Update: Pneumonia Vaccination Guidelines

CDC recommendations and a brief review of literature behind them

“Prevention is so much better than healing.”

Rev. Thomas Adams

Epidemiology Review:

- Estimated 13,500 cases of Invasive Pneumococcal Disease (IPD) in adults at least 65 y.o.
- Use of PCV13 in children indirectly reduced pneumococcal infections in adults.
  - IPD from serotypes unique to 13-valent decreased by ~50% since 2010.
- Estimated 20-25% of IPD and 10% of CAP in pts >65 y.o. are due to serotypes covered by PCV13.

Guidelines Prior to Last Month:

- For patients >65:
  - Naïve: single dose of PPSV23
  - PPSV prior to 65
    - Repeat PPSV23 at age 65 (at least 5 years after initial dose).

What is the problem with current strategy?

- PPSV23 is a free polysaccharide vaccine
  - Known there is limited duration of efficacy with this type.
  - Estimated to have duration of efficacy of 3-5 years!
- Observed “blunted” immune response with subsequent PPSV23 immunizations
- Therefore: hypothesis that repeated PPSV23 may not lengthen the duration of protection!

Background: What are the differences in Vaccines?

- PCV13 is a conjugate vaccine
  - Pneumococcal polysaccharide from 13 serotypes are covalently bonded, “conjugated” to nontoxic mutant diptheria toxin.
  - Serotypes: *1,3,4,5*,**6A**, *6B, 7F, 9V, 14, 18C, 19F, 19A, 23F*

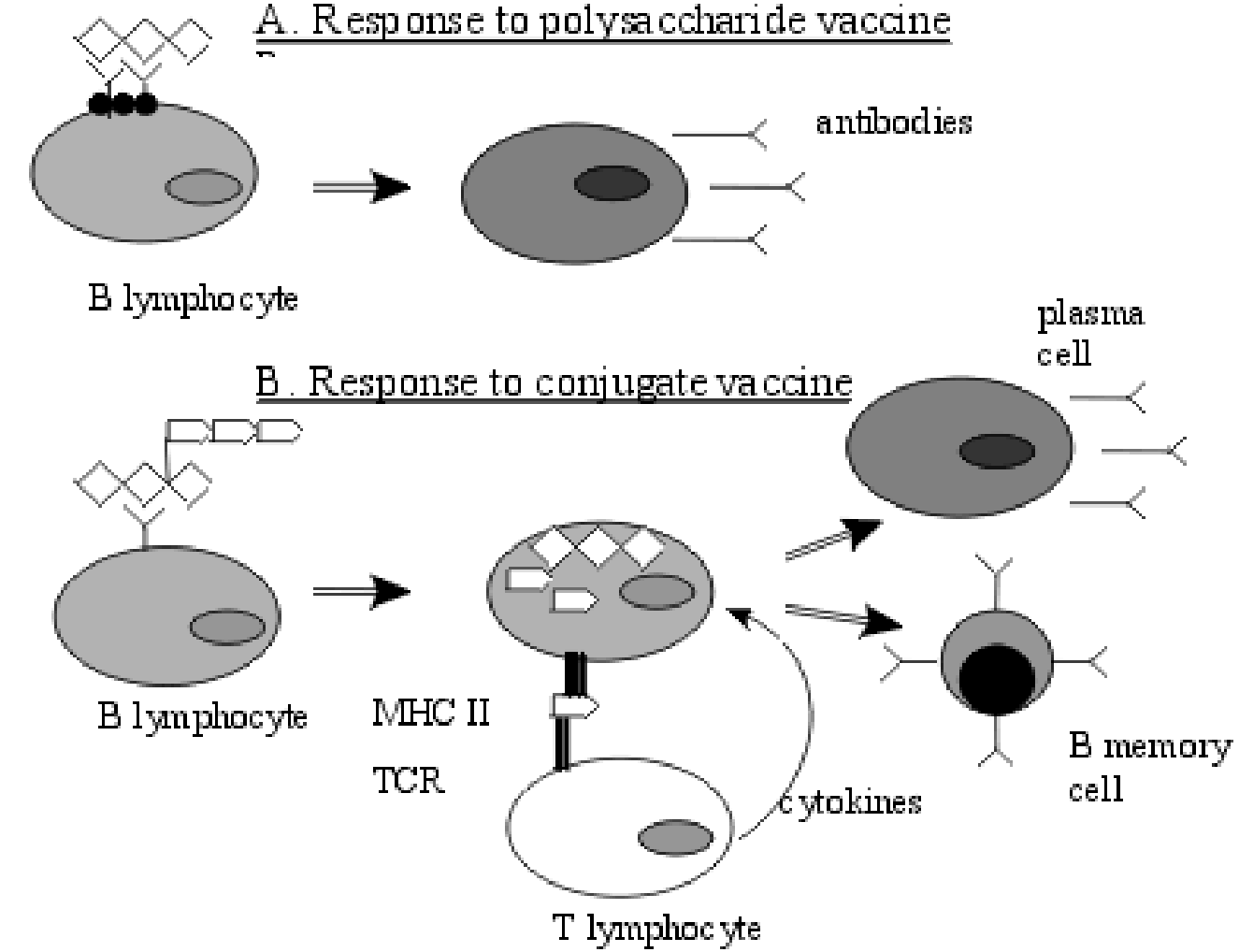
Background: What are the differences in Vaccines?

