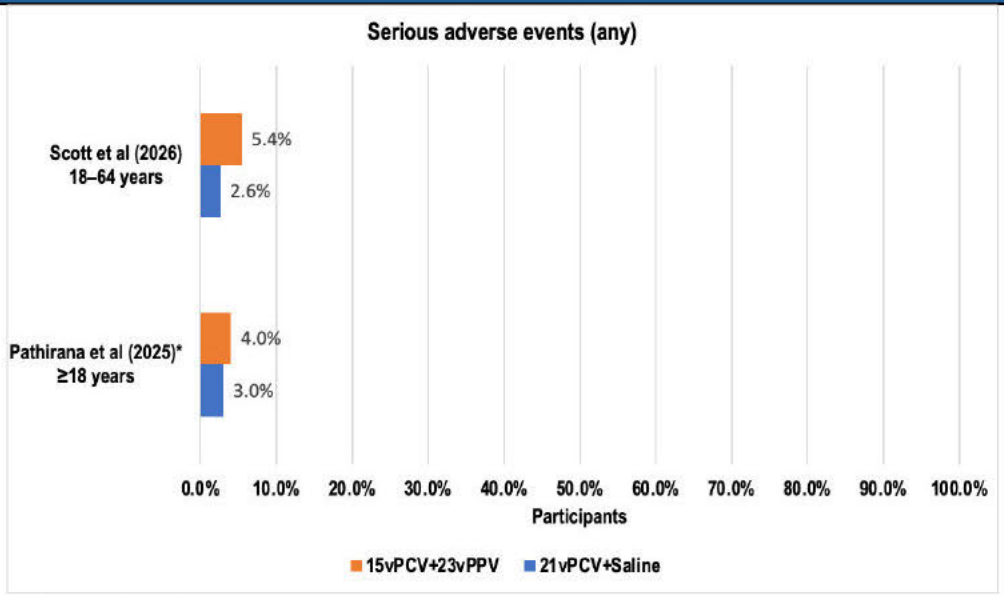
GRADE tables: Comparison of 21vPCV (V116) with 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

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

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

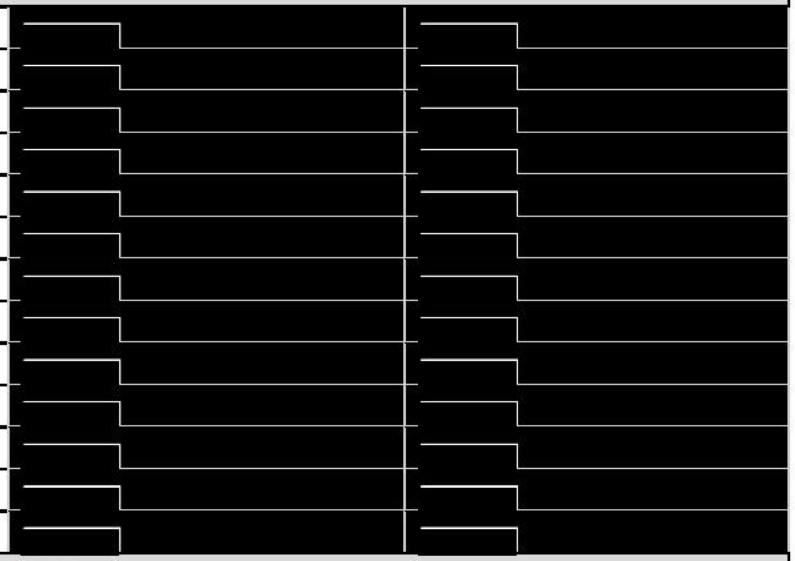
Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Any serious adverse events (SAEs) Follow-up: 6 months	 *Follow up = 3 months No cases were considered related to the vaccine	826 (2 RCTs)[1-4]	⨁⨁⨁⨁ High	21vPCV results in little to no difference in any SAEs compared to 15vPCV+23vPPV.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

<table>
<tr><th>Outcomes</th><th>Impact</th><th>No of participants (studies)</th><th>Certainty of the evidence (GRADE)</th><th>Interpretation</th></tr>
<tr>
<td>OPA GMT ratio

