Spring 5-7-2011

Comparison of Post-Licensure Safety Surveillance of 13-Valent Pneumococcal Conjugate Vaccine and 7-Valent Pneumococcal Conjugate Vaccine: Data from the Vaccine Advere Event Reporting System (Vaers)

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Public Health Thesis

Georgia State University Year 2011

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ABSTRACT

Comparison of Post-licensure safety surveillance of 13-Valent Pneumococcal Conjugate vaccine and 7-Valent Pneumococcal Conjugate vaccine: Data from the Vaccine Adverse Event Reporting System (VAERS).

Background: On February 24, 2010, Food and Drug Administration (FDA) licensed a 13-valent pneumococcal conjugate vaccine (Prevnar 13®, [PCV13]) for use among children aged 6 weeks--71 months. The Advisory Committee on Immunization Practices (ACIP) recommended PCV13 routine vaccination of all children aged 2--59 months, children aged 60--71 months with underlying medical conditions, with PCV13 replacing PCV7 for all doses.

Methods: We searched case reports to the Vaccine Adverse Event Reporting System (VAERS), a US passive surveillance system, for adverse events (AEs) reported after immunization with PCV13 vaccine from February 24, 2010 through February 24, 2011 for persons vaccinated from February 24, 2010 through December 31, 2010 and compared them with AEs reported by persons who were vaccinated with PCV7.

Results: VAERS received 1503 reports of AEs after PCV13; multiple vaccines were given in 79.0% of reports. One hundred eighty (11.9%) were coded as serious, including nineteen reports of death. The most frequently reported symptoms were injection site reactions, fever, irritability and vomiting. Seven hundred fifty-eight (50.4%) reports

comprised males. Most reports (37.7%) were from children 1-2 years. Total number of reports received for PCV13 was very similar to those received after vaccination with PCV7.

Conclusions: AEs reported to VAERS following 13-valent pneumococcal conjugate vaccine were consistent with AEs previously observed in pre-licensure trials. We did not identify any major safety concerns or outcomes.

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By

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M.D., LIBRE UNIVERSITY

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

2011

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ACKNOWLEDGEMENTS

I would like to sincerely thank my thesis committee members, Dr. Richard Rothenberg and Dr. Pedro Moro for their guidance and encouragement. Additionally I would like to thank Dr. Keith Klugman, Dr. Jane Gidudu and Dr. Frank DeStefano for their assistance and feedback.

AUTHOR'S STATEMENT

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CHAPTER I

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a lancet-shaped, gram-positive, facultative anaerobic bacteria first isolated by Pasteur in 1881. Pneumococcus is a common leading cause of bacteremia, meningitis and community acquired pneumonia among all ages, it is also a major cause of sinusitis and acute otitis media. Across Europe and North America, 30-100 cases of pneumonia per 100,000 people are expected each year (Heymann, 2008). The highest rates of invasive pneumococcal disease (IPD) occur among young children, especially those younger than 2 years of age; Bacteremic pneumonia accounts for 12%–16% of IPD. In the United States (U.S) Pneumococcus has become the leading cause of bacterial meningitis among children younger than 5 years of age and is a common cause of acute otitis media; by age 12 months, more than 60% of children have had at least one episode of acute otitis media (Atkinson et al., 2009).

On February 2000 the Food and Drug Administration (FDA) approved a 7-valent pneumococcal conjugate vaccine (Prevnar®, PCV7), the first pneumococcal conjugate vaccine licensed in the U.S to prevent invasive pneumococcal disease. In 2002, two years after licensure, PCV7 was also indicated and approved for active immunization of infants against otitis media caused by vaccine serotypes. Prior to licensure randomized clinical

trials were conducted in infants and children; good vaccine efficacy and a favorable safety profile were demonstrated (MMWR; December 10, 2010 / 59(RR11); 1-18). Prior to the introduction of PCV7, in children younger than 2 years the incidence of invasive pneumococcal disease was 166.9 per 100000 child years in the U.S (Robinson K et al., 2001). New conjugate vaccines may be able to prevent and reduce the burden of invasive pneumococcal disease as well as reducing the incidence rates of acute otitis media in young children

The World Health Organization (WHO) in 2007 recommended all countries to include pneumococcal conjugated vaccines to their national infant immunization programs (WHO position paper, 2007).

On February 24, 2010, the FDA licensed a 13-valent pneumococcal conjugate vaccine (Prevnar 13®, PCV 13), for prevention of IPD caused by the 13 pneumococcal serotypes covered by the vaccine and for prevention of otitis media caused by serotypes in the 7-valent pneumococcal conjugate vaccine formulation (Prevnar®, PCV7) (FDA Product approval information–CBER, 2010).

PCV13 is made by Pfizer Inc., the manufacturer of PCV7. The formulation and manufacturing process for the PCV13 vaccine was the same as that used for PCV7 vaccine, and the safety profile of licensed PCV13 was anticipated to be similar to that of PCV7, which has an excellent safety record.

The Advisory Committee on Immunization Practices (ACIP) recommended PCV13 for routine vaccination of all children aged 2-59 months, children aged 60-71 months with underlying medical conditions that increase their risk for pneumococcal disease or complications and children who previously received 1 or more doses of PCV7. PCV13 was slated to be a successor to PCV7 (MMWR; December 10, 2010 / 59(RR11);1-18).