- PPSV23:
  - Composed of purified capsular polysaccharides from 23 serotypes of pneumococcus
  - Serotypes: ***1***,2,***3,4,5,6B***, ***7F***,8,9N,***9V***,10A,11A,12F, ***14***,15B,17F, ***18C***, ***19F, 19A***,20,22F,***23F***,30

- Note the common serotypes (bold/italics).
- Recall: PCV13 includes serotype 6A (noted as used as outcome measure in studies reviewed later)

Background: Why does it matter?

- Conjugated vaccines:
  - Capsular polysaccharide conjugated to a carrier protein.
  - Converts from ***T-cell independent response to t-cell dependent*** response
  - More robust, longer lasting immune response.
  - Establish “Immune Memory”


A. Response to polysaccharide vaccine
antibodies
B lymphocyte
plasma cell
B. Response to conjugate vaccine
B lymphocyte
MHC II
TCR
cytokines
B memory cell
T lymphocyte
polysaccharide
protein molecule

Background: Evidence for conjugated vaccine (brief):

- Studies in children:
  - Pneumococcal conjugate vaccines (PCV7 and PCV13) effective in protection against invasive pneumococcal disease (IPD).
- Studies in immunocompromised:
  - PCV7 effective protection against vaccine-type IPD in HIV-infected adults.

Evidence (focused review):

- Enhanced immunogenicity of 13-valent when compared to 23-valent among pneumovax naïve (common serotypes). ***"Head to Head"***
- In patients immunized with 23-valent, addition of 13-valent (Booster?) 12 months later significantly more immunogenic than use of 23-valent booster. ***"Vaccine in Series"***

"Head to Head"

Jackson,LA et al. Vaccine 31 (2013) 3577-3584

- Randomized Double-Blind
- N = 831, adults 60-64 years old
  - Had a cohort of age 50-59 who received open label PCV13
- Received: PCV13 or PPSV23
- Outcomes: "anti-pneumococcal opsonophagocytic activity" (OPA) titers
  - 1 month and 1 year after vaccination
- Results: statistically significant OPA titers in 13-valent group.

Table 1
Baseline characteristics.

