13-valent Pneumococcal Conjugate Vaccine Use in Children 6 through 18 Years of Age with Immunocompromising Conditions: GRADE of Evidence

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Advisory Committee on Immunization Practices
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Policy question considered by Pneumococcal Working Group:

Should ACIP make a routine recommendation for PCV13 use among immunocompromised PCV13-naïve children 6 through 18 years of age?

Pneumococcal Working Group considerations for PCV13 for immunocompromised children 6 through 18 years old

- Existing recommendations for children & adults
- Burden of disease among different risk groups
- Proportion of cases of invasive pneumococcal disease (IPD) caused by serotypes in PCV13 and PPV23
- GRADE of evidence
  - Efficacy & effectiveness
  - Immunogenicity
  - Safety

ACIP Recommendations for PCV13 use in High Risk Children and Adolescents

- Routinely recommended for high risk children 6 weeks through 71 months of age
- 1 dose of PCV13 **may be** given to children aged 6-18 years
  - Anatomic or functional asplenia (sickle cell)
  - Cochlear implant, CSF leaks
  - 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

Category B, off-label

- Children with underlying medical conditions should receive PPV23 after PCV13
  - 1 dose of PPV23 at age ≥2 years
  - PPV23 at least 8 weeks after PCV13

- **MMWR Dec 2010**

ACIP Recommendations for PCV13 use in High Risk Adults

- Routinely recommended for PCV13-naïve adults 19 years of age or older
  - Anatomic or functional asplenia, (sickle cell)
  - Cochlear implant, CSF leaks
  - Immunocompromised (e.g. HIV, nephrotic syndrome)
- PPSV23-naïve adults
  - 1 dose of PCV13
  - PPV23 at least 8 weeks after PCV13
- Adults who have received PPV23 previously
  - 1 dose of PCV13 at least one year after PPSV23
  - If additional PPSV23 doses needed, at least 8 weeks after PCV13 dose and at least 5 years after previous PPSV23 dose

Category A

- **MMWR Oct 2012**

Rationale for Routine PCV13 Use in High Risk Children and Adolescents

- On January 25, 2013, FDA approved PCV13 for all children 6 through 17 years of age
- Children with immunocompromising conditions: small proportion of the population with very high risk of disease
- May provide protection in addition to recommended PPSV23
- Routine recommendation may improve vaccine uptake in these high-risk populations
- Harmonize the language with PCV13 recommendations for high risk adults (Category A)

GRADE Process Followed by the Work Group

1. Formulate specific policy question
2. Identify & rank relative importance of outcomes
3. Summarize all evidence for critical & important outcomes including NNV, where possible
4. Assess quality of evidence for each outcome
5. Summarize quality of evidence across outcomes
6. Review health economic data
7. Assess the balance of risks & benefits
8. Determine the recommendation category

Step 1. Formulate specific policy question

"Should PCV13 be administered routinely to children 6 through 18 years old with immunocompromising conditions?"

- Population: PCV13-naïve children 6-18 years-old with immunocompromising conditions, functional or anatomic asplenia (including sickle cell disease), CSF leaks, or cochlear implants
- Intervention: Pneumococcal conjugate vaccine (PCV13) administered as a single dose injection
- Control: Placebo
- Outcomes: See Step 2

Step 2: Critical & Important Outcomes Identified by the Pneumococcal Work Group

Outcome	Importance	Include in Evidence Profile?	Data available?
Invasive disease*	Critical	Yes	Yes
Pneumonia (non-bacteremic)	Critical	Yes	Yes
Hospitalizations	Critical	Yes	No
Deaths	Critical	Yes	Yes
Immunogenicity	Critical	Yes	Yes
Serious adverse events	Critical	Yes	Yes
Systemic adverse events	Critical	Yes	Yes
Office visits	Important	No	
Local reactions	Important	No	
Cost-effectiveness	Important	No	

*Sterile site isolation

GRADE Process Followed by the Work Group

1. Formulate specific policy question
2. Identify & rank relative importance of outcomes
3. **Summarize all evidence for critical outcomes including NNV, where possible**
4. **Assess quality of evidence for each outcome**
5. Summarize quality of evidence across outcomes
6. Review health economic data
7. Assess the balance of risks & benefits
8. Determine the recommendation category

Step 3: Critical Outcome: Invasive Pneumococcal Disease (IPD)

- Efficacy trial among HIV-infected adults ≥15 years of age in Malawi
- Double-blind, randomized, placebo-controlled
- IPD = isolation of pneumococcus from a normally sterile site
- All enrolled subjects (n=496) had recovered from documented IPD
  2 doses of PCV7 given 4 weeks apart

Endpoint	Vaccine Efficacy (95% CI)
PCV7-serotype IPD	**74**% (30%--90%)

French N, et.al. *N Engl J Med* 2010;362:812-22.

