GRADE tables: Comparison of 21vPCV (V116) with 20vPCV in non-Indigenous adults aged ≥70 years without 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 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

<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>Any serious adverse events (Any SAEs)

Follow-up: 6 months</td><td>There was no difference in proportion of any SAEs between 21vPCV or 20vPCV groups among those 50 years and over. Platt et al 2024 (STRIDE-3): n=19/1177, 1.6% (95%CI: NR) in 21vPCV group; n= 24/1175, 2.0% (95%CI: NR) in 20vPCV group</td><td>2,329
(1 RCT)[1,2]</td><td>⊕⊕⊕⊕
High[a]</td><td>21vPCV results in little to no difference in any SAEs compared to 20vPCV</td></tr>
<tr><td>OPA GMT ratio

Follow-up: 30 days</td><td>Table 1a: 95% CI for OPA GMT ratios (21vPCV vs. 20vPCV) 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">Platt et al (2024; STRIDE-3)
≥50 years</th></tr>
<tr><td>PCV</td><td>21vPCV</td><td>20vPCV</td></tr>
<tr><td>N</td><td>1179</td><td>1177</td></tr>
<tr><td>Shared STs</td><td colspan="2"></td></tr>
<tr><td>3</td><td colspan="2">1.40–1.72</td></tr>
<tr><td>6A</td><td colspan="2">0.68–0.88</td></tr>
<tr><td>7F</td><td colspan="2">0.95–1.18</td></tr>
<tr><td>8</td><td colspan="2">1.25–1.53</td></tr>
</table></td><td>2300
(1 RCT)[1-3]</td><td>⊕⊕⊕⊕
High[a]</td><td>21vPCV results in little difference in OPA GMT ratios for the 10 shared STs with 20vPCV as the ratios all met a non-inferiority margin of LCI>0.675.

21vPCV results in greater OPA GMT ratios for all 11 STs unique to 21vPCV, except for 15C which still met the non-inferiority margin of LCI>0.675.</td></tr>
</table>

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact		No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	10A	0.75–0.93			There is no data available on the STs unique to 20vPCV or cross reactions STs.
	11A	1.39–1.72			
	12F	0.92–1.21			
	19A	0.69–0.84			
	22F	0.72–0.92			
	33F	1.01–1.32			
	Unique STs: 20v-non-21v				
	1	NR			
	4	NR			
	5	NR			
	6B	NR			
	9V	NR			
	14	NR			
	18C	NR			
	19F	NR			
	23F	NR			
	15B*	NR			
	Unique STs: 21v-non-20v				
	9N	4.12–5.04			
	15A	2.91–3.74			
	15C	1.77–2.34			

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

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

16F	5.16–6.41
17F	14.90–19.09
20A	8.66–10.79
23A	6.86–9.55
23B	8.48–12.00
24F	33.87–44.25
31	18.68–25.18
35B	5.59–6.80

^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.

Table 1b: 95% CI for OPA GMT ratios (21vPCV vs. 20vPCV) for shared and unique serotypes at Day 30 shaded by estimates that favour 21vPCV*^

Study	**Platt et al (2024; STRIDE-3) ≥50 years**	
PCV	21vPCV	20vPCV
N	1179	1177
Shared STs		
3	1.40–1.72	
6A	0.68–0.88	
7F	0.95–1.18	

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact		No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	8	1.25–1.53			
	10A	0.75–0.93			
	11A	1.39–1.72			
	12F	0.92–1.21			
	19A	0.69–0.84			
	22F	0.72–0.92			
	33F	1.01–1.32			
	Unique STs: 20v-non-21v				
	1	NR			
	4	NR			
	5	NR			
	6B	NR			
	9V	NR			
	14	NR			
	18C	NR			
	19F	NR			
	23F	NR			
	15B*	NR			
	Unique STs: 21v-non-20v				
	9N	4.12–5.04			
	15A	2.91–3.74			