Characteristic	60–64 Year age group PCV13 *N* = 417	PPSV23 *N* = 414	50–59 Year Age group PCV13 *N* = 403
Female, %	53.5	60.9	61.8
Race, %			
White	96.4	94.2	95.0
Black	1.0	2.2	3.5
Asian	0.7	1.4	1.0
Other	1.0	1.4	0.2
American Indian or Alaska Native	1.0	0.5	0.2
Native Hawaiian or Other Pacific Islander	0	0.2	0
Hispanic or Latino, %	2.2	3.1	2.0
Mean age, years (SD)	61.8 (1.4)	61.7 (1.4)	54.4 (2.9)

"Head to Head" trial: table 2 OPA GMT 1 month after vaccination

Table 2
Comparison of pneumococcal OPA GMTs 1 month after vaccination with PCV13 and PPSV23 in subjects 60–64 years of age and 1 month after PCV13 in subjects 50–59 years of age.

Serotype	60–64 Year age group		Vaccine comparison (PCV13 vs PPV23)		50–59 Year age group	Group comparison (50–59 yr/60–64 yr)	
	PCV13 n^a = 359–404	PPSV23 n^a = 367–402			PCV13 n^a = 350–384		
	GMT[b]	GMT[b]	Ratio[c]	(95% CI[d])	GMT[b]	Ratio[e]	(95% CI[f])
1	146	104	1.4	(1.10, 1.78)	200	1.4	(1.08, 1.73)
3	93	85	1.1	(0.90, 1.32)	91	1.0	(0.81, 1.19)
4	2062	1295	1.6	(1.19, 2.13)	2833	1.4	(1.07, 1.77)
5	199	162	1.2	(0.93, 1.62)	269	1.4	(1.01, 1.80)
6B	1984	788	2.5	(1.82, 3.48)	3212	1.6	(1.24, 2.12)
7F	1120	405	2.8	(1.98, 3.87)	1520	1.4	(1.03, 1.79)
9V	1164	407	2.9	(2.00, 4.08)	1726	1.5	(1.11, 1.98)
14	612	692	0.9	(0.64, 1.21)	957	1.6	(1.16, 2.12)
18C	1726	925	1.9	(1.39, 2.51)	1939	1.1	(0.86, 1.47)
19A	682	352	1.9	(1.56, 2.41)	956	1.4	(1.16, 1.69)
19F	517	539	1.0	(0.72, 1.28)	599	1.2	(0.87, 1.54)
23F	375	72	5.2	(3.67, 7.33)	494	1.3	(0.94, 1.84)
6A	2593	213	12.1	(8.63, 17.08)	4328	1.7	(1.30, 2.15)

[a] n = Number of subjects with a determinate OPA titer to the given serotype.
[b] GMTs were calculated using all evaluable subjects with available data for the specified blood draw.
[c] Ratio of GMTs PCV13 to PPSV23 is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.
[d] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13–PPSV23).
[e] Ratio of GMTs, 50–59 years to 60–64 years, is calculated by back transforming the mean difference between vaccine cohorts on the logarithmic scale.
[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (50–59 years–60–64 years).

Non-inferiority of PCV13 relative to PPSV23: lower limit of 95% CI for GMR (Ratio) > 0.5 (met by all common serotypes!)

Statistically significant if lower limit of of 95% CI > 1.0 (>2.0 for 6A) (met in 8 of 12 common serotypes)

Adverse events and side effects:

- Severe Pain at injection site:
  - Significantly higher in PPSV23 group ($p = 0.003$)
- Mild pain at injection site:
  - Significantly higher in PCV13 group ($p = 0.005$)
- 50-59 y.o. group reported more pain and limitation to arm movement with PCV13 than in older group.
- All adverse effects similar
  - 16.7% for PPSV23 vs. 17% PCV13.
- No deaths attributed to vaccines.

“Vaccine In Series”

Jackson, LA et al Vaccine 31 (2013) 3585-3593

- Randomized double blind
- N = 936 adults > 70 years old with PPSV23 < 5yrs
- Randomized to PCV13 or 23-valent at year 0.
- All received PCV13 at year 1
- Results:
  - OPA titers higher in the PCV13 group (10/12 common serotypes).
  - Pts receiving PPSV23 at enrollment had less response than PCV13 patients.

