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Efficacy of 9-Valent Pneumococcal Conjugate Vaccine against Radiographically-confirmed Pneumonia among Children before and after 24 Months of Age in South Africa

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A research report submitted to Faculty of Health Sciences,

University of the Witwatersrand, in partial fulfilment of the requirements

for the degree of Master of Science in the field of Epidemiology and Biostatistics

Johannesburg – September 2013

DECLARATION

I declare that this research report is my own work. I submitted it in partial fulfilment of the requirements for the Degree of Master of Science in the field of Epidemiology and Biostatistics, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other university.



Ahmed Mohamed Mahmoud Elamin Sept. 22nd 2013

DEDICATION

I dedicate this work to my mother (Amna Awad'Allah) who taught me the love of knowledge.

ABSTRACT

Introduction

Streptococcus pneumoniae (the pneumococcus) is a leading cause of death in under-five children. The HIV/AIDS epidemic in sub-Saharan Africa contributes substantially to the pneumonia burden in the region. Vaccination against pneumococcus is a core component of the pneumococcal disease control program. It is a good, practical and cost-effective option to overcome some of the difficulties in facing the factors which facilitate the occurrence of pneumococcal disease. The aim of this study was to assess the persistence of efficacy of 9-valent pneumococcal conjugate vaccine (PCV9) against radiographically-confirmed pneumonia among children over 24 months of age in comparison to children before 6 months and between 6 and 24 months of age in South Africa.

Materials and methods

The study was an analytic cohort study using secondary data of a randomised controlled trial (RCT) of PCV9 from the Respiratory and Meningeal Pathogens Research Unit (RMPRU), University of the Witwatersrand. STATA and Epi-info computer software programs were used in the analysis.

Findings

Three thousand seven hundred PCV9 trial participants, who had chest x-ray records, form the cohort of the study. Overall PCV9 efficacy against radiographically-confirmed pneumonia was 7%. PCV9 was more efficacious against radiographically-confirmed pneumonia in 6 to 24

month of age children (21%) compared to under-6 month (0%) and beyond-24 month of age children (-5%). Partial PCV9 vaccination was more efficacious against radiographically-confirmed pneumonia than full vaccination. The association between partial and complete vaccination and radiographically-confirmed pneumonia was not statistically significant, however. HIV infection profoundly affected the efficacy of PCV9 in all age groups. Other factors which were associated with radiographically-confirmed pneumonia were clinical pneumonia, more than two previous pneumonia admissions and presence of pneumonia predisposing factors.

Conclusion and recommendations

PCV9 vaccination had limited efficacy against radiographically-confirmed pneumonia. However, it was more effective against radiographically-confirmed pneumonia in 6 to 24 month old children. Partial vaccination was more efficacious than a full course (given at 6, 10 and 14 weeks of age). Adoption of two primary doses of PCV9 with one booster dose, in-depth studies to investigate the factors that affect PCV9 efficacy, raising awareness about the potential effect of these factors on radiographically-confirmed pneumonia and the improvement of HIV/AIDS interventions are recommended.

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TABLE OF CONTENTS

	DECLARATION	I
	DEDICATION	II
	ABSTRACT	III
	ACKNOWLEDGEMENT	V
	TABLES OF CONTENTS	VI
	LIST OF FIGURES	IX
	LIST OF TABLES	X
	ACRONYMS	XII
1.	**CHAPTER 1: INTRODUCTION**	1
1.1	Background	1
1.1.1	The South African under-five mortality rate	3
1.1.2	Childhood pneumonia	4
1.1.3	Pneumococcal vaccines	6
1.1.4	Radiographically-confirmed pneumonia	8
1.2	Statement of the problem	9
1.3	Justification of the study	9
1.4	Efficacy and effectiveness of PCV against various childhood pneumococcal disease syndromes	10
1.5.1	Study aim	14
1.5.2	Study objectives	14
2.	**CHAPTER 2: METHODOLOGY**	15
2.1	Study design and data source	15
2.2	Study area and population	15
2.3	Recruitment of participants for the RCT and data collection	16
2.4	Study Sample	16
2.5	Data management and analysis concepts	17
2.6.1	Main exposures of interest	18
2.6.2	Other considered/potential confounding exposures	19
2.7	Study outcome of interest	20
2.8	Ethical clearance	20
3.	**CHAPTER 3: RESULTS**	21
3.1	Description of the participating children	21
3.1.1	Distribution of radiographically-confirmed pneumonia in the	21

	participating children	
3.1.2	Demographic characteristics of the participating children	21
3.1.3	Anthropometric measurements of the participating children	22
3.1.4	HIV status of the participating children	23
3.1.5	PCV9 vaccination status of the participating children	24
3.1.6	Distribution of pneumococcal disease in the participating children	24
3.1.7	Distribution of pneumonia predisposing risk factors, hospitalization in the last two weeks and pneumonia previous admissions in the participating children	24
3.2	characteristics of children of with and without radiographically-confirmed pneumonia	25
3.2.1	Demographic characteristics of children with and without radiographically-confirmed pneumonia	25
3.2.2	Anthropometric measurements of children with and without radiographically-confirmed pneumonia	27
3.2.3	Radiographically-confirmed pneumonia according to HIV status of the participating children	28
3.2.4	Radiographically-confirmed pneumonia in children diagnosed with and without pneumococcal disease syndromes	29
3.2.5	Radiographically-confirmed pneumonia in children with history of previous pneumonia admissions, previous hospitilization and pneumonia predisposing factors in different age groups	29
3.3	Efficacy of PCV9	32
3.3.1	Overall efficacy of PCV9	32
3.3.2	Efficacy of PCV9 in different age groups	32
3.3.3	Trend of efficacy of PCV9 through age groups	32
3.3.4	Efficacy of PCV9 against radiographically-confirmed pneumonia in fully and partially vaccinated children in different age groups	33
3.3.5	Overall efficacy of PCV9 in HIV infected and un-infected children	35
3.3.6	PCV9 efficacy against radiographically-confirmed pneumonia according to HIV status and age groups	35
3.3.7	Efficacy of PCV9 against radiographically-confirmed pneumonia in children with different characteristics/medical conditions	39
3.3.7.1	Sex	39
3.3.7.2	Pneumococcal disease syndromes	39

3.3.7.3	Previous pneumonia admissions and hospitalization history	39
3.3.7.4	Pneumonia predisposing factors	40
3.3.8	The power of the study	43
3.3.9	Factors that affect association between age groups and radiographically-confirmed pneumonia	43
3.3.9.1	Factors associated with radiographically-confirmed pneumonia in < 6 month of age children	46
3.3.9.2	Factors associated with radiographically-confirmed pneumonia in 6 to 24 month of age children	47
3.3.9.3	Factors associated with radiographically-confirmed pneumonia in > 24 month of age children	49
4	**CHAPTER 4: DISCUSSION**	51
4.1	Overall study findings	51
4.2	Overall PCV9 efficacy against radiographically-confirmed pneumonia	52
4.3	Efficacy of PCV9 in different age groups	52
4.3.1	PCV9 efficacy of PCV9 in under-6 month children	53
4.3.2	PCV9 efficacy of PCV9 in 6 to 24 month children	55
4.3.3	PCV9 efficacy in beyond-24 month children	56
4.4	PCV9 efficacy in partially and fully vaccinated children	58
4.6	Factors predictive of radiographically-confirmed pneumonia	59
4.7	Limitations	60
4.8	Conclusion	60
4.9	Recommendations	61
5	**REFERENCES**	63
6	**APPENDIXES**	73

LIST OF FIGURES

Figure	Title	Page
1.1	South Africa Antenatal Clinic HIV prevalence (%) 1990-2009	4
3.1	Percentage of children with first-episode radiographically-confirmed pneumonia, in different age groups	22
3.2	Median age (and IRQ) of children with and without radiographically-confirmed pneumonia in PCV9 vaccinated and un-vaccinated cohort	26
3.3	Distribution of radiographically-confirmed pneumonia, PCV9 vaccination and HIV infection in different age groups	27
3.4	Trend of PCV9 efficacy in different age groups	33

LIST OF TABLES

No.	Title	Page
1.1	Comparison of sub-Saharan Africa regional U5MR to other regional U5MRs	2
3.1	Distribution of children according to different parameters	23
3.2	Median age (and IQR) of children with and without radiographically-confirmed pneumonia	25
3.3	Anthropometric parameters at hospitalization of children with and without radiographically-confirmed pneumonia	28
3.4	Radiographically-confirmed pneumonia distribution according to HIV status of the participating children	29
3.5	Radiographically-confirmed pneumonia in children with history of more than two pneumonia admissions, presence of predisposing factors and history of hospitilization in different age groups	31
3.6	Overall efficacy of PCV9 against radiographically-confirmed pneumonia in under 5 participating children	32
3.7	Efficacy of PCV9 against radiographically-confirmed pneumonia in fully vaccinated children in different age groups	34
3.8	Efficacy of PCV9 efficacy against radiographically-confirmed pneumonia in partially vaccinated children in different age groups	34
3.9	Overall efficacy of PCV9 in HIV infected and un-infected participating children	35
3.10	Intent-to-treat analysis of PCV9 efficacy against radiographically-confirmed pneumonia in HIV-uninfected children in different age groups	37
3.11	Per protocol analysis of PCV9 efficacy against radiographically-confirmed pneumonia in HIV-uninfected children in different age groups	37
3.12	Intent-to-treat analysis of PCV9 efficacy against radiographically-confirmed pneumonia in HIV-infected children in different age groups	38
3.13	Per protocol analysis of PCV9 efficacy against radiographically-confirmed pneumonia in HIV-infected children in different age groups	38
3.14	Efficacy of PCV9 against radiographically-confirmed pneumonia in children with different characteristics in different age groups	42
3.15	Un-adjusted bi-variate and adjusted multi-variable logistic regression models of the association between radiographically-confirmed pneumonia and age groups	45
3.16	Adjusted multi-variable logistic regression model of radiographically-confirmed pneumonia and potential independent variables in under 6	46

month of age children
3.17 Adjusted multi-variable logistic regression model of radiographically-confirmed pneumonia and potential independent variables in 6 to 24 month of age children 48
3.18 Adjusted multi-variable logistic regression model of radiographically-confirmed pneumonia and potential independent variables in children older than 24 month of age 49

ACRONYMS

AC	Alveolar consolidation
AIDS	Acquired immunodeficiency syndrome
ANC	Antenatal clinic
ART	Anti-retroviral therapy
BVDV	Bovine viral diarrhoea virus
CEE/CIS	Central Eastern Europe/Commonwealth of Independent States
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence interval
CRM197	cross-reactive material/mutant 197
CSF	Cerebrospinal fluid
DTP-3	Diphtheria–tetanus–pertussis-3
EPI	Expanded Programme on Immunization
Epi-Info	Statistics computer software, version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA)
HAART	Highly active antiretroviral therapy
Hib	Haemophilus influenza type b
HIV	Human immunodeficiency virus
IPD	Invasive pneumococcal disease
IQR	Interquartile range
ITT	Intent-to-treat
Kg	Kilogram
MCV1	Measles containing vaccine 1st dose
MCV2	Measles containing vaccine 2nd dose
MDG	Millennium Developmental Goal
mg	Microgram
mL	Millilitre
MPS	Meningococcal polysaccharide
NVTs	Non-vaccine serotypes
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PCV7	7-valent Pneumococcal conjugate vaccine
PCV9	9-valent Pneumococcal conjugate vaccine
PMTCT	Prevention of mother-to-child transmission

PP	Per protocol
PPV	Pneumococcal polysaccharide vaccine
RCT	Randomized controlled trial
RH	Reproductive health
RMPRU	Respiratory and Meningeal Pathogens Research Unit
RR	Relative risk
RRV	Rhesus rotavirus
SD	Standard deviation
STATA	Statistics computer software (STATA Corp LP, College Station, Texas, USA)
TB	Tuberculosis
UNAIDS	The Joint United Nations Program on HIV/AIDS
UNICEF	United Nations Children's Fund
USA	United States of America
U5MR	Under five mortality rate
VAR	Vaccine-attributable reduction
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

This chapter describes the global, regional and South African burden of disease caused by *Streptococcus pneumoniae*. It gives an overview of the global experiences regarding the efficacy of pneumococcal conjugate vaccine (PCV) against pneumococcal disease. It describes the role of the x-ray as a tool in the diagnosis of paediatric pneumonia and discusses the importance of knowing the long-term (beyond 24 months) protective effect of PCV against radiographically-confirmed pneumonia in order to optimize the scheduling of vaccine doses.