An important factor to assess during pre-licensure is the detail evaluation of vaccine safety. For PCV7 and PCV13 no major safety problems were identified, however it is impossible to identify all safety concerns during clinical trials and there is always a possibility of not detecting some unusual adverse events. Clinical trials and post-licensure safety surveillance are critical to maintaining public health and trust in the Pneumococcal 13-valent Conjugate Vaccine. Due to the increased number of subjects exposed to the product after licensure investigators must continue to monitor, evaluate and characterize the potential adverse events of the product. This will allow for detection of unexpected adverse events and establish product's safety profile thus help for decision making.

Being able to distinguish events that could be potentially related to a vaccine and those that occur coincidentally is crucial. The quick identification and characterization of any adverse reactions to the vaccine can help distinguish between causal and no causal events.

This investigation will focus on and summarize the potential adverse events following immunization with PCV13 reported to the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system and primary method to detect vaccine safety signals. Frequencies of adverse events occurring following immunization with PCV13 and adverse events previously reported with PCV7 will be compared, taking into account possible bias, confounding, and probable associations. Although causality between vaccines and adverse events is not assessed by VAERS, it can detect signals, unusual or unexpected product-event combinations for more rigorous investigation using more appropriate epidemiological study designs (Zhou W, et al. 2003).

This examination uses data from a passive surveillance system that has important limitations and is subject of to both underreporting and over reporting, particularly in the first year after introduction of a new product (Rosenthal S, et al., 1995). Despite the limitations, VAERS has played an important role in monitoring adverse events following immunization. Its ability to detect adverse signals, for example, was demonstrated by uncovering an association between Rotavirus vaccine (Rotashield®) and Intussusception (MMWR February 6, 2009 / 58(RR02);1-25). Due to these limitations causality cannot be determined; other epidemiologic studies must be used for confirmation.

1.1 Background

During pre-licensure randomized clinical trials assessed the safety of both Pneumococcal conjugated vaccines PCV7 and PCV13, showing favorable results in about 19,000 young

children who received PCV7 and approximate 5,000 infants who received PCV13 (FDA. Product approval information–CBER, 2010). At introduction, PCV13 is indicated for active immunization for the prevention of invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. PCV13 is also indicated for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A (FDA, product approval information –CBER, 2010).

In the post-licensure period, a similar safety favorable results was provided for the first two years of PCV7 when comparing PCV7 to other vaccines after an estimated distribution of 31.5 million doses of PCV7 within the U.S. Adverse events described in children younger than 18 years old vaccinated with PCV7 were minor and similar to those observed in pre-licensure trails (Robert P. Wise et al., 2004). In 2008 a systematic review of 42 studies regarding the pre-and post-licensure safety profile of pneumococcal conjugate vaccines did not identify major safety issues with pneumococcal vaccines (Frank DeStefano et al., 2008). Although some hospitalizations were caused by reactive airway disease seen in PCV7 and 9-Valent Pneumococcal Conjugate vaccine recipients compared to controls (Black S et al., 2000 and Klugman et al., 2003) the outcome of extensive studies in the U.S. did not corroborate such an association (FDA. Product approval information–CBER, 2010).

The safety profile of PCV13 was assessed in 13 clinical trials; Approximately 15,000 doses were given to 5,000 healthy infants 6 weeks through 15 months of age and the

comparison group of 2,760 children received at least 1 dose of PCV7. The most commonly reported adverse reactions (≥20 % of subjects) were redness, swelling and tenderness at the injection site, fever, decreased appetite, irritability, increased sleep, and decreased sleep. No imbalance of serious adverse events following vaccination were observed when compared to PCV7. The most frequently reported local reaction was tenderness, and the most frequently reported systemic adverse event was irritability. In the largest U.S. safety study, moderate fever occurred at a statistically significantly higher rate in PCV13 recipients compared to PCV7 recipients after the second dose. This finding was not observed in smaller studies. Across all studies, four subjects died due to sudden infant death syndrome-SIDS (3 received PCV13). There were no consistent trends identified (FDA. Vaccines: approved products. PCV13).

The severity of local and systemic reactions after vaccination with PCV13 and PCV7 were alike. Thus, the data suggest that the safety profiles of PCV13 and PCV7 were comparable in pre-licensure studies (MMWR March 12, 2010 / 59(09);258-261), suggesting that the safety profile of licensed PCV13 will be similar to that of PCV7 vaccine.

1.2 Purpose of Study

This investigation aimed to assess the potential adverse events reported to VAERS following immunization with PCV13 in the first year of post-licensure and to compare

clinically significant adverse events following receipt of PCV13 with those that have been observed after PCV7.

This study will help to ascertain the safety profile of PCV13, detect potential safety signals that might be of public health importance and the need for additional studies for clarification and to inform vaccine benefit-risk decision making.

1.3 Research Questions

In order to review the safety profile and investigate the most frequently reported adverse events after vaccination with PCV13 the following questions must be addressed:

What are the most common adverse events reported to VAERS following immunization with PCV13 during the first year post-licensure?

What are the frequencies when comparing adverse events of PCV13 with PCV7's safety profile?

Are adverse events reported after vaccination with PCV13 the same as those expected and listed in the package insert?

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Pneumococcal Vaccines in the U.S.

Worldwide pneumonia is the most common cause of deaths related to pneumococcal disease. The World Health Organization estimates that approximately 1.9 million children die each year as a result of an acute respiratory infection, mainly pneumonia. (Mulholland K et al., 2003) although this might be an underestimate since the majority of the childhood deaths occur at home without autopsy. The introduction of new and better vaccines to protect against pneumococcal disease can have considerable impact in reducing mortality.

