Safety of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged ≥65 years old

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Disclaimer

- Findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the CDC and FDA

Topics

- Background on 13-valent pneumococcal conjugate vaccine (PCV13) use in adults
- Adverse events following PCV13 reported to the Vaccine Adverse Event Reporting System (VAERS) in adults aged ≥65 years old
- PCV13 safety in adults aged ≥65 years old in the Vaccine Safety Datalink (VSD)

Background

- December 2011: PCV13 was approved by the FDA for use in adults aged ≥50 years[1]
- June 2012: ACIP recommends routine use of PCV13 in series with PPSV23, for adults aged ≥19 years with immunocompromising conditions[2]
- August 2014: ACIP recommends both PCV13 and PPSV23 should be administered routinely in series to all adults aged ≥65 years[3]

[1] https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm201665.htm

[2] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm

[3] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6337a4.htm

Background: PCV13 in adults aged ≥65 years

- August 2014: ACIP recommends both PCV13 and PPSV23 should be administered routinely in series to all adults aged ≥65 years[1]
  - Pneumococcal vaccine-naïve persons. Adults aged ≥65 years who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23. The dose of PPSV23 should be given 6–12 months after a dose of PCV13. If PPSV23 cannot be given during this time window, the dose of PPSV23 should be given during the next visit. The two vaccines should not be coadministered, and the minimum acceptable interval between PCV13 and PPSV23 is 8 weeks.
  - Previous vaccination with PPSV23. Adults aged ≥65 years who have previously received ≥1 doses of PPSV23 also should receive a dose of PCV13 if they have not yet received it. A dose of PCV13 should be given ≥1 year after receipt of the most recent PPSV23 dose. For those for whom an additional dose of PPSV23 is indicated, this subsequent PPSV23 dose should be given 6–12 months after PCV13 and ≥5 years after the most recent dose of PPSV23.

[1] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6337a4.htm

Background: Pre-licensure clinical trials and post-licensure monitoring of PCV13

- Pre-licensure clinical trial data and post-licensure safety monitoring of PCV13 in adults has been reassuring
  - Pre-licensure randomized controlled trials in PPSV23-naïve and PPSV23-experienced adults aged ≥50 years[1,2]
  - Post-licensure observational studies in elderly adults[3,4]
  - Vaccine Adverse Event Reporting System (VAERS) review of reports in adults aged ≥19 years from 2012-2015[5]

[1] Jackson LA, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine. 2013; 31:3577–8; [2] Jackson LA, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine. 2013;31:3585–93; [3] Orsi A et al. [Immunization campaign with 13-valent Pneumococcal Conjugate Vaccine in adults in Liguria Region, Italy: one year post-introduction preliminary results]. Epidemiol Prev. 2014;38(6 Suppl 2):66-72; [4] Durando P, et al. Safety and tolerability of 13-valent pneumococcal conjugate vaccine in the elderly. Hum Vaccin Immunother. 2015;11:172-7; [5] Haber et al. Post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged ⩾19years old in the United States, Vaccine Adverse Event Reporting System (VAERS), June 1, 2012-December 31, 2015. Vaccine. 2016;34:6330-6334

Vaccine Adverse Event Reporting System (VAERS) review

Objective of VAERS review

- Describe the safety profile of reports submitted to the Vaccine Adverse Event Reporting System (VAERS) following PCV13 in adults aged ≥65 years

Vaccine Adverse Event Reporting System (VAERS)[1]

Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

[1] Co-managed by CDC and FDA (http://vaers.hhs.gov)

Methods

- Searched VAERS database for PCV13 reports from August 2014 through December 2017
  - Restricted to U.S. reports in adults aged ≥65 years
- Serious reports defined as those documenting death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability[1]
- Signs and symptoms of adverse event coded using Medical Dictionary for Regulatory Activities (MedDRA)[2] Preferred Terms (PTs)
  - PTs are not mutually exclusive
    - A single report may be assigned more than one PT

[1] Based on the Code of Federal Regulations 21 CFR 600.80

[2] https://www.meddra.org/

Methods (cont.)