1.1. Background

Sub-Saharan Africa is largely lagging behind all other regions on most health and developmental indicators[1]. Together with the South Asian region, they are the only regions where under-5 mortality rate (U5MR), which is a very sensitive indictor for health status and well-being of populations and countries, exceeded 50 per 1000 live births in 2011. The South Asian region's U5MR was 62 per 1000 live births, while that of the sub-Saharan African region was 160 per 1000 live births[2]. Eighty-two percent of approximately seven million annual global under-five deaths occurred in these two regions in 2011, with about half of all under-five childhood deaths occurring in the sub-Saharan African region [3].

The sub-Saharan African region U5MR was 593%, 552%, 193%, 348%, 593% and 2667% greater, compared to the average U5MRs in Latin America, East Asia, South Asia and Pacific, the Middle East, Central Eastern Europe/Commonwealth of Independent States CEE/CIS and

industrial countries/regions in which U5MRs were 27, 29, 83, 46, 27 and 6 per 1000 live births in 2006, respectively[2]. Moreover, the U5MR in sub-Saharan Africa was 222% and 113% greater, compared to the global and combined developing countries U5MR estimates (Table 1.1)[2].

Table 1.1: Comparison of sub-Saharan African regional U5MR to other regional U5MRs

Region	U5MR (per 1000 live births)	U5MR (%) in sub-Saharan Africa region compared to other regions
Sub-Saharan Africa	160	100 % (reference)
Latin America	27	593 %
East Asia	29	552 %
South Asia and Pacific	83	193 %
Middle East	46	348 %
CEE/CIS	27	593 %
Industrial countries	6	2667 %
Developing countries	142	113 %
Global	72	222 %

The high U5MR of the sub-Saharan African region results from multiple factors; however, the high human immunodeficiency virus (HIV) prevalence in the region is one of the major factors. The region embodies the majority of global HIV/AIDS cases, and 23.5 million (68%) of the 34.2 million global HIV/AIDS cases occurred in the region in 2011[4].

Further factors, which contribute to high U5MR in the region, include low socioeconomic status of most of the region's population, weak health systems, low immunization coverage against the major vaccine-preventable infectious causes of death (including measles[5], *S.*

pneumoniae, Haemophilus influenza type b [Hib][6], diarrhoeal disease[5], tetanus[5] and TB[5]), and the burden of neglected tropical diseases[7 8].

Good immunization coverage was not accomplished in the past decade, varying from region to region and from country to country. Global diphtheria-tetanus-pertussis 3rd dose (DTP-3) immunization coverage has increased during the past decade to a level of around 78%. It fell in the World Health Organization (WHO) African Region to be lower than 69% by 2004[9]. Global and African measles containing vaccine 1st dose (MCV1) immunization coverage was 84% and 75% in 2011, respectively[10]. South African coverage of MCV1 and measles containing vaccine 2nd dose (MCV2) in 2001 was 68% and 57%, respectively. Over the past decade, in response to measles outbreaks, the coverage has increased nationally to 95% and 83% in 2010, respectively[11].

1.1.1. The South African under-five mortality rate

The U5MR in South Africa was 62 per 1000 live births in 2009, a rate which was the same as in 1990[12]. It rose after 1990 and then started to decline in 2003[13]. This unchanged U5MR has arisen despite improvement in the accessibility of health services to the black majority of South Africa and an overall improvement of the average South African's socioeconomic situation, which occurred after the Apartheid era, in the early 1990s[14]. The rapid increase in the national HIV/AIDS epidemic eroded the initial reduction in U5MR that was anticipated to occur following on these positive political and economic changes[14]. The antenatal clinic (ANC) HIV prevalence among South African women, which is a reasonable proxy of the general

population's HIV prevalence, increased during the same time period from 0.8% in 1990 to 29.4% in 2009 (Figure 1)[15].

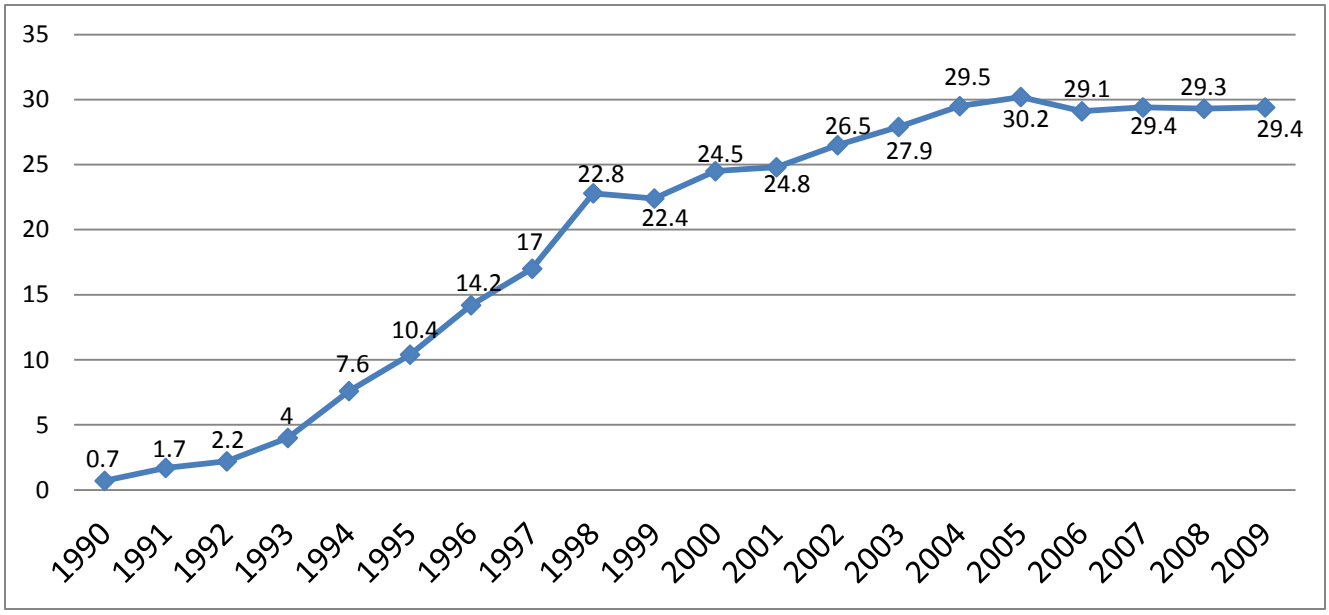


Figure 1.1: South African antenatal clinic HIV prevalence (%) 1990 – 2009

Source: South African Department of Health – UNAIDS Report on the Global AIDS Epidemic|2010

1.1.2. Childhood Pneumonia

Pneumonia kills more children under five years of age than any other disease[6]. Pneumonia is estimated to claim the lives of 700,000 to 1.6 million children every year, globally[5 16]. These pneumonia-associated deaths contribute to 18% of annual under-five childhood mortality[5].

The wide occurrence of malnutrition, low birth weight, lack of good coverage of measles immunization, lack of exclusive breast-feeding, indoor air pollution, and overcrowding in developing countries are the main risk factors for pneumonia [17 18]. These factors are difficult to address effectively within a short time period. They need long term, wide spectrum,

comprehensive interventions including poverty alleviation policies and social development of impoverished rural/peripheral areas.

Streptococcus pneumoniae is a major cause of pneumonia globally, and causes a substantial burden of disease in the developing world. The sub-Saharan Africa region has the highest estimated burden of pneumococcal disease; during 2006, 45% of the global pneumonia-associated deaths occurred in the region[19].

The HIV/AIDS epidemic in sub-Saharan Africa contributes substantially to the pneumonia burden in the region. Immune-suppression arising as a consequence of HIV infection predisposes HIV-infected individuals to opportunistic infections, including pneumococcal disease. HIV-infected persons are at significantly greater risk for pneumococcal disease compared to immune-competent persons. In South Africa, pneumonia claims the lives of 6% of HIV-uninfected under-five children and 33% of those who are HIV infected[20]. Half of all children hospitalized with pneumonia in South Africa are HIV-infected[21]. Children living with HIV/AIDS are up to 40 times more likely to develop invasive pneumococcal disease (IPD) compared to HIV-uninfected children[22 23]. Other conditions, including sickle-cell anaemia[24], nephrotic syndrome[25], cancer [26], and other chronic diseases are also associated with increased risk of serious pneumococcal disease.

Data from a vaccine trial indicates that in Africa, pneumococcus may be responsible for over 50% of severe pneumonia cases, and probably a higher proportion of fatal cases[27]. IPD is the

most serious pneumococcal infection syndrome. It occurs when pneumococci invade normally sterile sites of the body (e.g. cerebrospinal fluid [CSF] causing meningitis; blood, causing bacteraemia; and the pleural cavity, causing pleural effusion).

Emergence of pneumococcal serotypes with antimicrobial resistance is a challenge facing pneumonia treatment and control. Fifteen to 30% of *S. pneumoniae* isolates worldwide are multi-drug resistant (i.e., resistant to three or more classes of antibiotics) [28]. In some areas of the USA, Europe, and East Asia, the prevalence of macrolide resistance in pneumococcal isolates has been reported to be as high as 35% or more[29]. In South Africa, 40% of community-acquired pneumococcal isolates and 95% of hospital-acquired pneumococcal isolates were found to be non-susceptible to penicillin, and resistance to chloramphenicol, tetracycline, and erythromycin occurred in 9%, 12%, and 4% of all isolates, respectively[30]. The proportion of penicillin non-susceptible pneumococci with cefotaxime minimum inhibitory concentrations greater than or equal to 0.5 μg/ml increased from 0% in a 1986 study to 21.5% in a 1989/1991 study [30].

1.1.3. Pneumococcal vaccines

Vaccination against pneumococcus is a core component of the pneumococcal disease control program. It is a good, practical and cost-effective option to overcome some of the difficulties that face the addressing of the factors which facilitate pneumococcal disease, especially in developing countries.

There are two kinds of pneumococcal vaccines: pneumococcal polysaccharide vaccine (PPV) and PCV. PPV, first licenced in 1977, was the first vaccine introduced to prevent pneumococcal disease. It initially contained 14 polysaccharide antigens of pneumococcal serotypes. An improved formulation of PPV, containing polysaccharide epitopes of 23 pneumococcal serotypes was licensed in 1983. PPV is given to children older than two years and adults with underlying risk factors for severe pneumococcal disease. It is, however, not immunogenic in children younger than two years of age and does not elicit memory immune responses.

PCV is a pneumococcal polysaccharide vaccine conjugated to a carrier protein, such as cross-reactive material/mutant 197 (CRM197). This conjugation elicits a T-cell dependent immune response, which is mature in young infants and contributes to the development of memory immune responses[31]. Heptavalent PCV (PCV7), which contains antigen derived from pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, was licensed in the USA in early 2000. Substantial declines in the rate of IPD and pneumonia have been associated with the introduction of PCV in the USA [32 33 34]. New formulations of PCV vaccine including 9-valent, 10-valent, 11-valent and 13-valent are available. 9-valent PCV (PCV9) includes serotypes 1 and 5, which are not included in PCV7 and are important causes of IPD throughout the world [35].

PCVs have been incorporated into EPI schedules in many countries, and have been demonstrated to control disease caused by pneumococcus. The crude efficacy of PCV against IPD in under-five children was found to be high (65-85%) in several studies which have been

conducted in the USA[34 36], Europe[37], Asia[38] and sub-Saharan Africa[23 39]. Furthermore, results have shown that PCV vaccination is an effective intervention aganist different devastating pneumococcal complications.

The Department of Health in South Africa introduced PCV in the EPI in September 2008[40] in order to combat the burden of pneumococcal disease in young infants in the country. Two primary PCV doses are given at 6 and 14 weeks of age with one booster dose at 9 month, i.e. a 2+1 vaccination schedule[41]. This intervention aims to contribute to the reduction of the country's relatively high under-five childhood mortality and to achieve the Fourth Millennium Development Goal (MDG4) of reducing under-five mortality by two thirds of the 1990 levels by the year 2015.

1.1.4. Radiographically-confirmed pneumonia

Chest x-ray is used widely to diagnose pneumonia and other pulmonary diseases and infections. According to the WHO, radiographically-confirmed pneumonia is defined as pneumonia associated with chest radiograph–confirmed alveolar consolidation (AC)[42]. AC is defined as the presence of a dense opacity that could be a fluffy consolidation of a portion of a lobe, a whole lobe, or the entire lung. Often, it contains air bronchograms and sometimes it is associated with pleural effusion. Air bronchograms are air-filled bronchi seen as radiolucent, branching bands within pulmonary densities, and indicates that the surrounding lung parenchyma is consolidated. Pleural effusion is a collection of fluid in the pleural space, which may be large enough to obscure a region of AC opacity on chest x-ray [43].

Radiological diagnosis of pneumonia is difficult in children, especially in young children with interstitial pneumonia[44].

1.2. Statement of the problem

The burden of pneumococcal disease (including radiographically-confirmed pneumonia) is greater in HIV infected children[45]. Emergence of pneumococcal serotypes with resistance to antibiotics undermines the role of clinical interventions in the treatment of pneumococcal infections, and enhances the role which PCV could play in the control of radiographically-confirmed pneumonia.