The first pneumococcal vaccine trials began in 1911. The first pneumococcal vaccine was licensed in the United States in 1977 and included 14 serotypes. In 1983, a 23-valent pneumococcal polysaccharide vaccine (PPSV23) was licensed and replaced the 14-valent vaccine. It was recommended for all patients 65 years of age or older and for children 2 years of age or older. However, PPSV23 vaccine immunogenicity was insufficient owing to a lack of a good T-cell independent immune response and the vaccine was therefore was less effective in preventing pneumococcal disease in children. A 7-valent conjugate pneumococcal vaccine (PCV7, Prevnar®) was licensed in the U.S in 2000, using capsular

polysaccharides from selected serotypes conjugated to a protein carrier to stimulate a T-cell dependent immune response. PCV7 induces both a systemic and mucosal immune response to prevent nasopharyngeal colonization by bacteria (Edwards et al., 2003). Ninety pneumococcal serotypes have been identified. It is estimated that about 62% of invasive disease worldwide is caused by the 10 most common serotypes (Atkinson et al., 2009). In 2010 the 13-valent pneumococcal vaccine (PCV13, Prevnar 13®) was licensed in the U.S covering for thirteen serotypes including those in PCV7 vaccine and six additional serotypes (Table 1).

Table 1. Pneumococcal Vaccines Licensed for Immunization and Distribution in the U.S.

Vaccine	Trade name	Manufacturer	Year Licensed	Age group
Pneumovax 23 - Pneumococcal Vaccine, Polyvalent	Pneumovax 23®	Merck & Co, Inc	1983	All adults aged ≥65 years and those adults aged 19--64 years with underlying medical conditions that put them at greater risk for serious pneumococcal infection
Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)	Prevnar®	Wyeth Pharm. Inc	2000	≥2 months, ACIP also recommends children aged 24--59 months who are either unvaccinated or who have a lapse in PCV7 administration
Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)	Prevnar 13®	Wyeth Pharm. Inc (acquired by Pfizer Inc, 2010)	2010	All children aged 2--59 months. ACIP also recommends PCV13 for children aged 60--71 months with underlying medical conditions that increase their risk for pneumococcal disease or complications

2.2 Pneumococcal vaccines safety studies

There are currently several studies and clinical trials of pneumococcal conjugated vaccines that provide information on vaccine safety. Furthermore, post-marketing surveillance for PCV13 is in progress.

The safety of pneumococcal vaccines was established in pre-and post-licensure clinical trials in different countries. In a clinical trial conducted in South Africa, a 9-valent pneumococcal conjugate vaccine (PCV9) was administered to approximately 20,000 children with high prevalence of human immunodeficiency virus (HIV). Investigators reported viral pneumonia being more frequent in children who received the PCV9 vaccine than in children who received placebo; in addition, asthma was found to be more frequent in PCV9 recipients than in placebo recipients (Klugman et al., 2003). However in a study of PCV9 conducted in Gambia, asthma was not a frequently reported adverse event following vaccination (Cutts et al., 2005). In the U.S. the most comprehensive evaluation of PCV7 during pre-licensure was conducted at Northern California Kaiser Permanente (NCKP). Adverse events reported after vaccination occurred less frequently compared to studies previously done in Africa, and asthma was not associated with PCV7 (FDA. Product approval information –CBER, 2010). In the first two years post-licensure of PCV7, adverse events reported to VAERS in patients less than 18 years old after immunization with PCV7 were minor and similar to those occurring in pre-licensure clinical trials (Wise et al., 2004). In a systematic review of 42 studies regarding PCV7 safety profile in several industrialized and developing countries, investigators did not

identify major safety problems with pneumococcal vaccines (DeStefano et al., 2008). None of the previous studies found increased risk of death following immunization with pneumococcal conjugated vaccine and no major safety problems were identified. The World Health Organization recommended incorporating pneumococcal conjugate vaccine to all immunization programs (WHO, 2007)

Since the introduction of PCV7 vaccination, invasive pneumococcal disease (IPD) has decreased in children less than 5 years (Whitney et al., 2006) although an small increase (about 5 per 100,000) of IPD in the general population was detected and was determined to be caused by serotype 19A not included in PCV7 vaccine. However since 2002 the overall rates of IPD have level off to approximate 22-25 cases per 100,000 in children less than 5 years old (Pilishvili et al., 2010).

2.3 Monitoring Vaccine Safety

The National Childhood Vaccine Injury Act (NCVIA) of 1986 was enacted to manage the claims of people that reported adverse events or death after immunizations, and thus help to take care of financial liabilities as well as supervise market supply. The act required health professionals and vaccine manufacturers to report to the U.S. Department of Health and Human Services specific adverse events that occur after the administration of routinely recommended vaccines (National Childhood Vaccine Injury Act of the Public Health Service).

The Centers for Disease Control and Prevention (CDC) has vaccine safety post licensure monitoring systems in place to detect and respond to a potential adverse events following immunization.

VAERS is a national passive surveillance system and is operated by the CDC and the Food and Drug Administration (FDA) to accept reports from health care providers, vaccine manufacturers, the public and others on possible adverse events following immunization.

