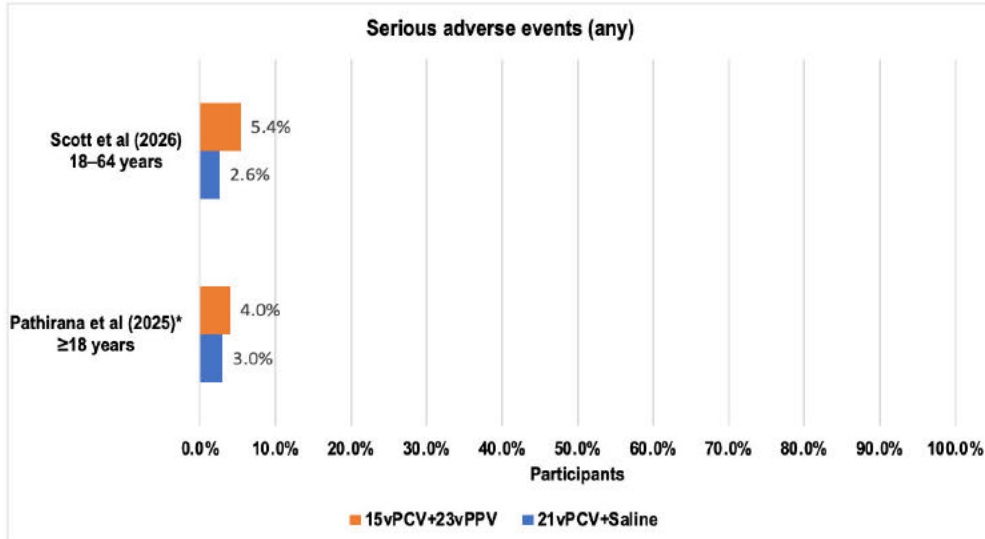


GRADE tables: Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

NCIRS is conducting GRADE assessments in support of the Australian Technical Advisory Group on Immunisation (ATAGI) and making results available on the Centre's website. Please read this material as a supplement to the [Australian Immunisation Handbook pneumococcal disease](#) chapter.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions																
Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions Intervention: 21vPCV (V116) + saline Comparison: 15vPCV+23vPPV																
Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation												
Any serious adverse events (Any SAEs) Follow-up: 6 months	Serious adverse events (any) <table><caption>Serious adverse events (any) - Data from Forest Plot</caption><thead><tr><th>Study</th><th>Age Group</th><th>15vPCV+23vPPV (%)</th><th>21vPCV+Saline (%)</th></tr></thead><tbody><tr><td>Scott et al (2026)</td><td>18-64 years</td><td>5.4%</td><td>2.6%</td></tr><tr><td>Pathirana et al (2025)*</td><td>≥18 years</td><td>4.0%</td><td>3.0%</td></tr></tbody></table> *Follow up = 3 months No cases were considered related to the vaccine	Study	Age Group	15vPCV+23vPPV (%)	21vPCV+Saline (%)	Scott et al (2026)	18-64 years	5.4%	2.6%	Pathirana et al (2025)*	≥18 years	4.0%	3.0%	826 (2 RCTs) ¹⁻⁴	⊕⊕⊕○ Moderate ^a	21vPCV likely results in little to no difference in any SAEs compared to 15vPCV+23vPPV.
Study	Age Group	15vPCV+23vPPV (%)	21vPCV+Saline (%)													
Scott et al (2026)	18-64 years	5.4%	2.6%													
Pathirana et al (2025)*	≥18 years	4.0%	3.0%													

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation				
OPA GMT ratio Follow-up: 30 days	Table 1a: 95% CI for OPA GMT ratios (21vPCV vs. 15vPCV+23PPV) for shared and unique serotypes at Day 30 shaded by non-inferiority (using 3 different thresholds) and superiority margins^*		828 (2 RCTs) ^{1,2}	⊕⊕⊕⊕○ Moderate ^a	21vPCV likely results in little to no difference in OPA GMT ratios for the 13 shared STs with 15vPCV+23vPPV as all ratios met a non-inferiority margin of LCI>0.675 except 8 and 19A in one study which only met the non-inferiority margin of LCI>0.51. 21vPCV likely results in greater OPA GMT ratios for all 9 STs unique to 21vPCV, except for 15C in one study which still met the non-inferiority margin of LCI>0.675. There is no data available on the STs unique to 23vPPV.			
	Study	CSR P007 (2023) ≥18 years				CSR P008 (2024) 18–64 years		
	PCV	21vPCV				15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV
	N	156				156	386	130
	Shared STs							
	3							
	6A							
	7F							
	8							
	9N							
	10A							
	11A							
	12F							
	17F							
	19A							
	20/20A							
22F								
33F								