“Vaccine in Series”: table 1

Table 1
Baseline characteristics.

Characteristic	PCV13 N = 463	PPSV23 N = 473
Female (%)	47.7	49.7
Race (%)		
White	95.9	96.0
Black	2.6	2.1
Asian	0.6	1.7
Other	0.4	0
American Indian or Alaska Native	0.2	0.2
Native Hawaiian or Other Pacific Islander	0.2	0
Hispanic or Latino	0.6	1.1
Any chronic underlying diseases (%)	36.9	48.4
Cardiovascular disease	18.4	21.8
Liver diseases	0.9	0.4
Pulmonary diseases	13.0	9.5
Diabetes mellitus	15.3	16.1
Renal and urinary disorders	5.2	3.6
Mean age (years (SD))	76.7 (4.6)	76.7 (4.5)
Range (years)	70.1 (95.5)	70.0 (94.7)
70–74 years (%)	42.5	43.6
75–79 years (%)	33.7	33.4
≥80 years (%)	23.8	23.0

Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SD, standard deviation.

Table 2
Comparison of pneumococcal OPA GMTs 1 month after PCV13 vs. PPSV23 given at year 0.

Serotype	PCV13 vs. PPSV23			
	PCV13 n^a = 400–426	PPSV23 n^a = 395–445	Vaccine comparison	
	GMT[b]	GMT[b]	GMT ratio[c]	(95% CI[d])
1	**81**	**55**	**1.5**	**(1.17, 1.88)**
3	55	49	1.1	(0.91, 1.35)
4	**545**	**203**	**2.7**	**(1.93, 3.74)**
5	**72**	**36**	**2.0**	**(1.55, 2.63)**
6B	**1261**	**417**	**3.0**	**(2.21, 4.13)**
7F	**245**	**160**	**1.5**	**(1.07, 2.18)**
9V	**181**	**90**	**2.0**	**(1.36, 2.97)**
14	280	285	1.0	(0.73, 1.33)
18C	**907**	**481**	**1.9**	**(1.42, 2.50)**
19A	**354**	**200**	**1.8**	**(1.43, 2.20)**
19F	**333**	**214**	**1.6**	**(1.17, 2.06)**
23F	**158**	**43**	**3.7**	**(2.69, 5.09)**
6A	**903**	**94**	**9.6**	**(7.00, 13.26)**

Serotypes in bold demonstrated a statistically significantly greater OPA response in PCV13 recipients compared with PPSV23 recipients.

[a] n = Number of subjects with a determinate OPA antibody titer to the given serotype.

[b] GMTs were calculated using all evaluable subjects with available data for both the specified blood draw.

[c] Ratio of GMTs (PCV13 to PPSV23) is calculated by back transforming the mean difference between vaccine groups on the logarithmic scale.

[d] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (PCV13–PPSV23).

- After year-zero vaccination:
  - PCV13 with statistically significant greater immunogenicity vs. PPSV23 for 10 of 12 common serotypes.

Definition of outcomes:

- Non-inferiority if lower limit of 95% CI > 0.5.
- ***Statistically significant higher response if lower limit of 95% CI >1***
- Statistically significant lower response if upper limit of 95% CI < 1

Table 4
Comparison of pneumococcal OPA GMTs 1 month after PPSV23/PCV13 (year 1) vs. PCV13 (year 0) and PCV13/PCV13 (year 1) vs. PPSV23/PCV13 (year 1).

