Safety of Pneumococcal Polysaccharide Vaccine (Pneumovax23®) in the Vaccine Adverse Event Reporting System (VAERS)

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The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of CDC

Purpose

- To provide the Advisory Commission on Childhood Vaccines (ACCV) with a review of the safety of Pneumococcal Polysaccharide Vaccine (Pneumovax23®) as it considers making a recommendation for the Vaccine Injury Compensation Program to cover adult immunizations

Outline

- Pneumococcal polysaccharide vaccine (Pneumovax23®) background
- VAERS analysis
- Summary and conclusions

Background: Pneumococcal Polysaccharide Vaccine (Pneumovax23®)

- **Antigen content**
  - 25 micrograms of 23 capsular polysaccharide types of *Streptococcus pneumoniae* (pneumococcus)
  - Serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F*
    - Cause 88% of bacteremic pneumococcal disease and provides cross-reactivity for additional types that account for 8% of bacteremic disease
- **Indication**
  - For prevention of pneumococcal disease caused by the 23 serotypes in the vaccine
  - Approved for persons ≥50 years, and for persons ≥2 years at increased risk for pneumococcal disease
  - Not approved for use in children less than 2 years of age since they do not develop an effective immune response

*13-valent pneumococcal conjugate vaccine (PCV13) contains serotypes in yellow above as well as 6A and 19A

Timeline for Pneumococcal Polysaccharide Vaccine Recommendations in the U.S.

1983 — ACIP Recommendations for PPV23

1984 — ACIP Recommendations for PPV23

1997 — ACIP Recommendations for PPV23

2000 — ACIP Recommendations for PPSV23 in adults ages 19-64 and in children ages 2-18 (after completing all doses of PCV13)

2010 — ACIP Recommendations for adults (incorporate PCV13 recommendations)

2011 — ACIP Recommendations for children 6-18 (incorporates PCV13 recommendations)

2012

2013

1983
Pneumovax-23 (Merck) licensed for ages ≥2

Pnu-Immune (Wyeth Lederle) licensed 1983 till 2002

2000
PCV7 (Wyeth) licensed for infants and young children (2, 4, 6,12-15 mo. age)*

2010
PCV13 licensed for children 6 weeks to 5 years

2011
PCV13 licensed for adults ≥50 years

2013
PCV13 licensed for children 6-17 years old

*Pneumococcal conjugate vaccines were developed because polysaccharide vaccines are not adequately immunogenic in young children to protect against pneumococcal disease.

ACIP=Advisory Committee on Immunization Practices

Pneumovax23® Pediatric Recommendations[1,2]

- **Children ages 2 years to 18 years**
  - **Immunocompetent with chronic conditions (1 dose)**
    - **Chronic heart or lung disease, diabetes mellitus, cerebrospinal fluid leaks, cochlear implants**
    - **Alcoholism, chronic liver disease, cigarette smoking (in children ages 6-18 years)**
  - **Functional or anatomic asplenia (2 doses, 5 years apart)**
    - **Sickle cell disease/other hemaglobinopathies; congenital or acquired asplenia**
  - **Immunocompromised (2 doses, 5 years apart)**
    - **Congenital or acquired immunodeficiencies, HIV, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, multiple myeloma**

1.CDC ACIP Recommendations June 28, 2013 at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6225a3.htm
2.CDC ACIP Recommendations Dec. 10, 2010 at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5911a1.htm

Pneumovax23® Adult Recommendations[1,2]

- **Adults ages 19-64**
  - **Immunocompetent with chronic conditions (1 dose)**
    - Chronic heart disease, chronic lung disease, diabetes mellitus, cerebrospinal fluid leaks, cochlear implants
    - alcoholism, chronic liver disease including cirrhosis, cigarette smoking
  - **Functional or anatomic asplenia (2 doses, 5 years apart)**
    - Sickle cell disease/other hemaglobinopathies; congenital or acquired asplenia
  - **Immunocompromised (2 doses, 5 years apart)**
    - Congenital or acquired immunodeficiencies, HIV, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, multiple myeloma
- **All adults ≥ 65**
  - One dose regardless of previous history

1.CDC ACIP Recommendations Sept. 3, 2010, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5934a3.htm
2.CDC ACIP Recommendations Oct. 12, 2012 available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm

Adverse Events from Prelicensure Studies Summarized in Package Insert (Pneumovax23®)*

- Most common adverse reactions, reported in >10% of subjects
  - Local reactions
    - Injection-site pain/soreness/tenderness (60%)
    - Injection-site swelling/induration (20%)
    - Injection-site erythema (16%)
  - Systemic reactions
    - Headache (18%)
    - Asthenia and fatigue (13%)
    - Myalgia (12%)

*http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM257088.pdf

Adverse Events from Prelicensure Studies Summarized in Package Insert (Pneumovax23®)* cont.