- Descriptive analysis
- Clinical review of reports for select pre-specified conditions of interest
  - Guillain-Barré syndrome (GBS), anaphylaxis, and death
- Empirical Bayesian data mining
  - Used to detect disproportional reporting
  - Identifies adverse events reported more frequently than expected after vaccine of interest compared with other vaccines in the VAERS database

PCV13 reports to VAERS in adults ≥65 years, Aug 2014-Dec 2017

Characteristics	N (%)
Total reports[1]	5,822
Female	4,387 (75)
Male	1,363 (23)
Unknown sex	72 (2)
Serious reports[2]	348 (6)
Median age [range] in years	72 [65-100]
Median onset interval [range] in days	1 [0-608]
Received PCV13 alone	4,189 (72)

- In reports documenting ≥1 co-administered vaccines, the most common were: high-dose inactivated influenza (n=884), zoster vaccine live (n=204), and Tdap (n=87)

[1] U.S. primary reports (foreign reports excluded)

[2] Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability

Most common signs and symptoms[1] in reports to VAERS following PCV13 in adults ≥65 years, Aug 2014-Dec 2017

PCV13 given alone (72%)	N (%)
Injection site erythema	1,176 (28)
Erythema	815 (20)
Injection site pain	771 (18)
Injection site swelling	735 (18)
Pain	582 (14)
Fever	577 (14)
Pain in extremity	569 (14)
Injection site warmth	487 (12)
Chills	389 (9)
Pruritus	378 (9)

PCV13 given w/other vaccines	N (%)
Injection site erythema	413 (25)
Injection site swelling	271 (17)
Injection site pain	263 (16)
Erythema	254 (16)
Pain in extremity	246 (15)
Pain	189 (12)
Injection site warmth	185 (11)
Fever	171(11)
Peripheral swelling	148 (9)
Pruritus	136 (8)

[1] Coded using the MedDRA Preferred Terms; more than one MedDRA Preferred Term may be assigned to a single report (i.e., not mutually exclusive)

Clinical review of reports for select pre-specified conditions of interest

Reports of Guillain-Barré Syndrome (GBS) after PCV13 in adults ≥65 years to VAERS, Aug 2014-Dec 2017

Characteristics	N (%)
Total GBS reports	39
Female / male	17 (44) / 22 (56)
Median age [range] in years	73 [65-89]
Median onset interval [range] in days	11 [0-56]
Viral respiratory illness 2-4 wks prior to onset of GBS symptoms	9 (23)
Met Brighton Collaboration criteria[1] for GBS[2] - Level 1 (16), Level 2 (8), Level 3 (2)	26 (67)
Received PCV13 alone	25 (64)
Received ≥1 co-administered vaccines - High-dose influenza (9), trivalent or quadrivalent inactivated influenza (4), Japanese encephalitis (1), typhoid (1), zoster vaccine live (1)	14 (36)

[1] Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.
[2] Remaining reports (13) had insufficient information to confirm diagnosis and apply Brighton Collaboration criteria for GBS

Reports of anaphylaxis after PCV13 in adults ≥65 years to VAERS, Aug 2014-Dec 2017

Characteristics	N
Total anaphylaxis reports	4
Female / male	3 / 1
Age range	65-94 years
Onset interval range	0-3 days
Received PCV13 alone[1]	3

[1] One case report documented co-administration of PCV13 and high-dose influenza vaccine

- 1 anaphylaxis case report met Brighton Collaboration[2] Level 1 criteria (highest level of diagnostic certainty)
  - 94 year-old female received only PCV13 only and within a "few hours" experienced angioedema, upper airway swelling and respiratory distress
- Remaining 3 case reports had insufficient information to confirm diagnosis and apply Brighton Collaboration criteria for anaphylaxis

[2] Ruggeberg et al. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data Vaccine. 2007 Aug 1;25(31):5675-84

Reports of death after PCV13 in adults ≥65 years to VAERS, Aug 2014-Dec 2017

Characteristics	N (%)
Total reports	26
Female / male	14 (54) / 12 (46)
Verified by autopsy or certificate of death	25 (96)
Median age [range] in years	80 [68-94]
Median time from vaccination to death [range] in days	13 [0-143]
Received PCV13 alone	21 (81)
Received co-administered vaccines High-dose influenza (3), quadrivalent inactivated influenza (1), zoster vaccine live (1)	5 (19)