Chest x-ray is a routine diagnostic method that is used widely to diagnose pneumonia. Crude PCV9 efficacy against radiographically-confirmed pneumonia has been estimated[39]. Without knowing the durability of PCV-induced protection against radiographically-confirmed pneumonia, evidence-based decision-making on the number of PCV doses required to induce sustained protection against this disease will be difficult to determine.

1.3. Justification of the study

Many trials have been conducted to assess the crude efficacy of PCV in the prevention of pneumococcal disease in children under five years of age. The results are encouraging. Moreover, PCV reduces the burden of hospitalization due to virus-associated pneumonia, which indicates that pneumococcal and respiratory viral co-infections are an important cause for pneumonia hospitalisation in children in developing country settings [46].

Radiographically-confirmed pneumonia is widely used in pneumonia diagnosis. Lack of concrete evidence on the durability of PCV efficacy against radiographically-confirmed pneumonia justifies the study of the long-term efficacy of PCV against radiographically-confirmed pneumonia in under-five children beyond the age of 24 months. Before rationalising the number of doses of PCV, the durability and persistence of protection (against radiographically-confirmed pneumonia) attributable to PCV, needs to be quantified. It is crucial for health care policy makers to know how long PCV efficacy persists in order to schedule vaccine booster doses, to secure on-going protection against radiographically-confirmed pneumonia.

1.4. Efficacy and effectiveness of PCV against various childhood pneumococcal disease syndromes

Introduction of PCV7 in the USA largely reduced pneumonia admissions among under-two children; four years after introduction of PCV7, there was a 39% decline in all-causes pneumonia admissions[32]. Examination of trends in pneumococcal meningitis was carried out from 1998 through 2005 using active, population-based surveillance data from eight sites in the USA. It showed that the incidence of pneumococcal meningitis declined from 1.13 to 0.79 cases per 100,000 persons between 1998–1999 and 2004–2005 (a 30.1% decline, $p<0.001$). Among children younger than two years of age, the incidence decreased by 64.0% ($p<0.001$) during the study period [47].

Different randomised controlled trials (RCTs) and other comparative studies have been conducted in developed and developing countries to measure PCV efficacy against different pneumococcal disease manifestations and complications. Different end-points/outcomes were used to measure PCV efficacy, and different results were published. Some of them focused on IPD while others focused on non-IPD syndromes, including pneumonia and acute otitis media.

A trial was conducted between 1997 and 1999 in Navajo and White Mountain Apache Indian reservations (in Alaska and southwest USA) to study the efficacy of PCV7 against IPD. In per protocol (PP) analysis, which includes only the participants who were fully vaccinated, the efficacy was found to be 76.8%. In the intent-to-treat (ITT) analysis, which includes every participant who was fully or partially vaccinated, vaccine efficacy was 82.6%[33].

In Israel, a RCT showed that PCV9 delayed the child-month period to develop a first episode of pneumococcal disease by 7%. It also showed a 15%, 16%, and 17% reduction in upper respiratory tract infection, lower respiratory tract infection and otitis media, respectively, amongst vaccinees compared to placebo recipients, as well as a 17% overall reduction in antibiotic use [48].

PCV9 efficacy has also been evaluated in under-five children in sub-Saharan Africa, where it was demonstrated to reduce the incidence of IPD and radiographically-confirmed pneumonia in HIV-infected and uninfected children under five years of age. In The Gambia, a low HIV-

prevalence African setting, PCV9 efficacy was found to be 77% efficacious against IPD caused by vaccine serotypes and 50% against disease caused by all pneumococcal serotypes in HIV-uninfected children between one and five years of age. Vaccine efficacy was found to be 37% against radiographically-confirmed pneumonia by PP analysis and 36% by ITT analysis. The first episode of radiographically-confirmed pneumonia was reduced by 7% amongst vaccinees. PCV9 efficacy was 15% against all-cause admissions and 16% against under-five childhood mortality[39].

A higher level of protection against pneumococcal disease syndromes has been found in under-five children in South Africa where a RCT was conducted in Soweto (Johannesburg) to evaluate the efficacy of PCV9 [23]. PCV9 reduced the incidence of the first episode of IPD by 83% in HIV-uninfected children and by 65% in HIV-infected children. Among HIV-uninfected children, PCV9 reduced the incidence of first episode radiographically-confirmed pneumonia by 20% in the ITT analysis and 25% in the PP analysis. The overall reduction (regardless of HIV infection status) in children was 72% and 17% against IPD and radiographically-confirmed pneumonia, respectively. PCV9 reduced the incidence of IPD due to penicillin-resistant serotypes by 67%, and that caused by trimethoprim-sulfamethoxazole resistant serotypes by 56% [23]. Radiographically-confirmed pneumonia vaccine attributable reduction (VAR) was 100 cases, 909 cases and 155 cases per 100,000 child-years in HIV-uninfected, HIV-infected and all children irrespective of the HIV status, respectively [45].

In Asia, a RCT was conducted in Bohol, The Philippines, to evaluate the efficacy of 11-valent PCV (PCV11)[38]. It showed that PCV11 efficacy against radiographically-confirmed pneumonia, using PP analysis, was 22.9%, 34% and 2.7% in 3 to 23 month, 3 to 11 month and 12 to 23 month age groups, respectively. By ITT analysis, the efficacy was found to be 16% in the age group under two years and 19.8% in the under 12-month age group.

A historical cohort study was conducted among Australian indigenous children, which showed that the effectiveness of PCV7 against the first episode of pneumonia was between 16% and 24% following a third dose of the vaccine [49]. A narrative review of the randomized, controlled, double-blind studies and systematic reviews of efficacy of pneumococcal vaccines among Australian children showed that PCV7 was expected to prevent >80% of IPD and IPD-associated mortality. It may also prevent 6% of all pneumonia, 18% of radiographically-confirmed pneumonia, 6% of all otitis media and 20% to 40% of tympanostomy tube procedures [50].

Most of the PCV studies were aiming to measure the overall reduction in pneumococcal disease attributable to PCV in children under-five years of age. A few trials (conducted in non-African countries) investigated the trend of PCV efficacy across different age-specific strata. The trial of Bohol (Philippines) investigated the trend of radiographically-confirmed pneumonia in children under two years of age [38]. It was found that PCV11 efficacy was maximal during the first year of vaccination and then started to decline gradually. In South Africa, the duration of the protective effect of PCV9 remains unknown [23]. However, efficacy is

expected to decline over time. Serotype replacement (by strains of pneumococcus not included in existing PCV preparations) may erode PCV effectiveness in vaccinated children [51].

1.5.1. Study aim

The aim of this study was to assess the persistence of efficacy of PCV9 against radiographically-confirmed pneumonia among children under five years of age admitted to Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, South Africa. Age strata utilised in the efficacy analyses were children over 24 months of age, compared to younger children (6 weeks to 6 months, and 6 to 24 months).

1.5.2. Study objectives

- To measure the protective effect of PCV9 against radiographically-confirmed pneumonia in <6 month, 6 to 24 month and 24 to 60 month old (CHBAH) admitted children who had participated in the RCT of PCV9 in Soweto, South Africa, between 1998 and 2005.
- To measure the protective effect of PCV9 against radiographically-confirmed pneumonia in HIV-infected and uninfected (CHBAH) admitted children before 6 months, between 6 and 24 months and older than 24 months of age in Soweto, South Africa.
- To study factors (including PCV9) which affect the occurrence of radiographically-confirmed pneumonia in (CHBAH) admitted children before 6 months, between 6 and 24 months and older than 24 months of age in Soweto, South Africa.

CHAPTER 2

METHODOLOGY

This chapter will discuss the methodology of the study, which includes study design, study population, source of the data, management of the data and data analysis concepts.

2.1. Study design and data source

The study was an analytic cohort study using secondary data derived from the PCV9 RCT which was conducted by the Respiratory and Meningeal Pathogens Research Unit (RMPRU) in Soweto between 1998 and 2005. The treatment arm of the trial included PCV9-vaccinated children and the control arm included PCV9-unvaccinated children (i.e. trial placebo recipients). The primary endpoints/outcomes were the first episode of IPD and/or radiographically-confirmed pneumonia[23]. For the purposes of this secondary analysis, the hypothesis was that PCV9-induced immunity would be eroded with time, and that vaccine efficacy against radiographically-confirmed pneumonia would consequently be decreased in older children.

2.2. Study area and population

The study area was Soweto, a township located south-west of Johannesburg, in the Gauteng Province of South Africa. The population of Soweto is estimated to be 1.5 million people, 120,000 of whom are under five years of age. The community of Soweto is served by Chris Hani Baragwanath Academic Hospital (CHBAH), a 3200 bed hospital which serves more than

90% of children in Soweto (the study catchment area). Children born in Soweto between 2nd March 1998 and 30th October 2000 comprised the study population (N=39,836).

2.3. Recruitment of participants for the RCT and data collection

Children, born within the time-frame mentioned above, and who were 28 to 84 days old, were eligible to participate in the RCT. They were recruited and randomized to receive the intervention (PCV9 or placebo) at 21 vaccination centres in Soweto. The vaccine doses were administered at approximately 6, 10 and 14 weeks of age. Data relating to the study primary end-points were collected through twenty-four hour active surveillance, which was conducted at the paediatric admissions ward at CHBAH. Clinical data of the admitted study participants (regardless of clinical syndrome) were matched with the demographic information of the children who had been enrolled into the RCT, which was recorded at the time of the recruitment into the study. Only children admitted in the hospital who were enrolled and assigned to vaccine or placebo trial arms at Soweto vaccination centres, were included in the analysis[23].

2.4. Study Sample

The study sample was drawn from the 39,836 children who were enrolled in the double-blind RCT. All (3,754) children with information (records), including chest x-ray readings, and between 6 weeks and 5 years, constituted the study sample eligible for this secondary analysis.

The total number of children's records which included chest x-ray information was 5,730. Some of the children had more than one record, because they were admitted on more than one occasion. Only records reflecting the first episode of radiographically-confirmed pneumonia and the records of the first visit amongst children without radiographically-confirmed pneumonia were drawn for analyses: this comprised 3,754 children. Fifty-four children were excluded because they were older than 5 years when admitted at CHBAH. Therefore, 3,700 children (1,929 vaccine recipients, 1,766 placebo recipients (the control group) and 5 were with unknown vaccination status) form the cohort on which all analyses were based.

2.5. Data management and analysis concepts

Data were obtained, with permission, from the main PCV9 RCT database and imported into STATA, version 11.0 (STATA Corp LP, College Station, Texas, USA) for analysis. Epi-info software, version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) was used to calculate the PCV9 efficacy trend across different age groups. Missing variables, duplication, and outliers were checked. Duplicates, which were due to multiple admissions of the participants, were identified. Children who had clinical data recorded during admission with first episode radiographically-confirmed pneumonia were identified. The first visit of children who did not develop radiographically-confirmed pneumonia was also included for the analysis. Age at admission was calculated by subtracting the date of birth from the date of admission, and represented in months.

The analysis was conducted according to the ITT principle, which includes all children who received at least one dose of the vaccine, and by PP analysis, which includes only children who received the full course (three doses) of PCV9.

Uni-variate analysis was done by one-way table analysis to calculate frequency distribution of different characteristics, while bivariate analysis was conducted by Chi squared test, Wilcoxon rank-sum test, and logistic regression. Detecting factors which influenced the occurrence of radiographically-confirmed pneumonia was conducted by forward stepwise logistic regression.

Vaccine efficacy was measured by calculating the incidence rate (attack rate) of radiographically-confirmed pneumonia among vaccinated and un-vaccinated children and determining the percentage reduction in attack rate of disease among vaccinated children compared to un-vaccinated children. The formula {(1-RR) × 100} was used, where RR is the relative risk of radiographically-confirmed pneumonia among vaccinated compared to un-vaccinated children.

Overall power of the study and in different age groups was calculated using STATA.

2.6.1. Main exposures of interest

- PCV9 vaccination was defined as the receipt of PCV9 by the child. A full course of vaccination comprised three doses, given at 6, 10 and 14 weeks of age.
- Age of the children was defined as the age of the children when they developed the main outcome of interest (radiographically-confirmed pneumonia).

- HIV status was defined as HIV status (HIV-infected or uninfected) of the participating child when he/she was admitted in the hospital. HIV infection was attributed in children who had a positive HIV serologic test if they were ≥18 months of age, or a positive HIV PCR if they were <18 months of age.