- **Most common adverse reactions after revaccination**
  - **Local reactions**
    - **Injection-site pain/soreness/tenderness (77%)**
    - **Injection-site swelling (40%)**
    - **Injection site erythema (35%)**
  - **Systemic reactions**
    - **Headache (18%)**
    - **Asthenia/fatigue (18%)**
    - **Myalgia (17%)**

*http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM257088.pdf

Selected Post-Marketing Studies

Study (year)	Design	Vaccine	Study Group	Main Safety Findings
Jackson, et al. (1999)[1]	Prospective comparative intervention study	Pneu-Immune (Lederle)	> 1400 participants of a group health cooperative. Ages of participants were 50 to 74.	Revaccinated vaccinees more likely than primary to report large local injection site reaction (≥ 10.2 cm within 2 days of vaccination: 11% (55/513) vs. 3% (29/901) (relative risk [RR], 3.3; 95% confidence interval [CI], 2.1-5.1). These reactions resolved by a median of 3 days following vaccination. No serious adverse events reported in either group.
Törling, et al. (2003)[2]	Prospective revaccination study	PPSV23 (brand not stated)	61 persons (ages 56-88) with history of hospitalization for pneumonia and previous PPSV23. No comparison group.	Local reactions occurred in 63%. 10% of total stated local reactions affected daily activity. No serious adverse events reported.
Lin, et al. (2005)[3]	Prospective vaccination study	2 doses of PCV7 and 1 dose of PPSV23 (controls-1 dose of PCV7 and 1 dose of PPSV23). Either Pnu-Immune or Pneumovax	25 pediatric solid organ transplant recipients between 2 and 18 years of age and 23 healthy age matched controls	Systemic and injection-site reactions were comparable between the 2 groups. 17 to 21% of transplant recipients reported fussiness, headache, loss of appetite after 23V, somewhat more than the control subjects.

1. Jackson LA, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA* 1999 Jan 20;281(3):243-8.
2. Törling J, et al. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. *Vaccine* 2003 Dec. 8;22(1):96-103.
3. Lin PL, et al. Safety and immunogenicity of the American Academy of Pediatrics--recommended sequential pneumococcal conjugate and polysaccharide vaccine schedule in pediatric solid organ transplant recipients. *Pediatrics* 2005 Jul;116(1):160-7.

Selected Post-Marketing Studies (continued)

Study (year)	Design	Vaccine	Study Group	Main Safety Findings
Abzug, et al. (2006)[1]	Multicenter prospective	2 doses PCV & 1 dose PPSV23	263 children ages 2 to <19 receiving HAART* for HIV. No comparison group.	Two PCVs and 1 PPSV23 were immunogenic and safe in HIV-infected children 2 to <19 years who were receiving HAART[2]
Burwen, et al, (2007)[3]	Retrospective database	Flu & PPSV23	Medicare Administrative Databases	Pneumococcal vaccinees had a statistically significant increased rate of hospitalizations for cellulitis and abscess of arm with an incidence rate of 2.5 cases per 100,000 vaccinees. Cellulitis and abscess of arm incidence rate was 5.4 per 100, 000 persons vaccinated if had a previous pneumococcal vaccine within 5 years.

1.Abzug MJ, et al. Immunogenicity, safety, and predictors of response after a pneumococcal conjugate and pneumococcal polysaccharide vaccine series in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J*. 2006 Oct;25(10):920-9.
2.HAART-highly active antiretroviral therapy
3. Burwen DR, et al. Evaluating adverse events after vaccination in the Medicare population. *Pharmacoepidemiol Drug Saf*. 2007 Jul;16(7):753-61.