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
continued OPA GMT ratio Follow-up: 30 days	Table 1a (continued)			
	Unique STs: 23v-non-21v			
	1	NR	NR	
	2	NR	NR	
	4	NR	NR	
	5	NR	NR	
	6B	NR	NR	
	9V	NR	NR	
	14	NR	NR	
	15B*	NR	NR	
	18C	NR	NR	
	19F	NR	NR	
	23F	NR	NR	

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation																		
continued OPA GMT ratio Follow-up: 30 days	Table 1a (continued) <table><tr><th colspan="2">Unique STs: 21v-non-23v</th></tr><tr><td>15A</td><td></td></tr><tr><td>15C</td><td></td></tr><tr><td>16F</td><td></td></tr><tr><td>23A</td><td></td></tr><tr><td>23B</td><td></td></tr><tr><td>24F</td><td></td></tr><tr><td>31</td><td></td></tr><tr><td>35B</td><td></td></tr></table> ^Yellow = non-inferiority LCI>0.5; Orange = non-inferiority LCI>0.675; Blue= superiority LCI>2 *Note: Sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 15vPCV, 23vPPV or 21vPCV. There was no data provided for this.	Unique STs: 21v-non-23v		15A		15C		16F		23A		23B		24F		31		35B				
Unique STs: 21v-non-23v																						
15A																						
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23B																						
24F																						
31																						
35B																						

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation																																					
continued OPA GMT ratio Follow-up: 30 days	Table 1b: 95% CI for OPA GMT ratios (21vPCV vs. 15vPCV+23vPPV) for shared and unique serotypes at Day 30 shaded by estimates that favour 21vPCV^* <table><tr><th>Study</th><th colspan="2">CSR P007 (2023) ≥18 years</th><th colspan="2">CSR P008 (2024) 18-64 years</th></tr><tr><th>PCV</th><th>21vPCV</th><th>15vPCV + 23vPPV</th><th>21vPCV</th><th>15vPCV + 23vPPV</th></tr><tr><th>N</th><td>156</td><td>156</td><td>386</td><td>130</td></tr><tr><th colspan="5">Shared STs</th></tr><tr><td>3</td><td colspan="4" rowspan="15"></td></tr><tr><td>6A</td></tr><tr><td>7F</td></tr><tr><td>8</td></tr><tr><td>9N</td></tr><tr><td>10A</td></tr><tr><td>11A</td></tr><tr><td>12F</td></tr><tr><td>17F</td></tr><tr><td>19A</td></tr><tr><td>20/20A</td></tr><tr><td>22F</td></tr><tr><td>33F</td></tr></table>	Study	CSR P007 (2023) ≥18 years		CSR P008 (2024) 18-64 years		PCV	21vPCV	15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV	N	156	156	386	130	Shared STs					3					6A	7F	8	9N	10A	11A	12F	17F	19A	20/20A	22F	33F			
	Study	CSR P007 (2023) ≥18 years		CSR P008 (2024) 18-64 years																																					
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Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation																																																	
continued OPA GMT ratio Follow-up: 30 days	Table 1b (continued)																																																				
	<table><tr><th colspan="3">Unique STs: 23v-non-21v</th></tr><tr><td>1</td><td>NR</td><td>NR</td></tr><tr><td>2</td><td>NR</td><td>NR</td></tr><tr><td>4</td><td>NR</td><td>NR</td></tr><tr><td>5</td><td>NR</td><td>NR</td></tr><tr><td>6B</td><td>NR</td><td>NR</td></tr><tr><td>9V</td><td>NR</td><td>NR</td></tr><tr><td>14</td><td>NR</td><td>NR</td></tr><tr><td>15B*</td><td>NR</td><td>NR</td></tr><tr><td>18C</td><td>NR</td><td>NR</td></tr><tr><td>19F</td><td>NR</td><td>NR</td></tr><tr><td>23F</td><td>NR</td><td>NR</td></tr><tr><th colspan="3">Unique STs: 21v-non-23v</th></tr><tr><td>15A</td><td colspan="2" rowspan="10"></td></tr><tr><td>15C</td></tr><tr><td>16F</td></tr><tr><td>23A</td></tr><tr><td>23B</td></tr><tr><td>24F</td></tr><tr><td>31</td></tr><tr><td>35B</td></tr></table>		Unique STs: 23v-non-21v			1	NR	NR	2	NR	NR	4	NR	NR	5	NR	NR	6B	NR	NR	9V	NR	NR	14	NR	NR	15B*	NR	NR	18C	NR	NR	19F	NR	NR	23F	NR	NR	Unique STs: 21v-non-23v			15A			15C	16F	23A	23B	24F	31	35B		
	Unique STs: 23v-non-21v																																																				
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^Red=UCI<1; Green = LCI>1; Blue = LCI>2																																																					
*Note: Sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 15vPCV, 23vPPV or 21vPCV. There was no data provided for this.																																																					

*Red=UCI<1; Green = LCI>1; Blue = LCI>2

*Note: Sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 15vPCV, 23vPPV or 21vPCV. There was no data provided for this.

