Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for Pneumococcal Vaccines for Adults aged ≥65 years

Methods: GRADE was used to evaluate 13-valent Pneumococcal Conjugate Vaccine (PCV13) for routine use among adults aged ≥65 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 all adults aged ≥65 years?" The intervention evaluated was a single dose of PCV13 compared to a dose of 23-valent polysaccharide vaccine (PPSV23).

The benefits considered critical outcomes in GRADE included prevention of invasive pneumococcal disease (IPD), pneumococcal community-acquired pneumonia, and hospitalizations due to pneumococcal disease. Evidence used to evaluate efficacy of PCV13 against IPD and pneumococcal pneumonia was from the randomized placebo-controlled trial (RCT) conducted among approximately 85,000 adults aged ≥65 years in Netherlands (CAPiTA).[2] Evidence was not available for the critical outcome of hospitalizations due to pneumococcal disease. In addition, vaccine-induced immunogenicity was considered as an important outcome; immunogenicity evidence was assessed using two phase III RCTs of PCV13 compared to PPSV23, which measured antibody responses by opsonophagocytic assay (OPA) and four RCTs of PCV7 compared to PPSV23, which measured antibody responses by enzyme-linked immunosorbent assay (ELISA).[3-8]

The harms considered were overall serious adverse events (SAE), deaths and systemic adverse events including fatigue, rash, new generalized muscle pain, and use of medications to treat fever. Safety of PCV13 was evaluated based on 6 RCTs in immunocompetent adults, compared to PPSV23.[9]

Evidence type for each critical outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, and imprecision.

Table 1a. Benefits of 13-valent Pneumococcal Conjugate Vaccine in Adults aged ≥65 years: Invasive Pneumococcal Disease and Community-Acquired Pneumonia

Outcome	No. of subjects (# studies)	Incidence in unvaccinated (cases/100,000)	Vaccine efficacy (95% CI)	Number Needed to Vaccinate [a]
PCV13-serotype Invasive Pneumococcal Disease	Approximately 85,000 adults (1 RCT)[2]	6.5[10]	74% (30-90%) [b]	20,400 (16,950-37,000)
Inpatient community-acquired pneumonia	Approximately 85,000 adults (1 RCT)[2]	137.5[11] [c]	45% (14-65%)	1,620 (1,110 - 5,130)
Outpatient community-acquired pneumonia	Approximately 85,000 adults (1 RCT)[12]	201[9] [c]	45% (14-65%)	1,110 (760-3,500)
Total community-acquired pneumonia	Approximately 85,000 adults (1 RCT)[2]	--	--	656 (454-2,110)

[a] Number needed to vaccinate or NNV=1 / (baseline rate – vaccinated rate)
[b] Vaccine Efficacy versus placebo
[c] Baseline estimates assume 10% of all CAP due to PCV13 types

Table 1b. Benefits of 13-valent Pneumococcal Conjugate Vaccine in Adults aged ≥65 years: Immunogenicity[a]

Study	No. of subjects	Population	Immunogenicity Results
Jackson et al 2013[3]	818	60 to 64 years PPSV23 Naïve	PCV13 > PPSV23 for 9/13 types (OPA) PCV13=PPSV23 for 4/13 types (OPA)
Jackson et al 2013[4]	879	≥70 years PPSV23 >5 years previously	PCV13>PPSV23 for 11/13 types (OPA) PCV13=PPSV23 for 2/13 types (OPA)
Goldblatt et al 2009[5]	599	50 to 80 years No PPSV23 within the past 5 years	PCV7 = PPSV23 for 3/7 types (ELISA) PCV7 > PPSV23 for 3/7 types (ELISA) PCV7<PPSV23 for 1/7 types (ELISA)
De Roux et al 2008[6]	217	>70 years PPSV Naïve	PCV7 = PPSV23 for 1 type (ELISA) PCV7>PPSV23 for 6/7 types (ELISA)
Ridda et al 2009[7]	241	>60 years, frail PPSV Naïve	PCV7 = PPSV23 for 4/4 types tested (ELISA) Comparisons of other 3 types not done
Miernyk et al 2009[8]	203	55 to 70 years, Alaska Native PPSV Naïve	PCV7 = PPSV23 for 4/4 types tested (ELISA) Comparisons of other 3 types not done