VAERS Review

Objective

- Describe the safety profile of Pneumovax23® in the Vaccine Adverse Event Reporting (VAERS)

Vaccine Adverse Event Reporting System (VAERS) (co-managed by CDC and FDA)*

Strengths

- National data; accepts reports from anyone
- Rapid signal detection; rare adverse events (AE)
- Collects information about vaccine, characteristics of vaccinee, adverse event†
- Data available to public

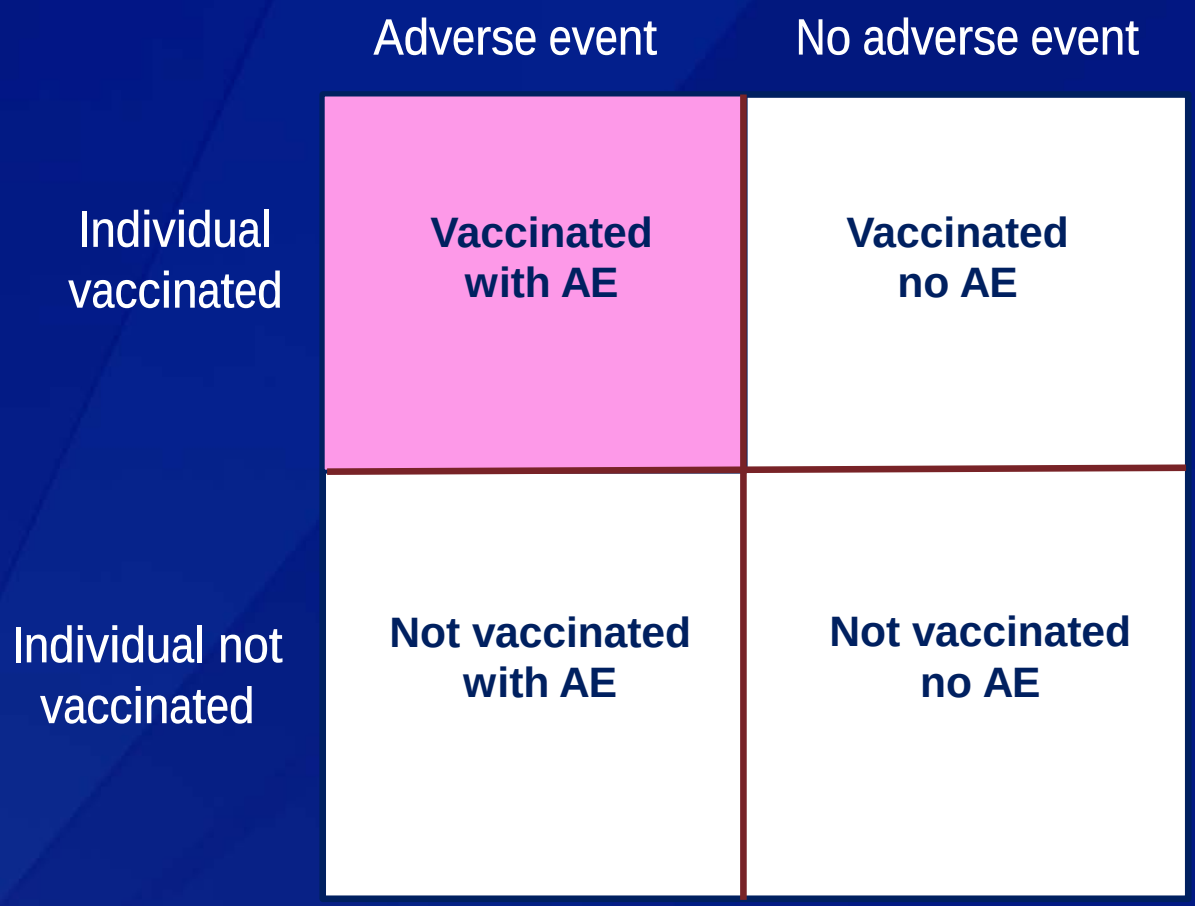
Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Generally cannot assess if vaccine caused an AE
- Lack of unvaccinated comparison group
- Pregnancy status not included on VAERS form
- Cannot calculate rates of occurrence of adverse events

*VAERS website: http://vaers.hhs.gov

†Some reports have no adverse event

Limitations of VAERS data



- **VAERS only contains info in pink cell (i.e., incomplete population data)**
  - **Not able to calculate rates of occurrence of adverse events**
  - **Not able to determine increased risk**
  - **Not able to calculate vaccination coverage**