Serotype	PPSV23/PCV13 vs. PCV13			PCV13/PCV13 vs. PPSV23/PCV13		
	PPSV23/PCV13 n^a = 338–367 GMT[b]	PCV13 n^a = 400–426 GMT[b]	Vaccine comparison GMT ratio[c] (95% CI[d])	PCV13/PCV13 n^a = 347–370 GMT[b]	PPSV23/PCV13 n^a = 338–367 GMT[b]	Vaccine comparison GMT ratio[c] (95% CI[d])
1	*34*	*81*	*0.4 (0.33, 0.54)*	**76**	**34**	**2.2 (1.74, 2.82)**
3	*33*	*55*	*0.6 (0.49, 0.74)*	**55**	**33**	**1.7 (1.36, 2.03)**
4	*267*	*545*	*0.5 (0.36, 0.67)*	**472**	**267**	**1.8 (1.29, 2.42)**
5	*42*	*72*	*0.6 (0.44, 0.76)*	**56**	**42**	**1.4 (1.03, 1.79)**
6B	*721*	*1261*	*0.6 (0.42, 0.78)*	**1565**	**721**	**2.2 (1.61, 2.94)**
7F	*120*	*245*	*0.5 (0.34, 0.71)*	**185**	**120**	**1.5 (1.05, 2.24)**
9V	*72*	*181*	*0.4 (0.27, 0.59)*	**158**	**72**	**2.2 (1.47, 3.32)**
14	*194*	*280*	*0.7 (0.51, 0.95)*	238	194	1.2 (0.89, 1.68)
18C	*513*	*907*	*0.6 (0.43, 0.74)*	**975**	**513**	**1.9 (1.45, 2.49)**
19A	*248*	*354*	*0.7 (0.56, 0.86)*	**339**	**248**	**1.4 (1.11, 1.68)**
19F	*180*	*333*	*0.5 (0.40, 0.72)*	**311**	**180**	**1.7 (1.30, 2.30)**
23F	*87*	*158*	*0.6 (0.39, 0.78)*	**310**	**87**	**3.6 (2.57, 4.93)**
6A	*549*	*903*	*0.6 (0.44, 0.83)*	**1134**	**549**	**2.1 (1.54, 2.77)**

Serotypes in italics demonstrated a statistically significantly lower OPA response following PCV13 administered after PPSV23 compared to the initial PCV13 administration.
Serotypes in bold demonstrated a statistically significantly greater OPA response following 2 administrations of PCV13 compared to PCV13 given after PPSV23.

[a] n = Number of subjects with a determinate OPA antibody titer to the given serotype.
[b] GMTs were calculated using all evaluable subjects with available data for both the specified blood draws.
[c] Ratio of GMTs is calculated by back transforming the mean difference between vaccine group/sequence on the logarithmic scale.
[d] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures.

- For PPSV23 before PCV13 OPA GMT significantly lower than PCV13 at year zero (Left table).
- If got PCV13 at year 0 and year 1 then significantly greater OPA GMT for 12 of 13 serotypes (Right table)
- Recall: all patients in this study received PPSV23 at most 5 years before enrollment
  - Left table demonstrates “blunted response.” Suggests better immunogenicity with PCV13.

Adverse events and safety

- Significantly higher proportion of subjects vaccinated with PPSV23 with local injection reactions.
- No significant difference in either group for local infections with year 1 PCV13 vaccination
- PPSV23 group with significantly increased:
  - Fatigue, rash, new/aggravated generalized muscle weakness.
- Significantly higher vomiting in the PPSV23/PCV13 group vs. PCV13/PCV13.

Coming Down The Pike

- Evidence the PCV13 is sufficient?
  - CAPiTA trial
    - Aim to demonstrate prevention of 1st CAP with PCV13 vaccine
    - N = 84,000 Netherlands residents > 65 y.o.
    - 1:1 randomization to PCV13 or PLACEBO
    - Presented at ACIP 2014 (I was unable to find the results and not specifically quoted in the CDC guideline paper).