2.6.2. Other considered/potential confounding exposures

- Sex: of the participating child (male of female);
- Weight: was defined as the weight (in kilograms) of the participating child when he/she was admitted in the hospital;
- Height: was defined as the height (in centimetres) of the participating child when he/she was admitted in the hospital;
- Head circumference: was defined as the circumference of the participating child's head around the occipital bone, to the most anterior portion of the frontal bone (in centimetres) when he/she was admitted in the hospital;
- Predisposing medical cause for pneumonia: was defined as the diagnosis of either an underlying cardiac condition (e.g. ventricular septal defect), chronic lung disease, prematurity (born before completing 37 weeks of gestational age), or post-maturity (born after 42 weeks of gestational age);
- Hospitalization in the last two weeks: was defined as a history of hospitalization within two weeks of the current hospitalization episode;

- Previous pneumonia admission: was defined as history of previous hospital admission due to pneumonia.

2.7. Study outcome of interest

The main outcome of interest was the first episode of radiographically-confirmed pneumonia, defined as the presence of parenchymal changes consistent with AC, with or without secondary changes (complications e.g. pleural effusion), which was diagnosed when the child was admitted to the hospital. Radiographs were read independently by a paediatrician and a radiologist. Discordant chest x-ray interpretations were reviewed by a paediatrician and a radiologist who were members of a WHO expert reading panel, and their decision was considered final[23].

2.8. Ethical Clearance

The Human Research Ethics Committee (Medical) of the University of the Witwatersrand approved the secondary analysis of the PCV9 study database for the purposes of this research project (Appendix 1). Additional informed consent was not required.

CHAPTER 3

RESULTS

This chapter, besides describing the study cohort, investigates PCV9 efficacy against radiographically-confirmed pneumonia and the impact of HIV on PCV9 efficacy. It also studies the factors that influence the relationships between radiographically-confirmed pneumonia as an outcome and PCV9 vaccination. These potential factors included: age (groups), HIV infection status, demographic characteristics, and underlying disease states, which predispose to pneumonia. Investigation of these relationships was conducted by means of bi-variate analysis and multi-variable logistic regression analysis.

3.1. Description of the participating children

3.1.1. Distribution of radiographically-confirmed pneumonia in the participating children

Twenty six percent (n=950) of the 3,700 children admitted with different medical complaints and in whom x-ray outcomes were available, had positive findings of AC on their x-ray radiographs (Table 3.1). Nineteen percent (285/1,495), 26% (417/1,595) and 41% (248/610) of under 6 month children, 6 to 24 month children and older than 24 month children had radiographically-confirmed pneumonia, respectively (Figure 3.1).

3.1.2. Demographic characteristics of the participating children

Forty-four percent (n=1,621) of the 3,700 children were female. Nineteen percent (n=703) of the children were born pre-term, 81% (n=2,993) were born term and less than 1% (n=3) were born post-term (Table 3.1).

The majority, 83% (n=3,090) of the children were under-24 months of age. Forty percent (n=1,495) were under 6 months of age, 43% (n=1,595) were between 6 and 24 months of age and 17% (n=610) were between 24 and 60 months of age (Table 3.1). The median age of the children at hospital admission/data collection was 8.4 months (IQR 3.7 - 18.2 months).

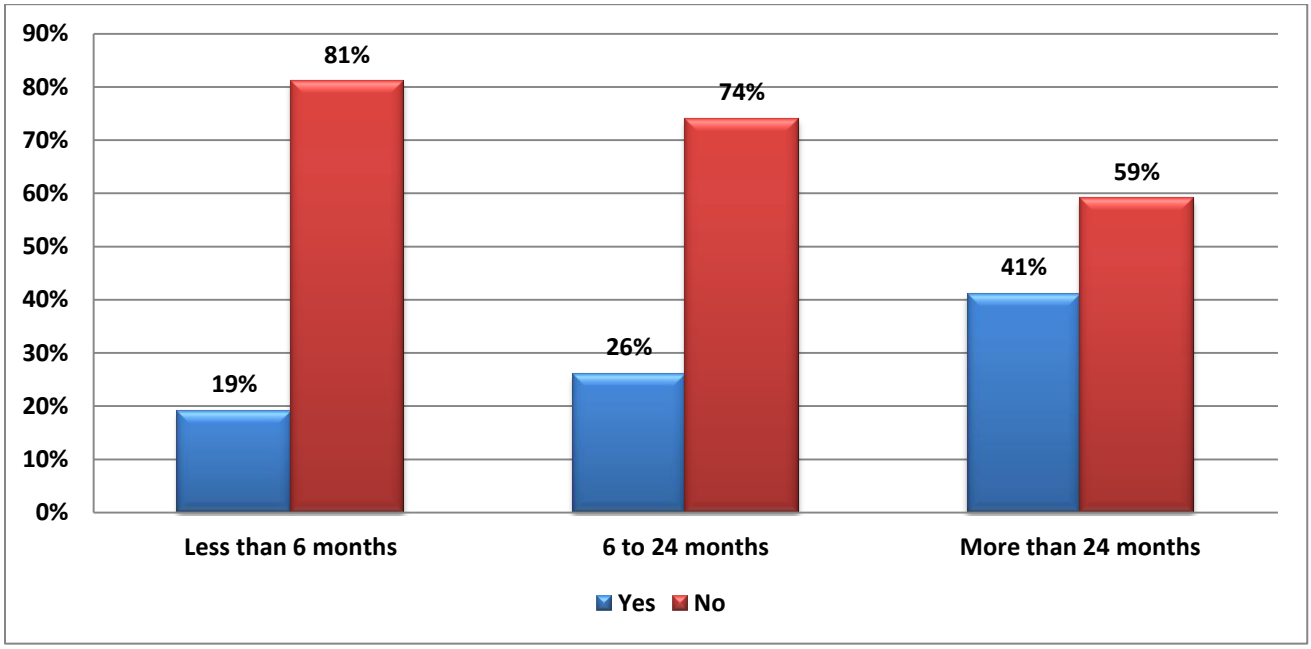


Figure 3.1 Percentage of children with first-episode radiographically-confirmed pneumonia, in different age groups

3.1.3. Anthropometric measurements of the participating children

The median birth weight of the children (available in only 493 [13%] of the cohort) was 3.0 kg (IQR 2.6 - 3.3 kg). Median weight (available in only 1,505 [40.7%] of the children), height (n=3,577) and head circumference (n=3,556) at the hospitalisation episode evaluated for the purposes of this secondary analysis were 9.5 kg (IQR 6.5 - 11.7 kg), 67 cm (IQR 58 - 78 cm) and 45 cm (IQR 41 - 48 cm), respectively (Table 3.1).

Table 3.1: Distribution of children according to different parameters

Parameter		Number	%
Radiographically-confirmed pneumonia	Yes	950	26
	No	2750	74
Sex	Male	2079	56
	Female	1621	44
Maturity at birth	Pre-term	703	19
	Term	2993	81
	Post-term	3	<1
Age categories	Under 6 month	1495	40
	6 to 24 month	1595	43
	24 month and older	610	17
HIV infection	Yes	988	28
	No	2501	72
PCV9 vaccination	Fully vaccinated	1206	33
	Partially vaccinated	599	16
	Un-vaccinated	1886	51
Pneumococcal disease diagnosis	Clinical pneumonia	3054	83
	IPD	16	< 1
	No pneumococcal disease	630	17
Pneumonia predisposing factors	Yes	758	21
	No	2852	79
Hospitalized during the last two weeks	Yes	275	7.5
	No	3392	92.5
Previous pneumonia admissions	Yes	357	10
	No	3271	90
Median age		8.4 months (IQR 3.7 -18.2 months)	
Median birth weight		3.0 kg (IQR 2.6 - 3.3 kg)	
Median weight		9.5 kg (IQR 6.5 - 11.7 kg)	
Median height		67 cm (IQR 58 - 78 cm)	
Median head circumference		45 cm (IQR 41 - 48 cm)	

3.1.4. HIV status of the participating children

HIV infection status was known in 3,489 (94.3%) of the 3,700 children. Of those with defined HIV infection status, 28% (n=988) were HIV-infected (Table 3.1); 46% (n=459) of them were

under-6 months old, 34% (n=336) were 6 to 24 months old and 20% (n=193) were beyond 24 months of age.

3.1.5. PCV9 vaccination status of the participating children

Forty-nine percent (n=1,805) of 3,691 children were PCV9 vaccinated (9 children had undetermined vaccination status), and 67% (n=1,206) of the PCV9 recipients completed the full (three) doses of vaccination (Table 3.1).

3.1.6. Distribution of pneumococcal disease in the participating children

The vast majority 83% (n=3,054) of the participating children were diagnosed with clinical pneumonia. Less than 1% (n=16) were diagnosed with IPD (meningitis/septicaemia), and 17% (n=630) were found to be free from pneumococcal disease (Table 3.1).

3.1.7. Distribution of pneumonia predisposing risk factors, hospitalization in the last two weeks and previous pneumonia admissions in the participating children

Twenty-one percent (n=758) of 3,610 children in whom data were available had predisposing factors (including pre/post maturity, an underlying cardiac condition or chronic lung disease), which contributed towards pneumonia diagnosis and 7.5% (n=275) had been hospitalized during the last two weeks (33 observations were missing) (Table 3.1). Ten percent (n=357) of children had previously been admitted with pneumonia.

3.2. characteristics of children with and without radiographically-confirmed pneumonia

3.2.1. Demographic characteristics of children with and without radiographically-confirmed pneumonia

Twenty-six percent (n=539) of the 2,078 male children and 25% (n=411) of 1,621 female children were diagnosed with radiographically-confirmed pneumonia.

Older children were at greater risk of developing radiographically-confirmed pneumonia; the median age of children with radiographically-confirmed pneumonia was 12.7 months (IQR 4.9 - 24.9 months), while that of children without radiographically-confirmed pneumonia was 7.2 months (IQR 3.5 - 16.1 month), p<0.001 (Table 3.2).

The median age of vaccinated children who were diagnosed with and without radiographically-confirmed pneumonia was 12.3 months (IQR 4.47 – 25.9 months) and 7 months (IQR 3.5 – 15.9) p<0.001 , respectively (Figure 3.2). The median age of un-vaccinated children who were diagnosed with and without radiographically-confirmed pneumonia was 12.9 months (IQR 5.3 – 24.1 months) and 7.4 months (IQR 3.5 – 16.3 months), respectively.

Table 3.2: Median age (and IQR) of children with and without radiographically-confirmed pneumonia

Radiographically-confirmed pneumonia	Age of children (month)	IQR	p value†
Yes	12.7	4.9 - 24.9	< 0.001
No	7.2	3.5 - 16.1	

†Wilcoxon rank-sum test

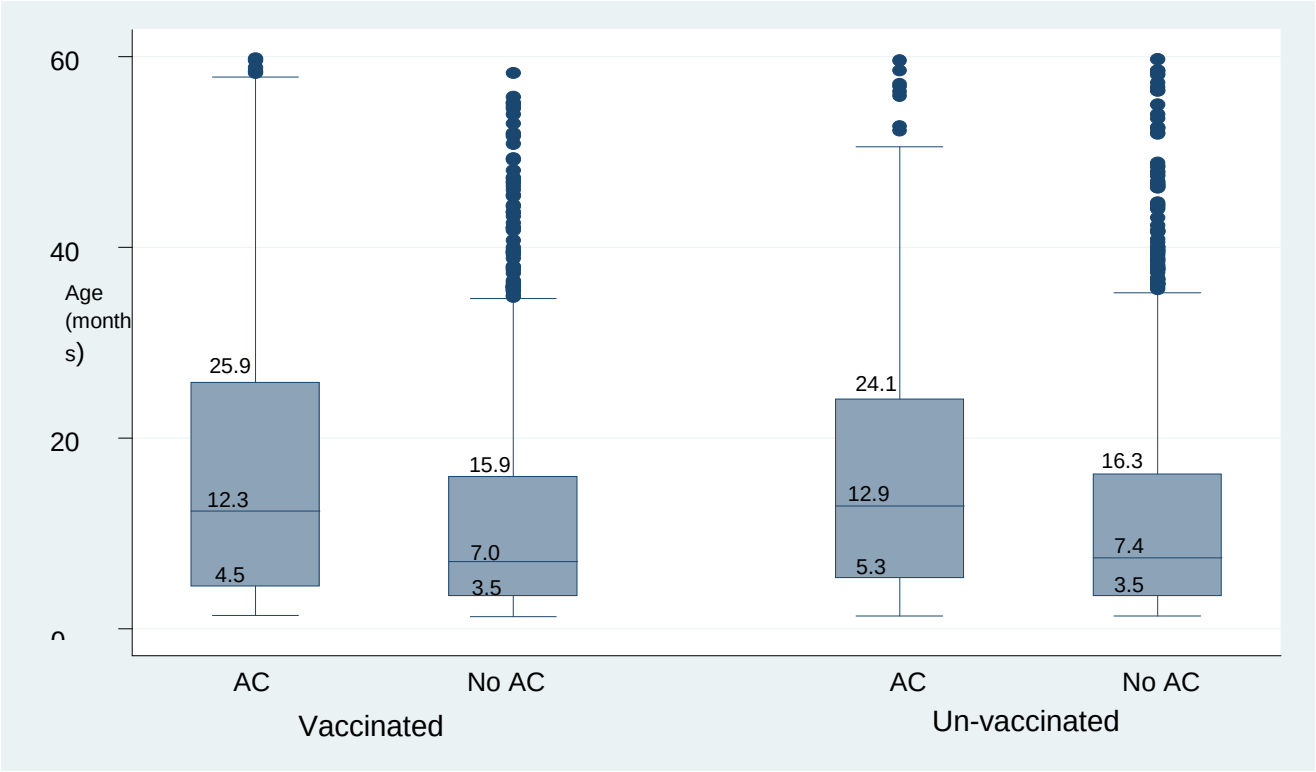


Figure 3.2: Median age (and IQR) of children with and without radiographically-confirmed pneumonia in PCV9 vaccinated and un-vaccinated cohort

The attack rate of radiographically-confirmed pneumonia differed in the different age groups. Although the percentage of vaccinated children in the different age groups was approximately the same, the rate of the disease was greater in children older than 24 months compared to younger children, and in 6 to 24 month olds than in under-6 month old children (Figure 3.1). The association between age groups and radiographically-confirmed pneumonia was statistically significant (<0.001). Moreover, the higher HIV infection prevalence in hospitalized under-6 month old children compared to 6 to 24 month children did not increase the prevalence of radiographically-confirmed pneumonia in this, youngest age group (Figure 3.3).