2.4 The Vaccine Adverse Events Reporting System (VAERS)

The Vaccine Adverse Events Reporting System (VAERS) is a passive reporting system used to monitor vaccine safety. It was established in 1990 and is jointly administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS accepts reports of adverse events after vaccination from vaccine manufacturers, healthcare providers, vaccine recipients, and others. VAERS generally cannot assess whether a vaccination caused an adverse event, but can identify possible vaccine safety problems for further investigation (Varricchio F et al., 2004).

VAERS is the largest United States post-licensure surveillance system and has provided useful information on the safety profile of pneumococcal vaccines in the general population of children and adults. Because of its size and national scope, VAERS can

provide information on rare adverse events that may not be detected in pre-licensure clinical trials.

VAERS serves as the U.S. "early warning" system for potential vaccine safety concerns (signal detection) about adverse events and reported frequencies compared to what would be expected to be associated with the use of an specific product (Table 2).

Table 2. Signal Detection

Data Source	Strengths	Limitations
VAERS	Nationwide Near real-time Detection of rare or unexpected events Lot specific surveillance Data mining	Underreporting Consistency Variable quality of reported information Specifics on vaccines used Variable reporting biases Poorly defined denominators No controls

VAERS uses the Medical Dictionary for Regulatory Activities (MedDRA) to code the signs and symptoms about reported adverse events on each report (MedDRA Maintenance and Support Service Organization). Reports may have multiple MedDRA codes and might include simultaneous vaccinations.

Reports are classified as serious, based on the Code of Federal Regulations (FDA, 21CFR 314.80) if they result in death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, or if a congenital anomaly is reported (FDA., Postmarketing reporting of adverse experiences; 1997). All serious events are reviewed.

This regulatory definition of a serious report does not always reflect the severity of an outcome. Reports are usually submitted by electronic mail by accessing http://www.vaers.org, regular mail or fax. All serious adverse events and deaths are followed up by FDA and CDC medical officers and epidemiologists.

2.5 Recommendations for 13-Valent Pneumococcal Conjugate vaccine

PCV13 is part of the U.S recommended immunization schedule for persons aged 0 through 6 years (Figure 1). PCV13 is approved for use among children aged 6 weeks--71 months and recommended as a four dose series at ages 2, 4, 6, and 12-15 months. PCV13 will succeed PCV7. On February 24, 2010, PCV13 was recommended (MMWR December 10, 2010 / 59(RR11);1-18) by the Advisory Committee on Immunization Practices (ACIP) for routine vaccination of:

- All children aged 2--59 months (Appendix A: Tables 3, 4 and 5).
- Children aged 60--71 months with underlying medical conditions that increase their risk for pneumococcal disease or complications (Appendix A: Table 6).
- Children who previously received 1 or more doses of PCV7.
- Unvaccinated children and children incompletely vaccinated with PCV7-- Transition from PCV7 to the PCV13 immunization program (Appendix A: Table 7)

Chapter III

METHODOLOGY

3.1 Data Source

We searched and reviewed reports of adverse events after PCV13 submitted to the Vaccine Adverse Event Reporting System (VAERS).

We searched for reports received by February 24, 2011 for persons vaccinated with PCV13 from February 24, 2010 through December 31, 2010. In order to assess the reporting trends and whether the proportions of reports received after PCV13 immunization were similar to PCV7 in previous years we went back avoiding seasonal pattern and reviewed safety data, U.S VAERS reports for adverse events reported following PCV7 from February 24, 2000 through February 24, 2001, persons vaccinated with PCV7 from February 24, 2000 through December 31, 2000. The total number of adverse events was stratified for PCV13 and PCV7. The numbers of deaths, non-fatal serious and non-serious reports were determined. Non-US reports were excluded.

We used information from VAERS which included demographics on the recipient (age, sex, etc,), type of vaccine, vaccination date, manufacturer, vaccine lot number, doses previously received, date of onset of symptoms and description of the event. Onset interval is the number of days from the time of vaccination to the onset of earliest reported symptoms.

Crude reporting rates for VAERS adverse events per 100,000 doses of vaccine were calculated by dividing the number of events occurring within the 12 months after PCV13 vaccination by total doses of PCV13 vaccine distributed in the United States. To calculate reporting rates, distribution data (total doses of PCV13 vaccine distributed) provided by vaccine manufacturer were used as an estimate of total doses administered to U.S. and as "denominator" to estimate reporting rates.

Based on pre- and post-licensure safety data on pneumococcal conjugate vaccines, special attention was paid to respiratory events that followed PCV13 vaccination including reactive airway disease and asthma (DeStefano F et al.,2008). A pre-specified group of combined MedDRA preferred terms was used as a search criterion to select potential asthma and reactive airway disease reports (bronchospasm, wheezing, asthma, status asthmaticus, reversible airway obstruction, bronchial hyper reactivity, asthmatic crisis, infantile asthma and respiratory distress).

3.2 Statistical Analysis

Descriptive statistics were used to describe the epidemiology of reports submitted to the VAERS, a national passive surveillance database for the U.S.

The VAERS database use standardized coding terms that are assigned after review of each report by trained personnel. Most reports receive multiple codes.

Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to Institutional Review Board review and informed consent requirements.

Chapter IV

RESULTS

4.1 Frequencies and Descriptive Statistics

From February 24, 2010, through February 24, 2011, VAERS received 1,503 reports of adverse events following receipt of PCV13; 180/1,503 or 11.9% reports were described as serious including 19 fatalities and most of the reports were described as non-serious (1,323/1,503 or 88%). From February 24, 2000, through February 24, 2001, a total of 963 reports were received after PCV7 vaccination; 114 (11.8%) were serious; including 23 reports of death, and 849 (88%) reports were non-serious. The number of death reports received over the first year after PCV13 licensure (19/1,503 or 1.3%) was less than the first post licensure year for the PCV7 group (23/963 or 2.4%). The percentage of serious reports after vaccination with PCV13 was lower compared to PCV7 (Table 8).

