical and financial support of the WHO's country office. The country is subdivided into health zones comprised of health centers and referral hospitals. Suspect cases are notified and investigated in health centers and hospitals with sample collection when

applicable; the sample is then sent to the laboratory for analysis. The data are scrubbed and entered by the data managers at each level. For this study, the data abstracted were collected in the three sentinel surveillance sites for the years 2009- July 2013. This is a credible source of data for pneumococcal disease in the DRC, as the sentinel sites are the places where most of the suspected pneumococcal disease patients are referred.

All data were obtained from the DRC's ministry of health. A letter was sent to the immunization authority requesting data and permission to use available data in this study. The letter was stamped, approved, and returned (Appendix B). As mentioned above, the data came from the three sentinel sites were suspect cases for pneumococcal diseases visit and were hospitalized.

Operationalization of Constructs

Number of instances (observed, not observed). Number of instances (observed, not observed) is defined as number of cases or occurrences determined by scientific observation (Ammer, 2013). Number of instances (observed, not observed) was measured at the nominal level. Part 5 on the case investigation form was used to measure number of instances (observed, not observed) for invasive pneumococcal disease. Each question on the case investigation survey was scaled on a nominal scale with results from different tests specifically culture LCR, Latex, and PCR. 1 = *Influenzae*, 2 = S. *pneumoniae*, 3 = *N. meningitidis*, 4 = *other organism*, 5 = *Negative*. Number of instances (observed, not observed) was extracted from archival sources, meaning that the data were gathered at a previous time.

Province type (Kinshasa, Katanga). Province type is defined as a territory governed as an administrative or political unit of a country or empire (Dictionary.com,

n.d.). Province type (Kinshasa, Katanga) was measured at the nominal level: 1 = *Kinshasa* and 2 = *Katanga*. Questions included in Part 1, providing the general information on the case investigation survey questionnaire, were used to measure province type (Kinshasa, Katanga). Each question on the case investigation questionnaire was scaled at the nominal level. Province type (Kinshasa, Katanga) was extracted from archival sources, meaning the data were gathered at a previous time.

Sex. Sex is defined as either of the two main categories (male and female) into which humans and most other living things are divided on the basis of their reproductive functions. Sex is used to refer to the biological function (Gentile, 1993). Sex was measured at the nominal level. Part 1 of the questions on the case investigation form was used to measure sex: 1 = *male*, and 2 = *female*. Sex was extracted from archival sources, meaning the data were gathered at a previous time.

Table 4

Operationization of Constructs

Variable	**Variable Values**	**Questions**
Province type	Kinshasa/ Katanga	Part 1
Number of instances	Observed/not observed	Part 5
Sex	1=Male 2= Female	Part 1
Age group	1= < 2 years 2= 2-5years	Part 1

Data Analysis Plan

The data were analyzed using the SPSS version 21 to evaluate the impact of the pneumococcal conjugate vaccine. The aim was to determine whether or not the introduction of the pneumococcal conjugate vaccine reduced invasive pneumococcal disease incidence. SPSS 21.0 was used to conduct and tabulate data cleaning and analyses of the archival data and to provide summary statistics where applicable including the mean, central tendency, variance, and standard deviation. Logistic regression analyses were used to evaluate the research questions and to assess whether the number of incident cases increased or decreased with age and gender, (observed, not observed) and province type (Kinshasa, Katanga). Archival data were obtained on number of incident cases of invasive pneumococcal disease by province type to create a 2 x 2 contingency table. Logistic regression was appropriate to analyze the impact of vaccination on the disease incidence, given the variables (province type and number of incidence) were scaled at the nominal level.

RQ1: What is the difference in the number of incident cases of invasive pneumococcal disease in children between the Kinshasa province following the introduction of PCV13 and a comparison group in the Katanga province where the vaccine was not introduced?

Directional Hypothesis 1:

$H_0$1: There is no difference in the number of incident cases of invasive pneumococcal disease in children between the Kinshasa province following the introduction of PCV 13 and the Katanga province where the vaccine was not introduced.

H_a1: Children in Kinshasa province where the PCV 13 was introduced showed a decrease in the number of incident cases of invasive pneumococcal disease as compared to the children of the same age in the Katanga province where the vaccine was not introduced.

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: province type: (Kinshasa, Katanga)
- Statistical analysis: Chi-square test of independence

RQ2: Is there an association between age and incident cases of invasive pneumococcal disease in children among the Kinshasa province (PCV13) and Katanga province (control)?

Directional Hypothesis 2:

H_02: There is no association between age and incident cases of invasive pneumococcal disease in children controlling for province (intervention vs. control)

H_a2: Older children (2-5 years) were more likely to contract invasive pneumococcal disease in the control province compared to the PCV13 intervention province

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: Province type: (Kinshasa, Katanga)
- Covariate: Age
- Statistical analysis: Logistic regression

RQ3: Is there an association between gender and incident cases of invasive pneumococcal disease in children among the Kinshasa province (PCV13) and Katanga province (control)?

Directional Hypothesis 3:

$H_0$3: There is no association between gender and incident cases of invasive pneumococcal disease in children controlling for province (intervention vs. control)

H_a3: Males were more likely to contract invasive pneumococcal disease in the control province compared to the PCV13 intervention province.

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: Province type: (Kinshasa, Katanga)
- Covariate: Gender
- Statistical analysis: Logistic regression

Threats to Validity

External Validity

The sample may not have been the best representation of the population, because it only included patients who visited three hospitals among many; however, it was assumed to be representative because the three hospitals were chosen for pneumococcal diseases referral sites, and the most important information was the lab result. Additionally, the timing of the data collection could affect the way people were thinking when taking the survey. Finally, the condition of the sick child could have been a distraction for the parents; people might have wanted the health care worker to quickly attend to their sick children.

Internal Validity

Chi-square and logistic regression might not have been the only options to test the research questions, but they were the best options and the most accurate inferential statistical tests for this study because I was trying to determine if there was a significant association between a binomial and a categorical variable. Also, the immunization status might have been confounding; children might present the disease even though they are vaccinated, but they might not have had the appropriate number of doses to be immunized. Also, the quantitative design used in this study to answer the research questions might not have been exhaustive; this study has benefited from a qualitative aspect in describing the circulating serotypes of pneumococcal disease in the DRC to see if they were covered in the PCV 13 vaccine.

Ethical Procedures

The data abstracted for this study were archival surveillance data without personal identifying information, as provided by the immunizing authority. The data had unique identification codes. The data were obtained from the ministry of health. Permission was received from the government of the DRC for use of the archival data in the study (Appendix B). Walden IRB approval was sought after approval of the proposal and was obtained, the IRB approval number was 09-04-15-0202213. I reviewed archival data in electronic copies; therefore, there was no direct contact with the participants. The data were cleaned before analysis and will be permanently deleted from my computer 5 years after the study. Any hard copy will be shredded.

Summary and Transition

I described the methodology in Chapter 3 to help me to understand the relationship between the vaccination with PCV 13 and the reduction of pneumococcal disease in the DRC. In this chapter, the use of chi square analysis and logistic regression as valid means to analyze was discussed, as well as threat to validity, the ethical concerns, and the procedure for data abstraction. Chapter 4 covers the data abstraction process, an analysis of the data, and the interpretation of the results.

Chapter 4: Result

Introduction

The purpose of this study was to determine whether there was an association between the introduction of PCV13 and new cases of pneumococcal disease in two provinces in central Africa. I examined the relationship between DRC provinces' childhood immunization rates for pneumococcal vaccine and the incidence of invasive pneumococcal disease. The research involved a sample of children who lived in the DRC and who were immunized with PCV13 starting in April 2011 as recorded in an official regional immunization record in the Kinshasa province and a comparison group of the same age in the Katanga province where the vaccine was not introduced. The research population was obtained from the archival data collected in the three sentinel surveillance sites in the municipalities of Kalembelembe, Kingasani in Kinshasa, province of Kinshasa, and the hospital of Sendwe in the town of Lubumbashi, province of Katanga from 2009 to July 2013. Three research questions were used to guide this quantitative study. The variables of interest included age, gender, location, and lab results.

This chapter starts with a summary of the applied statistical methods and the results consisting of a detailed description of the evaluated participants. I then present the descriptive statistics of the sample and a review of the independent variables in relation to the dependent variable. The descriptive statistics of the sample are followed by the data analyses using a chi square test of independence and logistic regression to determine if the vaccination made a difference in the incidence of pneumococcal disease in the population moderated by sex, gender, and province type. Finally, this chapter concludes with a summary of my findings.

Data Cleaning

Prior to analyzing the research questions, data screening and data cleaning were undertaken to ensure the variables of interest met appropriate statistical assumptions. Upon review, it was found that 110 participants of the 490 in the data set were missing critical information such as age, gender, or lab results. These participants were removed from the analysis. The total number of participants used in the study was 380.