Step 3: Critical Outcome: Invasive Pneumococcal Disease (IPD)

- Double-blind, randomized, placebo-controlled
- Efficacy trial among HIV-infected and HIV-uninfected children in South Africa
- IPD = isolation of pneumococcus from a normally sterile site
- PCV9 at 6, 10, and 14 weeks of age (n=19,922) or placebo (n=19,914)

Endpoint	Vaccine Efficacy (95% CI)
PCV9-serotype IPD	**65**% (24%--86%)*

*VE among children with HIV-infection

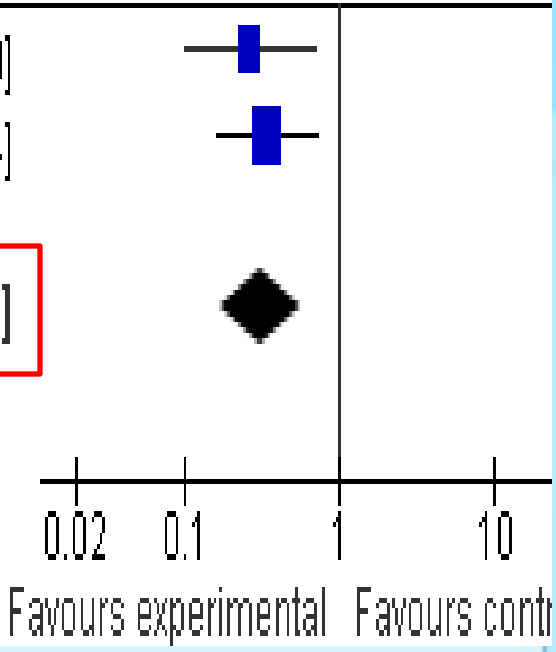
Klugman, K et.al. *N Engl J Med* 2003

Step 3: Critical Outcome: Invasive Pneumococcal Disease (IPD)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
French	5	248	19	248	42.2%	0.26 [0.10, 0.69]
Klugman	9	19922	26	19914	57.8%	0.35 [0.16, 0.74]
Total (95% CI)		20170		20162	100.0%	0.31 [0.17, 0.56]
Total events	14		45			

Heterogeneity: $Chi^2 = 0.19$, $df = 1$ ($P = 0.66$); $I^2 = 0\%$

Test for overall effect: $Z = 3.84$ ($P = 0.0001$)



French N, et.al. *N Engl J Med* 2010
Klugman, K et.al. *N Engl J Med* 2003

What effect might we expect among HIV-infected children 6-18 years old in the U.S.*?*

Number-Needed-to Vaccinate=

$1 / (Rate_{unvaccinated} - Rate_{vaccinated})$

- $Rate_{unvaccinated}$ = 1,265 cases per 100,000[1]
- Efficacy PCV13-type IPD = **69**% (44%--83%)[2]
- $Rate_{vaccinated}$ = 392 per 100,000 (215--708)

NNV = 115 (95--180)

[1]Incidence of PCV13 type IPD among children <19 years with HIV/AIDS in the US, CDC unpublished data 2009

[2]Summary VE estimate from 2 RCTs: Klugman 2003 and French 2010

Step 3: Critical Outcome: Invasive Pneumococcal Disease (IPD)

- Observational population-based study assessing the effect of PCV7 on IPD among children with sickle cell disease
- PCV7 histories linked to IPD data for n=1257 children ≤10 years old with confirmed hemoglobinopathies
- Stratified survival analysis to estimate PCV7 effect on IPD rates while accounting for herd immunity
- VE for ≥1 dose of PCV7 was estimated to be **81.4% (19-96%)** controlling for the presence of herd immunity in the 2 years after PCV7 licensure

Adamkiewicz et al. *Pediatrics* 2008

Step 4. Quality of Evidence for Invasive Pneumococcal Disease

Outcome	Design (# studies)	Risk of bias	Inconsis-tency	Indirectness	Impreci-sion	Quality of Evidence
IPD	RCT (2)	No serious	N/A	Very serious	No serious	**3**
IPD	Observational (1)	No serious	N/A	No serious	No serious	**3**

Indirectness due to

1) different population (Malawi, adults, IPD survivors, limited ARVs[1] or South Africa, infants[2])
2) different intervention (PCV7, 2 doses or PCV9, 3 doses)