IgG GMC ratio Follow-up: 30 days	Table 2a: 95% CI for IgG GMC ratios (21vPCV vs. 15vPCV+23vPPV) for shared and unique serotypes at Day 30 shaded by non-inferiority (using 3 different thresholds) and superiority margins ^{^*}					828 (2 RCT) ^{1,2} ⊕⊕⊕○ Moderate^a 21vPCV likely results in little to no difference in IgG GMC ratios for the 13 shared STs with 15vPCV+23vPPV as all ratios met a non-inferiority margin of LCI>0.675 except 8 and 6A which each only met the non-inferiority margin of LCI>0.51 in one study. 21vPCV likely results in greater IgG GMC ratios for all 8 STs unique to 21vPCV, except for 15C which only met the non-inferiority criteria of LCI>0.675 in one study. There is no data available on the STs unique to 23vPPV.	
	Study		CSR P007 (2023) ≥18 years		CSR P008 (2024) 18-64 years		
	PCV	21vPCV	15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV		
	N	156	156	386	130		
	Shared STs						
	3						
	6A						
	7F						
	8						
	9N						
	10A						
	11A						
	12F						
	17F						
	19A						
	20/20A						
	22F						
	33F						
	Unique STs: 23v-non-21v						
	1	NR		NR			
	2	NR		NR			
	4	NR		NR			
	5	NR		NR			
	6B	NR		NR			
	9V	NR		NR			
	14	NR		NR			
	15B*	NR		NR			
	18C	NR		NR			
19F	NR		NR				
23F	NR		NR				

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions				
Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions				
Intervention: 21vPCV (V116) + saline				
Comparison: 15vPCV+23vPPV				
Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
<i>continued</i> IgG GMC ratio Follow-up: 30 days	Table 2a (continued)			
	Unique STs: 21v-non-23v			
	15A			
	15C			
	16F			
	23A			
	23B			
	24F			
	31			
	35B			
^Yellow = non-inferiority LCI>0.5; Orange = non-inferiority LCI>0.675; Blue= superiority LCI>2 *Note: sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 15vPCV, 23vPPV or 21vPCV. There was no data provided for this.				

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact					No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
continued IgG GMC ratio Follow-up: 30 days	Table 2b: 95% CI for IgG GMC ratios (21vPCV vs. 15vPCV+23vPPV) for shared and unique serotypes at Day 30 shaded by estimates that favour 21vPCV ^{A*}							
	Study	CSR P007 (2023) ≥18 years		CSR P008 (2024) 18-64 years				
	PCV	21vPCV	15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV			
	N	156	156	386	130			
	Shared STs							
	3							
	6A							
	7F							
	8							
	9N							
	10A							
	11A							
	12F							
	17F							
	19A							
	20/20A							
	22F							
	33F							

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact			No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
continued IgG GMC ratio Follow-up: 30 days	Table 2b (continued)					
	Unique STs: 23v-non-21v					
	1	NR	NR			
	2	NR	NR			
	4	NR	NR			
	5	NR	NR			
	6B	NR	NR			
	9V	NR	NR			
	14	NR	NR			
	15B*	NR	NR			
	18C	NR	NR			
	19F	NR	NR			
	23F	NR	NR			

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
<i>continued</i> IgG GMC ratio Follow-up: 30 days	Table 2b (<i>continued</i>)			
	Unique STs: 21v-non-23v			
	15A			
	15C			
	16F			
	23A			
	23B			
	24F			
	31			
	35B			
^a Red=UCI<1; Green = LCI>1; Blue = LCI>2 [*] Note: sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 15vPCV, 23vPPV or 21vPCV. There was no data provided for this outcome.				

^aRed=UCI<1; Green = LCI>1; Blue = LCI>2

* Note: sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 15vPCV, 23vPPV or 21vPCV. There was no data provided for this outcome.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact				No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation	
% of participants ≥4-fold rise in OPA GMT Follow-up: 30 days	Table 3: % participants ≥4 fold-rise in OPA GMT pre- to 30 days post-vaccination ^{^*}				828 (2 RCT) ¹⁻⁴	⊕⊕○○ Low ^{a,b}	21vPCV may result in little to no difference in the % participants with ≥4-fold rise in OPA GMT for 12/12 shared serotypes, except for 7F which in one study may have a greater proportion of participants. 21vPCV may result in an increase in the % participants with ≥4-fold rise in OPA GMT for 8/8 unique serotypes, except for 15C which in one study had no significant difference despite a higher point estimate. There is no data available on the STs unique to 23vPPV except 15B, which may result in little to no difference.	
	Study	CSR P007 (2023) ≥18 years		CSR P008 (2024) 18-64 years				
	PCV	21vPCV	15vPCV + 23vPPV	21vPCV				15vPCV + 23vPPV
	N	156	156	386				130
	Shared STs							
	3							
	6A							
	7F							
	8							
	9N							
	10A							
	11A							
	12F							
	17F							
	19A							
	20/20A							
22F								
33F								