3.2.2. Anthropometric measurements of children with and without radiographically-confirmed pneumonia

The median birth weight of children who were hospitalised with first-episode radiographically-confirmed pneumonia and those who were not was 3 kg (IQR, 2.5-3.2 kg) and 3 kg (IQR, 2.6-3.4 kg), respectively. Anthropometric parameters at hospitalisation of the children, stratified by presence of radiographically-confirmed pneumonia, are tabulated in Table 3.3 and reflect the older age of children admitted with radiographically-confirmed pneumonia.

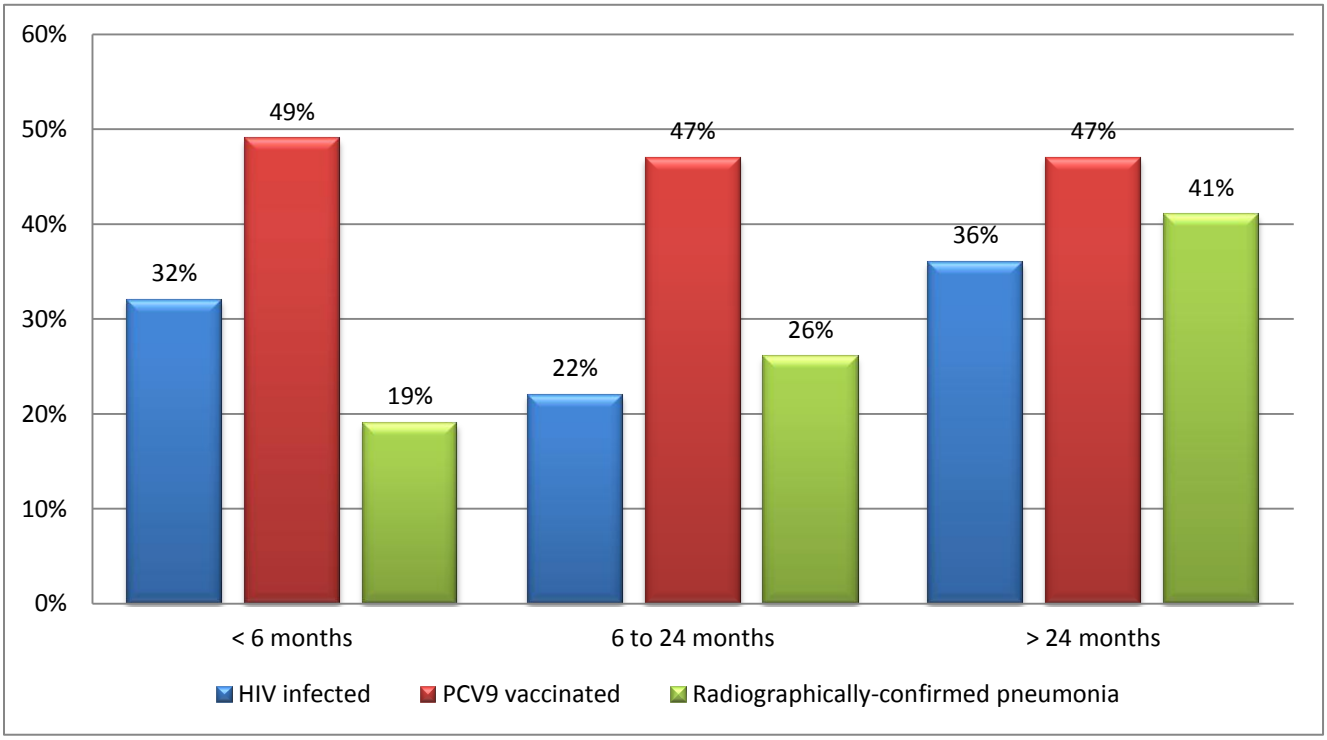


Figure 3.3: Distribution of radiographically-confirmed pneumonia, PCV9 vaccination and HIV infection in different age groups

The association between radiographically-confirmed pneumonia and anthropometric measures (weight, height and head circumference) was statistically significant. The median weight of children with and without radiographically-confirmed pneumonia was 10 kg (IQR

7.1 – 12 kg) and 9.2 kg (IQR 6.2 – 11.5 kg), respectively. The median height of children with and without the disease was 71 cm (IQR 60 – 83 cm) and 66 cm (IQR 58 -78 cm), respectively. The median head circumference of children with and without the disease was 45 cm (IQR 41.5 – 48 cm) and 44 cm (IQR 41 – 48 cm), respectively (Table 3.3).

Table 3.3: Anthropometric parameters at hospitalization of children with and without radiographically-confirmed pneumonia

Parameter		Radiographically-confirmed pneumonia		P-value†
		Yes	No	
Birth weight	N=3,700	3 (2.5 – 3.2)	3 (2.6 – 3.4)	0.087
Weight (kg), Median (IQR)	n=1,505	10.0 (7.1 - 12.0)	9.2 (6.2 - 11.5)	0.001
Height (cm), Median (IQR)	n=3,577	71 (60 - 83)	66 (58 - 78)	<0.001
Head circumference (cm), Median (IQR)	n=3,556	45 (41.5 - 48)	44 (41 - 48)	<0.001

†Wilcoxon rank-sum test

3.2.3: Radiographically-confirmed pneumonia according to HIV status of the participating children

HIV-infected children had a 4-fold (95% CI 3.45 - 4.77, p<0.001) increased odds of being admitted with radiographically-confirmed pneumonia compared to HIV-uninfected children (Table 3.4).

Under-6 month HIV-infected children had a 5-fold (95% CI 2.73 – 10.83, p<0.001) increased odds of being diagnosed with radiographically-confirmed pneumonia compared to HIV-uninfected under-6 month children (Tables 3.16). Six to 24 months and 24 month and older HIV infected children had a 3-fold (95% CI 2.01 - 5.33, p<0.001) and 4-fold (95% CI 2.83 –

7.21, p<0.001) increased odds, respectively, of being diagnosed with radiographically-confirmed pneumonia compared to 6 to 24 and 24 months and older HIV-uninfected children (Table 3.17 and Table 3.18).

Table 3.4: Radiographically-confirmed pneumonia distribution according to HIV status of the participating children

HIV infection	Radiographically-confirmed pneumonia		OR (95% CI), P value
	No. of cases; total children	Attack rate	
Yes	468; 988	0.47	4.1 (3.45 – 4.77), <0.001
No	454; 2,501	0.18	

3.2.4. Radiographically-confirmed pneumonia in children diagnosed with and without pneumococcal disease syndromes

Not surprisingly, children diagnosed with (clinical) pneumonia had a 4-fold increased odds (OR 4.1, 95% CI, 3.1 - 5.5, p<0.001) to have radiographically-confirmed pneumonia compared to those who were not diagnosed with clinical pneumonia. Children diagnosed with IPD had about 2-fold increased odds (OR 1.8, 95% CI 0.5 – 6.3, p=0.368) of having radiographically-confirmed pneumonia compared to children who were not diagnosed with IPD.

3.2.5. *Radiographically-confirmed pneumonia in children with history of previous pneumonia admissions, previous hospitilization and pneumonia predisposing factors in different age groups*

Children who had been admitted before (on more than two occasions) due to pneumonia had more than 3-fold increased odds of being diagnosed with radiographically-confirmed pneumonia compared to children without such admission history (OR 3.25; 95% CI 2.58 - 4.08, p<0.001) (Table 3.5).

Children who were recognised to have factors predisposing them to develop pneumonia, had an increased odds of being diagnosed with radiographically-confirmed pneumonia compared to children who did not have these pneumonia predisposing factors (OR 2.68; 95% CI 2.26 - 3.19, p<0.001). Similarly, children who had been hospitalised in the last two weeks had a nearly 2-fold increased odds of being diagnosed with radiographically-confirmed pneumonia compared to children without a history of previous hospitalization (OR 1.96, 95% CI 1.52 – 2.5, p<0.001) (Table 3.5).

Table 3.5: Radiographically-confirmed pneumonia in children with history of more than two pneumonia admissions, presence of predisposing factors and history of hospitilization in different age groups

Characteristics		<6 month n (%)	6 to 24 month n (%)	>24 month n (%)	All ages n (%)	OR in the comparison of 'All ages' (95% CI)	P-value
More than 2 previous pneumonia admissions	Yes	15 (23)	90 (50)	70 (63)	175 (49)	3.25 (2.58 - 4.08)	<0.001†
	No	263 (19)	314 (23)	170 (35)	747 (23)		
Pneumonia predisposing factors	Yes	80 (27)	140 (46)	98 (63)	318 (42)	2.68 (2.26 - 3.19)	<0.001
	No	198 (17)	261 (21)	146 (33)	605 (21)		
Hospitalization in the last two weeks	Yes	28 (23)	56 (51)	23 (55)	107 (39)	1.96 (1.52 – 2.50)	<0.001
	No	254 (19)	356 (24)	223 (40)	833 (25)		

†Chi squared test

3.3. Efficacy of PCV9

3.3.1. Overall efficacy of PCV9

The overall efficacy of PCV9 against radiologically-defined AC, regardless of HIV status and age group, was 7% (Table 3.6). The association between PCV9 vaccination and radiographically-confirmed pneumonia was not statistically significant, however (p=0.140).

Table 3.6: Overall efficacy of PCV9 against radiographically-confirmed pneumonia in under 5 participating children

Number of diseased and total children		Attack rate		Relative risk (V/U)	PCV9 efficacy
Vaccinated (V)	Un-vaccinated (U)	(V)	(U)	RR	(1 - RR) × 100
434; 1,766	515; 1,929	0.25	0.27	0.93**	7%

** p=0.140

3.3.2. Efficacy of PCV9 in different age groups

PCV9 was not efficacious in protecting against radiographically-confirmed pneumonia in children under the age of 6 months. Efficacy against this clinical end-point increased with increasing age, such that in those 6 to 24 months of age, PCV9 vaccine reduced radiographically-confirmed pneumonia by 21% (95% CI 20.8% - 21.2%) among the vaccinated group compared to the unvaccinated group. The effect was no longer observed in children older than 24 months of age, where a 5% increase in radiographically-confirmed pneumonia in the PCV9 vaccinated group was demonstrated (Figure 3.4 and Table 3.14).

3.3.3. Trend of efficacy of PCV9 through age groups

There was no linear trend in the efficacy of PCV9 against radiographically-confirmed pneumonia in different age groups. The vaccine was efficacious for the prevention of radiographically-confirmed pneumonia in the 6 to 24 month age group only. It was non-

efficacious in those under-6 months, and appeared to be a risk factor for the disease process in children older than 24 months of age (Figure 3.4, Table 3.14).