[1]French N, et.al. *N Engl J Med* 2010
[2]Klugman, K et.al. *N Engl J Med* 2003
[3]Adamkiewicz et al. *Pediatrics* 2008

Step 3: Critical Outcome: Pneumonia and Death

- Double-blind, randomized, placebo-controlled
- Efficacy trial among HIV-infected and HIV-uninfected children in South Africa
- Pneumonia = radiologically-confirmed alveolar consolidation (WHO definition)
- PCV9 at 6, 10, and 14 weeks of age (n=19,922) or placebo (n=19,914)

Endpoint	Vaccine Efficacy (95% CI)
Radiologically-confirmed pneumonia	**13**% (-7%--29%)[1]
All-cause mortality	**6**% (P=0.63) [1,2]
Mortality attributable to pneumonia	4% (P=0.73) [3]

[1]VE among children with HIV-infection
[2]166 deaths among vaccine recipients and 176 among controls;
[3]153 deaths in the vaccinated group and 160 in the control group

Klugman, K et.al. *N Engl J Med* 2003

Step 4. Quality of Evidence for Pneumonia and Death

Outcome	Design (# studies)	Risk of bias	Inconsis-tency	Indirectness	Impreci-sion	Quality of Evidence
Pneumo nia	RCT (1)	No serious	N/A	Very serious	No serious	**3**
Death	RCT (1)	No serious	N/A	Very serious	No serious	**3**

Indirectness due to

1) different population (South Africa, infants[1])
2) different intervention (PCV9, 3 doses)

[1]Klugman, K et.al. *N Engl J Med* 2003

Step 3: Immunogenicity: Phase III

- Safety and immunogenicity of PCV13 in subjects with SCD previously immunized with PPSV23 (>6 months prior)
- Diagnosis of SCD by hemoglobin (Hb) electrophoresis or PCR: HbSS, HbSC, HbSD, HbSE, and HbSβ-thal
- Open-label, single-arm study in children 6 through 17 years of age (N=158) who received 2 doses of PCV13 given 6 months apart
- Serotype-specific IgG concentrations and OPA titers measured prior to and 28-42 days after each dose

Courtesy of Pfizer; Protocol 6096A1-3014-WW (B1851013)

Step 3: Immunogenicity: Phase III, OPA

	Before Dose 1		After Dose 1			
Serotype	GMT	(95% CI)	GMT	(95% CI)	GMFR	(95% CI)
PCV7						
4	255	(150.5, 432.4)	2637	(2046.8, 3398.5)	10.3	(6.13, 17.44)
6B	684	(405.9, 1153.3)	7643	(6238.1, 9363.9)	11.2	(6.60, 18.91)
9V	299	(167.2, 533.6)	2391	(1691.3, 3380.8)	8.0	(4.49, 14.25)
14	649	(431.8, 976.5)	2248	(1841.7, 2744.5)	3.5	(2.31, 5.19)
18C	486	(261.0, 903.3)	3996	(2779.4, 5744.9)	8.2	(4.48, 15.13)
19F	82	(44.4, 151.9)	1460	(1030.7, 2069.2)	17.8	(9.90, 31.92)
23F	38	(22.6, 63.6)	1527	(1121.2, 2080.1)	40.3	(22.85, 70.99)
Non PCV7						
1	7	(5.4, 8.4)	53	(38.4, 74.3)	7.9	(5.64, 11.11)
3	14	(10.5, 19.0)	114	(90.4, 143.7)	8.1	(5.92, 11.07)
5	11	(7.8, 14.3)	274	(194.5, 386.0)	26.1	(17.03, 39.85)
6A	251	(146.8, 430.1)	7371	(6065.7, 8956.1)	29.3	(16.99, 50.61)
7F	367	(230.7, 584.2)	3305	(2828.6, 3861.7)	9.0	(5.51, 14.70)
19A	140	(99.8, 197.2)	1489	(1179.9, 1879.4)	10.6	(7.38, 15.25)

Courtesy of Pfizer; Protocol 6096A1-3014-WW (B1851013)