<i>continued</i> % of participants ≥4-fold rise in OPA GMT Follow-up: 30 days	Table 3 (continued)				
	Unique STs: 23v-non-21v				
	1	NR	NR	NR	NR
	2	NR	NR	NR	NR
	4	NR	NR	NR	NR
	5	NR	NR	NR	NR
	6B	NR	NR	NR	NR
	9V	NR	NR	NR	NR
	14	NR	NR	NR	NR
	15B*				
	18C	NR	NR	NR	NR
	19F	NR	NR	NR	NR
	23F	NR	NR	NR	NR
	Unique STs: 21v-non-23v				
	15A				
	15C				
	16F				
	23A				
	23B				
	24F				
	31				
	35B				
	^Green = point estimate favours intervention and CIs do not overlap; White = CIs overlap *Note: sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 15vPCV, 23vPPV or 21vPCV. There was no statistically significant difference between the responses for 6C in either study: P007 - 21vPCV = vs 15v+23v = ; P008 21vPCV = vs 15v+23v =).				

% participants ≥4-fold rise in IgG GMC Follow-up: 30 days	Table 4: % participants ≥4 fold-rise in IgG GMC pre- to 30 days post vaccination^{^*}				
	Study	CSR P007 (2023) ≥18 years		CSR P008 (2024) 18-64 years	
	PCV	21vPCV	15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV
	N	156	156	386	130
	Shared STs				
	3				
	6A				
	7F				
	8				
	9N				
	10A				
	11A				
	12F				
	17F				
	19A				
	20/20A				
	22F				
	33F				
	Unique STs: 23v-non-21v				
	1	NR	NR	NR	NR
	2	NR	NR	NR	NR
	4	NR	NR	NR	NR
	5	NR	NR	NR	NR
	6B	NR	NR	NR	NR
	9V	NR	NR	NR	NR
	14	NR	NR	NR	NR
	15B*				
	18C	NR	NR	NR	NR
	19F	NR	NR	NR	NR
	23F	NR	NR	NR	NR
	Unique STs: 21v-non-23v				
	15A				
	15C				
	16F				
828 (2 RCT) ^{1,2}					⊕⊕⊕○ Moderate^a
					21vPCV likely results in little to no difference in the % participants with ≥4-fold rise in IgG GMC for 12/12 shared serotypes in one study, however in the other study STs 11A, 12F, 17F likely results in a significantly greater proportion of participants with ≥4-fold rise in IgG and 19A likely results in a significantly lower proportion. 21vPCV likely results in an increase in the % participants with ≥4-fold rise in IgG GMC for 8/8 unique serotypes, except for 15A which in one study likely results in little to no difference. There is no data available on the STs unique to 23vPPV except 15B which in one study likely results in little to no difference, and in the other study is borderline significantly lower.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
23A 23B 24F 31 35B ^aGreen = point estimate favours intervention and CIs do not overlap; Orange = point estimate favours comparator and CIs are borderline; white = CIs overlap [*]Note: Sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 15vPCV, 23vPPV or 21vPCV. There was no statistically significant difference between the responses for 6C: 21vPCV = [REDACTED] vs 15vPCV+23vPPV = [REDACTED] in P007 and 21vPCV = [REDACTED] vs 15vPCV+23vPPV = [REDACTED] in P008.				