Follow-up: 30 days</td>
<td>
Table 1a: 95% CI for OPA GMT ratios (21vPCV vs. 15vPCV+23vPPV) for shared and unique serotypes at Day 30 shaded by non-inferiority (using 3 different thresholds) and superiority margins^
<table>
<tr><th>Study</th><th colspan="2">CSR P007 (2023) ≥18 years</th><th colspan="2">CSR P008 (2024) ≥18 years</th></tr>
<tr><td>PCV</td><td>21vPCV+Saline</td><td>15vPCV + 23vPPV</td><td>21vPCV+Saline</td><td>15vPCV + 23vPPV</td></tr>
<tr><td>N</td><td>155</td><td>155</td><td>386</td><td>130</td></tr>
<tr><td colspan="5">Shared STs</td></tr>
<tr><td>3</td><td colspan="4" rowspan="13">  </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>
<tr><td colspan="5">Unique STs: 23v-non-21v</td></tr>
<tr><td>1</td><td colspan="2">NR</td><td colspan="2">NR</td></tr>
</table>
</td>
<td>828
(2 RCTs)[1,2]</td>
<td>⊕⊕⊕⊕
High</td>
<td>21vPCV 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 which only met the non-inferiority margin of LCI>0.51 in one study.

21vPCV results in greater OPA GMT ratios for all 8 STs unique to 21vPCV, except for 15C which still met the non-inferiority margin of LCI>0.675 in one study</td>
</tr>
</table>

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact			No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	2	NR	NR			There is no data available on the STs unique to 23vPPV.
	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	[redacted]				
	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 20vPCV or 21vPCV. There was no data provided for this outcome.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation

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 or 15vPCV+23vPPV^

Study	CSR P007 (2023) ≥18 years		CSR P008 (2024) ≥18 years	
PCV	21vPCV	15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV
N	155	155	386	130
Shared STs				
3	[redacted]			
6A				
7F				
8				
9N				
10A				
11A				
12F				
17F				
19A				
20/20A				
22F				
33F				
Unique STs: 23v-non-21v				
1	[redacted]		[redacted]	

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	[redacted]			

* 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 20vPCV or 21vPCV. There was no data provided for this outcome.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
continued **OPA GMT 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^			

Study	**CSR P007 (2023) ≥18 years**		**CSR P008 (2024) ≥18 years**	
PCV	21vPCV	15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV
N	155	155	386	130
Shared STs				
3	[redacted]			
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	

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact			No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	9V	NR	NR			
	14	NR	NR			
	15B*	NR	NR			
	18C	NR	NR			
	19F	NR	NR			
	23F	NR	NR			
	Unique STs: 21v-non-23v					
	15A	[redacted]				
	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 20vPCV or 21vPCV. There was no data provided for this outcome.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation

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 or 15vPCV+23vPPV^

Study	CSR P007 (2023) ≥18 years		CSR P008 (2023) ≥18 years	
PCV	21vPCV	15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV
N	156	156	386	130
Shared STs				
3	[redacted]			
6A				
7F				
8				
9N				
10A				
11A				
12F				
17F				
19A				
20/20A				
22F				
33F				
Unique STs: 23v-non-21v				
1	NR		NR	

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact			No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	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	[redacted]				
	15C					
	16F					
	23A					
	23B					
	24F					
	31					
	35B					

