Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) of Pneumococcal Vaccines for Immunocompromised Children Aged 6 through 18 Years

Methods: GRADE was used to evaluate 13-valent Pneumococcal Conjugate Vaccine (PCV13) for routine use among immunocompromised children aged 6 through 18 years.

Evidence of benefits, harms, values and preferences, and cost-effectiveness were reviewed in accordance with GRADE methods.[1] The primary policy question was "Should PCV13 be administered routinely to children aged 6 through 18 years with immunocompromising conditions?" Due to the limited body of evidence on vaccine efficacy and safety among persons with most immunocompromising conditions and varying formulations of pneumococcal conjugate vaccines (PCV), 7-,9-, and 13-valent PCVs were evaluated using data for HIV-infected adults and children, and children with sickle cell disease. Studies with PCV7 and PCV9 were used as a proxy when no PCV13 studies were available; PCV7 and PCV9 have the same formulation as PCV13 with 7 antigens in common. The benefits considered in GRADE included critical outcomes of prevention of invasive pneumococcal disease (IPD), pneumococcal pneumonia, death, and hospitalizations due to pneumococcal disease; vaccine-induced immunogenicity was considered an important outcome. The harms considered were serious adverse events and systemic adverse events. Evidence type for each critical or important outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, and imprecision.

Evidence used to evaluate efficacy of PCV13 to prevent IPD was from two randomized controlled trials (RCT): PCV9 among HIV-infected children in South Africa[2] and of PCV7 among HIV-infected adults in Malawi.[3] The effectiveness of PCV13 against IPD was assumed to be the same as that estimated from a pre/post observational study of PCV7 in children <10 years with sickle cell disease (SCD).[4] Evidence used to evaluate efficacy of PCV13 to prevent critical outcomes of pneumonia and death was from the same RCT in South Africa among HIV-infected children.[2] Evidence was not available for critical outcome of hospitalizations. There are two studies on immunogenicity for children with SCD: an unpublished pre/post study of immunogenicity of PCV13 in children aged 6 through 18,[5] and a published immunogenicity study of PCV7 and PPSV compared to PPSV alone.[6] There are three published studies for HIV-infected children: one pre/post study and two clinical trials for immunogenicity of PCV.[7-9] Four RCTs of PCV7 have been conducted in HIV-infected adults.[10-13] Safety of PCV13 was evaluated based on a pre/post study in children with SCD[5] and three RCTs of PCV7 in HIV-infected adults.[10-12]

Table 1. Benefits: 13-valent Pneumococcal Conjugate Vaccine in immunocompromised older children:

Outcome	No. of subjects (# studies)	Incidence in unvaccinated (cases/100,000)	Incidence in vaccinated (cases/100,000)	Vaccine efficacy (95% CI)	Absolute risk per 100,000	Number needed to vaccinate
Invasive Pneumococcal Disease	RCTs in HIV-infected individuals					
	39,836 (1 RCT of PCV9, HIV+ children, South Africa)[2]	131	45	65% (24, 86)[a]	N/A	N/A
	496 (1 RCT of PCV7, HIV+ adults, Malawi)[3]	7,661	2,016	74% (30, 90)[b]	N/A	N/A
		197[c]	61[d]	69% (44, 83)[e]	135[d]	736[d]
	Retrospective cohort study in children <10 years with sickle cell disease[4]					
	1,247	1.7	0.5	81% (19, 96)[f]	N/A	N/A
Death	39,836 (1 RCT of PCV9, HIV+ children, South Africa)[2]	884	833	6% (P-value =0.63)[a]	N/A	N/A
Pneumonia	39,836 (1 RCT of PCV9, HIV+ children, South Africa)[2]	1,049	914	13% (-7, 29)[a]	N/A	N/A
Immunogenicity- Antibody response to vaccine serotypes						