[a] Immunogenicity: Antibody response to vaccine serotypes, compared to PPSV23

Table 2. Harms of 13-valent Pneumococcal Conjugate Vaccine in Adults aged ≥65 years

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Risk Difference per 1000 (95% CI)
Serious adverse events (SAE)				
Overall serious adverse events	6,000 (6 RCTs)[9]	--	0.2-1.1%	No difference [a]
Deaths	6,000 (6 RCTs)[9]	--	16/6000 (0.3%)[b]	No difference [a]
Systemic Adverse Events				
Fatigue	3 RCTs & PCV13 phase III[9] [c]	43.3% [d]	34.0%	-9.3 (-16.4, -2.2)
Rash		16.4% [d]	7.3%	-9.1 (-14.3, -4.0)
New generalized muscle pain		44.7% [d]	36.8%	-7.9 (-15.2,-0.6)
Medications to treat fever		17.5% [d]	8.6%	-8.9 (-16.6,-1.9)

[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
[d] Controls received PPSV23

Table 3. Evidence Type for Benefits and Harms: 13-valent Pneumococcal Conjugate Vaccine in Adults aged ≥65 years

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type [a]
Benefits [b]						
Invasive Pneumococcal Disease	1 RCT	No serious	Not applicable	Serious [c]	No serious	2
Community-acquired pneumonia	1 RCT	No serious	Not applicable	No serious	No serious	1
Immunogenicity	6 RCT	No serious	No serious	Serious [d]	No serious	2
Harms						
Systemic adverse events	3 RCTs	No serious	No serious	No serious	No serious	1

[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] Immunogenicity data which was considered an important outcome did not contribute to overall evidence type.

[c] Indirectness due to different comparison group: 1) Placebo instead of PPSV and 2) PPSV efficacy against IPD among older adults = 50-80%

[d] Indirectness due to different outcome (antibody response without correlates of protection)

Table 4. Summary of Evidence for 13-valent Pneumococcal Conjugate Vaccine in Adults aged ≥65 years

Comparison	Outcome	Study design	Findings	Evidence type	Overall evidence type [a]
PCV13 vs. no vaccination	IPD	1 RCT	Decreased risk among vaccinated	2	2
PCV13 vs. no vaccination	Pneumonia	1 RCT	Decreased risk among vaccinated	1	
PCV7 or PCV13 vs. PPSV23	Immunogenicity	6 RCTs	Response better for PCV than PPSV23 or no difference	2	
PCV13 vs. PPSV23	Serious and systemic adverse events	3 RCTs	No difference or decreased risk with PCV13	1	

[a] Overall evidence type is based on the weakest evidence type among the critical outcomes. This did not include immunogenicity data which was considered an important outcome.

Table 5. Considerations for Formulating Recommendations for 13-valent Pneumococcal Conjugate Vaccine in Adults aged ≥ 65 years

Key factors	Comments
Evidence type/quality for benefits and harms	Data on efficacy against most critical outcomes available
Balance of benefits versus harms	Benefits outweigh harms Short-term: No uncertainty about the balance Long-term: Indirect (herd) effects of infant vaccination expected to further reduce burden of pneumococcal disease in adults.
Values	General consensus reached on which outcomes are critical to prevent
Cost-effectiveness	Short-term: The net benefits are worth the costs Long-term: Uncertainty about whether the net benefits are worth the costs due to continued indirect effects
Summary	The evidence supporting PCV13 vaccination of adults was determined to be type 2 (moderate level of evidence). The recommendation was designated as Category A.

The ACIP Pneumococcal Work Group concluded that broader serotype protection can be achieved through use of both PCV13 and PPSV23 among adults ≥65 years of age; 20-25% of IPD among adults in this age group is caused by PCV13 serotypes, and an additional 38.5% by serotypes in PPSV23 not included in PCV13.[10] Conversely, PCV13 use among older adults will protect against inpatient community-acquired pneumonia.[2] 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.[3-8] Although the optimal interval for PCV13 followed by PPSV23 has not been directly studied, studies evaluating the immune response following a sequence of PCV7 or PCV13 followed by PPSV23 with intervals of 2, 6,

12 months, or 3-4 years demonstrated that following the PPSV23 dose, antibody levels were higher than the pre-PCV baseline, and a non-inferior response was observed when compared with post-PCV antibody levels.[5,8,13,14] 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 according to expert opinion.

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