Methods

- Included US VAERS reports following Pneumovax23® or pneumococcal polysaccharide vaccine (PPSV23) brand unknown after 2002
- Reports received from January 1, 1990 – January 31, 2014
- Dates vaccinated January 1, 1990 – December 31, 2013
- Excluded PPSV23 brand name “Pnu-Immune”
  - Pnu-Immune has not been used in the US since 2002 and constitutes ~10% of PPSV23 reports in VAERS
- Signs, symptoms, or diagnosis coded using Medical Dictionary for Regulatory Activities (MedDRA)*
- Descriptive statistics: age, serious†, non-serious, deaths

* http://www.meddra.org/

† Serious reports classified based on Code of Federal Regulations: death, life threatening, hospitalization, prolonged hospitalization, permanent disability

Pneumovax23® VAERS Reports – All Ages

Characteristics	N (%)
Number of reports	25,168
Serious	2129 (8)
Female	16,871 (67)
Type of reporter	
Healthcare provider	10,462 (42)
Other	6,319 (25)
Manufacturer	5152 (20)
Patient/Parent	2576 (10)
Age groups (years)	
0-2 (not approved for this age group)	940 (4)
2-5	427 (2)
6-12	550 (2)
13-18	390 (2)
19-64	11,040 (44)
65+	10,546 (42)

Pneumovax23® VAERS Reports by Age Groups and Serious Status[1,2]

Age	Deaths N (%)	Serious non-fatal[2] N (%)	Non-serious N (%)	Total N (%)
2 to 18 years	4 (0.3)	234 (17)	1129 (83)	1367 (100)
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2 to 4 years	0 (0)	55 (16)	280 (84)	335 (100)
5 to 18 years	4 (0.4)	179 (17)	849 (82)	1032 (100)
19 to 64 years	23 (0.2)	997 (9)	10,020 (91)	11,040 (100)
65+ years	38 (0.4)	696 (7)	9812 (93)	10,546 (100)
Total	66 (0.3)	2063 (8)	23,039 (92)	25,168 (100)

1-Not shown: 1275 (5%) reports with age not reported/unknown and 940 (4%) report with age 0 to <2 years
2-Includes life threatening illness, inpatient hospitalization, prolongation of an existing hospitalization, or permanent disability

Top 10 MedDRA Terms* in Children ages 2 to 18 Years

MedDRA Codes Serious reports	N=238 (%)
Pyrexia	172 (72)
White blood cell count increased	95 (40)
Cellulitis	93 (39)
Injection site pain	87 (37)
Injection site erythema	82 (34)
Injection site swelling	67 (28)
C-reactive protein increased	49 (21)
Erythema	46 (19)
Blood culture negative	44 (18)
Vomiting	44 (18)

MedDRA Codes Non-serious reports	N=1129 (%)
Pyrexia	476 (42)
Injection site erythema	344 (30)
Injection site pain	269 (24)
Injection site swelling	219 (19)
Erythema	183 (16)
Pain	167 (15)
Injection site oedema	123 (11)
Injection site warmth	105 (9)
Oedema peripheral	101 (9)
Vomiting	93 (8)

- MedDRA terms are not mutually exclusive.
- All of these symptoms or related symptoms are listed in the package insert except “blood culture negative.”

Co-administered Vaccines with Pneumovax23® in Children 2 to 18 years (N=1367), VAERS

Vaccine	N (%)
Pneumovax23® administered alone	***613 (45)***
Trivalent inactivated influenza (TIV)	377 (28)
DTaP	78 (6)
H1N1 inactivated influenza	18 (1)
DTaP-IPV-Hib (Pentacel)	10 (0.7)
DTP	9 (0.7)
DT	8 (0.6)
Live attenuated influenza vaccine (LAIV)	8 (0.6)