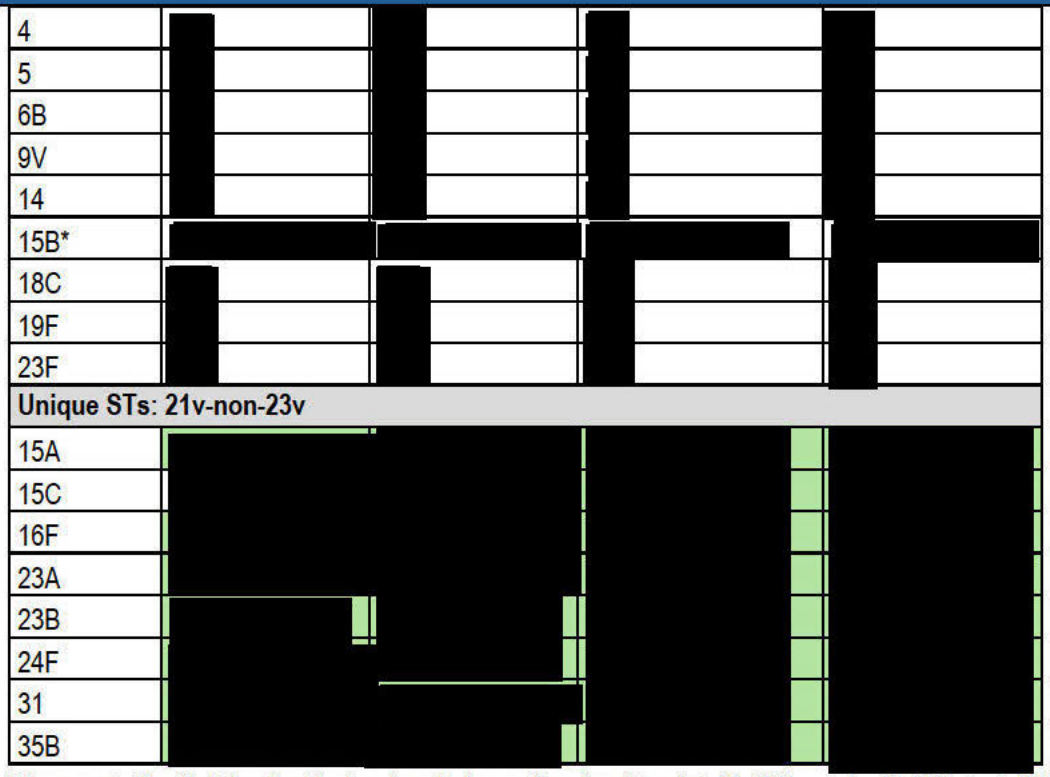
^red=UCI<1; green = LCI>1; blue = LCI>2
* Note: sponsor claims cross protection for 15B though it is not contained in the 21vPCV vaccine formulation. Sponsor also claims cross protection of ST 6C which is not contained in either 20vPCV or 21vPCV. There was no data provided for this outcome.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

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**: % of participants ≥4-fold rise in OPA GMT pre- to 30 days post-vaccination^	828 (2 RCT)[1,2]	⊕⊕⊕◯ Moderate[a]	21vPCV likely results 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 likely results 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

Study	CSR P007 (2023) ≥18 years		CSR P008 (2024) ≥18 years	
PCV	21vPCV	15vPCV + 23vPPV	21vPCV	15vPCV + 23vPPV
N	156	156	386	130
Shared STs				
3	[redacted]	[redacted]	[redacted]	[redacted]
6A				
7F				
8				
9N				
10A				
11A				
12F				
17F				
19A				
20/20A				
22F				
33F				
Unique STs: 23v-non-21v				
1	[redacted]	[redacted]	[redacted]	[redacted]
2				

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions				
Patient or population: Adults aged ≥18 years with risk conditions **Intervention**: 21vPCV (V116) + saline **Comparison**: 15vPCV+233vPPV				
Outcomes	**Impact**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
	 ^Green=a significantly higher (i.e. CIs do not overlap) proportion of participants in 21vPCV group had ≥4-fold rise in OPA GMT pre- to post–vaccination compared with 15vPCV+23vPPV participants * 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 20vPCV or 21vPCV. There was no statistically			except 15B, which may result in little to no difference.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	significant difference between the responses for 6C in either study: P007 - [redacted] P008 [redacted]			

Table 4: % of 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	[redacted]	[redacted]	[redacted]	[redacted]
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