Step 3: Immunogenicity: Phase III, ELISA

	Before Dose 1		After Dose 1			
Serotype	GMC	(95% CI)	GMC	(95% CI)	GMFR	(95% CI)
PCV7						
4	1.01	(0.80, 1.27)	6.97	(5.65, 8.60)	6.91	(5.27, 9.06)
6B	5.78	(4.87, 6.86)	27.25	(22.09, 33.61)	4.72	(3.80, 5.85)
9V	3.01	(2.56, 3.53)	9.31	(7.83, 11.07)	3.10	(2.60, 3.70)
14	6.30	(4.78, 8.30)	34.63	(27.77, 43.18)	5.50	(4.05, 7.46)
18C	1.40	(1.14, 1.73)	7.83	(6.41, 9.56)	5.58	(4.47, 6.97)
19F	4.46	(3.60, 5.53)	21.26	(16.65, 27.14)	4.76	(3.77, 6.03)
23F	2.77	(2.35, 3.27)	18.25	(14.52, 22.95)	6.58	(5.12, 8.46)
Non PCV7						
1	1.57	(1.26, 1.95)	5.64	(4.61, 6.90)	3.60	(2.90, 4.46)
3	1.02	(0.83, 1.25)	2.06	(1.77, 2.41)	2.03	(1.78, 2.31)
5	4.14	(3.58, 4.78)	7.19	(6.19, 8.35)	1.74	(1.56, 1.94)
6A	4.62	(3.91, 5.46)	18.93	(15.22, 23.56)	4.10	(3.32, 5.05)
7F	2.16	(1.80, 2.59)	9.46	(8.17, 10.96)	4.38	(3.62, 5.30)
19A	8.16	(7.03, 9.48)	26.82	(22.16, 32.46)	3.28	(2.73, 3.96)

Courtesy of Pfizer; Protocol 6096A1-3014-WW (B1851013)

Step 3: Immunogenicity in HIV+

- Published studies in HIV-infected adults and children included
  - 2 RCTs in infants (4-dose PCV7 or 3-dose PCV9)
  - pre/post study in PPSV pre-immunized 2-18 year old, 2-dose PCV7
  - 4 RCTs among adults; CD4 $\geq$200; comparisons to PPSV23
- PCV does elicit an immune response in HIV-infected children and adults
- Significantly higher response in PCV arm vs. placebo
- Response following a single dose of PCV is as good or better than PPV23 (both in vaccine naive or previously vaccinated adults)

Step 4. Quality of Evidence for Immunogenicity

Outcome	Design (# studies)	Indirectness	Other considerations	Quality of Evidence
Immuno-genicity	PCV7 RCT HIV+ Adults (4) and children (2)	Very serious	No serious	3
	Pre/post (2) SCD children (PCV13) and HIV+ children (PCV7)	No Serious	No Serious	3

Indirectness due to different population (adults) and different intervention (PCV7 or PCV9)

Step 3. Critical outcome: Safety

- Published studies in HIV-infected adults and children included
  - 2 RCTs in infants (4-dose PCV7 or 3-dose PCV9)
  - 3 RCTs among adults; CD4 $\geq$200; comparisons to PPSV23
- No serious adverse events reported
- Mild, self-limited secondary effects
- Severe induration, erythema, fever, limited leg movement
- No significant differences in systemic adverse events reported in PCV vs. control arm

Step 3. Critical outcome: Safety

Study Description	Outcomes (within 7 days of dose 1)	Proportion in PCV13 vaccinated
PCV13 Phase III pre/post study; 2 doses of PCV13; 6 to 18 years old with SCD*	Vomiting (any) Diarrhea (any) Headache (any) Fatigue (any) Muscle pain (any) Joint pain (any) Fever ≥38.0°C	15.4% 13.3% 53.6% 66.1% 74.8% 39.8% 26.0%

- Severe systemic events reported by more than 10% of subjects after dose 1 included headache (11 subjects, 12.0%), fatigue (13 subjects, 14.4%), and muscle pain (9 subjects, 10.1%)
- After dose 1, 13 (8.2%) subjects reported severe AEs. The most frequently reported severe AEs were sickle cell anemia with crisis (7 subjects [4.4%]), acute chest syndrome (2 subjects) and pyrexia (2 subjects)
- No life-threatening AEs were reported during the study period

***Courtesy of Pfizer,** Safety and Immunogenicity of Prevnar 13 in Children with Sickle Cell Disease (SCD) Previously Immunized with PPSV23

Step 4. Quality of Evidence for Serious and Systemic Adverse Events

Outcome	Design (# studies)	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Quality of Evidence
Serious & systemic adverse events	RCT (5) Pre/post (1)	No serious	No serious	Very serious None	No serious	**3**

Indirectness due to different intervention (PCV7, PCV9)

Step 5. Summarize quality of evidence across outcomes

Outcome	Study Design	Findings	Quality of Evidence	Overall Quality of Evidence
IPD	RCT (2)	Decreased risk among vaccinated	3	3
Pneumonia	RCT (1)	Decreased risk (non-significant) among vaccinated	3	
Death	RCT (1)	No change in outcome	3	
Antibody response to vaccine types	Pre/post (2); RCT (7)	Increases in antibody titers post-vaccination	3	
SAE	Pre/post RCT (5)	No serious adverse events	3	