Description of the Sample

This study's sample consisted of 380 children who were 5 years of age or under located in the DRC who have visited surveillance sites complaining of signs and symptoms that correspond with the case definition of pneumococcal disease during 2009–July 2013. Data were abstracted from a valid sample of 380 participants. Specifically, there was not much difference between the number of participants who were males (51.1%, *n* = 194) and those who were females (48.9%, *n* =186); additionally, 64.2% of the participants were under 2-years-old (n =244), 35.8% were between 2- and 5-years-old (*n* = 136), and 21.6% of the participants came from the province of Katanga (*n* = 82) and 78.4% came from the province of Kinshasa (*n* = 298). Described in Table 5 are frequency and percent statistics of participants' gender, age groups, and province type.

Table 5

Frequency and Percent Statistics of Participants' Gender, Age Groups, and Province Type

Variables	Frequency	Percent
Gender		
Male	194	51.1
Female	186	48.9
Age Groups		
< 2 years	244	64.2
2 – 5 years	136	35.8
Province type		
Katanga	82	21.6
Kinshasa	298	78.4

Note: total *N*= 380

Table 6

Frequency of Participants' Gender, Age Groups by Province Type

		Province type		Total
		Katanga	Kinshasa	
Gender	Male	45	149	194
	Female	37	149	186
Age group	< 2 years	67	177	244
	2-5 years	15	121	136

Note: total N= 380

Population and Sample

The population of interest consisted of (a) children included in the archival surveillance data of the sentinel surveillance sites, (b) children of an age where the disease is common, and (c) children presumed to have had the symptoms of an invasive pneumococcal disease. The sample did not include children who had visited other hospitals in the provinces of Kinshasa and Katanga.

Analysis of Research Questions

The research questions were evaluated using chi-square test of independence and logistic regression to determine if there is a difference between number of children diagnosed with the disease (observed, not observed) and province type (Kinshasa, Katanga), gender (male, female), and age groups.

The dependent variable for the analyses was the number of incident cases as measured by the case investigation questionnaire and defined in Chapter 3. The independent variables were province (Katanga, Kinshasa) type, gender (male, female), and age groups.

Research Questions and Hypotheses.

The research questions were the following:

RQ1: What is the difference in the number of incident cases of invasive pneumococcal disease in children between the Kinshasa province following the introduction of PCV13 and a comparison group in the Katanga province where the vaccine was not introduced?

Directional Hypothesis 1:

$H_0$1: There is no difference in the number of incident cases of invasive pneumococcal disease in children between the Kinshasa province following the introduction of PCV 13 and the Katanga province where the vaccine was not introduced.

H_a1: Children in Kinshasa province where the PCV 13 was introduced showed a decrease in the number of incident cases of invasive pneumococcal disease as compared to the children of the same age in the Katanga province where the vaccine was not introduced.

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: province type: (Kinshasa, Katanga)
- Statistical analysis: Chi-square test of independence

RQ2: Is there an association between age and incident cases of invasive pneumococcal disease in children among the Kinshasa province (PCV13) and Katanga province (control)?

Directional Hypothesis 2:

$H_0$2: There is no association between age and incident cases of invasive pneumococcal disease in children controlling for province (intervention vs. control)

H_a2: Older children (2-5 years) were more likely to contract invasive pneumococcal disease in the control province compared to the PCV13 intervention province

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: Province type: (Kinshasa, Katanga)
- Covariate: Age

- Statistical analysis: Logistic regression

RQ3: Is there an association between gender and incident cases of invasive pneumococcal disease in children among the Kinshasa province (PCV13) and Katanga province (control)?

Directional Hypothesis 3:

$H_0$3: There is no association between gender and incident cases of invasive pneumococcal disease in children controlling for province (intervention vs. control)

H_a3: Males were more likely to contract invasive pneumococcal disease in the control province compared to the PCV13 intervention province.

- Dependent variable: Number of incident cases (observed, not observed)
- Independent variable: Province type: (Kinshasa, Katanga)
- Covariate: Gender
- Statistical analysis: Logistic regression

Before conducting the following analyses, the data were assessed using an analytic strategy in that the variables were first evaluated for missing data, skewness and Kurtosis, univariate outliers, normality, and linearity. Subsequently, chi-square and logistic regression analyses were run to determine if any significant difference existed between the variables of interest.

Chi-square test of independence analysis for research question1

Using SPSS 21, chi-square analysis was conducted to determine if a significant difference existed in the number of incidence cases of invasive pneumococcal diseases in children between the Kinshasa province following the introduction of PCV13 vaccine and a comparison group in the Katanga province where the vaccine was not introduced.

Because *P* value = 0.000 < 0.05, I reject the null hypothesis. At α=0.05 level of significance, there is enough evidence to conclude that a significant difference existed in the number of incident cases of invasive pneumococcal diseases between the Kinshasa province following the introduction of PCV 13 vaccine and a comparison group in the Katanga province where the vaccine was not introduced (χ^2= 12.302; *p* <0.001). The number of incident cases of invasive pneumococcal disease was significantly higher among children in the province of Katanga where the PCV 13 vaccine was not introduced. Summarized details are displayed in Tables 7 and 8.

Table7

*2X2 Table Showing Count and Expected Count by Province Type. Final result * Province type Crosstabulation*

			Province type		Total
			Katanga	Kinshasa	
Final result	Observed	Count	20	29	49
	Not Observed	Count	62	269	331
Total		Count	82	298	380

Table 8

Summary of Chi-Square Analysis for Research Question 1

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-square	12.302[a]	1	.000		
Continuity Correction[b]	11.032	1	.001		
Likelihood Ratio	10.812	1	.001		
Fisher's Exact Test				.001	.001
Linear-by-Linear Association	12.270	1	.000		
N of Valid Cases	380				

Note: a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 10.57.

b. Computed only for a 2x2 table

N= 380

Figure 1 displays the distribution of final results by province type.

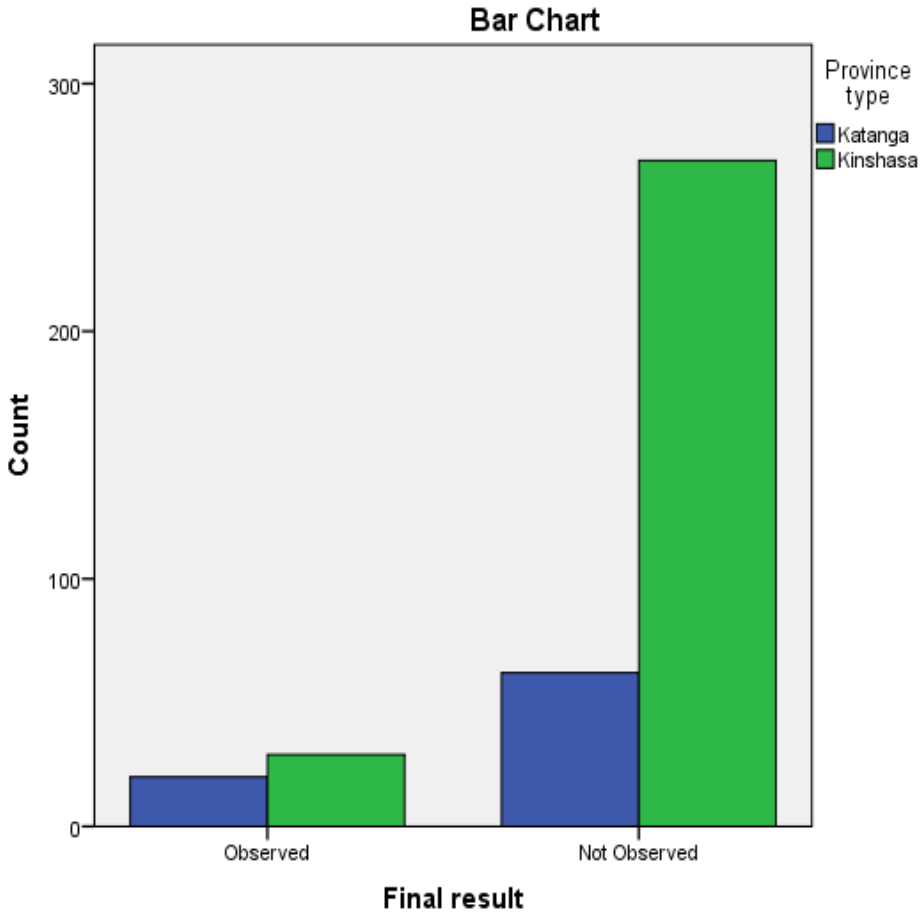

Figure 1: Distribution of final result by province type

Logistic Regression Analyses

Logistic regression analyses were conducted to determine if there were significant differences in number of incident cases between provinces and between males and females for the age groups < 2 years and 2-5 years. Specifically, Analysis 2-3 evaluated differences in incident cases of invasive pneumococcal disease (dependent variable). The independent variables were gender (male, female), age groups (<2 years old and 2 – 5 years old), and province type (Katanga, Kinshasa). The predictor variable for the two regression analyses was number of incident cases as defined in Chapter 3. The

moderating variable for Analysis 2 was age groups (<2-years-old and 2-5-years-old). The moderating variable for Analysis 3 was gender (male, female).