Causes of death among verified[1] deaths after PCV13 in adults ≥65 years reported to VAERS, Aug 2014-Dec 2017 (n=25)

- Cerebrovascular accident (6)
- Septic shock (5)
- Coronary artery disease (3)
- Chronic obstructive pulmonary disease (3)
- myocardial infarction (1)
- Congestive heart failure (1)
- Colon infarction (1)
- Pulmonary embolism (1)
- Influenza (1)
- Medullary paralysis (1)
- Parkinson's disease (1)
- Cryptococcal meningitis (1)

[1] Verified by autopsy or death certificate

Empirical Bayesian data mining

- Empirical Bayesian data mining did not show any unexpected disproportional reporting for PCV13-MedDRA PT pairings for adults aged ≥65 years old compared to other vaccines[1]

[1] Data provided by FDA/CBER Division of Epidemiology

Summary of VAERS review

- VAERS received 5,822 reports following PCV13 in adults aged ≥65 years during August 1, 2014 through December 31, 2017
  - Most (94%) reports were non-serious
    - Similar to other vaccines given in this age group
  - Most frequently reported adverse events were injection site reactions (i.e., swelling, erythema, and pain) and fever
  - No unexpected data mining findings
  - No new safety signals or unexpected patterns observed
- During the analytic period, approximately 29 million PCV13 doses were distributed for the ≥65 year-old U.S. population[1]

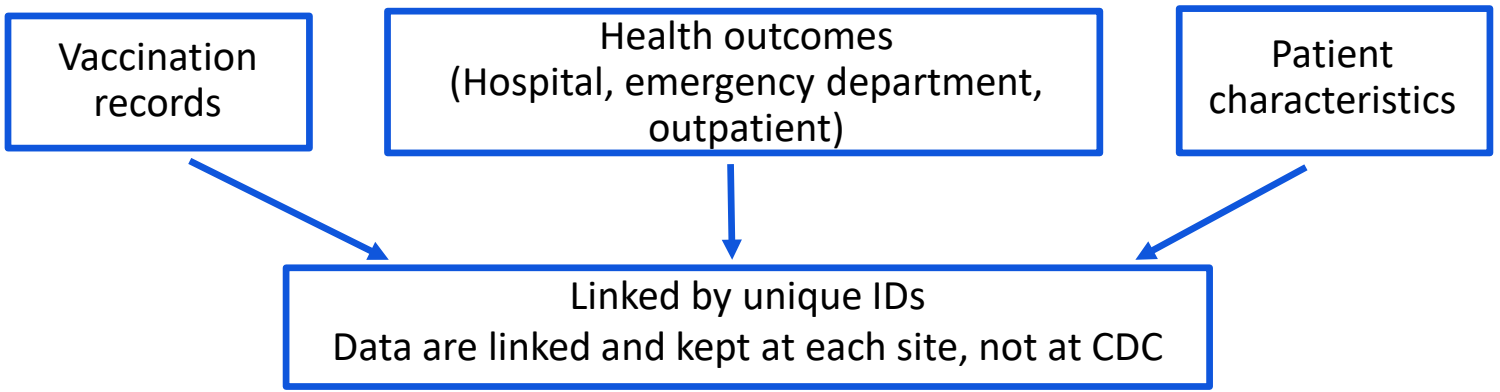
[1] Pfizer, personal communication

Vaccine Safety Datalink (VSD) study[1]

[1] Slides adapted from a previous presentation by Hung Fu Tseng, Kaiser Permanente Southern California/Vaccine Safety Datalink

Vaccine Safety Datalink (VSD)

- Established in 1990
- Collaboration between CDC and several integrated healthcare plans
- Data on over 10 million persons per year (~3% of U.S. population)
- Links vaccination data to health outcome data



Objective of VSD study

- To examine a large cohort of adults aged ≥65 years old for evidence of an increased risk of adverse events (AEs) requiring medical attention following vaccination with PCV13 compared to PPSV23

Methods

- Cohort study
- 6 Vaccine Safety Datalink (VSD) sites
- Study period: January 1, 2011 to September 30, 2015
- “Exposed” doses
  - First dose of PCV13 received by active members aged ≥65 years old during January 1, 2015 to August 15, 2015
- “Unexposed” doses
  - First dose of PSV23 received by active members of the same age group during January 1 to August 15 of each year between 2011 and 2015

Methods (cont.)