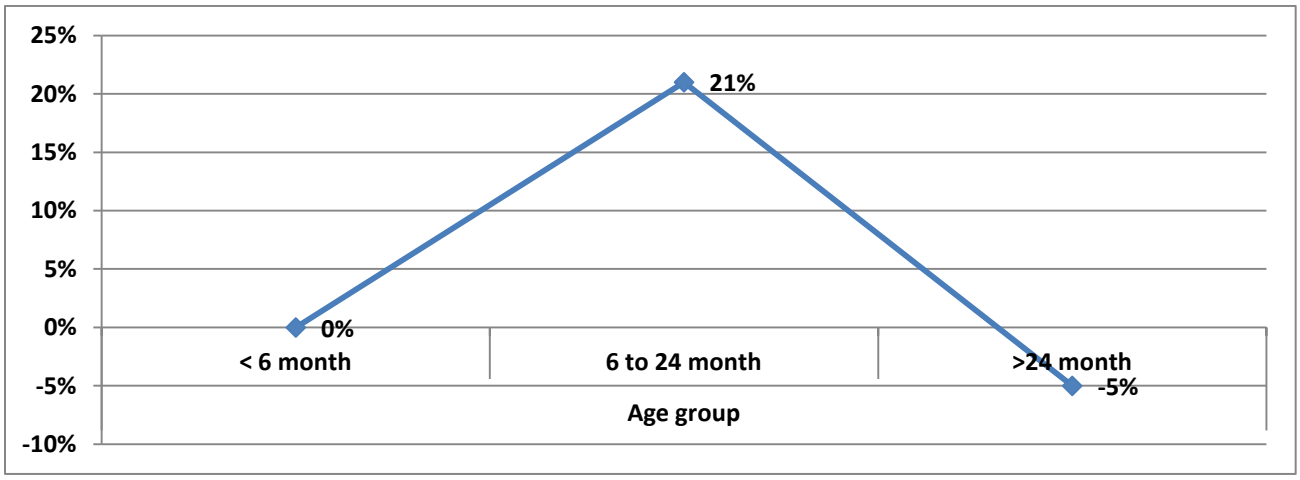


Figure 3.4: Trend of PCV9 efficacy in different age groups

3.3.4. Efficacy of PCV9 against radiographically-confirmed pneumonia in fully and partially vaccinated children in different age groups

The efficacy of PCV9 against radiographically-confirmed pneumonia in fully vaccinated children <6 months, 6 to 24 months and >24 months was 0%, 18% and -3%, respectively (Table 3.7). The efficacy in the same groups for children which were partially vaccinated was 10%, -29% and -3%, respectively (Table 3.8). The associations between the PCV9 vaccination and the disease in all these different age groups children were not statistically significant, however.

The PCV9 efficacy against radiographically-confirmed pneumonia in fully and partially vaccinated children, was 0% ($p>0.05$) and 26% ($p<0.05$), respectively. Fully vaccinated children had an increased odds of being admitted with first-episode of the disease compared to children who received a partial course of PCV9 (OR 1.50; 95% CI, 1.17-1.93, p 0.001).

Table 3.7: Efficacy of PCV9 against radiographically-confirmed pneumonia in fully vaccinated children in different age groups

Age group	Number of diseased and total children		Attack rate		Relative risk (V/U)	PCV9 efficacy
	Vaccinated (V)	Un-vaccinated (U)	(V)	(U)	RR	(1 - RR) × 100
Less than 6 months	41; 208	145; 737	0.20	0.20	1.00***	0%
6 to 24 months	166; 721	235; 828	0.23	0.28	0.82**	18%
Beyond 24 months	114; 277	128; 321	0.41	0.40	1.03***	-3%
All groups	321; 1,206	508; 1,886	0.27	0.27	1.00***	0%

*<0.001; ** < 0.05; *** > 0.05

Table 3.8: Efficacy of PCV9 efficacy against radiographically-confirmed pneumonia in partially vaccinated children in different age groups

Age group	Number of diseased and total children		Attack rate		Relative risk (V/U)	PCV9 efficacy
	Vaccinated (V)	Un-vaccinated (U)	(V)	(U)	RR	(1 - RR) × 100
Less than 6 months	98; 546	145; 737	0.18	0.20	0.90***	10%
6 to 24 months	16; 45	235; 828	0.36	0.28	1.29***	-29%
Beyond 24 months	4; 8	128; 321	0.50	0.40	1.03***	-3%
All age groups	118; 599	508; 1,886	0.20	0.27	0.74*	26%

*<0.001; ** < 0.05; *** > 0.05

3.3.5. Overall efficacy of PCV9 in HIV infected and un-infected children

Overall efficacy of PCV9 in HIV-infected and HIV-uninfected children was –7% and 20% respectively (Table 3.9).

Table 3.9: Overall efficacy of PCV9 in HIV infected and un-infected participating children

HIV infection	Number of diseased and total children		Attack rate		Relative risk (V/U)	PCV9 efficacy (1 - RR) × 100
	Vaccinated (V)	Un-vaccinated (U)	(V)	(U)		
Yes	224; 461	243; 526	0.49	0.46	1.07**	- 7%
No	198; 1,206	256; 1,291	0.16	0.20	0.80*	20%

* p=0.543 ** p=0.027

3.3.6. PCV9 efficacy against radiographically-confirmed pneumonia according to HIV status and age groups

The crude PCV9 efficacy in HIV-uninfected and HIV-infected children was 20% and –7%, respectively. In HIV-uninfected children, the PCV9 efficacy against radiographically-confirmed pneumonia was 7%, 19% and 13% in under-6 month olds, 6 to 24 month olds and those older than 24 months, respectively, in the ITT analysis. This indicates that PCV9 would prevent the occurrence of 7, 19 and 13 cases of radiographically-confirmed pneumonia, in under-6, 6 to 24 and beyond-24 month-old children, respectively, in every hundred cases in these age groups of unvaccinated children if they were vaccinated. The PCV9 efficacy was 14%, 19% and 13% in the same age groups in the PP analysis (Table 3.10 and Table 3.11). In HIV-infected children, the PCV9 efficacy against radiographically-confirmed pneumonia was -13%, 7% and -16% in under-6 month, 6 to 24 month and those older than 24 months of age, respectively, in the ITT analysis (Table 3.12), and -42%, 4% and -15% in the same age groups in the PP analysis (Table 3.13).

The negative efficacy of the vaccine in under-6 month and beyond-24 month HIV-infected children indicates that the vaccine in these age groups had no protective effect against radiographically-confirmed pneumonia, and that receipt of PCV9 may have been associated with enhanced risk of radiographically-confirmed pneumonia. PCV9 efficacy of -16% in HIV-infected children older than 24 months of age indicates that PCV9 vaccination would be associated with an additional 16 cases of radiographically-confirmed pneumonia (in every hundred cases) amongst HIV-infected placebo recipients, if they were vaccinated.

Table 3.10: Intent-to-treat analysis of PCV9 efficacy against radiographically-confirmed pneumonia in HIV-uninfected children in different age groups

Age group	Number of diseased and total children		Attack rate		Relative risk (V/U)	PCV9 efficacy
	Vaccinated (V)	Un-vaccinated (U)	(V)	(U)	RR	(1 - RR) × 100
Less than 6 months	61; 488	69; 493	0.13	0.14	0.93	7%
6 to 24 months	96; 567	128; 606	0.17	0.21	0.81	19%
Beyond 24 months	41; 151	59; 192	0.27	0.31	0.87	13%

Table 3.11: Per protocol analysis of PCV9 efficacy against radiographically-confirmed pneumonia in HIV-uninfected children in different age groups

Age group	Number of diseased and total children		Attack rate		Relative risk (V/U)	PCV9 efficacy
	Vaccinated (V)	Un-vaccinated (U)	(V)	(U)	RR	(1 - RR) × 100
Less than 6 months	17; 142	113; 839	0.12	0.14	0.86	14%
6 to 24 months	92; 549	132; 623	0.17	0.21	0.81	19%
Beyond 24 months	40; 148	60; 195	0.27	0.31	0.87	13%

Table 3.12: Intent-to-treat analysis of PCV 9efficacy against radiographically-confirmed pneumonia in HIV-infected children in different age groups

Age group	Number of diseased and total children		Attack rate		Relative risk (V/U)	PCV9 efficacy
	Vaccinated (V)	Un-vaccinated (U)	(V)	(U)	RR	(1 - RR) × 100
Less than 6 months	77; 223	72; 235	0.35	0.31	1.13	-13%
6 to 24 months	74; 144	105; 192	0.51	0.55	0.93	7%
Beyond 24 months	73; 94	66; 99	0.78	0.67	1.16	-16%

Table 3.13: Per protocol analysis of PCV9 efficacy against radiographically-confirmed pneumonia in HIV-infected children in different age groups

Age group	Number of diseased and total children		Attack rate		Relative risk (V/U)	PCV9 efficacy
	Vaccinated (V)	Un-vaccinated (U)	(V)	(U)	RR	(1 – RR)× 100
Less than 6 months	21; 48	128; 410	0.44	0.31	1.42	-42%
6 to 24 months	71; 137	108; 199	0.52	0.54	0.96	4%
Beyond 24 months	69; 90	68; 101	0.77	0.67	1.15	-15%

3.3.7. Efficacy of PCV9 against radiographically-confirmed pneumonia in children with different characteristics/medical conditions

3.3.7.1. Sex

The overall PCV9 efficacy in boys and girls was 7% and 11%, respectively (p> 0.05). There was no difference in PCV9 efficacy between boys and girls in the under-6 month age group. In this age group, the efficacy of the vaccine against radiographically-confirmed pneumonia was 0% regardless of gender. In 6 to 24 month boys and girls, the efficacy was 11% and 28%, respectively. In the beyond-24 month old age group, the efficacy was negative in both sexes (Table 3. 4).

3.3.7.2. Pneumococcal disease syndromes

Among children under 6 months of age, the efficacy of PCV9 against radiographically-confirmed pneumonia was 4% and 100%, in children diagnosed with clinical pneumonia and in children diagnosed with IPD, respectively (Table 3.14). In children between 6 to 24 months of age, the efficacy was 16% in children diagnosed with clinical pneumonia (Table 3.14). In children older than 24 months of age the efficacy was -6% in children diagnosed with clinical pneumonia.

3.3.7.3. Previous pneumonia admissions and hospitalization history

The crude PCV9 efficacy in children with a history of more than two previous pneumonia admissions was 8% (p<0.001). It was the same efficacy in children without such history (p <0.001). PCV9 efficacy against radiographically-confirmed pneumonia in children under 6

months of age was 12% in the children with a history of more than two previous pneumonia admissions, and it was -6% in children without a previous pneumonia history. In children between 6 to 24 months old, the PCV9 efficacy was 22% in children with a history of a previous pneumonia admission and 20% in children without such a medical history. In children older than 24 months, the efficacy was -12% in children with a history of previous pneumonia admission and -3% in children without a previous pneumonia history.

The crude PCV9 efficacy in children with and without hospitalization history during the last two weeks was 7% and 4%, respectively. In children under six months of age, the efficacy of PCV9 against radiographically-confirmed pneumonia was 16% in children with a history of hospitalization in the last two weeks and it was -6% in children without this history. In 6 to 24 month old children, PCV9 efficacy against radiographically-confirmed pneumonia was 2% and 18% in children with and without a history of recent hospitalization, respectively. In children older than 24 months of age, it was -6% and -8%, respectively (Table 3.14).

3.3.7.4. Pneumonia predisposing factors

The crude efficacy of PCV9 in children with and without pneumonia predisposing factors was -10% and 13%, respectively. In under-6 month old children, the efficacy of PCV9 against radiographically-confirmed pneumonia in children with pneumonia predisposing factors (which included prematurity, post-maturity, cardiac conditions and chronic pulmonary disease) was 4%. The vaccine was not efficacious against radiographically-confirmed pneumonia in children who did not have these risk factors, in whom the efficacy was 0%. In 6

to 24 month old children, the efficacy of the vaccine was 2% in children with these pneumonia predisposing factors and 22% in children without these predisposing factors. In children older than 24 months of age, the efficacy was -17% in children with predisposing factors. No efficacy was detected in children beyond-24 months of age, who were free of these predisposing factors (Table 3.14).

Table 3.14: Efficacy of PCV9 against radiographically-confirmed pneumonia in children with different characteristics in different age groups

Characteristics		Less than 6 month				6 to 24 month				Beyond 24 month			
		Attack rate		(1 – RR)	**Power**	Attack rate		(1 – RR)	**Power**	Attack rate		(1 – RR)	**Power**
		Vacc.	Un-vacc.	× 100		Vacc.	Un-vacc.	× 100		Vacc.	Un-vacc.	× 100	
Sex	Male	0.20	0.20	0%		0.25	0.28	11%		0.40	0.38	-5%	
	Female	0.18	0.18	0%		0.21	0.29	28%		0.44	0.42	-5%	
Pneumococcal disease	Clinical pneumonia	0.21	0.22	4%		0.27	0.32	16%		0.51	0.48	-6%	
	IPD	0.00	0.25	100%		….	0.17	….		0.50	….	….	
	No disease	0.00	0.00			0.00	0.00			0.00	0.00		
Presence of factors predisposing to pneumonia	Yes	0.27	0.28	4%		0.45	0.46	2%		0.68	0.58	-17%	
	No	0.17	0.17	0%		0.18	0.23	22%		0.33	0.33	0%	
Hospitalization in the last 2 weeks	Yes	0.21	0.25	16%		0.50	0.51	2%		0.57	0.54	-6%	
	No	0.19	0.18	-6%		0.22	0.27	18%		0.41	0.38	-8%	
More than 2 previous pneumonia admissions	Yes	0.21	0.24	12%		0.43	0.55	22%		0.66	0.59	-12%	
	No	0.19	0.18	-6%		0.20	0.25	20%		0.36	0.35	-3%	
Overall		0.19	0.19	0%	**0%**	0.23	0.29	21%	**76%**	0.42	0.40	-5%	**6%**

(1 – RR) × 100 = PCV9 Efficacy; Vacc. = vaccinated; Un-vacc. = un-vaccinated

3.3.8. The power of the study

The overall power of the study for the purposes of establishing PCV9 efficacy against radiographically-confirmed pneumonia was 27%. Among under-6 month children, the power of the study was 0%; the study was unable to demonstrate a difference in attack rate of radiographically-confirmed pneumonia between vaccinated and non-vaccinated under-6 month old children. In 6 to 24 month children, the power of the study was 76% and it was 6% in children older than 24 months of age (Table 3.14).