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

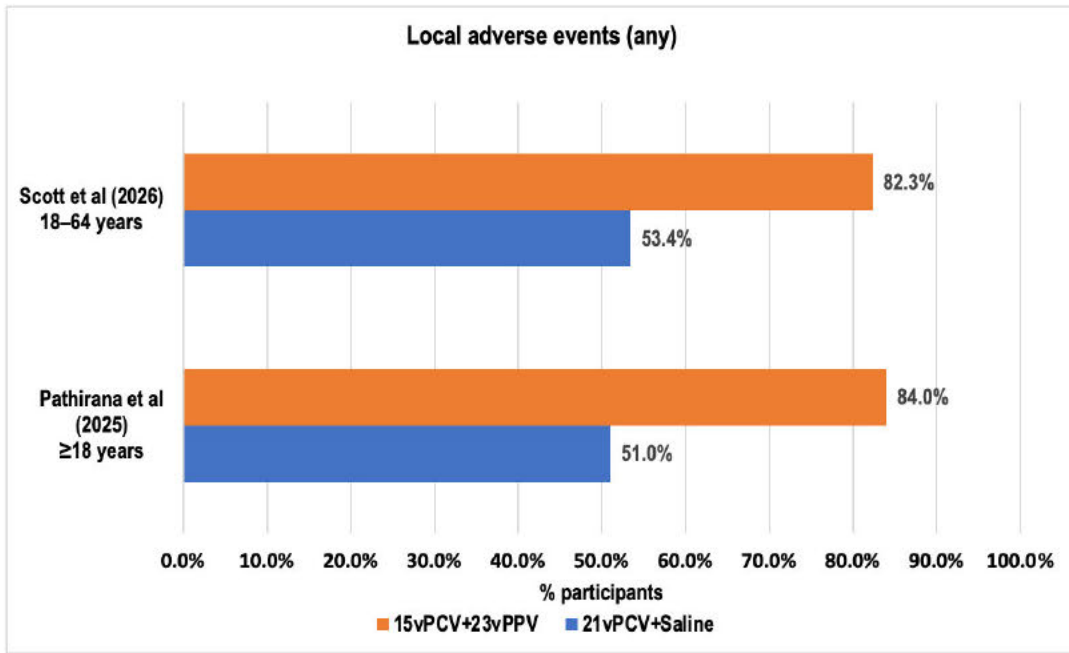
Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation									
Any systemic adverse events (AEs) Follow-up: 5 days	Systemic adverse events <table><thead><tr><th>Study</th><th>15vPCV+23vPPV (%)</th><th>21vPCV (%)</th></tr></thead><tbody><tr><td>Scott et al (2026) 18-64 years</td><td>68.5%</td><td>51.6%</td></tr><tr><td>Pathirana et al (2025) ≥18 years</td><td>59.0%</td><td>63.0%</td></tr></tbody></table>	Study	15vPCV+23vPPV (%)	21vPCV (%)	Scott et al (2026) 18-64 years	68.5%	51.6%	Pathirana et al (2025) ≥18 years	59.0%	63.0%	826 (2 RCTs) ¹⁻⁴	⊕⊕○○ Low ^{a,c}	21vPCV may result in little to no difference in any systemic AEs compared to 15vPCV+23vPPV.
Study	15vPCV+23vPPV (%)	21vPCV (%)											
Scott et al (2026) 18-64 years	68.5%	51.6%											
Pathirana et al (2025) ≥18 years	59.0%	63.0%											

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation						
Any local adverse events (any local AEs) Follow-up: 5 days	Local adverse events (any)  <table><caption>Local adverse events (any) - % participants</caption><thead><tr><th>Study</th><th>15vPCV+23vPPV</th><th>21vPCV+Saline</th></tr></thead><tbody><tr><td>Scott et al (2026) 18-64 years</td><td>82.3%</td><td>53.4%</td></tr><tr><td>Pathirana et al (2025) ≥18 years</td><td>84.0%</td><td>51.0%</td></tr></tbody></table> 826 (2 RCTs) ¹⁻⁴ ⊕⊕⊕○ Moderate^a 21vPCV likely results in a reduction in any local AEs compared to 15vPCV+23vPPV.	Study	15vPCV+23vPPV	21vPCV+Saline	Scott et al (2026) 18-64 years	82.3%	53.4%	Pathirana et al (2025) ≥18 years	84.0%	51.0%
Study	15vPCV+23vPPV	21vPCV+Saline								
Scott et al (2026) 18-64 years	82.3%	53.4%								
Pathirana et al (2025) ≥18 years	84.0%	51.0%								

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Patient or population: Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions

Intervention: 21vPCV (V116) + saline

Comparison: 15vPCV+23vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Explanations a. Downgraded as ethnicity of study population not reflective of population of interest (Aboriginal and Torres Island peoples) b. Some concerns in the missing outcome domain c. Serious inconsistency between studies for intervention arm Abbreviations: 21vPCV= 21-valent pneumococcal conjugate vaccine; 15vPCV= 15-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; AEs=adverse events; CI=confidence interval; GMC= geometric mean concentrations; GMT=geometric mean titres; IgG=Immunoglobulin G; LCI=lower confidence interval; NR= not reported; OPA=opsonophagocytic activity; RCTs=randomised controlled trials; SAEs= serious adverse events; ST= serotype; UCI=upper confidence interval.				
GRADE Working Group grades of evidence <i>High certainty:</i> We are very confident that the true effect lies close to that of the estimate of the effect <i>Moderate certainty:</i> We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. <i>Low certainty:</i> Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. <i>Very low certainty:</i> We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.				