Logistic Regression Analysis for research question2

Using SPSS 22, binary logistic regression analysis was conducted to determine if a significant difference existed in the number of incidence cases of invasive pneumococcal diseases in children aged up to 5 years between the Kinshasa province following the introduction of PCV13 vaccine and a comparison group of the same age in the Katanga province where the vaccine was not introduced.

Table 9

Block 0: Beginning Block for Research Question 2. Iteration History[a,b,c]

Iteration		-2 Log likelihood	Coefficients Constant
Step 0	1	300.730	1.484
	2	292.262	1.855
	3	292.129	1.909
	4	292.129	1.910
	5	292.129	1.910

Note: a. Constant is included in the model.

b. Initial -2 Log Likelihood: 292.129

c. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 10

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	1.910	.153	155.755	1	.000	6.755

Table 11

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	Province type(1)	12.302	1	.000
		Ag groups(1)	4.356	1	.037
	Overall Statistics		14.383	2	.001

Block 0: Beginning Block. Tables 9, 10 and 11 suggests that if I knew nothing about my variables and guessed that older children (2-5 years) will be more likely to contract invasive pneumococcal disease in the control province compared to the PCV13 intervention province, I would be correct 87.1% of the time. The variable not in the equation table means that both variables improve the model, with province type slightly better than age groups, as both are significant and if included would add to the predictive power of the model.

Table 12

Block 1: Method=Enter for research question 2. Iteration History[a,b,c,d]

Iteration			Coefficients		
		-2 Log likelihood	Constant	Province type(1)	Agegroups (1)
Step 1	1	291.915	1.736	-.539	-.211
	2	279.464	2.374	-.890	-.429
	3	278.925	2.570	-.985	-.543
	4	278.923	2.586	-.989	-.555
	5	278.923	2.586	-.989	-.555

Note : a. Method: Enter

b. Constant is included in the model.

c. Initial -2 Log Likelihood: 292.129

d. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 13

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	13.207	2	.001
	Block	13.207	2	.001
	Model	13.207	2	.001

Block 1 Method = Enter displayed in tables 12 and 13 present the results when the predictors province type and age groups are included. SPSS prints a classification table which shows how the classification error rate has not changed from the original 87.1%. By adding the variables we can still predict with 87.1% accuracy (see classification Table 14 below).

Table 14

Classification Table[a]

Observed			Predicted		
			Final result		Percentage
			Observed	Not Observed	Correct
Step 1	Final result	Observed	0	49	.0
		Not Observed	0	331	100.0
	Overall Percentage				87.1

Note: a. The cut value is .500

Model chi-square is used to test the overall significance. It is the difference between –2log likelihood for the best-fitting model and –2log likelihood for the null hypothesis model

There are two hypotheses to test in relation to the overall fit of the model:

H0: The model is a good fitting model.

H1: The model is not a good fitting model.

The –2log likelihood value from the Model Summary table below is 278.923.

In our case model chi square has 2 degrees of freedom, a value of 13.207 and a probability of $p < 0.01$. Thus, the indication is that the model has a poor fit, with the model containing only the constant indicating that the predictors do have a significant effect and create essentially a different model.

Table 15

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	278.923[a]	.034	.064

Note: a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

The Model summary in table 15 provides some approximations of the coefficient of determination R2.

Here the Cox and Snell's R-Square is indicating that 3.4% of the variation in the dependent variable is explained by the logistic model. The Nagelkerke modification that does range from 0 to 1 is a more reliable measure of the relationship. Nagelkerke's R2 is normally higher than the Cox and Snell measure and is the most-reported of the R-squared estimates. In our case it is 0.064, indicating a weak relationship of 6.4% between the predictors and the prediction.

Table 16

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	.165	2	.921

Table 17

Contingency Table for Hosmer and Lemeshow Test

		Final result = Observed		Final result = Not Observed		Total
		Observed	Expected	Observed	Expected	
Step 1	1	17	17.474	50	49.526	67
	2	3	2.526	12	12.474	15
	3	21	20.526	156	156.474	177
	4	8	8.474	113	112.526	121

Tables 16 and 17 showed that Our H-L statistic has a significance of .921 which means that it is not statistically significant and therefore our model is quite a good fit. This desirable outcome of non-significance indicates that the model prediction does not significantly differ from the observed.

Table 18

Variables in the Equation

		B	SE	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
								Lower	Upper
Step 1[a]	Province Type (1)	-.989	.330	9.010	1	.003	.372	.195	.709
	Age groups (1)	-.555	.370	2.249	1	.134	.574	.278	1.186
	Constant	2.586	.324	63.699	1	.000	13.280		

Note: a. Variable(s) entered on step 1: Province type, Age groups.

The Wald statistic displayed in table 18 has a chi-square distribution.

In the variable in the equation table, we note that Province type contributed significantly to the prediction (p = .003) which is less than .05 (we reject the null hypothesis) but Age groups did not (p = .134), we accept the null hypothesis.

The Exp (B) value associated with Province type is .372 meaning that participants are 0.4 time more likely to belong to the Observed group. The Exp (B) value associated with Age groups is 0.574; participants are 0.6 time more likely to belong to the observed group.

In this study age group is 0.6 times as important as province type in determining the decision (see above).

Table 19

Correlation Matrix

		Constant	Province type(1)	Agegroups(1)
Step 1	Constant	1,000	-.214	-.796
	Province type(1)	-.214	1.000	-.183
	Agegroups(1)	-.796	-.183	1.000

The Correlation Matrix table 19 shows the correlations between each of the predictor variables and the constant.

```
             Step number: 1

             Observed Groups and Predicted Probabilities

     200 +                                                                                                    +
         I                                                                                                    I
         I                                                                                        N           I
F        I                                                                                        N           I
R    150 +                                                                                        N           +
E        I                                                                                        N           I
Q        I                                                                                        N   N       I
U        I                                                                                        N   N       I
E    100 +                                                                                        N   N       +
N        I                                                                                        N   N       I
C        I                                                                                        N   N       I
Y        I                                                                         N              N   N       I
      50 +                                                                         N              N   N       +
         I                                                                         N              N   N       I
         I                                                                         N              O   N       I
         I                                                                         O         N    O   O       I
Predicted ---------+---------+---------+---------+---------+---------+---------+---------+---------+----------
  Prob:   0        .1        .2        .3        .4        .5        .6        .7        .8        .9         1
  Group:  OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOONNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN

          Predicted Probability is of Membership for Not Observed
          The Cut Value is .50
          Symbols: O - Observed
                   N - Not Observed
          Each Symbol Represents 12.5 Cases.
```

Figure 2. Probability of membership

Figure 2 shows how our full model predicts membership. Accuracy is shown by the unusually clarity in the middle.

Results Analysis 2

Using SPSS 21.0, Analysis 2 was evaluated using Binary Logistic regression analysis to determine if a significant relationship existed between the number of incident cases between the Kinshasa province where PCV 13 was introduced and the Katanga province where the vaccine was not introduced, and if that relationship was moderated by Age group. Results indicated that a

test of the full model against a constant only model was statistically significant, indicating that there is a difference in incident cases of invasive Pneumococcal diseases

between the Kinshasa province and the Katanga province (chi square = 13.207, p < .01 with df = 2).

Nagelkerke's R2 of .064 indicated a weak relationship between prediction and grouping. Prediction success overall was 87.1% (100% for Not observed and 0% for Observed. The Wald criterion demonstrated that only province type made a significant contribution to prediction (aOR 0.372, 95% CI 0.709-0.195, P=0.003). Age group was not a significant predictor (aOR 0.574, 95% CI 1.186-0.278, P= .134)

Logistic Regression Analysis for research question 3

Table 20

Block 0: Beginning Block for analysis 3. Iteration History[a,b,c]

Iteration		-2 Log likelihood	Coefficients Constant
Step 0	1	300.730	1.484
	2	292.262	1.855
	3	292.129	1.909
	4	292.129	1.910
	5	292.129	1.910

Note: a. Constant is included in the model.

b. Initial -2 Log Likelihood: 292.129

c. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 21

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	1.910	.153	155.755	1	.000	6.755

Table 22

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	Province type(1)	12.302	1	.000
		Gender(1)	.000	1	.996
	Overall Statistics		12.323	2	.002

Block 0: Beginning Block. Tables 20, 21and 22 suggests that if we knew nothing about our variables and guessed that Males will be more likely to contract invasive pneumococcal disease in the control province compared to the PCV13 intervention province we would be correct 87.1% of the time. The variable not in the equation table tells us that both variables improve the model, with Province type slightly better than Age groups, as both are significant and if included would add to the predictive power of the model.