Among all, the most frequently reported adverse events following immunization were injection site erythema (25.5%, 15.2%), pyrexia (24.2%, 32.0%) and injection site swelling (19.4%, 5.5%) for PCV13 and PCV7, respectively (Table 9). Other common adverse events reported after PCV13 were irritability, injection site pain and vomiting. No unexpected serious events or death appeared to be associated with PCV13 or PCV7. In the analysis among serious reports, pyrexia (38.9%, 28.9%), irritability (36.1%, 11.4%) and vomiting (35.6%, 8.8%) were the most frequently reported adverse events for

PCV13 and PCV7, respectively (Table 10). The median age (<1 year) were the same for PCV13 and PCV7 whereas the median onset interval was 2 and 1 day for PCV13 and PCV7 respectively.

The percentage of persons receiving the pneumococcal vaccine alone with no other antigens was higher for PCV13 compared to PCV7; In 323 of 1,503 reports (21%) PCV13 was the only vaccine administered, the remaining 79% of reports described simultaneous vaccination of PCV13 with a variety of other vaccines. Whereas 324 of 963 reports (34%) noted PCV7 administration without simultaneous vaccinations.

Most of the adverse events reported in both groups happened within one day of vaccination. For PCV13, of the 1380 reports that included onset interval, 545 (36%) occurred on the day of vaccination compared to PCV7 reports whereas 927 reports including onset interval, 347 (36%) occurring the same day of vaccination. The median age of recipients reporting adverse events to VAERS after immunization with PCV13 and PCV7 was the same (<1 year). 50% (758/1503) and 51% (493/963) of reports received were in males for PCV13 and PCV7, respectively; for the PCV13 reports, 48% were in females and 1% were reports with unspecified gender whereas for the PCV7, 45% were in females and 3% reports had unspecified gender.

There were no significant differences in reporting practices to VAERS by recipients. The majority of reports following PCV13 (941/1503, or 63%) were submitted by the healthcare provider, compared to 39% reports submitted by providers after vaccination

with PCV7. Other additional sources of reporting included manufacturer (7%, 23%), patients or parents (4%, 3%), state health clinics (3%, 6%), and "others" (23%, 3%) for PCV13 and PCV7, respectively. The proportions of reported adverse events found for all reports received after vaccination with PCV13 were lower for calculated age group <6 months and 6-11 months (22% and 10% vs. 25% and 22%) compared to PCV7; for the calculated age group 3-5 years the proportion was greater (29% vs. 8%) compared to PCV7.

Table 8. Characteristics of the Vaccine Adverse Event Reporting System (VAERS) U.S. reports following receipt of PCV13 vaccine February 24, 2010 through February 24, 2011 (n=1503) and PCV7 vaccine February 24, 2000 through February 24, 2001 (n=963)

Characteristic	PCV13	PCV7
All reports	n=1503	n=963
Serious reports	11.9% (180/1503)	11.8% (114/963)
Deaths	1.2% (19/1503)	2.4% (23/963)
Recipients age in years [a] (median [range])	1.0 (0 – 75.0)	1.0 (0 – 80.0)
Onset interval in days [b] (median [range])	1.0 (0 – 91.0)	1.0 (0 – 204.0)
Male reports [c]	50.4% (758/1503)	51.1% (493/963)
Vaccine given alone	21.0% (323/1503)	33.6% (324/963)
Reports with MedDRA [d] term coded for "wheezing"	2.1 % (31/1503)	0.7% (7/963)
Reports with MedDRA [d] term coded for "asthma" [e]	2.4 % (36/1503)	0.9 % (9/963)
Age group		
< 6 mos	21.6% (325/1503)	25.3% (244/963)
6-11 mos	9.5% (143/1503)	22.1% (213/963)
1-2 years	37.7% (567/1503)	41.3% (398/963)
3-5 years	28.8% (433/1503)	7.6% (74/963)
>=6 years	0.68% (11/1503)	1.8% (18/963)
Unknown	1.6% (25/1503)	1.6% (16/963)

[a] Age unknown for 25 and 16 reports for PCV13 and PCV7 respectively.

[b] Onset unknown for 123 and 36 reports for PCV13 and PCV7 respectively. Days from the time of vaccination to the onset of the earliest reported symptoms.

[c] Gender unknown for 21 and 32 reports for PCV13 and PCV7 respectively.

[d] The Medical Dictionary for Regulatory Activities (MedDRA) was used to code symptoms and/or conditions described in each report.

[e] Asthma Combined MedDRA PTs: Bronchospasm, wheezing, asthma, status asthmaticus, reversible airway obstruction, bronchial hyperreactivity, asthmatic crisis, infantile asthma, respiratory distress.

Table 9. Most common reported frequencies of adverse events occurring after vaccination with PCV13 (PCV13) and PCV7 (Prevnar®); ALL reports.