GRADE evidence profile

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Any serious adverse events (SAEs) (follow-up: 6 months)									
2	Rando mised trials	Not serious	Not serious	Serious ^a	Not serious	None	The rate of SAEs was 2.6% for 21vPCV and ranged from 3.9% to 5.4% for 15vPCV+23vPPV. No SAEs were considered by study investigators to be related to the vaccine. ¹⁻⁴	⊕⊕⊕○ Moderate	CRITICAL
OPA GMT ratio (Follow-up: 30 days)									
2	Rando mised trials	Not serious	Not serious	Serious ^a	Not serious	None	The OPA GMT ratio 30 days following vaccination for shared serotypes ranges from [REDACTED]. In the P008 study, all serotypes met a non-inferiority margin of a lower CI of >0.675. In the P007 study, serotypes 8 and 19A did not meet a non-inferiority margin of a lower CI of >0.675, however, they met a non-inferiority margin of a lower CI of >0.50. For 21v-non-23v serotypes (15A, 15C, 16F, 23A, 23B, 24F, 31, 35B), the OPA GMT ratio 30 days following vaccination ranged from [REDACTED]. All serotypes, except 15C in only the P007 study, met a superiority margin of a lower CI of >2. For serotypes 15B and 6C that are considered cross-reactive, i.e. similar enough to those targeted by the vaccine to potentially provide some level of protection, the OPA GMT ratio was not measured. ^{1,2}	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
IgG GMC ratio (follow-up: 30 days)									
2	Rando mised trials	Not serious	Not serious	Serious ^a	Not serious	None	The IgG GMC ratio 30 days following vaccination for shared serotypes ranges from [REDACTED]. All serotypes met a non-inferiority margin of a lower CI of >0.675, except 8 and 6A which met a non-inferiority margin of a lower CI of >0.50. For 21v-non23v serotypes (15A, 15C, 16F, 23A, 23B, 24F, 31, 35B), the IgG GMC ratio 30 days following vaccination ranged from [REDACTED]. All serotypes met a superiority margin of a lower CI of >2, except for 15C in the P008 study which met the non-inferiority criteria of LCI >0.675. For serotypes 15B and 6C that are considered cross-reactive, i.e. similar enough to those targeted by the vaccine to potentially provide some level of protection, the IgG GMC ratio was not measured. ^{1,2}	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
%of participants ≥4-fold rise in OPA GMT (follow-up: 30 days)									
2	Rando mised trials	Serious ^b	Not serious	Serious ^a	Not serious	None	The proportion of participants with ≥4-fold rise of OPA GMT pre- to post-vaccination for shared serotypes ranged from [redacted] for 21vPCV recipients and from [redacted] for 15vPCV+23vPPV recipients. For the unique 21vPCV serotypes (15A, 15C, 16F, 23A, 23B, 24F, 31, 31B), the proportion of participants with ≥4-fold rise of OPA GMT pre- to post-vaccination ranged from [redacted] for 21vPCV and from [redacted] for 15vPCV+23vPCV. For serotypes 15B and 6C that are considered cross-reactive i.e. similar enough to those targeted by the vaccine to potentially provide some level of protection the proportion of participants with ≥4-fold rise in OPA GMT pre- to post-vaccination for ST 15B ranged from [redacted] for 21vPCV and [redacted] for 15vPCV+23vPPV, and for ST 6C ranged from [redacted] for 21vPCV and [redacted] for 15vPCV+23vPPV. ¹⁻⁴	⊕⊕○○ Low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
% of participants ≥4-fold rise in IgG GMC (follow-up: 30 days)									
2	Rando mised trials	Not serious	Not serious	Serious ^a	Not serious	None	The proportion of participants with ≥4-fold rise of IgG GMC pre- to post-vaccination for shared serotypes ranged from [REDACTED] for 21vPCV recipients and from [REDACTED] for 15vPCV+23vPPV recipients. For the unique 21vPCV serotypes (15A, 15C, 16F, 23A, 23B, 24F, 31, 31B), the proportion of participants with ≥4-fold rise of IgG GMC pre- to post-vaccination ranged from [REDACTED] for 21vPCV and from [REDACTED] for 15vPCV+23vPCV. For serotypes 15B and 6C that are considered cross-reactive i.e. similar enough to those targeted by the vaccine to potentially provide some level of protection the proportion of participants with ≥4-fold rise in IgG GMC pre- to post-vaccination for ST 15B ranged from [REDACTED] for 21vPCV and [REDACTED] for 15vPCV+23vPPV, and for ST 6C ranged from [REDACTED] for 21vPCV and [REDACTED] for 15vPCV+23vPPV. ¹⁻⁴	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Any systemic adverse events (follow-up: 5 days)									
2	Randomised trials	Not serious	Serious ^c	Serious ^a	Not serious	None	The rate of systemic adverse events ranged from 51.6% to 63.2% for 21vPCV recipients and 59.4% to 68.5% for 15vPCV+23vPCV recipients. Fatigue, headache and muscle pain were most common. ^{1,2}	⊕⊕○○ Low	IMPORTANT
Any local adverse events (follow-up: 5 days)									
2	Randomised trials	Not serious	Not serious	Serious ^a	Not serious	None	The rate of local adverse events was 51.0% to 53.4% for 21vPCV recipients and 82.3% to 83.9% for 15vPCV+23vPPV recipients. Injection site pain and swelling was most common. ^{1,2}	⊕⊕⊕○ Moderate	IMPORTANT
Explanations									
a. Downgraded as ethnicity of study population not reflective of population of interest (Aboriginal and Torres Island peoples)									
b. Some concerns in the missing outcome domain									
c. Serious inconsistency between studies for intervention arm									
Abbreviations: 21vPCV=21-valent pneumococcal conjugate vaccine; 15vPCV=15-valent pneumococcal conjugate vaccine; 23vPPV=23-valent pneumococcal polysaccharide vaccine; GMC=geometric mean concentrations; GMT=geometric mean titres; IgG=Immunoglobulin G; OPA=opsonophagocytic activity; SAEs=serious adverse events; ST=serotype									