3.3.9. Factors that affect the association between age groups and radiographically-confirmed pneumonia

Unadjusted logistic regression analysis showed that there was a statistically significant relationship between radiographically-confirmed pneumonia and age groups. Both 6 to 24 and beyond-24 month children were at higher risk of radiographically-confirmed pneumonia compared to under-6 month old children (Table 3.15). Children 6 to 24 months old had 1.5 times the odds of developing the disease compared to children under-6 months (OR 1.5; 95% CI 1.27 - 1.79, $p<0.001$), while children older than 24 months had 2.91 times the odds of the disease compared to under-6 month children (OR 2.91; 95% CI 2.38 - 3.57, $p<0.001$).

Adjusted multi-variable (forward stepwise) logistic regression analysis showed that certain factors significantly affect the association between radiographically-confirmed pneumonia and age groups. These predicting factors were HIV infection, associated clinical pneumonia,

history of a previous admission due to pneumonia and the presence of factors which predispose towards pneumonia (Table 3.15).

HIV-infected children were at higher risk of radiographically-confirmed pneumonia compared to HIV-uninfected children (OR 3.66, 95% CI 2.72 – 4.93, p<0.001). Children who were diagnosed with clinical pneumonia were at higher risk of radiographically-confirmed pneumonia compared to children in whom a diagnosis of clinical pneumonia was not made (OR 3.5, 95% CI 2.2 - 5.6, p<0.001). On the other hand, the analysis showed that there was no association between IPD and radiographically-confirmed pneumonia (OR 1.03, 95% CI 0.07 – 13.91, p=0.995).

Children with a history of previous admission for pneumonia were at higher risk of radiographically-confirmed pneumonia compared to children without such a history (OR 1.85, 95% CI 1.27 - 2.70, p=0.002). Children with factors which predispose to pneumonia were at higher risk of radiographically-confirmed pneumonia compared to children who did not have these risk factors (OR 2.13, 95% CI 1.52 – 2.94, p<0.001).

There was no association between sex, PCV9 vaccination and hospitalization history and radiographically-confirmed pneumonia (Table 3.15).

Table 3.15: Un-adjusted bi-variate and adjusted multi-variable logistic regression model of the association between radiographically-confirmed pneumonia and age groups

Independent variable	Bi-variate model		Multi-variable model	
	OR	p value	OR	p value
Female			1	Reference
Male			2.92	0.533
Under-6 months age group	1	Reference	1	Reference
6 to 24 months age group	1.50	<0.001	1.88	**0.001**
Beyond-24 months age group	2.91	<0.001	3.45	**<0.001**
Weight			1.01	0.667
Height			1.00	0.591
Head circumference			1.00	0.887
HIV-uninfected			1	Reference
HIV-infected			3.66	**<0.001**
PCV9 un-vaccinated			1	Reference
PCV9 fully vaccinated			1.06	0.672
PCV9 partially vaccinated			1.49	0.148
No pneumococcal disease			1	Reference
Clinical pneumonia			3.5	**<0.001**
IPD			1.03	0.995
Absence of predisposing cause forpneumonia			1	Reference
Presence of predisposing cause forpneumonia			2.13	**0.002**
No hospitalization in the last 2 weeks			1	Reference
Hospitalization in the last 2 weeks			1.15	0.617
< 2 previous admissions of pneumonia			1	Reference
≥ 2 previous admissions of pneumonia			1.83	**0.014**

3.3.9.1. Factors associated with radiographically-confirmed pneumonia in children <6 months of age

In children under 6 months of age, adjusted multi-variable (forward stepwise) logistic regression analysis showed that the predicting factors which had a statistically significant association with radiographically-confirmed pneumonia were HIV infection and the presence of factors which are known to predispose children to pneumonia.

Table 3.16: Adjusted multi-variable logistic regression model of radiographically-confirmed pneumonia and potential independent variables in children under 6 months of age

Independent variable	Multi-variable model	
	OR	p value
Female	1	Reference
Male	1.64	0.174
Weight	0.97	0.261
Height	1.00	0.980
Head circumference	0.97	0.714
HIV-uninfected	1	Reference
HIV-infected	5.13	**<0.001**
PCV9 un-vaccinated (placebo recipient)	1	Reference
PCV9 fully vaccinated	1.15	0.785
PCV9 partially vaccinated	1.41	0.361
No pneumococcal disease	1	Reference
Clinical pneumonia	…..	……
IPD	…..	…..
Absence of predisposing cause for pneumonia	1	Reference
Presence of predisposing cause for pneumonia	3.13	**0.005**
No hospitalization in the last 2 weeks	1	Reference
Hospitalization in the last 2 weeks	1.70	0.461
< 2 previous admissions of pneumonia	1	Reference
≥ 2 previous admissions of pneumonia	0.56	0.598

The HIV-infected under 6 month children had a 5-fold higher odds of developing radiographically-confirmed pneumonia compared to HIV-uninfected children (OR 5.13, 95% CI 2.54 – 10.35, p<0.001) (Table 3.16). The occurrence of radiographically-confirmed pneumonia was positively related to pneumonia predisposing causes. Infants under-6 months of age who had pneumonia predisposing factors had a 3-fold greater odds of developing radiographically-confirmed pneumonia compared to children of the same age without these predisposing causes (OR 3.13; 95% CI 1.43 to 7.14, p=0.005) (Table 3.16).

3.3.9.2. Factors associated with radiographically-confirmed pneumonia in children 6 to 24 months of age

Variables significantly predictive of radiographically-confirmed pneumonia in children between 6 and 24 months of age included HIV infection, clinical pneumonia and presence of pneumonia predisposing factors (Table 3.17).

HIV-infected children in this age group had a 3-fold higher odds of radiographically-confirmed pneumonia compared to HIV-uninfected children of the same age group (OR 3.04, 95% CI 1.85 to 4.98, p<0.001). Six to 24 month old children with clinical pneumonia were more likely to be diagnosed with radiographically-confirmed pneumonia compared to 6 to 24 children without clinical pneumonia (OR 2.63, 95% CI 1.27 to 5.56, p=0.009).

Six to 24 month old children with pneumonia predisposing factors had a 2-fold increased likelihood (OR 2.44, 95% CI 1.43 to 2.50 4.17, p=0.001) of radiographically-confirmed pneumonia compared to 6 to 24 children without these factors.

Table 3.17: Adjusted multi-variable logistic regression model of radiographically-confirmed pneumonia and potential independent variables in children 6 to 24 month of age

Independent variable	Multi-variable model	
	OR	p value
Female	1	Reference
Male	0.93	0.734
Weight	1.10	0.125
Height	1.00	0.689
Head circumference	0.89	0.063
HIV-uninfected	1	Reference
HIV-infected	3.04	**<0.001**
PCV9 un-vaccinated (placebo recipient)	1	Reference
PCV9 fully vaccinated	1.26	0.300
PCV9 partially vaccinated	0.61	0.382
No pneumococcal disease	1	Reference
Clinical pneumonia	2.63	**0.009**
IPD	…..	…..
Absence of predisposing cause for pneumonia	1	Reference
Presence of predisposing cause for pneumonia	2.44	**0.001**
No hospitalization in the last 2 weeks	1	Reference
Hospitalization in the last 2 weeks	1.35	0.510
< 2 previous admissions of pneumonia	1	Reference
≥ 2 previous admissions of pneumonia	1.82	0.065

3.3.9.3. Factors associated with radiographically-confirmed pneumonia in children >24 months of age

In children older than 24 months, adjusted multi-variable logistic regression showed that only HIV infection, clinical pneumonia and history of more than two previous pneumonia admissions were significantly associated with radiographically-confirmed pneumonia (Table 3. 18).

Table 3.18: Adjusted multi-variable logistic regression model of radiographically-confirmed pneumonia and potential independent variables in children older than 24 month of age

Independent variable	Multi-variable model	
	OR	p value
Female	1	Reference
Male	0.67	0.082
Weight	0.99	0.680
Height	0.99	0.639
Head circumference	1.02	0.480
HIV-uninfected	1	Reference
HIV-infected	4.09	**<0.001**
PCV9 un-vaccinated (placebo recipient)	1	Reference
PCV9 fully vaccinated	1.09	0.721
PCV9 partially vaccinated	2.00	0.484
No pneumococcal disease	1	Reference
Clinical pneumonia	3.03	**<0.001**
IPD	1.14	0.929
Absence of predisposing cause for pneumonia	1	Reference
Presence of predisposing cause for pneumonia	1.61	0.076
No hospitalization in the last 2 weeks	1	Reference
Hospitalization in the last 2 weeks	0.93	0.876
< 2 previous admissions of pneumonia	1	Reference
≥ 2 previous admissions of pneumonia	0.54	**0.036**

In HIV-infected children older than 24 months of age, the odds of radiographically-confirmed pneumonia was 4-fold greater (OR 4.09, 95% CI 2.53 to 6.61, p<0.001) compared to HIV-uninfected children. Children diagnosed with clinical pneumonia had approximately a 300% increased odds to be diagnosed with radiographically-confirmed pneumonia compared to children without clinical pneumonia (OR 3.33, 95% CI 1.79 to 6.25, p=0.001). Children older than 24 months of age with a history of more than two previous admissions for pneumonia had about two-fold increased odds (OR 1.85, 95% CI 0.96 to 3.23, p=0.036) of radiographically-confirmed pneumonia compared to children without such a history.

CHAPTER 4

DISCUSSION

In this chapter the findings, including efficacy of PCV9 against radiographically-confirmed pneumonia in different age groups and according to different factors that may influence the occurrence of the disease, are discussed. The associations of radiographically-confirmed pneumonia and the potential predicting factors are studied in different age groups in order to find a logical and sound explanation of the study findings. Conclusions are drawn from the study findings, and certain interventions are recommended.

4.1. Overall study findings

PCV9 vaccination in children under five years of age had a limited role in the prevention of radiographically-confirmed pneumonia. Vaccine efficacy against radiographically-confirmed pneumonia seemed to be higher in 6 to 24 month age group compared to the under-6 month and beyond-24 month age groups. The association between the PCV9 vaccination and radiographically-confirmed pneumonia was profoundly affected by pneumonia risk factors, primarily HIV infection. Other factors associated with radiographically-confirmed pneumonia included age, clinical diagnosed pneumonia, previous pneumonia admissions, and presence of pneumonia predisposing factors (which included prematurity, post-maturity, cardiac conditions and chronic pulmonary disease).

Partial vaccination was found to be more efficacious against radiographically-confirmed pneumonia. Children may fail to respond adequately to immunization with PCV9, when they receive full (three) doses of the vaccine.

4.2. Overall PCV9 efficacy against radiographically-confirmed pneumonia

The overall efficacy of PCV9 was 7%. This estimate is at the extreme lower end of confidence interval of PCV efficacy against radiographically-confirmed pneumonia (25.5%; 95% CI 6.5 - 40.7%, p=0.011) previously observed in the USA [52]. However, it is very low compared to the findings of the RCT which was conducted in The Gambia, in which PCV9 efficacy against radiographically-confirmed pneumonia was 37% (95% CI 27 - 45)[39].

4.3. Efficacy of PCV9 in different age

The analysis findings show that the efficacy of PCV9 against radiographically-confirmed pneumonia seemed to be lower in older children than in younger children; calculation of median age of PCV9 vaccinated children shows that those who developed radiographically-confirmed pneumonia were older than those who did not (Table 3.2). However, the median age of PCV9 unvaccinated children shows that children who developed radiographically-confirmed pneumonia are also older than children who did not (Figure 3.2). Moreover, although the percentage of vaccinated children in the different age groups was approximately equal, the incidence rate of radiographically-confirmed pneumonia was greater in older children than in younger ones (Figure 3.3).