- Outcomes included:
  - Cardiovascular events
  - Bell's palsy
  - Guillain-Barré syndrome (GBS)
  - Syncope
  - Erythema multiforme
  - Thrombocytopenia
  - Cellulitis and infection
  - Allergic reaction
  - Anaphylaxis
- Risk windows varied by events, and were censored at membership disenrollment or receipt of another vaccine

Methods (cont.)

- Possible confounders included:
  - Age at vaccination
  - Sex
  - VSD site
  - Healthcare utilization
  - Charlson comorbidity score[1] (predicts one-year mortality)
  - Concomitant vaccination
  - Calendar month

- Analysis included the inverse probability of treatment weighting (IPTW) approach to adjust for the differences between the exposed (PCV13) and the unexposed (PPSV23) that may be associated with the risk of adverse events

[1]Charlson ME et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

Study population / VSD sites

	PPSV23 (N=232,591)	PCV13 (N=313,136)
HMO Site		
NCK	85794 (36.89%)	77382 (24.71%)
KPC	15278 (6.57%)	23875 (7.62%)
MFC	4604 (1.98%)	12645 (4.04%)
NWK	12256 (5.27%)	25063 (8%)
SCK	96227 (41.37%)	160958 (51.4%)
GHC	18432 (7.92%)	13213 (4.22%)

- NCK (Norther California Kaiser Permanente), KPC (Kaiser Permanente Colorado), MFC (Marshfield Clinic), NWK (Northwest Kaiser Permanente), SCK (Southern California Kaiser Permanents), GHC (Group Health Cooperative, now Kaiser Permanente Washington)
- Six subjects with missing or other gender were excluded

Results: RRs for medically attended AE for PCV13 v. PPSV23

Adverse Event (risk window)	PPV23 AE counts (N = 232591)	PCV13 AE counts (N = 313136)	Unadjusted RR	95% Wald Confidence Limits		IPTW Adjusted RR	95% Wald Confidence Limits	
G1. Cardiovascular events (1-42)								
Acute myocardial infarction	375	534	1.05	0.92	1.19	0.73	0.61	0.88
Acute pericarditis	8	6	0.55	0.19	1.59	0.90	0.27	2.94
Atrial fibrillation	430	702	1.20	1.06	1.35	0.67	0.57	0.80
Cardiomyopathy &heart failure	566	838	1.09	0.98	1.21	0.62	0.54	0.72
G2. Bell's Palsy (1-42)	57	69	0.89	0.63	1.26	0.69	0.41	1.15
G3. Guillain-Barre Syndrome (1-42)	8	4	0.37	0.11	1.22	0.21	0.05	0.78
G4. Syncope (day 0)	75	22	0.22	0.14	0.35	0.13	0.07	0.25
G5. Erythema multiforme (1-42)	2	2	0.73	0.10	5.22	0.94	0.13	6.71
G6. Thrombocytopenia (1-28)								
Thrombocytopenia I	21	17	0.60	0.31	1.13	0.66	0.25	1.76
Thrombocytopenia II	100	96	0.71	0.53	0.94	0.44	0.31	0.61
G7. Cellulitis and infection (1-7)	1393	1915	1.02	0.95	1.09	0.89	0.81	0.98
G8. Allergic reaction (1-7)	70	49	0.52	0.36	0.75	0.47	0.30	0.73
G9. Anaphylaxis (0-1)	4	5	0.93	0.25	3.46	1.32	0.30	5.79

All anaphylaxis diagnoses at 0-1 days following vaccination were chart reviewed and one patient receiving 5 vaccines concomitantly, including PCV13, was confirmed as anaphylaxis

Sensitivity analysis

- Sensitivity analysis included:
  - Alternative comparison groups
    - Those received PPSV23 during 2015 (N = 25,536)
    - Those received PPSV23 from 2014 to 2015 (N=77,597)

- Sensitivity analysis did not affect the overall results

Conclusions

- Results of this VSD study of PCV13 safety in adults aged ≥65 years old do not support an increased rate of adverse events (for those adverse events studies) following PCV13 compared to PPSV23
- Findings should provide reassurance regarding continued use of PCV13 in this age group

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Thank you

For more information, contact CDC
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