Reported frequencies of adverse events occurring following administration of PCV13 and PCV7—All reports		
Adverse event	%	
	PCV 13*	PCV 7†
	(n = 1,503)	(n = 963)
Injection site erythema	25.5	15.2
Pyrexia	24.2	32.0
Injection site swelling	19.4	5.5
irritability	10.3	11.1
Injection site pain	9.8	5.5
Injection site warmth	9.8	3.5
Vomiting	9.2	6.7
Urticaria	7.5	10.0
Crying	7.4	3.7
Erythema	6.5	3.7
Rash	6.3	8.7
Body temperature increased	5.8	--
Injection site duration	5.2	2.9
Abbreviations: PCV13 = 13-valent pneumococcal polysaccharide-protein conjugate vaccine, PCV7 = 7-valent pneumococcal polysaccharide-protein conjugate vaccine, and NA = data not available.		
* ALL VAERS reports received following PCV13 immunization 2/24/10 through 2/24/11; vaccination date 2/24/10 through 12/31/10.		
† ALL VAERS reports received following PCV7 immunization 2/24/00 through 2/24/01; vaccination date 2/24/00 through 12/31/00.		

Table 10. Most common reported frequencies of Serious adverse events occurring after vaccination with PCV13 (PCV13) and PCV7 (Prevnar®)

Reported frequencies of adverse events occurring following administration of PCV13 and PCV7—Serious reports

PCV 13* (n=180) Adverse Event	%	PCV 7† (n=114) Adverse Event	%
PYREXIA	38.9	PYREXIA	28.9
IRRITABILITY	36.1	CONVULSION	20.2
VOMITING	35.6	APNOEA	12.3
BLOOD CULTURE NEGATIVE	22.8	IRRITABILITY	11.4
CONVULSION	20.6	LETHARGY	10.5
INTUSSUSCEPTION	19.4	CYANOSIS	9.6
DIARRHOEA	18.9	VOMITING	8.8
UNRESPONSIVE TO STIMULI	16.1	ANOREXIA	8.8
COUGH	16.1	SUDDEN INFANT DEATH SYNDROME	8.8
PLATELET COUNT INCREASED	15.6	COMA	7
ULTRASOUND ABDOMEN ABNORMAL	15.6	BACTERIAL INFECTION	7
CRYING	15.6	HYPOTONIA	7
WHITE BLOOD CELL COUNT INCREASED	13.9	PNEUMONIA	7
ENEMA ADMINISTRATION	12.8	FEBRILE CONVULSION	5.3
CULTURE URINE NEGATIVE	12.8	SOMNOLENCE	5.3
LYMPHOCYTE PERCENTAGE DECREASED	12.2	PALLOR	5.3
SOMNOLENCE	12.2	RASH	5.3
HAEMATOCRIT DECREASED	12.2	LABORATORY TEST ABNORMAL	4.4
CHEST X-RAY ABNORMAL	12.2	CARDIAC ARREST	4.4
ELECTROENCEPHALOGRAM NORMAL	12.2	UPPER RESPIRATORY TRACT INFECTION	3.5
GAZE PALSY	12.2	DEHYDRATION	3.5
CHEST X-RAY NORMAL	12.2	AGITATION	3.5
HAEMATOCHEZIA	11.7	UNEVALUABLE EVENT	3.5
NEUTROPHIL PERCENTAGE INCREASED	11.7	STUPOR	3.5
COMPUTERISED TOMOGRAM NORMAL	11.7	STARING	3.5

Abbreviations: PCV13=13-valent pneumococcal polysaccharide-protein conjugate vaccine, PCV7= 7-valent pneumococcal polysaccharide-protein conjugate vaccine.

* Serious VAERS reports received following PCV13 immunization 2/24/10 through 2/24/11; vaccination date 2/24/10 through 12/31/10.
† Serious VAERS reports received following PCV7 immunization 2/24/00 through 2/24/01; vaccination date 2/24/00 through 12/31/00.

Chapter V

DISCUSSION AND CONCLUSION

5.1 Discussion

In the pre-licensure safety database, which includes approximately 15,000 doses and 5,000 recipients, no safety signals were identified. The available post-marketing data support an acceptable safety profile for PCV13. The great majority of reports in the first year after PCV13 licensure described minor signs and symptoms previously documented during clinical trials. The proportion of reports describing serious events (11.9%) was similar to that reported on a regular basis for other vaccines in the data system (14.3%) (Zhou W, et al. 2003). Nonetheless, further investigation for unusual reports of serious events (i.e. seizures), including requesting medical records for clinical review and follow up, continues to be a priority.

Although the total number of VAERS reports received following PCV13 vaccination was higher than the total reports received following PCV7 vaccination for all age groups in the previous year, the findings must be carefully interpreted since enhanced reporting to VAERS has been documented when a new vaccine is licensed and available to the public. In addition, an increase in adverse events that may attributable in part to heightened public perception and awareness (Zhou W et al., 2003). Finally, each VAERS report

usually includes multiple MedDRA codes and occasional duplicate coding or coding errors may appear, also many reported events may not be due to the vaccine.

Asthma and reactive airway disease have been found statistically important in previous pneumococcal studies (Klugman et al., 2003). This investigation looked for asthma and reactive airway disease reports using pre-specified MedDRA codes and demonstrated no difference in proportional reporting after PCV13 vaccination compared with PCV7 vaccine. Local reactions are very common after vaccination of any type and very often occur with minor symptoms and with no sequelae. Expected reports of pyrexia as a frequent adverse event were observed, however findings were similar in both groups and similar to previous studies of these vaccines. Fever is also a common symptom in children and not necessarily related to vaccination.