Table 23

Block 1: Method=Enter for research question 3. Iteration History[a,b,c,d]

Iteration		-2 Log likelihood	Coefficients		
			Constant	Province type(1)	Gender(1)
Step 1	1	293.228	1.601	-.587	.020
	2	281.675	2.090	-.982	.038
	3	281.297	2.199	-1.093	.046
	4	281.296	2.205	-1.098	.046
	5	281.296	2.205	-1.098	.046

Note : a. Method: Enter

b. Constant is included in the model.

c. Initial -2 Log Likelihood: 292.129

d. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Table 24

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	10.834	2	.004
	Block	10.834	2	.004
	Model	10.834	2	.004

Block 1 Method = Enter. Tables 23 and 24 presents the results when the predictors province type and genders are included. SPSS prints a classification table which shows how the classification error rate has not changed from the original 87.1%. By adding the variables we can still predict with 87.1% accuracy (see classification Table 25 below).

Table 25

Classification Table[a]

Observed			Predicted		
			Final result		Percentage Correct
			Observed	Not Observed	
Step 1	Final result	Observed	0	49	.0
		Not Observed	0	331	100.0
	Overall Percentage				87.1

Note: a. The cut value is .500

Model chi-square is used to test the overall significance. It is the difference between –2log likelihood for the best-fitting model and –2log likelihood for the null hypothesis model

There are two hypotheses to test in relation to the overall fit of the model:

H0: The model is a good fitting model.

H1: The model is not a good fitting model.

The –2log likelihood value from the Model Summary table below is 281.296.

In our case model chi square has 2 degrees of freedom, a value of 10.834and a probability of p= 0.004. Thus, the indication is that the model has a poor fit, with the model containing only the constant indicating that the predictors do have a significant effect and create essentially a different model.

Table 26

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	281.296[a]	.028	.052

Note: a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

The Model summary displayed in Table 26 provides some approximations of the coefficient of determination R2.

Here the Cox and Snell's R-Square is indicating that 2.8% of the variation in the dependent variable is explained by the logistic model. The Nagelkerke modification that does range from 0 to 1 is a more reliable measure of the relationship. Nagelkerke's R2 is normally higher than the Cox and Snell measure and is the most-reported of the R-squared estimates. In our case it is 0.052, indicating a weak relationship of 5.2% between the predictors and the prediction.

Table 27

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	.016	2	.992

Table 28

Contingency Table for Hosmer and Lemeshow Test

		Final result = Observed		Final result = Not Observed		Total
		Observed	Expected	Observed	Expected	
Step 1	1	9	9.198	28	27.802	37
	2	11	10.802	34	34.198	45
	3	15	14.802	134	134.198	149
	4	14	14.198	135	134.802	149

As displayed in Tables 27 and 28, our H-L statistic has a significance of .992 which means that it is not statistically significant and therefore our model is quite a good fit. This desirable outcome of non-significance indicates that the model prediction does not significantly differ from the observed.

Table 29

Variables in the Equation

		B	SE	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
								Lower	Upper
Step 1[a]	Province Type (1)	-1.098	.323	11.533	1	.001	.333	.177	.628
	Age groups (1)	.046	.312	.022	1	.882	1.047	.569	1.929
	Constant	2.205	.248	78.905	1	.000	9.066		

Note: a. Variable(s) entered on step 1: Province type, Gender.

The Wald statistic has a chi-square distribution.

In the variable in the equation table, Table 29 we note that province type contributed significantly to the prediction (p = .001) which is less than .05 (we reject the null hypothesis) but gender did not (p = .882), we accept the null hypothesis.

The Exp (B) value associated with Province type is .333 meaning that participants are 0.3 time more likely to belong to the Observed group. The Exp (B) value associated with Gender is 1.047; participants are 1 time more likely to belong to the observed group.

In this study Gender is 0.6 times as important as province type in determining the decision.

Table 30

Correlation Matrix

		Constant	Provincetype(1)	Gender(1)
Step 1	Constant	1.000	-.445	-.616
	Provincetype(1)	-.445	1.000	-.050
	Gender(1)	-.616	-.050	1.000

The Correlation Matrix table, Table 30 shows the correlations between each of the predictor variables and the constant.

```
              Step number: 1

              Observed Groups and Predicted Probabilities

     320 +
+
         I                                                                                   N
I
         I                                                                                   N
I
F        I                                                                                   N
I
R    240 +                                                                                   N
+
E        I                                                                                   N
I
Q        I                                                                                   N
I
U        I                                                                                   N
I
E    160 +                                                                                   N
+
N        I                                                                                   N
I
C        I                                                                                   N
I
Y        I                                                                                   N
I
      80 +                                                                     N             N
+
         I                                                                     N             N
I
         I                                                                     N             N
I
         I                                                                     O             O
I
Predicted ---------+---------+---------+---------+---------+---------+---------+---------+---------+--
--------
  Prob:   0       .1        .2        .3        .4        .5        .6        .7        .8        .9
1
  Group:
OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOONNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN

          Predicted Probability is of Membership for Not Observed
          The Cut Value is .50
          Symbols: O - Observed
```

N - Not Observed
Each Symbol Represents 20 Cases.

Figure 3: Membership probability

Figure 3 shows how our full model predicts membership. Accuracy is shown by the unusually clarity in the middle.

Results Analysis 3

Using SPSS 21.0, Analysis 3 was evaluated using Binary Logistic regression analysis to determine if a significant relationship existed between the number of incident cases between the Kinshasa province where PCV 13 was introduced and the Katanga province where the vaccine was not introduced, and if that relationship was moderated by Gender. Results indicated that a

test of the full model against a constant only model was statistically significant, indicating that there is a difference in incident cases of invasive Pneumococcal diseases between the Kinshasa province and the Katanga province (chi square = 10.834, p = .004 with df = 2).

Nagelkerke's R2 of 0.052 indicated a weak relationship between prediction and grouping. Prediction success overall was 87.1% (100% for Not observed and 0% for Observed. The Wald criterion demonstrated that only province type made a significant contribution to prediction (aOR 0.333, 95% CI 0.628-0.177, P=0.001). Gender was not a significant predictor (aOR 1.047, 95% CI 1.929-0.569, P= 0.882).

Descriptive analysis of S. Pneumoniae strains

The circulating Streptococcus Pneumoniae serotypes in the DRC include serotypes 1, 2, 5, 7C, 13, 15B, 19F, 22F, 23A, 23F and 33F. Only four of the 11 serotypes found

circulating in DRC are included in the PCV 13 vaccine. The results are displayed in table 31.

Table 31

Frequency of Streptococcus Pneumoniae serotypes

	Frequency	Valid Percent	Cumulative Percent
Unknown	31	63.3	63.3
S. Pneum ser 1	4	8.2	67.3
S. Pneum ser 2	2	4.0	71.4
S. Pneum ser 5	1	2.0	73.4
S. Pneum ser 15B	1	2.0	79.6
S. Pneum ser 19F	2	4.1	83.7
S. Pneum ser 23F	2	4.1	87.8
S. Pneum ser 33F	1	2.0	89.8
S. Pneum ser 7C	1	2.0	91.8
S. Pneum ser22F	1	2.0	93.9
S. Pneum ser23A	1	2.0	95.9
S. Pneum ser13	1	2.0	98.0
S. Pneum ser19F	1	2.0	100.0
Total	49	100.0	

Table 32 and figure 4 depicts the distribution of the Streptococcus Pneumoniae serotypes by province type. It should be noted that serotyping was not done for all positive cases for invasive pneumococcal disease; of the 49 positive cases 31 serotypes

were unknown. The majority of serotyping was conducted for the Kinshasa province with only one conducted for the Katanga cases.