Pediatric Death Reports after Pneumovax23® in VAERS

Co-administered Vaccines	Age	Sex	Onset interval	Cause of death or medical condition around time of death*	Medical History
None	6 years	Male	3.6 years	Sickle cell disease with fever; cause of death unknown May have developed pneumococcal sepsis around time of death	
Trivalent inactivated influenza (IIV3)	7 years	Female	3 days	Accidental asphyxiation	Lissencephaly - microcephaly Seizure disorder
None	~6 years	Female	5.8 years	Pneumococcal sepsis, hemoglobin sickle cell disease	
Meningococcal polysaccharide, IIV3, Hep B, MMR	18 years	Male	1 month	Neisseria meningitidis septicemia	

*Cause of death is based on review of autopsy report, death certificate or medical record

Top 10 MedDRA Terms* in Adults Ages 19 and Older

MedDRA Codes Serious reports	N=1754 (%)
Pyrexia	770 (44)
Injection site erythema	520 (30)
Cellulitis	515 (29)
Injection site pain	512 (29)
White blood cell count increased	454 (26)
Pain	373 (21)
Injection site swelling	369 (21)
Chills	353 (20)
Erythema	323 (18)
Pain in extremity	272 (16)

MedDRA Codes Non-serious reports	N=19,832 (%)
Injection site erythema	6119 (31)
Injection site pain	5161 (26)
Erythema	4498 (23)
Pyrexia	4418 (22)
Injection site swelling	4389 (22)
Pain	3795 (19)
Oedema peripheral	2624 (13)
Injection site warmth	2529 (13)
Pain in extremity	2522 (13)
Injection site oedema	1906 (10)

* MedDRA terms are not mutually exclusive. All of these symptoms or related symptoms are listed in the package insert.

Co-administered Vaccines with Pneumovax23® in Adults ages 19 and older (N=21,586), VAERS

Vaccine	N (%)
Pneumovax23® administered alone	***11,286 (52)***
Trivalent inactivated influenza (TIV)	8,291 (38)
Hepatitis B	151 (0.7)
Hepatitis A	147 (0.7)
H1N1 inactivated influenza	141 (0.7)
Hepatitis A & B Combined	78 (0.4)
DTAP	71 (0.3)
DT	43 (0.2)

Reports of Pneumovax23® administered during pregnancy

- 18 total reports
- Adverse events include
  - 2 reports of spontaneous abortions
  - 6 reports of cellulitis
  - 5 reports of local reactions
  - 4 reports of no adverse event
  - 1 report of gestational diabetes and chlamydia

- *Pregnancy Category C:* Animal reproduction studies have not been conducted with PNEUMOVAX 23. It is also not known whether PNEUMOVAX 23 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PNEUMOVAX 23 should be given to a pregnant woman only if clearly needed.
- ACIP-Pneumococcal polysaccharide vaccine should be considered for pregnant women at increased risk for infection.

Death Reports in Adults ages 19 and Older Following Pneumovax23®

- 61 total death reports
  - Median age 69 years old; range 23 to 98 years old
  - 43 confirmed with medical records, autopsy reports and/or death certificates
  - 18 had no records
- Body systems involved in the cause of death among the 43 confirmed death reports in adults
  - Cardiovascular (N=16)
  - Respiratory (N=11)
  - Other infectious (N=5)
  - Undetermined (N=4)
  - Other non-infectious (N=4)
  - Gastrointestinal (N=1)
  - Neurological (N=2)

Summary and Conclusions: Pneumovax23®

- From 1990 through 2013, VAERS has received 25,168 reports following Pneumovax23®
- Most reports (92%) were classified as non-serious
- Fever (47%) is the most commonly reported adverse event in children followed by injection site erythema (31%), injection site pain (26%), and injection site swelling (21%)
- Deaths reports in children are rare (4 total) and listed cause of death and information from medical records do not suggest a pattern of concern
- Injection site erythema (31%) and injection site pain (26%) are the most commonly reported adverse events in adults
- No concerning patterns were detected in VAERS for Pneumovax23® for children or adults

WHO Position Paper: 23-valent Pneumococcal Polysaccharide Vaccine*—2008

"On the basis of decades of use, PPV23 is considered safe both in terms of severe immediate reactions and potential long-term adverse consequences. Minor adverse reactions, such as transient redness and pain at the injection site, occur in 30–50% of those who have been vaccinated, more commonly following subcutaneous administration than intramuscular administration; low grade fever occurs infrequently. Local reactions may be more frequent in recipients of a second dose of the vaccine..."

*http://www.who.int/wer/2008/wer8342.pdf

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Thank You

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