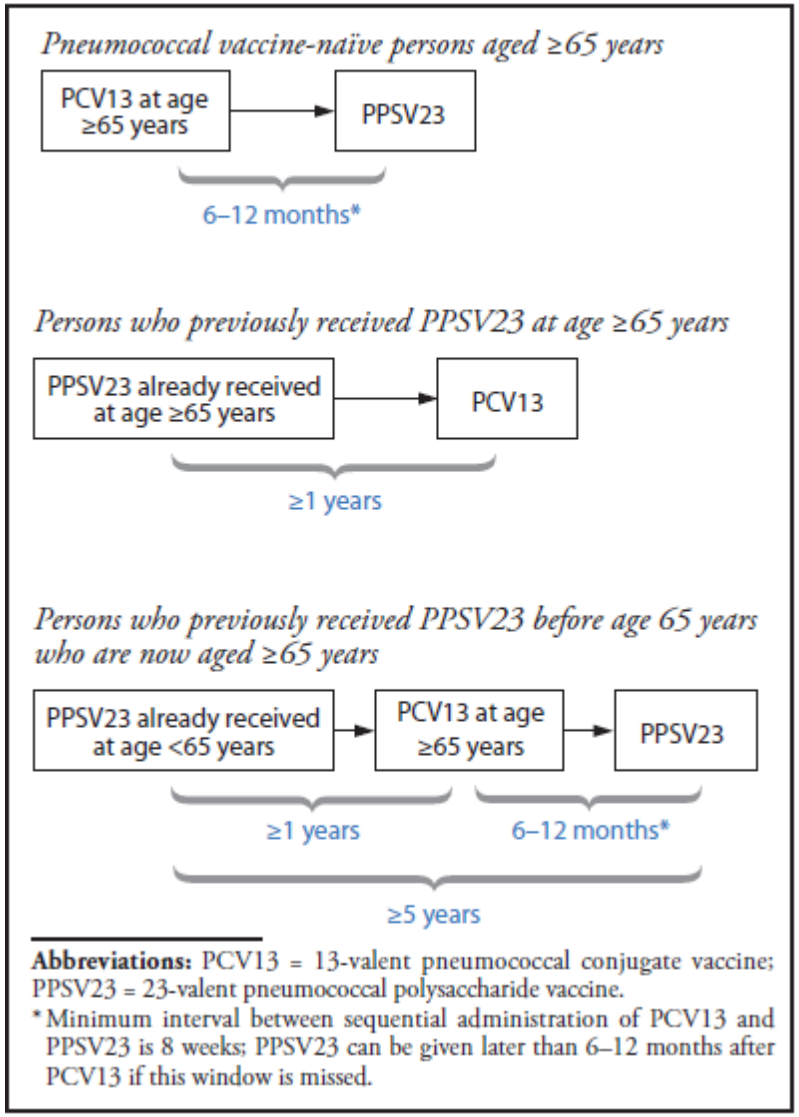
Conclusions:

- Invasive pneumococcal disease remains significant threat to morbidity and mortality.
- PPSV23 with decreasing effectiveness after 3-5 years.
- Conjugated vaccine have hypothetical benefits.
- PCV13 alone appears to be significantly more immunogenic than PPSV23
- Series vaccination of PCV13 after PPSV23 appears to be safe and effective means of increasing immunogenicity

New guidelines for patients >65:

- Pts with PPSV23 vaccine >65: administer 13 valent at least 1 year after PPSV23.
- Naïve patients: recommend initial PCV13 at age 65 then PPSV23 within 6-12 months
- Pt received PPSV23 prior to age 65 and now >65 y.o.: administer PCV13 followed by PPSV23 in 6-12 months.

BOX. Sequential administration and recommended intervals for PCV13 and PPSV23 for adults aged ≥65 years — Advisory Committee on Immunization Practices, United States



Abbreviations: PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

* Minimum interval between sequential administration of PCV13 and PPSV23 is 8 weeks; PPSV23 can be given later than 6–12 months after PCV13 if this window is missed.

Thank you

References available on request