ATAGI evidence to decision framework for 21vPCV compared with 15vPCV+23vPPV in Aboriginal and Torres Island peoples aged ≥50 years without risk conditions

Should 21vPCV be recommended as an alternative for or preferred over 15vPCV+23vPPV Aboriginal and Torres Island peoples aged ≥50 years without risk conditions for the prevention of pneumococcal disease?					
Population	Aboriginal and Torres Island peoples aged ≥50 years without risk conditions				
Intervention	21-valent pneumococcal conjugate vaccine (21vPCV) + saline				
Comparison	15-valent pneumococcal conjugate vaccine + 23-valent pneumococcal polysaccharide vaccine (15vPCV+23vPPV)				
Main outcomes	<i>Immunogenicity</i> OPA and IgG geometric mean titres: • OPA GMT ratios pre- to post-vaccination • IgG GMC ratios pre- to post-vaccination • % of participants ≥ 4-fold rise of GMT pre- to post-vaccination • % of participants ≥ 4-fold rise of GMC pre- to post-vaccination <i>Safety</i> • serious adverse events • local adverse events • systemic adverse events				
Setting	Australia, Belgium, Canada, Chile, France, Japan, New Zealand, Poland, South Africa, South Korea, Thailand and the United States				
Perspective	Individual				
ASSESSMENT					
Problem <i>Is the problem a priority?</i>					
Don't know	Varies	No	Probably no	Probably yes	Yes
• In Australia, in 2023, there were over 2200 notifications of invasive pneumococcal disease (IPD, the severe form of pneumococcal disease).⁵ Individuals with certain underlying risk conditions have increased risk of pneumococcal disease. Serotypes that cause pneumococcal disease in those with risk conditions is more diverse compared to others.					

- The use of PCV over several years, combined with high coverage, means certain non-vaccine serotypes have increased in Australia. In the current 13vPCV era, the additional serotypes in 21vPCV cause a considerable amount of residual IPD in adults aged ≥ 18 years.
- Extended-valency PCVs would likely improve pneumococcal disease prevention in adults.

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial
• Overall, there is evidence of a small effect at improving immunogenicity outcomes for 21v-non15v serotypes based on the OPA GMT ratios, IgG GMC ratios and % of participants with ≥ 4-fold rise in OPA GMT and IgG GMC. • Evidence for the shared serotypes between 21vPCV and 15vPCV+23vPPV suggests there is little to no difference in the immunogenicity. • No evidence is available on persistence of immunogenicity or effectiveness against clinical outcomes after 21vPCV.					

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial
• Undesirable effects include frequent rates of injection site adverse events and systemic adverse events, which are mostly of mild to moderate severity. In comparison, the rates of local and systemic adverse events are slightly lower than those seen after 15vPCV+23vPPV. • Rate of serious adverse events were low and comparable to 15vPCV+23vPPV. No serious adverse events were considered to be vaccine related.					

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Don't Know	Varies	Favours comparison	Probably favours comparison	Does not favour either comparison or intervention	Probably favours intervention	Favours intervention
• The overall balance of desirable and undesirable effects for the 21v-non15v+23v serotypes probably favours 21vPCV compared to 15vPCV+23vPPV • The overall balance of desirable effects of 21vPCV are comparable to 15vPCV+23vPPV for the shared serotypes and slightly favour 21vPCV for undesirable effects. • Undesirable effects are minor yet slightly higher in 15vPCV+23vPPV compared to 21vPCV.						