5.2 Study Limitations

VAERS is a passive surveillance system with limitations that include both under-reporting and biased reporting that can affect the outcome and analysis. More important, VAERS generally does not assess causality. Because VAERS accepts reports from any person, it is common to find duplicates or errors in reporting as well as missing data (i.e. demographics) in some cases. However VAERS has been used as an important surveillance tool and demonstrated to be very helpful when assessing vaccine safety

(MMWR February 6, 2009 / 58(RR02);1-25) and has a national capacity that permitted us to investigate in a large and diverse population.

This study assessed associations between adverse event reported to VAERS after vaccination with PCV13, however for a stricter and deeper analysis of direct associations of vaccination and adverse events an exhaustive clinical review of each serious report will be necessary to rule out similar reported clinical symptoms and signs in order to be able to establish cases and their association with safety concerns. Another limitation was the inability to calculate adjusted reporting rates for selected adverse events.

5.3 Recommendations

1. More surveillance and multidisciplinary approaches are needed to address the limitations of VAERS. Clinical review of medical records would help to understand better the nature of the adverse events reported.

2. Health professionals, health care providers and policy makers must develop and implement interventions to spread the knowledge to the general public regarding the safety of the vaccines as well as let people know about systems that are in place for continue monitoring vaccine safety issues in addition to insist in the benefits of and the need for immunizations against vaccine preventable diseases.

3. Encourage all healthcare personnel and public in general to use the VAERS system to report any clinically significant medical event that occurs after vaccination, even if the reporter cannot be sure that the event was caused by the vaccine. If no minor adverse event is unreported, the better the data captured and the higher the probability for a correct assessment, increasing the availability of information and continued monitoring of the safety of the PCV13 are key for ensuring optimal public health decisions and public confidence in the Pneumococcal 13-valent Conjugate Vaccine.

5.4 Conclusion

We were able to compare PCV13 and PCV7 risk profile. Among all reports, frequencies of solicited adverse events after vaccination with PCV13 were similar to those reported in prior studies and those currently listed in the package insert. No unexpected adverse events reported after PCV13 vaccination.

The safety profile of the PCV13 needs to be considered in the context of the benefits of vaccination, which includes the disease epidemiology and the vaccine effectiveness. Education about the recommendations, safety and importance of immunization with pneumococcal vaccines is fundamental to decrease disease rates.

APPENDIX A: Recommended schedule for use of PCV13

Table 3**.** Recommended schedule for use of 13-valent pneumococcal conjugate vaccine

Recommended schedule for use of 13-valent pneumococcal conjugate vaccine (PCV13) among previously unvaccinated infants and children by age at time of first vaccination		
Age at first dose (mos)	Primary PCV13 series*	PCV13 booster dose†
2--6	3 doses	1 dose at 12--15 mos
7--11	2 doses	1 dose at 12--15 mos
12--23	2 doses	NA
24--59 in healthy children	1 dose	NA
24--71 in children with certain chronic diseases or immunocompromising conditions§	2 doses	NA
Abbreviation: NA = not applicable * Minimum interval between doses is 8 weeks except for children vaccinated at age <12 months, for whom minimum interval between doses is 4 weeks. Minimum age for administration of first dose is 6 weeks. † Administered at least 8 weeks after the previous dose. § See Table 6 for a complete list of conditions.		

Table 4. Recommended schedule for use of 13-valent pneumococcal conjugate vaccine

Recommended schedule for administering doses of 13-valent pneumococcal conjugate vaccine (PCV13) to children aged <24 months by PCV vaccination history and age --- Advisory Committee on Immunization Practices, US, 2010		
Age at this visit (mos)	Vaccination history: total number of PCV7 and/or PCV13 doses received previously	Recommended PCV13 regimen*
2--6 mos	0 doses	3 doses, 8 weeks apart; fourth dose at age 12--15 mos
	1 dose	2 doses, 8 weeks apart; fourth dose at age 12--15 mos
	2 doses	1 dose, 8 weeks after the most recent dose; fourth dose at age 12--15 mos
7--11 mos	0 doses	2 doses, 8 weeks apart; third dose at 12--15 mos
	1 or 2 doses before age 7 mos	1 dose at age 7--11 mos, with a second dose at 12--15 mos, ≥8 weeks later
12--23 mos	0 doses	2 doses, ≥8 weeks apart

	1 dose before age 12 mos	2 doses, ≥8 weeks apart
	1 dose at ≥12 mos	1 dose, ≥8 weeks after the most recent dose†
	2 or 3 doses before age 12 mos	1 dose,≥8 weeks after the most recent dose†
	4 doses of PCV7 or other age-appropriate, complete PCV7 schedule	1 supplemental dose ≥8 weeks after the most recent dose
Abbreviation: PCV7 = 7-valent pneumococcal polysaccharide-protein conjugate vaccine. * Minimum interval between doses is 8 weeks except for children vaccinated at age <1 year, for whom minimum interval between doses is 4 weeks. † No additional PCV13 doses are indicated for children aged 12--23 months who have received 2 or 3 doses of PCV7 before age 12 months and at least 1 dose of PCV13 at age ≥12 months.		