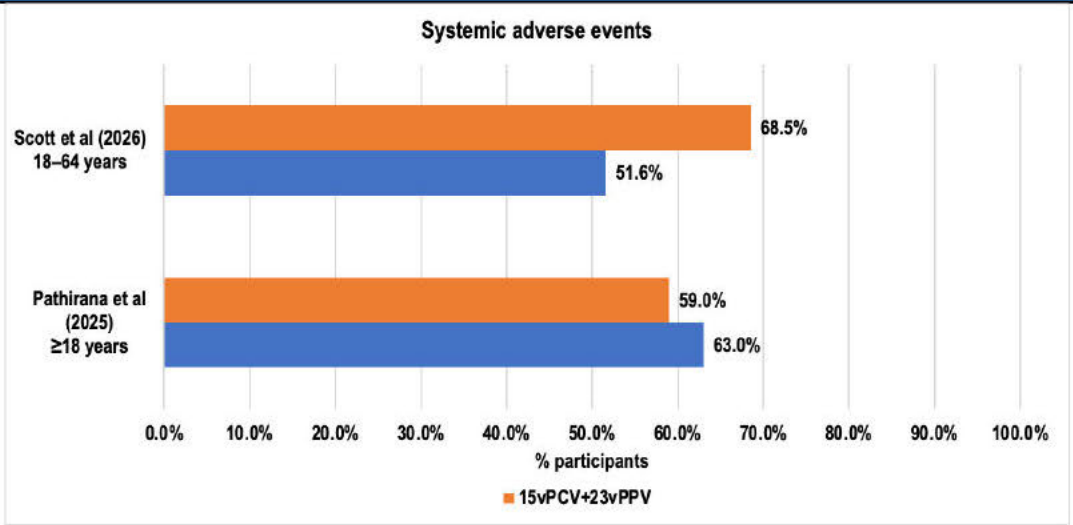
Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	6B NR NR NR NR 9V NR NR NR NR 14 NR NR NR NR 15B* [redacted] 18C NR NR NR NR 19F NR NR NR NR 23F NR NR NR NR **Unique STs: 21v-non-23v** 15A [redacted] 15C 16F 23A 23B 24F 31 35B ^Green=a significantly higher (i.e. CIs do not overlap) proportion of participants in 21vPCV group had ≥4-fold rise in OPA GMT pre- to post-vaccination compared with 15vPCV+23vPPV participants; Red = a significantly higher (i.e. CIs do not overlap) proportion of participants in 15vPCV+23vPCV group had ≥4-fold rise in OPA GMT pre- to post-vaccination compared with 21vPCV participants *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 20vPCV or 21vPCV. There was no statistically significant difference between the responses for 6C: [redacted]			

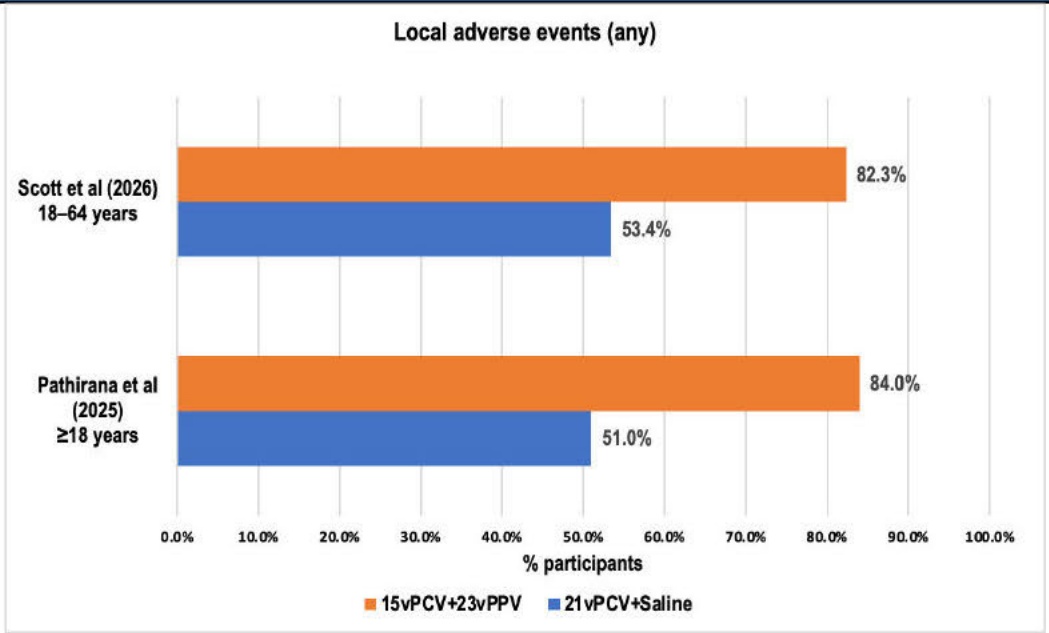
Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Any systemic adverse events (AEs) Follow-up: 5 days		826 (2 RCTs)[1-4]	⊕⊕⊕◯ Moderate[b]	21vPCV likely results in little to no difference in any systemic AEs compared to 15vPCV+23vPPV.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Any local adverse events (AEs) Follow-up: 5 days		826 (2 RCTs)[1-4]	⊕⊕⊕⊕ High	21vPCV results in a reduction in any local AEs compared to 15vPCV+23vPPV.