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- The certainty of evidence is moderate.
- For five out of the seven outcomes the certainty of evidence is moderate and for two outcomes it was low.
- The evidence was downgraded to moderate due to indirectness as ethnicity of study population not reflective of population of interest (Aboriginal and Torres Island peoples) the certainty of evidence was further downgraded to low either due to serious risk of bias due to missing outcome data (for % participants $\geq$ 4-fold rise in OPA GMT) or due to inconsistency between studies (for any systemic adverse events).

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Important uncertainty	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability
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- There is unlikely to be important uncertainty in how people value protection against pneumococcal disease.

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes
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- Vaccination to prevent pneumococcal disease appears to be acceptable in the Australian setting.
- In 2016, the vaccination uptake of the 23vPPV vaccine in adults aged ≥ 65 years was estimated to be 52%.⁶
- The 13vPCV program commenced in July 2020. Whilst the vaccine coverage for 13vPCV in adults aged over 70 years was 23.9% in 2021, this was likely more due to lack of awareness⁷ of pneumococcal vaccines and the program being relatively new, rather than a lack of acceptability of the intervention. Coverage increased in the following years, with vaccine coverage for 13vPCV in adults aged over 70 years 33.8% in 2022 and 37.6% in 2023. ⁵
- The coverage of 23vPPV doses following 13vPCV is not currently evaluated in National coverage reports.

Equity

What would be the impact on health inequities?

Don't know	Varies	Increased	Probably increased	Probably no impact	Probably reduced	Reduced
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- There is probably no impact of 21vPCV use over 20vPCV on health inequities
- Currently 13vPCV is funded under the National Immunisation Program pneumococcal program for adults aged ≥ 70 years without risk conditions. Neither 21vPCV nor 20vPCV are currently funded. However, if either of these vaccines were funded it probably reduce health inequities when compared to 13vPCV as more serotypes causing IPD would be covered.
- Based on Australian epidemiology data the serotypes causing IPD are consistent across population groups and use of 21vPCV would cover similar proportions of cases i.e. 81% in people aged ≥ 70 years and 84% in Aboriginal and Torres Island peoples aged ≥ 25 years.

- This program can be accessed via multiple immunisation providers such as GPs and pharmacies which supports equitable access. However, data is not currently investigated to determine if access is a barrier for pneumococcal vaccination in regional and remote areas.

Feasibility

Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes
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- There are minimal barriers to implementation, as the vaccine delivery system is already in use and this vaccine would likely replace the use of another vaccine for the individuals receiving it.

ATAGI recommendation

21vPCV is recommended preferentially to 15vPCV+23vPPV in those Aboriginal and Torres Island peoples aged ≥ 50 years without risk conditions.

Justification and considerations

- Rates of any systemic and any serious adverse events were generally comparable between 15vPCV+23vPPV and 21vPCV. A lower rate of local adverse events is observed following 21vPCV compared to 15vPCV+23vPPV.
- The evidence suggests that 21vPCV likely results in little difference in the immunogenicity outcomes for the shared serotypes compared to 15vPCV+23vPPV. However, there is some concern regarding downward drift in immunogenicity and a lower immune response for serotype 19A. The immune response for serotype 3 continues to be sub-optimal for 21vPCV, which is consistent with other lower valency pneumococcal conjugate vaccines.
- The sponsor claims cross protection for two serotypes: 15B and 6C. Data was provided for the % participants with greater than 4-fold rise in OPA and IgG to support this claim. As 15B is included in 15vPCV and both 21vPCV and 20vPCV provide cross-protection against 6C, there is no additional benefit to using 21vPCV for these two serotypes.
- Based on the current epidemiology of the top 20 serotypes causing IPD in Australia, ATAGI notes that the net-benefit of protection from increased coverage of disease-causing serotypes in 21vPCV outweighs loss of 19F and 4 and lower immune response of 19A. This is because the serotypes causing a significant proportion of IPD that are excluded from 21vPCV are included in 20vPCV, and the herd protection offered by vaccinating children with 20vPCV would provide protection against these three serotypes causing a significant proportion of IPD in Australia.
- ATAGI notes there is uncertainty regarding efficacy against clinical outcomes as only 4 serotypes in 21vPCV are shared with 13vPCV for which there is clinical efficacy data. This study is an immune-bridging study to a vaccine (15vPCV+23vPPV) that was only assessed via immune-bridging to 13vPCV (i.e., a bridge to a bridge immunogenicity study) with downward drift in immunogenicity for shared serotypes observed at each stage.

References

1. Merck Sharp & Dohme (MSD). A phase 3, randomized, double-blind, active comparator-controlled clinical study to evaluate the safety, tolerability, and immunogenicity of v116 in pneumococcal vaccine-naïve adults 18 to 64 years of age with increased risk for pneumococcal disease. [Clinical Study Report]. In press 2024.
2. Merck Sharp & Dohme (MSD). A phase 3, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of v116 in adults living with HIV. [Clinical Study Report]. In press 2023.
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