Table 5. Recommended schedule for use of 13-valent pneumococcal conjugate vaccine

Recommended schedule for administering doses of 13-valent pneumococcal conjugate vaccine (PCV13) to children aged ≥24 months by PCV vaccination history and age		
Age at this visit (mos)	Vaccination history: total number of PCV7 and/or PCV13 doses received previously before age 24 months	Recommended PCV13 regimen*
24--59 mos in healthy children	Unvaccinated or any incomplete schedule	1 dose, ≥ 8 weeks after the most recent dose
	4 doses of PCV7 or other age-appropriate, complete PCV7 schedule	1 supplemental dose, ≥8 weeks after the most recent dose
24--71 mos in children with underlying medical conditions†	Unvaccinated or any incomplete schedule of <3 doses	2 doses, the first dose ≥8 weeks after the most recent dose and a second dose ≥ 8 weeks later
	Any incomplete schedule of 3 doses	1 dose, ≥ 8 weeks after the most recent dose
	4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 supplemental dose, ≥8 weeks after the most recent dose
Abbreviation: PCV7 = 7-valent pneumococcal polysaccharide-protein conjugate vaccine. * Minimum interval between doses is 8 weeks. † For list of conditions, see Table 6.		

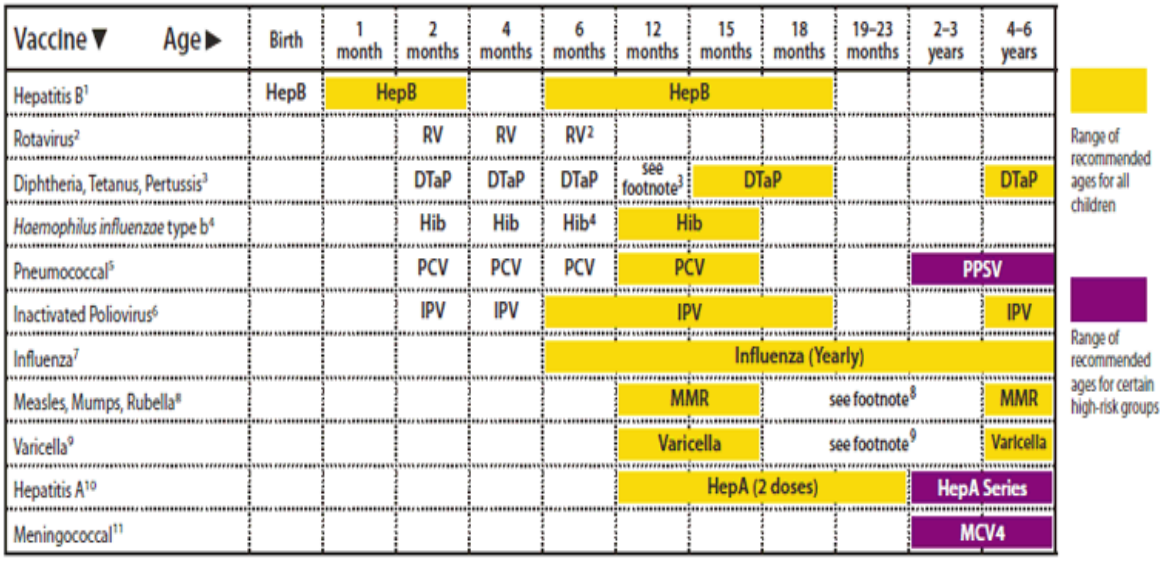
Table 6. Underlying medical conditions that are indications for pneumococcal vaccination

Underlying medical conditions that are indications for pneumococcal vaccination among children, by risk group --- Advisory Committee on Immunization Practices (ACIP), United States, 2010	
Risk group	Condition
Immunocompetent children	Chronic heart disease*
	Chronic lung disease†
	Diabetes mellitus
	Cerebrospinal fluid leaks
	Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies
	Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation
	Congenital immunodeficiency§
* Particularly cyanotic congenital heart disease and cardiac failure.	
† Including asthma if treated with prolonged high-dose oral corticosteroids.	
§ Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).	

Table 7. Recommended transition schedule

Recommended transition schedule from 7-valent pneumococcal conjugate vaccine (PCV7) to 13-valent vaccine (PCV13) vaccination among infants and children, according to number of previous PCV7 doses received --- Advisory Committee on Immunization Practices (ACIP), United States, 2010				
Infant series			Booster dose	Supplemental PCV13 dose
2 mos	4 mos	6 mos	≥12 mos*	14--59 mos†
PCV7	PCV13	PCV13	PCV13	---
PCV7	PCV7	PCV13	PCV13	---
PCV7	PCV7	PCV7	PCV13	---
PCV7	PCV7	PCV7	PCV7	PCV13
* No additional PCV13 doses are indicated for children age 12--23 months who have received 2 or 3 doses of PCV before age 12 months and at least 1 dose of PCV13 at age ≥12 months.				
† For children with underlying medical conditions (see Table 6), a single supplemental PCV13 dose is recommended through age 71 months				

FIGURE 1: Recommended immunization schedule for persons aged 0 through 6 years, U.S, 2011



Vaccine ▼ Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB			HepB						
Rotavirus[2]			RV	RV	RV[2]						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP	see footnote[3]	DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	Hib[4]	Hib					
Pneumococcal[5]			PCV	PCV	PCV	PCV				PPSV	
Inactivated Poliovirus[6]			IPV	IPV	IPV						IPV
Influenza[7]					Influenza (Yearly)						
Measles, Mumps, Rubella[8]						MMR		see footnote[8]			MMR
Varicella[9]						Varicella		see footnote[9]			Varicella
Hepatitis A[10]						HepA (2 doses)				HepA Series	
Meningococcal[11]										MCV4	

Range of recommended ages for all children

Range of recommended ages for certain high-risk groups

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