Table 32

S. Pneum serotypes by province

	Serotypes										
Province	S.1	S.2	S.5	S.7C	S.13	S.15B	S.19F	S.22F	S.23A	S.23F	S.33F
Katanga	0	0	1	0	0	0	0	0	0	0	0
Kinshasa	4	2	0	1	1	1	3	1	1	2	1
Total	4	2	1	1	1	1	3	1	1	2	1

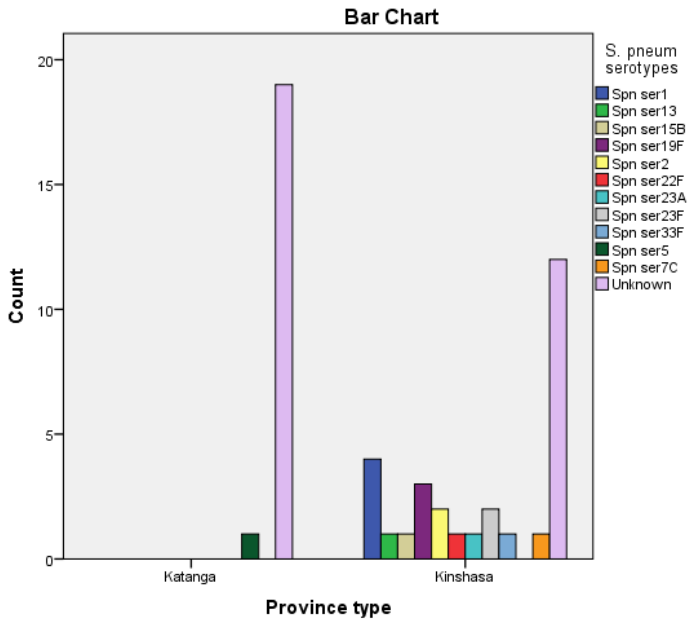

Figure4. Serotypes distribution by province

Serotypes distribution was also analyzed by province and by age groups and later by province and by gender. The results showed that more serotyping was done in the < 2 years age group but that age group also has the most unknown serotypes. As for gender

the distribution is about the same for both males and females. Results are displayed in figures 5 and 6. When the analysis was done by crossing age groups and gender, I noted that males had more serotyping done in the < 2 years of age. Results are depicted in figure 7.

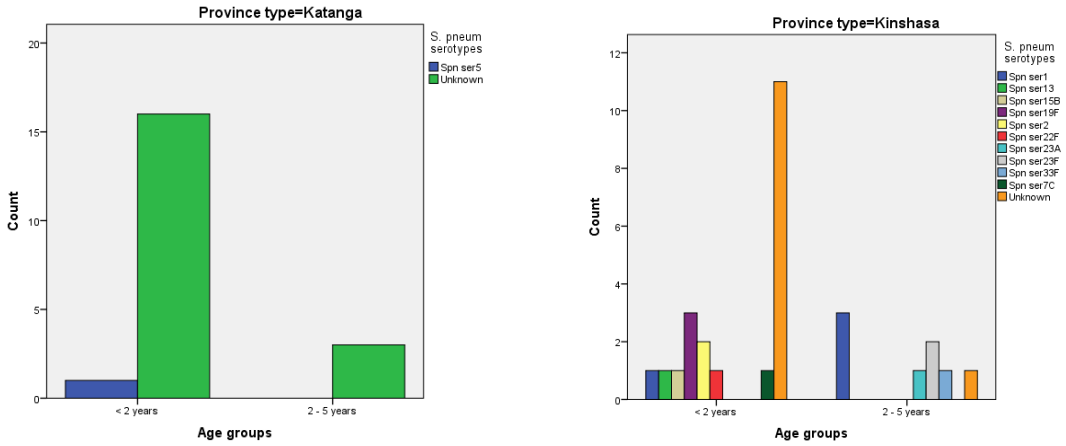

Figure5. Serotypes distribution by province and by age groups

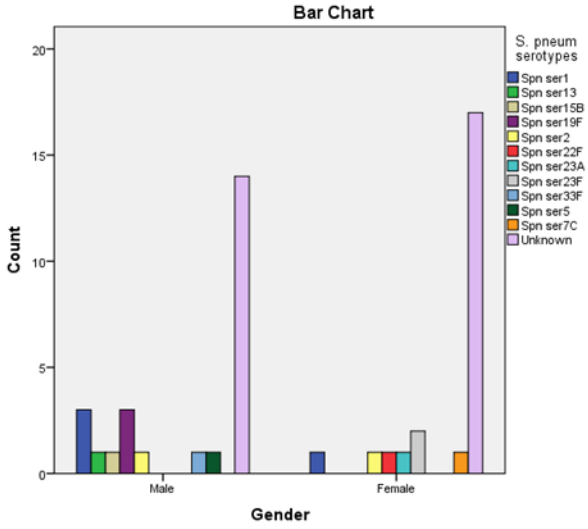

Figure 6. Serotype distribution by gender

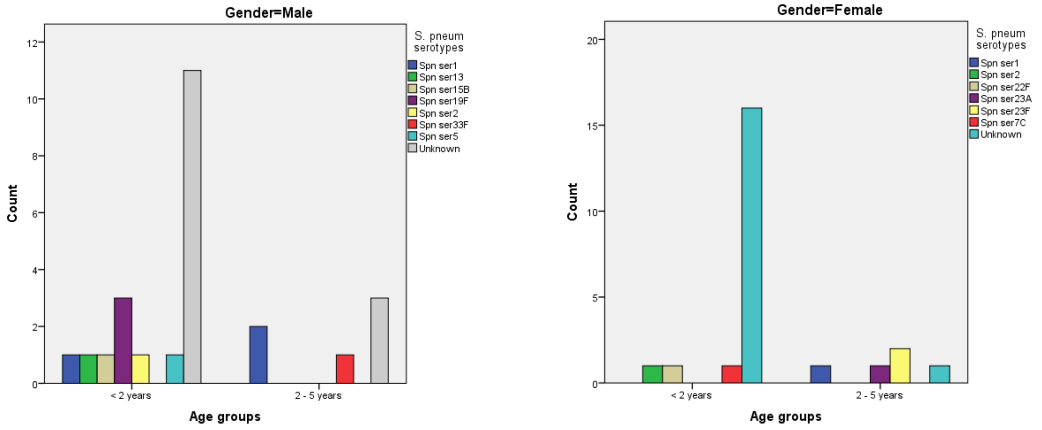

Figure7. Serotype distribution by gender and by age groups

PCV13 vaccination coverage in Kinshasa province for the years 2011, 2012 and 2013 is displayed in figure 8. The coverage for the first dose of PCV13 is good for 2012 and 2013, it's below 80 % for 2011, and this can be explained by the fact that 2011 was the first year of introduction. The third dose is barely at 80% for 2012 but less than 80% for 2011 and 2013; the country had a shortage of vaccine during 2013.

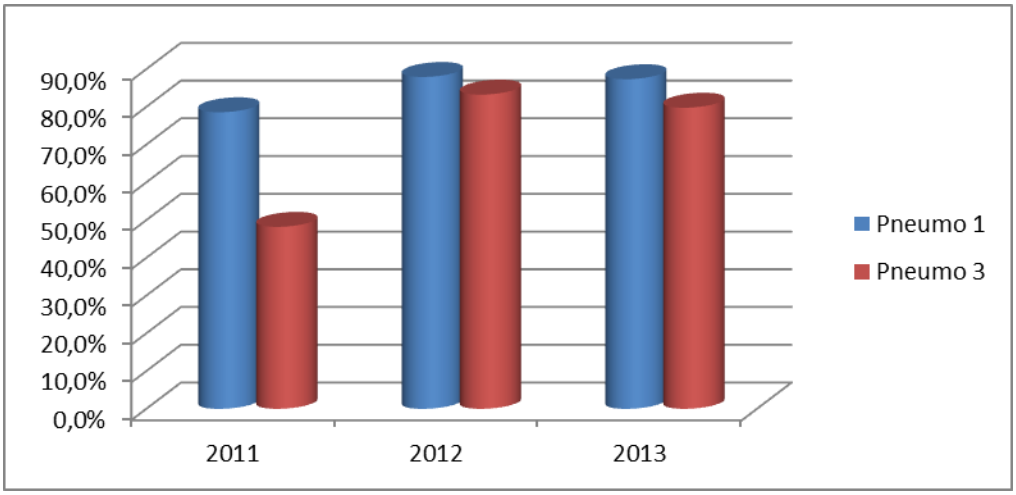

Figure 8. PCV 13 coverage in Kinshasa province for the years 2011, 2012 and 2013 (January-July 2013)

Summary and Transition

In summary, pneumococcal vaccination for young children has been shown to prevent serious illness, hospitalizations, and even death (Rodewald et al, 1999). According to the World Health Organization, the risk of serious pneumococcal disease remains high throughout the first 24 months of life (WHO, 2013). My intent for researching this topic was to examine the relationship between vaccination with PCV13 and the reduction in incidence of invasive pneumococcal diseases, and how this relationship might be affected by an individual's gender and age. The Chi-Square and Logistic Regression analysis conducted in the current study indicated that there was a significant relationship between vaccination with PCV13 and the reduction in incident cases for invasive pneumococcal diseases influenced by province type; however the relationship was not influenced by age group and gender. Table 15 provides a summary of the results for all analyses. There were no statistically significant relationships between any of the predictor variables, concluding that the predictor variables and the interaction effects do not have a significant effect on the outcome variable.