Step 6. Review health economic data

- **Cost effectiveness evaluated for adults with immunocompromising conditions (June 2012 ACIP)**
- **CEA indicated PCV13 immunization is cost-saving for four selected sub-populations evaluated in the model**
- **CEA not evaluated for children 6 through 18 years old**
  - Relatively small population of very high-risk individuals
  - Recommendation has a time-limited utility (PCV13-naïve persons only)

Step 7. Assess the balance of risks & benefits
Step 8. Determine Recommendation Category

Question	Response	
Is the evidence level/quality "Lower"?	**Yes**	Indirectness of evidence in RCTs; evidence from observational studies
Is there uncertainty about the balance of benefits versus harms & burdens?	**No**	Very high burden of disease in immunocompromised
Is there variability or uncertainty in what is important?	**No**	WG Consensus on critical outcomes
Is there uncertainty about whether the net benefits are worth the costs?	**Yes**	Uncertainty regarding key inputs needed for the cost-effectiveness analysis

Conclusions from the Pneumococcal Working Group

- Extremely high burden of disease among immunocompromised children 6 through 18 years old
- GRADE process led to conclusion that PCV13 is likely effective in this group & that benefits likely outweigh harms
- No additional data expected to influence GRADE conclusions for immunocompromised group
- Indirect effects of PCV13 use in children unlikely to eliminate PCV13 serotypes from immunocompromised persons

WG Decision: Benefits likely outweigh harms and PCV13 should be routinely recommended for PCV13-naïve children 6-18 years old with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants
(Category A, evidence type 3)

Acknowledgements

ACIP members

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Recommendations for Pneumococcal Vaccine use among Immunocompromised Children 6 through 18 years of age

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Respiratory Diseases Branch,

National Center for Immunizations and Respiratory Diseases

Advisory Committee on Immunization Practices

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Proposed indications for PCV13

- PCV13-naïve children 6 through 18 years of age
  - Anatomic or functional asplenia (including sickle cell disease)
  - 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
  - Cochlear implant, CSF leaks

Prevention of pneumococcal disease among children 6 through 18 years old with immunocompromising conditions

- A single dose of PCV13 is recommended for children aged 6–18 years who have not received PCV13 previously and who are at increased risk for invasive pneumococcal disease because of anatomic or functional asplenia, including sickle cell disease, immunocompromising conditions such as HIV-infection, cochlear implant, or cerebrospinal fluid leaks, regardless of whether they have previously received PCV7 or PPSV23.
- Recommendations for PPSV23 use for children in this age group remain unchanged

Recommendation for PCV13 and PPSV23

- **PPSV23-naïve children:**
  - PCV13 dose is recommended to be given before PPSV23, whenever possible
  - PPSV23 should be given **at least 8 weeks** after a dose of PCV13 (MMWR 2010)
  - Recommendations for 2nd dose of PPSV remain unchanged (MMWR 2010)
- **PPSV23-immunized children**
  - A dose of PCV13 should be given **at least 8 weeks** after the PPSV23 dose (MMWR 2010)
  - Total number and interval between PPSV23 doses unchanged from existing recommendations (MMWR 2010)

Current ACIP Recommendations for PPSV23 use Among High-Risk Children Aged 2–18 Years

Administration of PPSV23 After PCV13 Among Children Aged 2–18 Years Who Are at Increased Risk for Pneumococcal Disease

- Children aged ≥2 years with underlying medical conditions should receive PPSV23 after completing all recommended doses of PCV13. These children should be administered 1 dose of PPSV23 at age ≥2 years and at least 8 weeks after the most recent dose of PCV13
- Children who have received PPSV23 previously also should receive recommended PCV13 doses

Revaccination With PPSV23 Among Children at Highest Risk

- A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23 for children who have anatomic or functional asplenia, including SCD, HIV infection, or other immunocompromising condition. No more than 2 PPSV23 doses are recommended

MMWR 2010

ACIP vote

ACIP vote

Recommendation for PCV13-naïve children 6 through 18 years of age

On the basis of the presented information, the WG proposes the following recommendation for a vote

Proposed language:

"We recommend that children 6 through 18 years of age with immunocompromising conditions , functional or anatomic asplenia , CSF leaks or cochlear implants, and who have not previously received PCV13 receive a single dose of PCV13, regardless of whether they have previously received PCV7 or PPSV23"