Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for Pneumococcal Vaccines for Immunocompromised Adults

Methods: GRADE was used to evaluate 13-valent Pneumococcal Conjugate Vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) for routine use among immunocompromised adults.

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 adults with immunocompromising conditions?" For consistency, evidence for both PPSV23 (recommended for use since 1983) and PCV13 were evaluated by applying the GRADE framework. Due to the limited body of evidence on vaccine efficacy and safety among persons with most immunocompromising conditions, both vaccines were evaluated using data for HIV-infected adults. Additionally, studies with 7-valent pneumococcal conjugate vaccine (PCV7) were used as a proxy when no PCV13 studies were available; PCV7 has the same formulation as PCV13 but contains 6 fewer antigens. The benefits considered critical outcomes in GRADE included prevention of death, invasive pneumococcal disease (IPD), pneumococcal pneumonia, hospitalizations due to pneumococcal disease, and 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 a randomized controlled trial (RCT) of PCV7 among HIV-infected adults in Malawi.[2] Evidence was not available for critical outcomes of pneumonia, hospitalizations, or deaths. Immunogenicity of PCV13 compared to PPSV23 was evaluated based on 2 phase III RCTs among healthy adults[3] and 4 RCTs of PCV7 in HIV-infected adults.[4-7] Safety of PCV13 was evaluated based on 6 RCTs in immunocompetent adults.[3]

The evidence used to evaluate efficacy of PPSV23 compared to placebo against IPD, pneumonia, and deaths was drawn from one RCT among HIV-infected adults in Uganda[8] as well as 9 observational studies in the United States and Europe.[9-17] Evidence was not available for the critical outcome of hospitalization due to pneumococcal disease. Immunogenicity was evaluated in 2 RCTs and 2 observational studies among HIV-infected people.[4,7,18-20] Safety was assessed by review of post-licensure surveillance data.[21]

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

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[d]	Number Needed to Vaccinate
Invasive Pneumococcal Disease[a]	496 (1 RCT, HIV+ adults, Malawi) [2]	64[c]	17 [d]	74% (30, 90)[b]	47[d]	2128[d]
Immunogenicity- Antibody response to vaccine serotypes						
Outcome	**No. of studies**	**Number in PCV13 group**	**Number in PPSV23 group**	**Results**		
GMT[e] ratios	PCV13 phase III studies in immunocompetent adults					
	1 RCT[3]	370	370	Statistically significantly greater for PCV13 vs. PPSV23 for 9/13 serotypes; non-inferior response for all types		
	1 RCT[3]	462	462	Statistically significantly greater for PCV13 vs. PPSV23 for 11/13 serotypes; non-inferior response for all types		
	PCV7, in HIV+ adults					
% with ≥4-fold increase in GMT[e]	1 RCT[4]	15	16	GMTs higher for PCV7 vs. PPSV23 (stat. significance not assessed post 1st dose); % with ≥4-fold increase in GMT higher for PCV7 vs. PPSV23 for 4/5 serotypes (stat. significant for 1/4)		
% with ≥2-fold rise in IgG[f] levels and >1ug/ml)	1 RCT[5]	106	106	No significant difference in outcome between PCV7 and PPSV (OR[g]: 1.36, 95%CI 0.82-2.25)		
	1 RCT[6]	102	100	No significant difference in outcome between PCV7 and PPSV		
	1 RCT[7]	131	73	Greater response for PCV7 vs PPSV (57% vs 36%, respectively; OR: 2.6 [95% CI, 1.4–5.0])		

RCT, Randomized Controlled Trial.

[a] Caused by vaccine serotypes or type 6A

[b] Intention-to-treat analysis (vaccine efficacy estimated using hazard ratios)

[c] Incidence of PCV13 type IPD among adults with HIV/AIDS in the US, Active Bacterial Core surveillance, CDC unpublished 2009

[d] Incidence in vaccinated, absolute risk, and number needed to vaccinate was estimated using VE estimate from

RCT[2] and applying it to baseline incidence of PCV13 type IPD in the US population with HIV/AIDS
[e]GMT= Geometric Mean Titers
[f]IgG= immunoglobulin
[g]odds ratio

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

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Risk Difference per 1000 (95% CI)
Serious adverse events (SAE)				
Overall SAE	6,000[3]	N/A	0.2-1.1%	No difference[a]
Deaths	6,000[3]	N/A	16/6000 (0.003%)[b]	No difference[a]
Systemic Adverse Events				
Fatigue	3 RCTs[3]; PCV13 phase III[c]	43.3%	34.0%	-9.3 (-16.4, -2.2)
Rash		16.4%	7.3%	-9.1 (-14.3, -4.0)
New generalized muscle pain		44.7%	36.8%	-7.9 (-15.2,-0.6)
Use of medications to treat fever		17.5%	8.6%	-8.9 (-16.6,-1.9)
Mild, self- limited secondary effects	1 RCT[6]	20%	34%	P=0.07
	3 RCTs[4,5,18]			No serious adverse events; no differences in systemic adverse events reported

N/A, not applicable

[a] No difference between the treatment groups
[b] No deaths were considered vaccine related
[c] Significant differences reported for 2 out of 3 RCTs (4 out of 13 outcomes); only significant findings presented in the table

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

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type[a]
Benefits						
Invasive Pneumococcal Disease	RCT (1)	No serious	N/A	Very serious [b]	No serious	3
Antibody response to vaccine types	RCT (2)	No serious	No serious	Very serious [c]	No serious	3
Antibody response to vaccine types	RCT (4)	No serious	No serious	Serious [d]	No serious	2
Harms						
Systemic adverse events	RCT (3)	No serious	N/A	Serious [e]	No serious	2

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 population (Malawi), 2) different intervention (PCV7, 2 doses), and 3) different comparison group (placebo)