In Chapter 5, I cover a detailed discussion of these results as well as presented the study limitations, recommendations for future studies, and implications for social change.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this study was to determine whether there was an association between the introduction of PCV13 and new cases of pneumococcal disease in two provinces in central Africa and how this relationship might be influenced by an individual's gender and/or age. The findings of this study contribute to the existing body of literature (Chibuk, Robinson, & Hartfield, 2010; Ercan, Severge, Topkaya, Ercan, & Altınkaya, 2011; Poehling et al., 2006; Whitney et al., 2003) on the implications of vaccination with PCV13 in relation to invasive pneumococcal diseases by confirming or not the relationship with the reduction of the disease and by determining that most of the circulating serotypes in the African country are not covered by the PCV13 vaccine. Prior to the current study, no scholar has explored the association between vaccination with PCV13 and the reduction in invasive disease in the DRC. This research study filled that gap by offering a new perspective on the impact of the PCV13 vaccine to the field of public health. The study's sample consisted of children 5-years-old or less who live in the DRC and have visited the sentinel surveillance sites complaining of signs and symptoms corresponding with the case definition of pneumococcal disease during the years 2009-2013. The three research questions for this study integrated a chi-square analysis and two logistic regression analyses to determine the effect of vaccination of PCV13 on the reduction of invasive pneumococcal diseases and to determine if that effect is dependent on gender and age. This study was conducted to explore whether there was a relationship between vaccination with pneumococcal conjugate vaccine and reduction in invasive

pneumococcal diseases and how this might be affected by a child's gender or age. The design of this study was a quantitative, quasi-experimental research design. Data were derived from DRC's archival surveillance data for pneumococcal diseases collected from the established three sentinel surveillance sites.

Interpretation of Findings

In this study, a sample of 380 children located within the DRC was evaluated. Data were entered into SPSS 21.0 and were then tested using chi-square and logistic regression analysis to evaluate the research questions.

Results of Research Hypothesis 1

Using SPSS 21.0, Hypothesis 1 was evaluated using a chi-square to determine if there was a difference between incident cases in Kinshasa province following the introduction of PCV13 and the Katanga province where the vaccine was not introduced.

Results from Analyses 1 indicated that a significant difference existed in the number of incident cases of invasive pneumococcal diseases between the Kinshasa province following the introduction of PCV 13 vaccine and a comparison group in the Katanga province where the vaccine was not introduced ($\chi^2 = 12.302$; $p < 0.001$). Because P value = $0.000 < 0.05$, I rejected the null hypothesis. The number of incident cases of invasive pneumococcal disease is significantly higher among children in the province of Katanga where the PCV 13 vaccine was not introduced. Because the PCV13 vaccination coverage was higher than 80% in the Kinshasa province for the years 2012 and 2013, it is possible that the entire population was protected by heard immunity.

Results of Research Hypothesis 2

Using SPSS 21.0, Hypothesis 2 was evaluated using logistic regression to determine if a significant relationship existed between age and incident cases of invasive pneumococcal disease in children among the Kinshasa province following the introduction of PCV13 and Katanga province where the vaccine was not introduced.

Results from Analyses 2 indicated that no significant relationship existed between age and incident cases of invasive pneumococcal disease in children among the Kinshasa province following the introduction of PCV13 and Katanga province where the vaccine was not introduced (aOR 0.574, 95% CI 1.186-0.278, P= .134), but that there was a difference in incident cases of invasive pneumococcal diseases between the Kinshasa province and the Katanga province (χ^2= 13.207, $p < .01$ with df = 2) confirmed by (aOR 0.372, 95% CI 0.709-0.195, P=0.003).

Results of Research Hypothesis 3

Using SPSS 21.0, Hypothesis 3 was evaluated using logistic regression to determine if a significant relationship existed between gender and incident cases of invasive pneumococcal disease in children among the Kinshasa province following the introduction of PCV13 and Katanga province where the vaccine was not introduced.

Results from Analyses 3 indicated that no significant difference existed between gender and incident cases of invasive pneumococcal disease in children among the Kinshasa province following the introduction of PCV13 and Katanga province where the vaccine was not introduced (aOR 1.047, 95% CI 1.929-0.569, P= 0.882). Because P value = 0.882 > 0.05, I accepted the null hypothesis. At α=0.05 level of significance there was enough evidence to conclude that no significant difference existed between males

and females in the number of incident cases of invasive pneumococcal diseases in children between the Kinshasa province following the introduction of PCV 13 vaccine and the Katanga province where the vaccine was not introduced.

These results represent new findings in the DRC that contribute to the literature. Whitney et al. (2003) provided evidence that the pneumococcal conjugate vaccine seven valent (PCV7) induced a decline in the invasive disease in children, especially the less than 2 years of age, and may also reduce the burden of disease in adults. Poehling et al. (2006) observed a significant decrease of at least 60% in children less than 2 years of age after vaccination with PCV 7. Researchers have not been able to determine whether the association between the reduction in invasive disease after vaccination with the pneumococcal conjugate vaccine and gender exist. This may further lead the DRC's six remaining provinces and other African countries to introduce the vaccine. Additionally the findings have the potential to assist public health practitioners in promoting prevention of the invasive diseases by adopting childhood vaccination with the PCV13 vaccine. Evidence of the relationship between PCV13 and reduction in the incidence of invasive pneumococcal diseases was found for children 5 years of age or under, also an age where the disease is more frequent in DRC. This assisted with distinguishing the age group at risk of the disease and will help determine actions directed toward these particular children. The results in this study support prior research findings that had also affirmed the impact of pneumococcal conjugate vaccines on the reduction of the invasive diseases mostly in children < 2 years.

Strengths of the Study

In this study, I identified the age group most at risk for invasive pneumococcal diseases in the DRC, necessary to better direct interventions. The data obtained from the DRC government consisted of archival surveillance and vaccination data collected as part of the national surveillance system. The sample consisted of children 5 years of age and under who have visited a sentinel surveillance site complaining of symptoms of pneumococcal disease during the years 2009-2013. The data set files were in Excel and Access format, which were later imported into SPSS for analysis. For proper analysis, the data were checked for missing values and tested for normality.

Analytic guidelines were followed to conduct a power analysis in order to determine the minimum sample size needed. A minimum of 88 participants was required to produce an 80% probability of rejecting the null hypothesis (Faul et al., 2007). Further, all data collected are kept private and strictly confidential according to the public health laws requirements.

Limitations of the Study

The results of this study have a number of limitations that must be acknowledged as with most research. Despite these limitations to the study findings, the conclusions of the study make a contribution to the existing body of literature on this subject. First, the causal relationship between PCV 13 and the reduction in incidence cases of invasive pneumococcal diseases might not have been accurate in children based on the fact that only a weighted average of pneumococcal vaccination rates for children was used to estimate the coverage of children in Kinshasa province. The data provided did not include vaccination status of the participants with the number of doses. Secondly, serotyping was

not done for all positive cases, especially in the Katanga province; therefore, all possible circulating serotypes are unknown to identify if they were included in the PCV13 vaccine. Thirdly, there could be variations in pneumococcal vaccine effectiveness within different disease seasons; this needs to be taken into account. Finally, this was a quasi-experimental study that provided information in a limited time frame and may not predict future vaccination rates.

Generalizability

This study targeted only children who have visited one of the three sentinel surveillance sites, data from other cities were not included. This may have impacted the generalizability of my results because I only used patients visiting three hospitals among many; however, it was assumed to be generalizable because the three hospitals were chosen for pneumococcal diseases referral sites, and the most important information was the lab result. The sample consisted of children who were up to 5-years-old, residing in the DRC and had visited the sentinel sites in 2009 – 2013.

Validity

This study was conducted using an archived data that were originally collected with a case investigation form for pneumococcal disease designed by the DRC's ministry of health. The clinical and laboratory diagnostic of pneumococcal diseases were made based on the WHO's algorithm provided to member countries (WHO, 2012). Data from the case investigation form were collected as part of the normal surveillance system for pneumococcal diseases in DRC. Although the WHO (2012) considered the case investigation form a reliable and valid tool for diagnosing pneumococcal diseases, concerns with validity should be considered because I cannot determine whether the

timing of the data collection could have affected the way people are thinking when taking the survey. In addition, the condition of the sick child could have been a distraction for the parents.

Reliability

The pneumococcal diseases case investigation form is a reliable tool that is dependable and accurate (WHO, 2012). The DRC ministry of health is responsible for collecting and disseminating data necessary for planning and executing public health activities in the country. As a reliable source of the nationwide surveillance data for diseases, the DRC ministry of health facilitates through its specialized offices, community health planning, and monitoring prevention effectively. To generate reliable statistics, a minimum sample size of 88 participants was needed according to the power analysis. As a means to control reliability, 380 DRC national representations of those up to 5 years were sampled. However, the use of secondary data increases the probability of measurement error and data variance. Error can occur due to constructs and content validity of the data collected; however, standard error could have prevented errors to invalidate the secondary data. For instance, the case investigation questionnaire can have control over reliability because health care clinicians in the sentinel sites were onsite to assess clinical findings for pneumococcal diseases. Moreover, participants may have been improperly classified as not having pneumococcal diseases impacting this present study's reliability. Also as a researcher, my actions and attitude when collecting the data could have caused some measurement errors. Finally, quality control processes such as checking for missing and normality testing were done before statistical analysis to verify collection of correct data and ensure the data produces stable and consistent results.