Comparison of 21vPCV (V116) to 15vPCV+23vPPV in adults aged ≥18 years with risk conditions

Patient or population: Adults aged ≥18 years with risk conditions
Intervention: 21vPCV (V116) + saline
Comparison: 15vPCV+233vPPV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation

Explanations

a. Some concerns in missing outcome domain

b. 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

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: 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	Randomised trials	Not serious	Not serious	Not serious	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]	⊕⊕⊕⊕ High	CRITICAL
OPA GMT ratio (follow-up: 30 days)									
2	Randomised trials	Not serious	Not serious	Not serious	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 >0.67. In the P007 study, serotypes 8 and 19A did not meet a non-inferiority margin of a lower CI of >0.67, however, they 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 OPA GMT ratio 30 days following vaccination ranged from [redacted]. All serotypes, except 15C in only in 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]	⊕⊕⊕⊕ High	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	Randomised trials	Serious[a]	Not serious	Not serious	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 postvaccination ranged from [redacted] for 21vPCV and from [redacted] for 15vPCV+23vPCV. For serotypes 15B that is 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 ranged from [redacted] for 21vPCV and [redacted] for 15vPCV+23vPPV.[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	Randomised trials	Not serious	Not serious	Not serious	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 >0.67, except 8 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. 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]	⊕⊕⊕⊕ High	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
% participants ≥4 fold-rise in IgG GMC (follow-up: 30 days)									
2	Randomised trials	Not serious	Not serious	Not serious	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 postvaccination ranged from [redacted] for 21vPCV and from [redacted] or 15vPCV+23vPCV. For serotypes 15B that is 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 ranged from [redacted] for 21vPCV [redacted] for 15vPCV+23vPPV (15B). [1,2]	⊕⊕⊕⊕ High	IMPORTANT
Any systemic adverse events (follow-up: 5 days)									
2	Randomised trials	Not serious	Serious[b]	Not serious	Not serious	None	The rate of systemic adverse events ranged from 39.9% to 63.2% for 21vPCV recipients and 53.8% to 59.4% for 15vPCV+23vPCV recipients. Fatigue, headache and muscle pain were most common.[1-4]	⊕⊕⊕◯ Moderate	IMPORTANT
Any local adverse events (follow-up: 5 days)									

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	The rate of local adverse events was 51.0% to 53.4% for 21vPCV recipients and 82.0% to 83.9% for 15vPCV+23vPPV recipients. Injection site pain and swelling was most common.[1-4]	⨁⨁⨁⨁ High	IMPORTANT

Explanations

a. Some concerns in missing outcome domain

b. 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 adults aged ≥18 years with risk conditions

Should 21vPCV be recommended as an alternative for or preferred over 15vPCV+23vPPV in adults aged ≥18 years with risk conditions for the prevention of pneumococcal disease?	
Population	Adults aged ≥18 years with risk conditions
Intervention	21-valent pneumococcal conjugate vaccine (21vPCV)
Comparison	15-valent pneumococcal conjugate vaccine + 23-valent pneumococcal polysaccharide vaccine (15vPCV+23vPPV)
Main outcomes	*Immunogenicity* 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 *Safety* • serious adverse events • local adverse events • systemic adverse events
Setting	Australia, Canada, Chile, Japan, New Zealand, Poland, South Korea, and the United States
Perspective	Individual

ASSESSMENT

Problem
Is the problem a priority?

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. It is noted that the undesirable effects are after 15vPCV, before 23vPPV dose, are comparable 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 high.
- For five of the seven outcomes the certainty of evidence is high and for two it is moderate.
- For one outcome (% of participants ≥4-fold rise in OPA GMT), the certainty of evidence was downgraded to low due to serious risk of bias due to missing outcome data. For another outcome (systemic adverse events) the certainty of evidence was downgraded due to inconsistency between studies.

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

- 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

- 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 ≥18 years was estimated to be 52%.[6]
- The 13vPCV program commenced in July 2020. Whilst the vaccine coverage for 13vPCV in adults aged over 18 years was 23.9% in 2021, this was likely more due to lack of awareness[7] 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

- 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 compared to lower valency vaccines i.e. 81% in people aged ≥70 years and 84% in Aboriginal and Torres Island peoples aged ≥50 years.
- This program can be accessed via multiple immunisation providers such as GPs and pharmacies which supports equitable access. However, data is not currently available on whether access is a barrier for pneumococcal vaccination, particularly in regional and remote areas.

Feasibility
Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes

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 aged 18 years and over with 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 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.
- 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 observed at each stage.

References

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