Outcome	Study design	Number in study		Results
GMFR	PCV13 in children with SCD			
	Pre/Post[5]	158		A single dose of PCV13 was immunogenic in SCD patients; none to modest increases in titers post-dose 2 of PCV13 administered 6 months later vs. dose 1
	Study design	Number in PCV arm	Number in PPSV23 arm	
	PCV7 in children with SCD			
GMC	RCT[6] (2 doses of PCV7 +PPSV23 vs. PPSV23 only)	11	12	Significant increases in GMC post 1 dose PCV7, no additional benefit post dose 2 of PCV7; response as good or better for some serotypes post 1 dose PCV7 vs. PPSV23
	PCV7 in HIV+ adults			
% with ≥4-fold increase in GMT	RCT[10] (2 doses of PCV7 vs. PPSV23)	15	16	GMTs higher for PCV7 vs. PPSV23 (significance not assessed post 1st dose of PCV7); % with ≥4-fold increase in GMT higher for PCV7 vs. PPSV23 for 4/5 serotypes (significant for 1/4 serotypes)
% with ≥2-fold rise in IgG levels and >1µg/ml	RCT[11]	106	106	No significant difference in outcome between PCV7 and PPSV23 (OR: 1.36, 95%CI 0.82-2.25)
	RCT[12]	102	100	No significant difference in outcome between PCV7 and PPSV23
	RCT[13]	131	73	Greater response for PCV7 vs. PPSV23 (57% vs. 36%, respectively; OR: 2.6 [95% CI, 1.4–5.0])
	Study design	Number in PCV group	Number in placebo group	

	PCV7 in HIV+ children			
GMC	Pre/post[7]	225	N/A	76–96% achieved >0.5 µg/mL after 1 dose and 62–88% achieved >1.0 µg/mL after 2 doses of PCV7 for five serotypes tested
	RCT[8]	30	36	Proportion >0.35 µg/mL: 63-93% (1 month after 3rd dose of PCV9)[a]; Proportion ≥0.2 µg/mL and ≥0.35 µg/mL (5.3 years after 3rd dose of PCV9): 39-100% achieved ≥0.2 g/mL and 19-81% achieved ≥0.35 µg/mL for each of seven serotypes tested
	RCT[9]	30	15	>95% achieved 0.15 µg/mL and 80% achieved 0.5 µg/mL after 3rd PCV7 dose; 88–100% achieved a 4-fold rise after 3rd PCV7 dose for each of seven serotypes tested

[a]Vaccine efficacy for a 3-dose primary series of PCV9 administered at 6, 10, and 14 weeks of age
[b]Vaccine efficacy for 2 doses of PCV7 administered 4 weeks apart estimated using hazard ratios
[c]Incidence of PCV13 type IPD among children aged 6–18 years with HIV/AIDS in the US, Active Bacterial Core surveillance (ABCs), CDC unpublished 2007–09, ABCs incidence data was only used to compute the number needed to vaccinate and not used in the evidence profile
[d]Incidence in vaccinated, absolute risk, and number needed to vaccinate was estimated using VE estimate from two RCTs[2,3] and applying it to baseline incidence of PCV13 type IPD in the US population with HIV/AIDS
[e]Summary vaccine efficacy estimated using data from two RCTs[2,3]
[f]Vaccine effectiveness for ≥1 doses of PCV7 adjusted for herd effects
Abbreviations:
GMC= Geometric Mean Concentration
GMT= Geometric Mean Titers
IgG= Immunoglobulin G
OR= Odds Ratio
GMFR=Geometric Mean Fold Rise
N/A= Not applicable
RCT= Randomized Controlled Trial

Table 2. Harms: 13-valent Pneumococcal Conjugate Vaccine in immunocompromised children:

Outcome	Study design	Incidence in controls	Incidence in vaccinated	Comments
Serious adverse events (SAE)				
Overall SAE	1 Pre/Post,[5] 3 RCTs[10-12]	N/A	0	No serious adverse events reported
Deaths	1 Pre/Post,[5] 3 RCTs[10-12]	N/A	0	No deaths
Systemic Adverse Events				
		Proportion reporting		
Fatigue	Pre/post study, 2 doses, children with SCD[5]	66.1%		
Headache		53.6%		
New generalized muscle pain		74.8%		
Vomiting		15.4%		
Diarrhea		15.4%		
New generalized joint pain		39.8%		
	Study design	**Incidence in controls**	**Incidence in vaccinated**	**Comments**
Mild, self- limited secondary reactions	1 RCT[12]	20%	34%	P=0.07
	2 RCTs[10,11]	N/A	N/A	No serious adverse events; no differences in systemic adverse events reported

N/A= Not applicable
RCT= Randomized Controlled Trial

Table 3. Evidence Type for Benefits and Harms: 13-valent Pneumococcal Conjugate Vaccine in immunocompromised older children:

Outcome	Study design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type[a]
Benefits						
Invasive Pneumococcal Disease	RCT (2) Observational (1)	No serious No serious	No serious N/A	Very serious [b] No serious	No serious No serious	3 3
Pneumonia	RCT (1)	No serious	N/A	Very serious [b]	Serious	3
Death	RCT (1)	No serious	N/A	Very serious [b]	Serious	3
Antibody response to vaccine types	Pre/post (2)	No serious	No serious	No serious	No serious	3
	RCT (4) adults, RCT (2) children	No serious	No serious	Very serious [c]	No serious	3
Harms						
Systemic adverse events	Pre/post (1)	No serious	N/A	No serious	No serious	3
	RCT (5)	No serious	No serious	Very serious [c]	No serious	3

N/A= Not applicable

[a]Evidence type:

1= Randomized controlled trials (RCTs), or overwhelming evidence from observational studies.

2= RCTs with important limitations, or exceptionally strong evidence from observational studies.

3= Observational studies, or RCTs with notable limitations.

4= Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

[b]Indirectness due to 1) different intervention (PCV9, 3 doses; PCV7, 2 doses) and 2) different population (South Africa, infants; Malawi, adults)

[c]Indirectness due to 1) different intervention (PCV7 or PCV9) and 2) different population (adults)

Table 4. Summary of Evidence: 13-valent Pneumococcal Conjugate Vaccine in immunocompromised children:

Comparison	Outcome[a]	Study design (# studies)	Findings	Evidence type	Overall evidence type
PCV9 or PCV7 vs. No vaccination	Invasive Pneumococcal Disease	RCT (2)	Decreased risk among vaccinated	3	3
PCV9 vs. No vaccination	Pneumonia	RCT (1)	Decreased risk among vaccinated	3	
PCV9 vs. No vaccination	Death	RCT (1)	No change in outcome	3	
PCV13, PCV7, or PCV9 vs PPSV or placebo	Antibody response to vaccine types	Pre/post (2) RCT (6)	Increases in antibody titers post-vaccination	3	
PCV13 or PCV7	SAE[b]	Pre/Post (1) RCT (5)	No serious adverse events	3	

[a] Overall evidence type is based on the weakest evidence type among the critical outcomes. Evidence was not available and, evidence type could not be assessed for critical outcomes of hospitalizations due to pneumococcal disease
[b] SAE= Serious Adverse Events

Table 5. Considerations for Formulating Recommendations: 13-valent Pneumococcal Conjugate Vaccine in immunocompromised children:

Key factors	Comments
Evidence type for benefits and harms	Indirectness & lack of evidence for 3 of 4 critical disease outcomes
Balance between benefits and harms	Benefits outweigh harms Very high burden of disease in immunocompromised children
Value	ACIP pneumococcal work group consensus regarding the importance of preventing critical pneumococcal outcomes
Cost-effectiveness	Uncertainty regarding costs/benefits relative to PPSV23

Summary: Benefits are greater than potential harms. High values were placed on prevention of the morbidity and mortality of pneumococcal infection among immunocompromised children. (*recommendation category A; evidence type 3)*

The ACIP Pneumococcal Work Group concluded that broader serotype protection can be achieved through use of both PCV13 and PPSV23 among immunocompomised children 6 through 18 years old; 49% of IPD in this group is caused by PCV13 serotypes, and an additional 23% by serotypes in PPSV23 not included in PCV13. Evidence from immunogenicity studies demonstrate that antibody response is non-inferior or superior when PCV is given before PPSV23 compared to PPSV23 administration before PCV.[11,12,14] Although the optimal interval for PCV13 followed by PPSV23 has not been specifically studied, significant increases in antibody as well as non-inferior to superior response compared to PPSV23 alone has been observed when PPSV23 was given eight weeks after PCV7.[14] For children previously immunized with PPSV23, waiting at least 8 weeks after PPSV23 before giving a dose of PCV13 may provide a better immune response (expert opinion).

The Work Group concluded that Category A (desirable consequences clearly outweigh undesirable consequences) recommendation for the use of PCV13 (evidence type 3) among PCV13-naïve immunocompromised children is warranted because 1) there remains an extremely high burden of pneumococcal disease among immuocompromised children, and 2) indirect effects of PCV13 use in young children are unlikely to eliminate disease caused by PCV13 serotypes in older children with immunocompromising conditions.

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