Recommendations

Recommendations for Future Research

The results of this study provided a basis for a number of recommendations. Some recommendations for further research are grounded in the limitations listed above. To test this study's hypotheses, archival data during 2009 – 2013 was chosen from the DRC archival surveillance data set. The entire data set was used to reflect the entire population and to answer the research questions after data cleaning. To better the generalizability to the DRC population as a whole, a future study may consider including children who have visited other hospitals in the provinces of Kinshasa and Katanga as part of the larger group, or may examine these populations individually to gain insights into how they may be similar to or different from the participant who were eligible for inclusion in the study.

Additional recommendations for further research emerged from an examination of the results of this study in relation to the literature reviewed in Chapter Two. More research is needed to find more vaccines covering more serotypes. Further, data analysis involving circulating serotypes in DRC could add to the knowledge of serotypes not included in the vaccine.

Recommendations for Practice

Evidence showed that children less than five years are more at risk for invasive pneumococcal diseases, with an increased incidence in the less than 2 years age group (Knoll et al., 2009). It was also shown that the PCV13 had an impact in that age group and on the vaccine contained serotypes (CDC, 2012). Yet, despite the cost effectiveness many countries had not introduced the PCV13 in their childhood vaccination calendar. Often medical practitioners only treat the patients with antibiotics, very costly and not

always affordable especially in sub Saharan Africa. Ayieko et al., (2013) in their Assessment of Health Benefits and Cost-Effectiveness of 10-Valent and 13-Valent Pneumococcal Conjugate vaccination in Kenyan Children found that by investing annually $14million in the vaccine, 43% of infection with the disease could be avoided; this could help save $1.97 million in treatment cost and a 6.1 % reduction in child mortality; their findings showed that introducing the pneumococcal conjugate vaccine is highly cost effective. The mortality caused by invasive pneumococcal diseases is high due in part to reasons cited above but also to antibiotic resistance observed more and more (Ayieko et al., 2013). Therefore it is recommended that vaccination with Pneumococcal conjugates vaccines are put in priority in actions for reducing the morbidity and mortality caused by invasive pneumococcal diseases in countries. In addition, entire communities in the Kinshasa province could have been protected since the vaccination coverage assessed from the immunization data provided by the DRC's Ministry of health was at a good level to induce heard immunity.

Implications for Positive Social Change

It is expected that the conclusions of this study will translate into significantly impacting the way invasive pneumococcal disease, which leads to loss of life or poor quality of live is handled in the DRC. In 2009 the pneumococcal disease incidence was ≥ 3000 per 100,000 children less than 5-years of age in DRC; the mortality rate was between 300 and 500 per 100,000 children less than 5-years of age (Wang, 2009). Further, the results can be applied to the remaining provinces where the PCV13 vaccine was not introduced as well as the African countries who have not yet adopted the preventive measure. Recommending a broad utilization of PCV 13 vaccination as a

measure of preventing a deadly disease will contribute to improving the health of children in DRC in particular and of the entire world in general. This study focused on exploring whether there was a relationship between vaccination with PCV13 and the reduction of invasive pneumococcal diseases, and how this relationship was affected by an individual's gender and age. Understanding the connection between PCV13 vaccination and the reduction of the disease provided a basis on which to foster positive social change in DRC and Africa in general.

Also, the results of this study supported positive social change by broadening the understanding of a relationship between PCV13 and the reduction in incidence of invasive pneumococcal diseases in a place like DRC. This increased knowledge will positively enhance the general public's understanding of not only the burden of the diseases on children up to 5-years of age but also the way to prevent them effectively. Surveillance data in DRC showed circulation of non-vaccine serotypes 2, 7C, 13, 15B, 22F, 23A and 33F. The presence of circulating non vaccine serotypes in DRC suggested that there is a need for further research for a vaccine including more serotypes likely to continue decreasing the burden of invasive disease in children.

Conclusion

The consequences of invasive pneumococcal diseases are significant and evidenced by their yearly high mortality. This constitutes a public health problem that needs to be addressed. Pneumococcal disease can lead to severe health problems, including pneumonia, blood infections, and meningitis that can impair an individual's quality of life and cause death. Further, existing research indicates that there is a high incidence of pneumococcal diseases among children worldwide (CDC, 2011). Additionally,

antibiotics resistance has prompted the recommendation to place attention on prevention of the diseases; and the most cost effective prevention of pneumococcal disease in children is through vaccination with pneumococcal conjugate vaccine (Bergman et al., 2008). The most serotypes containing vaccine available to date is the pneumococcal conjugate vaccine thirteen valent (PCV13) containing 13 of the most disease causing streptococcus pneumoniae serotypes. By adopting the vaccine in the child's vaccination calendar, public health policy makers and healthcare practitioners can enable positive outcomes and enhance children quality of life in a cost-effective manner.

The results of this study provided strong evidence for decision-making that will change the lives of children residing in the DRC, who are up to 5-years of age by implementing practices that acknowledge and address the burden of pneumococcal diseases. This study reported ample statistical evidence to suggest an important role for PCV13 in the reduction of incidence of above cited diseases. However gender and age were found to have no significant impact on the relationship between PCV13 and the reduction of the disease incidence. A child that is completely vaccinated acquires immunity against vaccine preventable diseases (CDC, 2013); According to Esposito and Principi (2015), vaccination with PCV 13 can protect an entire community through heard immunity. The results of this study could suggest that more people where protected through heard immunity because the vaccination coverage with PCV13 in the Kinshasa province was over 80% for the years 2012-2013. Further, this study supported positive social change by broadening the understanding of a relationship between PCV13 and the reduction in incidence of invasive pneumococcal diseases in a place like DRC and provided guidance for public health policies and services.

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Appendix A: Map of the Democratic Republic of Congo

Appendix B: Authorization from the Ministry of Health of DRC

Dr Aissata Coulibaly Diaha
World Health Organization
diahaa@who.int
0817006424

To the Director of the EPI program in the Democratic Republic of Congo

Dear Director,

For my PhD in Epidemiology I chose to study the impact of vaccination with PCV 13 on the reduction of incident cases of diseases due to streptococcus pneumonia. To that effect I would like to obtain from the Ministry of Health the authorization to use the following data:

- Available data from the sentinel surveillance sites of Kalembelembe and Kingasani in the Kinshasa province and of Sendwe in the Katanga province for the years 2009 through 2013.
- Surveillance and vaccination data for the districts of Kalembelembe and Kingasani before and after the introduction of the vaccine and for Lubumbashi/district of Sendwe where the vaccine was not introduced for the years 2009-2013.
- Serotype data from the regional reference laboratory for the years 2009-2013.

Hoping to get a favorable answer, please accept my best regards.

Aissata Coulibaly

_____

Aissata C. Diaha, DDS, MPH, PhD candidate

He wrote OK for authorization and put his stamp of approval.

Dr Aissata Coulibaly Diaha

Organisation Mondiale de la Santé

diahaa@who.int

0817006424

A Monsieur le Directeur du Programme Elargi de Vaccination

En République Démocratique du Congo

Monsieur le Directeur,

Dans le cadre de mon PhD en Epidémiologie, j'ai choisi comme sujet de dissertation l'étude de l'impact de la vaccination avec le PCV 13 sur la réduction de l'incidence des maladies dues au streptococcus pneumoniae. A cet effet j'aimerais obtenir auprès du Ministère de la santé la permission d'utiliser les données suivantes:

1. Données disponibles des sites de surveillance sentinelle de Kalembelebe et Kingasani à Kinshasa et de Sendwe à Lubumbashi pour les années 2009-2013

2. Données de vaccination et de surveillance en provenance des districts de Kingasani, Kalembelebe avant et après l'introduction du vaccin et à Lubumbashi, district de Sendwe où le vaccin n'a pas été introduit pour les années 2009-2013

3. données de sérotypage des pneumocoques reçues du RRL (Laboratoire régional de référence) pour les années 2009-2013

Dans l'attente d'une suite favorable, veuillez accepter mes meilleures salutations.