The lower efficacy of PCV9 in older children as demonstrated in this analysis may have resulted as a function of the increased biological likelihood of developing radiographically-confirmed pneumonia in the older age group. Pathologists generally consider young children as being incapable of localizing lung inflammation to a single lobe of the lung. On an immunological and anatomical basis, older children are more likely to develop (and/or to be diagnosed) with (lobar) alveolar consolidation on chest x-ray than younger children[53]; therefore, older children (more likely to be admitted/diagnosed with lobar consolidation) would be erroneously considered to have lower PCV9 efficacy against radiographically-confirmed alveolar consolidation compared to younger children. According to a study which was conducted in Boston (USA), WHO criteria for diagnosing radiographically-confirmed pneumonia were ineffective for screening young children admitted to the emergency department. WHO criteria demonstrated poor sensitivity for the diagnosis of radiographically-confirmed pneumonia. Chest x-ray may therefore not be a sensitive screening tool for the diagnosis of pneumonia (especially in young) children [54].

4.3.1. PCV9 efficacy of PCV9 in under-6 month children

PCV9 was not efficacious against the occurrence of radiographically-confirmed pneumonia in children less than 6 month of age. Interference of the vaccine response due to maternal antibodies during the first months of life might explain in part the lower vaccine efficacy observed in this age group. Immaturity of the young child's immune system may also limit the effectiveness of vaccination.

Maternal antibodies might interfere with the development of an antibody response following vaccination with either a killed or an attenuated vaccine. A trial conducted between April 1997 and May 2000 on the Navajo and White Mountain Apache reservations in the southwestern United States found that maternal antibody was associated with a reduced infant response to PCV7[55 56].

Lack of PCV9 efficacy against radiographically-confirmed pneumonia in the under-6 month age group could also be one of the consequences of HIV infection. The association between radiographically-confirmed pneumonia and HIV infection was the strongest compared to other age groups (Table 3.15, Table 3.16 and Table 3.17), even though the HIV prevalence in this infant group was not the highest. The association between radiographically-confirmed pneumonia and HIV infection was comparatively weak in 24 months of age and older children, even though the HIV prevalence was the highest. Different strengths of association between HIV and radiographically-confirmed pneumonia in under-6 and in 24-months and older children could be due to differing immune system maturity in these two groups. The immune system in 24-month and older children group is more mature than that of under-6 month group and might provide some protection against pneumococcal disease. The association between HIV and radiographically-confirmed pneumonia in 6 to 24 month of age group was the weakest comparing to other two groups. This could be due to lowest HIV prevalence on this group.

Although HIV infection markedly influenced the occurrence of radiographically-confirmed pneumonia, there were other factors that are expected to have played a role in the disease occurrence, and hence the efficacy of PCV9. History of hospitalization and previous pneumonia admission could be proxy indicators of these (not yet studied) factors like socioeconomic status, mother and father education level, number of children in the family, etc. This might explain the lowest efficacy of PCV9 against radiographically-confirmed pneumonia in 24 month and above children, even though the association between HIV infection and radiographically-confirmed pneumonia was not the strongest one compared to children other age groups.

4.3.2. PCV9 efficacy of PCV9 in 6 to 24 month children

The efficacy of PCV9 was found to be the highest (21%) in the 6 to 24 month age group. The relatively higher power (76%) of the study in this age group compared to other (under-6 and beyond-24) groups may explain why PCV9 efficacy could only be demonstrated in this age-group.

As was the case in children older than 24 months of age, the efficacy of PCV9 in the 6 to 24 month age group was profoundly affected by HIV infection. The relatively high efficacy of PCV9 in the 6 to 24 month (compared to other age groups) may be due to fact that the HIV infection prevalence in 6 to 24 month age group was the lowest. The HIV infection rate was 220/1,000 in 6 to 24 month while it was 320/1,000 and 360/1,000 in under-6 and beyond-24 month age groups, respectively.

4.3.3. PCV9 efficacy in children older than 24 months of age

In 24 months and older children, the PCV9 efficacy was -5%, indicating that PCV9 vaccination was associated with an increased occurrence of radiographically-confirmed pneumonia. This finding is counter-intuitive. The higher likelihood of pneumococcal infection to be manifested with radiological changes in older children compared to younger children could partially explain the diminished PCV9 efficacy in children older than 24 month of age, as discussed above. Another reason that could explain this finding may be the limited power of the study to detect a difference in radiographically-confirmed pneumonia prevalence among vaccinated and unvaccinated children in this age group. Only 17% (n=610) of the study cohort children were 24 months of age and older.

HIV infection had a statistically significant association with radiographically-confirmed pneumonia. This could explain the negative protective effect of PCV9 in 24 month and older HIV-infected children where the HIV infection prevalence was the highest comparing to other age groups. The risk of HIV infection was strong enough to substantially confound the effect of PCV9 against radiographically-confirmed pneumonia in this age group. HIV-infected children older than 24 months of age had an approximately 4-fold increased odds of developing radiographically-confirmed pneumonia compared to HIV-uninfected children from the same age group.

The limited and poor antiretroviral therapy (ART) program in South Africa at the time of PCV9 efficacy trail (between 1998–2005)[57] might have indirectly reduced the efficacy of PCV9

against radiographically-confirmed pneumonia. ART, through suppression of HIV virus and halting the progression of HIV/AIDS, helps the immune system of HIV-infected children to recover and to respond positively to PCV vaccination. South Africa paediatric HIV infection in the absence of an ART program would have confounded and masked the ability of PCV9 to prevent radiographically-confirmed pneumonia[58]. The South African ART program was only implemented in April 2004, with initial sub-optimal coverage of HIV-infected children in need of ART [59].

Serotype replacement disease could be one of the factors that may reduce the efficacy of PCV. It occurs when pneumococcal serotypes which are included in PCV formulations are replaced by non-vaccine pneumococcal serotypes (NVTs), which establish themselves as the predominant pathogenic pneumococcal serotypes[60]. This phenomenon was observed following widespread use of PCV in the USA [61 62 63 64]. It occurs gradually over time when vaccination programs mature, which was not the case during South African PCV9 efficacy trial.

The statistically significant association between clinical pneumonia and history of previous pneumonia-related hospital admissions and radiographically-confirmed pneumonia in children older than 24 months of age is anticipated. The three respiratory disease categories (radiographically-confirmed pneumonia, clinical pneumonia and history of previous hospitalization for pneumonia) manifest in the occurrence of respiratory infection and would be expected to coexist.

4.4. PCV9 efficacy in partially and fully vaccinated children

An unanticipated finding in this analysis was that children who were partially vaccinated (receiving one or two doses of PCV9) were more protected against radiographically-confirmed pneumonia than those who were fully vaccinated. Three primary doses of PCV9 (given at 6, 10 and 14 weeks) without a booster vaccination series may not be a good option for establishing sufficient and durable efficacy against radiographically-confirmed pneumonia. A PCV schedule of two doses, given at 6 and 10 or 14 weeks with one booster dose at 9 months may engender greater PCV9 efficacy against radiographically-confirmed pneumonia than a 3-dose primary schedule. A two-dose primary schedule of PCV7 was found to confer equivalent efficacy against IPD compared to a 3-dose primary schedule[65 66]. The "2+1" schedule may be sufficient to provide protection against most PCV serotypes according to a study conducted in the UK, which showed a significant reduction in all infant IPD [67].

Introduction of a large amount of pneumococcal polysaccharide antigens through three full doses of PCV9 may overload, interact with, and suppress the immune system's ability to respond optimally to the vaccine by depleting the memory B-cell pool [68]. An immunogenicity study conducted in the UK to find the minimum schedule of PCV9 doses that could protect infants and toddlers demonstrated that 10% of healthy toddlers were nonresponsive to at least one serotype following three doses of PCV9 vaccination[69]. Feasibly, IPD could initiate similar immune paresis associated with PCV as it overburdens the immune system with a vast amount of pneumococcal capsular polysaccharide antigen. A study in the UK showed that

9.3% of young children who had IPD, failed to respond to over-immunization[70]. The same phenomenon was observed in the context of meningococcal polysaccharide (MPS) vaccination where there is increasing evidence that antibody hyporesponsiveness also could occur [71].

However, according to the findings of the current study, IPD could not be the reason of low efficacy of PCV9. Only 16 cases of IPD were observed in this study cohort (Table 3.1).

4.6. Factors predictive of radiographically-confirmed pneumonia

HIV infection and clinical pneumonia were found to be associated with radiographically-confirmed pneumonia in children older than 6 months of age (Tables 3.16 and 3.17). HIV infection depletes the immune system's capacity to contain infectious processes, chiefly by impacting on cell-mediated immune function; however, humoral immune processes (and production of antibodies in response to vaccination, which depends on a T-cell related mechanism in very young children, in particular) are also adversely affected in HIV-infected individuals [72 73 74]. This results in a sub-optimal response to PCV9 vaccination with consequent failure to establish sufficient vaccine-derived protective effect against radiographically-confirmed pneumonia.

Co-occurrence of radiographically-confirmed pneumonia, clinical pneumonia diagnosis, history of previous pneumonia hospital admissions and the presence of pneumonia predisposing factors was an anticipated finding.

4.7. Limitations

1. Chest x-ray is not a good diagnostic tool to differentiate between different kinds of (viral and bacterial) pneumonia. Therefore, viral pneumonia and other non-pneumococcal bacterial radiographically-diagnosed pneumonia may wrongly been classified as pneumococcal radiographically-confirmed pneumonia.
2. For the purposes of this secondary data analysis, a major limitation was the large number of missing data. For example, only 13% of children had recorded birth weight, about 40% of the children had recorded weight.
3. Only RCT enrolled children who were admitted to hospital and had chest x-ray records, were included in the accessing of PCV9 efficacy against radiologically-confirmed pneumonia. Children with pneumonia who may have attended peripheral clinics or the hospital outpatient department, or were asymptomatic, were not included in the analysis.
4. A lack of anthropometric data (weight-for-age and/or height-for-age percentiles) makes it difficult to investigate the influence of nutritional status on the occurrence of radiographically-confirmed pneumonia in children.

4.8. Conclusion

In the overall analysis, PCV9 vaccination had limited efficacy against radiographically-confirmed pneumonia. In children 6 weeks to 6 months of age and those older than 24 months of age, PCV9 was non-efficacious. However, it was efficacious against radiographically-confirmed pneumonia in the 6 to 24 month children age group. Partial

vaccination was more efficacious against radiographically-confirmed pneumonia than a full course (given at 6, 10 and 14 weeks of age) of vaccination.

HIV infection was the main factor that affected PCV9 efficacy against radiographically-confirmed pneumonia in all children, regardless of age group. Other factors that were associated with the occurrence of the disease were presence of pneumonia predisposing factors and history of previous pneumonia admissions.

Although PCV9 has been shown to be highly efficacious in terms of protecting HIV-infected and HIV-uninfected children from invasive disease caused by vaccine-serotype pneumococci, vaccine efficacy against non-specific disease end-points is less substantial [23 39 47]. However, PCV9 efficacy against radiographically-confirmed pneumonia may have greater public health impact than PCV9 efficacy against IPD as the public health burden of radiographically-confirmed pneumonia is far greater than the burden of IPD cases[75]. However, the burden of disease prevented by vaccination would it be better evaluated using outcome measures with high sensitivity, such as a clinical diagnosis of pneumonia[75].

4.9. Recommendations

This study aimed to assess the persistence of efficacy of PCV9 against radiographically-confirmed pneumonia among children over 24 months of age compared to children younger than 6 months and between 6 and 24 months of age in South Africa. In view of the findings presented above, the following recommendations are made:

1. Studies to investigate the efficacy of PCV in relation to potential predicting factors of pneumonia would assist in delineating clinical burden of disease and the public health impact of vaccination.
2. A two-dose primary schedule of PCV9 appears to be more efficacious than a three-dose primary schedule. It is also more cost-effective, reduces discomfort and gives space for introduction of new vaccines. The South African Department of Health adopted a two-dose primary schedule of PCV vaccination (with a booster dose at 9 months) in April 2009.
3. Improve access to HIV/AIDS related prevention, treatment and care services, including reproductive health (RH)/HIV/AIDS integrated services package.
4. Awareness raising campaigns should be carried out to educate mothers (and families) about the important role of other factors in the occurrence of childhood chest infection.

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6.APPENDIXS

6.1. Appendix 1: certificate of Ethical approval of PCV9 efficacy study

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Ahmed Elamin

CLEARANCE CERTIFICATE	M110948
PROJECT	Efficacy of 9-Valent Pneumococcal Conjugate Vaccine against Radiographically-Confirmed Pneomonia among Children before and after 24 Months of Age in South Africa
INVESTIGATORS	Dr Ahmed Elamin.
DEPARTMENT	School of Public Health
DATE CONSIDERED	30/09/2011
M110948+DECISION OF THE COMMITTEE*	Approved uncoditionally

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

DATE 30/09/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Peter Nyasulu

DECLARATION OF INVESTIGATOR(S)

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