[c] Indirectness due to 1) different population (immunocompetent) and 2) different outcome (antibody response without defined correlates of protection)

[d] Indirectness due to 1) different intervention (PCV7) and 2) different outcome (antibody response without defined correlates of protection)

[e] Indirectness due to 1)different population (Phase III studies of PCV13 in immunocompetent) or 2) different intervention (PCV7 published studies)

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

Comparison	Outcome	Study design (# studies)	Findings	Evidence type	Overall evidence type
PCV7 vs. No vaccination	Invasive Pneumococcal Disease	RCT (1)	Decreased risk among vaccinated	2/3	2/3[a]
PCV13 vs. PPSV23	Antibody response to vaccine types	RCT (2)	Response improved for PCV13 vs. PPSV23 or no difference	3	
PCV7 vs. PPSV23	Antibody response to vaccine types	RCT (4)	Response improved for PCV7 vs. PPSV23 or no difference	2	
PCV13 vs. PPSV23	Systemic adverse events	RCT (3)	No difference for SAE[b] Decreased risk for some systemic adverse events	2	

[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 death, hospitalizations due to pneumococcal disease, and pneumonia

[b] SAE= Serious Adverse Events

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

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 adults
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 adults. (*recommendation category B; evidence type 2/3)*

Table 6. Evidence type: 23-valent Pneumococcal Polysaccharide Vaccine in immunocompromised adults

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type[a]
Death	RCT (1)[8,22]	Serious [b]	N/A	Very serious [c]	Not serious	3
IPD[d]	RCT (1)[8]	Not serious	N/A	Very serious[c]	Not serious	3
	Observational (6)[9-13,17]	Serious [e]	Not serious	Not serious	Not serious	4
Pneumonia	RCT (1)[8]	Not serious	N/A	Very serious [c]	Not serious	3
	Observational (5)[11,12,14-16]	Serious [e]	Serious [f]	Not serious	Not serious	4
Antibody response to vaccine types	RCT (2)[4,7]	Not serious	Not serious	Serious [g]	Not serious	2
	Observational (2)[19,20]	Not serious	Not serious	Serious[g]	Not serious	3
Systemic adverse events	Post-licensure surveillance[21]	Not serious	Not serious	Not serious	N/A	3

[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] Inconsistent findings of the initial trial and a follow up study. Mortality assessed during a follow up study (Watera et al) showed improved mortality among vaccine recipients while initial study (French et al) had a null finding with respect to mortality

[c] Indirectness due to different population (highly immunosuppressed, no antiretroviral therapy)

[d] Invasive Pneumococcal Disease

[e] Observational studies overestimate effectiveness against all IPD or all-cause pneumonia

[f] Test of heterogeneity of odds ratios is highly significant (p=0.0002)

[g] No correlates of protection

Table 7. Summary of Evidence: 23-valent Pneumococcal Polysaccharide Vaccine in immunocompromised adults

Comparison	Outcome	Study design (# studies)	Findings	Evidence type	Overall evidence type[a]
PPSV23 vs. Placebo	Death	RCT (1)	Inconclusive data on efficacy against mortality	3	**3/4**
PPSV23 vs. Placebo or No vaccination	IPD[b]	RCT (1) Observational (6)	Negative efficacy among highly immunosuppressed adults; effectiveness against all IPD 49% (34%, 61%) from observational studies	3/4	
PPSV23 vs. Placebo or No vaccination	All-cause pneumonia	RCT (1) Observational (5)	Negative efficacy among highly immunosuppressed adults; effectiveness of 31% (27%, 36%) from observational studies	3/4	
PPSV23	Systemic adverse events	Post-licensure surveillance	PPSV23 appears safe for use among adults with HIV	3	

[a] Overall evidence type is based on the weakest critical outcomes evidence type. Evidence was not available and evidence type was not assessed for critical outcome of hospitalizations due to pneumococcal infections.
[b]Invasive Pneumoccal Disease

Table 8. Considerations for Formulating Recommendations: 23-valent Pneumococcal Polysaccharide Vaccine in immunocompromised adults

Key factors	Comments
Evidence type for benefits and harms	Inconsistent evidence for all-cause pneumonia; limited data from RCT not generalizable to the US HIV+ population
Balance between benefits and harms	Some uncertainty about benefits. Vaccine appears to be safe in this population
Value	ACIP pneumococcal work group consensus regarding the importance of preventing critical pneumococcal outcomes
Cost-effectiveness	Cost-effectiveness in the general adult population demonstrated; uncertainty around the assumptions utilized in cost-effectiveness analysis

Summary: Benefits are likely greater than harms. High values were placed on prevention of the morbidity and mortality of pneumococcal infection among immunocompromised adults.(*recommendation category B; evidence type 3/4)*

The ACIP Pneumococcal Work Group concluded that broader serotype protection can be achieved through use of both PCV13 and PPSV23 among immunocompomised adults; half of IPD in immunocompromised adults is caused by PCV13 serotypes, and an additional 21% 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.[5,6,18] 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.[18] For adults previously immunized with PPSV23, waiting at least 1 year after PPSV23 before giving a dose of PCV13 may provide a better immune response (expert opinion).

The Work Group concluded that Category A recommendation for the use of both PCV13 (evidence type 2/3) and PPSV23 (evidence type 3/4) among immunocompromised adults. Category A, (desirable consequences clearly outweigh undesirable consequences) is warranted because 1) there remains an extremely high burden of pneumococcal disease among immuocompromised adults; 2) indirect effects of PCV13 use in children are unlikely to eliminate PCV13 serotypes from the adult immunocompromised population, and 3) the GRADE process led to the conclusion that both PCV13 and PPSV23 are effective in this group & that benefits likely outweigh harms.

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