Aissata C. Diaha

Aissata C. Diaha, DDS, MPH, PhD candidate

Appendix C: Case Investigation Form

INFECTIONS BACTERIENNES INVASIVES – FORMULAIRE D'INVESTIGATION DE CAS SUSPECT

Nom du patient: _____ Date d'admission ____ /____ /__ ____ No. ID du cas: _____

Numero du dossier, si disponible _____ Nom de l'hôpital: _____

PARTIE 1: INFORMATION GENERALE

Sexe: Masculin ☐ **Féminin** ☐ **Age** M J **Date de naissance** J M A

Nom de père/de la mère: _____

ZS de Résidence: _____ Province/Région: _____

Ville/village:_____ Village/Quartier: _____

Adresse : _____ Numéro de téléphone mobile:_____

PARTIE 2: INFORMATION CLINIQUE

Date de début de la maladie: _____/_____/_____

Enfant hospitalisé? _____ (oui/non/pas connu) **Date d'admission: _____/_____/_____**

Diagnostic à l'admission #1_____ Diagnostic à l'admission #2 _____

Autres infections co-morbides :……..

Antibiotiques avant l'admission? _____ (oui/non/pas connu)

Le cas a-t-il eu des signes et symptômes suivants? (cochez tous s'appliquant)

Des convulsions	☐	Incapable de s'alimenter	☐	Antécédent de fièvre	☐	Stridor	☐
Altération de la conscience	☐	Respiration rapide	☐	Déshydratation	☐	Toux	☐
Difficulté de respiration	☐	Tirage sous costal	☐	Nuque raide	☐		
Fontanelle bombée	☐	Inconnu	☐	Autre: _____			

Cas répondant à la définition de cas suspect de méningite : Oui/ Non

LCR prélevé? ___ (oui/non) **Si oui, date et l'heure du prélèvement: _____/_____/_____ (_____:_____)**

Aspect de LCR au prélèvement:……Pression : goutte à goutte hyperbare

Autre Information (par exemple, pourquoi le LCR n'a pas été prélevé?)**: _____**

_____

PART 3: STATUT VACCINAL

Vaccination de routine? **O** **N** **I** **Vaccination pendant une campagne?**

Nbre

Vaccin Hib? ----- ------ ----- ---- **Vaccin Hib?** **O** **N** **I** **O: Oui**

Vaccin Pneumo? ----- ------ ----- ---- **Vaccin Pneumo?** **O** **N** I **N: Non**

Vaccin Meningococcique ----- ------ ----- ---- **Vaccin Meningococcique** **O** **N** I **I: Inconnu**

Dates des doses de **Routine Hib**: Dose #1___/____/___ Dose #2 ____/___/____ Dose #3 ____/____/____

Dates des doses de **Routine Pneumo**: Dose #1___/____/___ Dose #2 ____/___/____ Dose #3 ____/____/____

Dates des doses **Routine Meningococcal**: Dose #1__/___/___ Dose #2 ____/___/____ Dose #3 ___/____/____

Source d'information? Carte de vaccination Histoire orale ☐ registre ☐ Inconnue ☐

Commentaire :

Nom du patient: _____ Date d'admission ____ /____ /_____ No. ID du cas: _____

Numero du dossier, si disponible _____Nom de l'hôpital: _____

PARTIE 4: RESULTAT A LA SORTIE

Résultat a la sorite: Guéri ☐ **Date de sortie** (ou transfert or décès): ____/____/_____

(veuillez cocher (√) Décès ☐ Sorti contre l'avis médical ☐

Transfert ☐ inconnu ☐

Des séquelles à la sortie? O ☐ N ☐ I ☐ **Si oui, veuillez décrire**: _____

Classification finale à la sortie?

Pneumonie ☐ *Méningite* ☐ *Septicémie* ☐ *Autres* ☐ *Inconnu* ☐

Si autres, spécifier : _____

PART 5: RESULTATS DU LABORATOIRE

No d'identification de l'échantillon : _____

Date de réception du LCR au labo: ____/____/____ **L'heure de réception: (_____:___)**

Apparence du LCR: (cochez un) **Echantillon de LCR traité?** 1-Oui ☐ 2-Non ☐

1 - Claire ☐ Si non, raison de non-traitement?_____

2 - Trouble ☐

3 – Xanthos. ☐ **Résultat du LCR enregistré?** 1-Oui ☐ 2-Non ☐

4 – Purulent ☐ **Résultat de Gram:** Cocci G+ ☐ Cocci G- ☐ Coccobacille G- ☐

5 – Autres ☐ Indéterminé ☐

6 – Hémon. ☐ **LCR Protéine: _____** (cochez un) ≤100 ☐ >100 ☐

9 – Inconnu ☐ **LCR Glucose: _____** (cochez un) <40 ☐ 40-100 ☐ >100 ☐

Autres spécifiez : _____

Résultat culture de LCR

1-*H. influenzae* ☐

2-*S. pneumoniae* ☐

3-*N. meningitidis* ☐

4- Autre organisme ☐

5-Stérile ☐

6-Culture non faite

Latex traité? 1-Oui ☐ 2-Non ☐

1-Hib ☐

2-*S. pneumoniae* ☐

3-*N. meningitidis* ☐

4-*N. mening* W135 ☐

5-Négatif ☐

6-Autre non spec.

PCR fait? 1-Oui ☐ 2-Non ☐

1-*H. influenzae* ☐

2-*S. pneumoniae* ☐

3-*N. meningitidis* ☐

4-Négatif ☐

Autre test fait

Autre, spécifiez : _____

1-Binax ☐

2-Identification biochimie ☐

Num leucocytes: _____ (cochez un) <10 ☐ 10-100 ☐ >100 ☐

Non fait ☐

3-Optochine ☐

4- facteurs X et V ☐

5-Autre ☐

6-Pas d'autre test

Si autre, résultat : _____

PART 6: LABORATOIRE DE REFERENCE REGIONAL

L'isolé a-t-il été envoyé au LRR? ____(oui/non) **Si oui, date d'envoi: _____/_____/_____**

NOTES: _____

INFECTIONS BACTERIENNES INVASIVES – LABORATOIRE DE REFERENCE REGIONAL

Nom du patient: _____ Date d'admission ____ /____ /____ No. ID du cas: _____

Numero du dossier, si disponible _____Nom de l'hôpital: _____

LCR **No d'identification de l'échantillon : _____**

Echantillon envoyé au LNR? 1-Oui ☐ 2-Non ☐ **LCR stocké** 1-Oui ☐ 2-Non ☐

Comment était conservé?

Date d'envoi du résultat 1-(Congélateur -20ºC) ☐

du LCR au pavillon: ____/____/____ 2-(Congélateur -70ºC) ☐

Pathogène isolé du LCR 1- *S. pneumoniae* ☐ 2- *N. meningitidis* ☐ 3-Hib ☐ 4- Autre organisme ☐

Si autre, spécifiez : _____

Autre fluide stérile

Autre liquide stérile prélevé (autre que le sang et le LCR) 1-Oui ☐ 2-Non ☐ Quel ? _____

Résultat de la culture d'autre liquide stérile prélevé : _____

Isolat

Isolat envoyé au LRR? 1-Oui ☐ 2-Non ☐

Date d'envoie de l'isolat au LRR: _____/_____/_____ Date de réception par le LRR:

_____/_____/_____

Date d'envoi du résultat au labo national: _____/_____/_____ Date de réception: _____/_____/_____

Commentaire du labo national : _____

RÉSULTATS DU TEST DE SENSIBILITÉ ANTIMICROBIENNE

H. influenzae **Serotype identifié** 1-a ☐ 2-b ☐ 3-c ☐ 4-d ☐ 5-e ☐ 6-f ☐ 7-non typé ☐

Test fait? 1-Oui ☐ 2-Non ☐ (cochez 1-Sensible 2-Résistant 3-Intermediare)

Oxacilline (1mg)	☐	Chloramphenicol (30mg)	☐	Cefotaxime (30mg)	☐
Pénicilline (10U)	☐	Cotrimoxazole (25mg)	☐	Ciprofloxacine (5mg)	☐
Ampicilline (10U)	☐	Erythromycin (15mg)	☐	Autres : _____	

S. pneumoniae **Serotype identifié** _____

Test fait? 1-Oui ☐ 2-Non ☐ (cochez 1-Sensible 2-Résistant 3-Intermediare)

Oxacilline (1mg)	☐	Chloramphenicol (30mg)	☐	Cefotaxime (30mg)	☐
Pénicilline (10U)	☐	Cotrimoxazole (25mg)	☐	Ciprofloxacine (5mg)	☐
Ampicilline (10U)	☐	Erythromycin (15mg)	☐	Autres :_____	

N. mengitidis **Serogroup identifié** 1-A ☐ 2-C ☐ 3-Y ☐ 4-W135 ☐ 5-autre ☐

Test fait? 1-Oui ☐ 2-Non ☐ (cochez 1-Sensible 2-Résistant 3-Intermediare)

Oxacilline (1mg)	☐	Chloramphenicol (30mg)	☐	Cefotaxime (30mg)	☐
Pénicilline (10U)	☐	Cotrimoxazole (25mg)	☐	Ciprofloxacine (5mg)	☐
Ampicilline (10U)	☐	Erythromycin (15mg)	☐	Autres : _____	