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

<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></td><td>
<table>
<tr><td>15C</td><td>1.77–2.34</td></tr>
<tr><td>16F</td><td>5.16–6.41</td></tr>
<tr><td>17F</td><td>14.90–19.09</td></tr>
<tr><td>20A</td><td>8.66–10.79</td></tr>
<tr><td>23A</td><td>6.86–9.55</td></tr>
<tr><td>23B</td><td>8.48–12.00</td></tr>
<tr><td>24F</td><td>33.87–44.25</td></tr>
<tr><td>31</td><td>18.68–25.18</td></tr>
<tr><td>35B</td><td>5.59–6.80</td></tr>
</table>
^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.</td><td></td><td></td><td></td></tr>
<tr><td>**IgG GMC ratio**

Follow-up: 30 days</td><td>**Table 2a**: 95% CI for IgG GMC ratios (21vPCV vs. 20vPCV) for shared and unique serotypes at Day 30 shaded by non-inferiority (using 3 different thresholds) and superiority margins^*
<table>
<tr><td>**Study**</td><td colspan="2">**CSR P003 (2023) ≥50 years**</td></tr>
<tr><td>**PCV**</td><td>21vPCV</td><td>20vPCV</td></tr>
<tr><td>**N**</td><td>1179</td><td>1177</td></tr>
<tr><td>**Shared STs**</td><td colspan="2"></td></tr>
<tr><td>3</td><td colspan="2"></td></tr>
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(1 RCT)[1]</td><td>⊕⊕⊕⊕
High[a]</td><td>21vPCV results in little difference in IgG ratios for the 10 shared STs with 20vPCV as all ratios met a non-inferiority margin of LCI>0.675 except 19A which only met the non-inferiority margin of LCI>0.51.</td></tr>
</table>

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

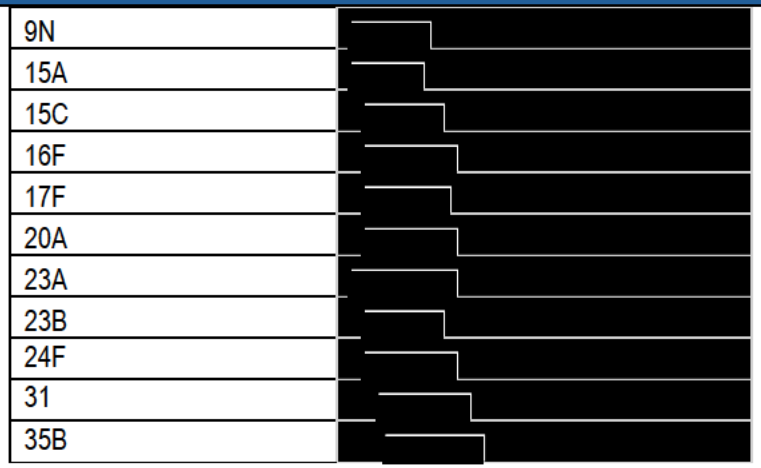
Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact		No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	6A	[redacted]			21vPCV results in greater IgG GMT ratios for all 11 serotypes unique to 21vPCV. There is no data available on the STs unique to 20vPCV.
	7F				
	8				
	10A				
	11A				
	12F				
	19A				
	22F				
	33F				
	Unique STs: 20v-non-21v				
	1	NR			
	4	NR			
	5	NR			
	6B	NR			
	9V	NR			
	14	NR			
	18C	NR			
	19F	NR			
	23F	NR			
	15B*	NR			
	Unique STs: 21v-non-20v				

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

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



^Orange= non-inferiority LCI>0.675; Yellow= non-inferiority LCI>0.51; 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.

Table 2b: 95% CI for IgG GMC ratios (21vPCV vs. 20vPCV) for shared and unique serotypes at Day 30 shaded by estimates that favour 21vPCV^*

Study	CSR P003 (2023) ≥50 years	
PCV	21vPCV	20vPCV
N	1179	1177
Shared STs		

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions				
Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions **Intervention**: 21vPCV (V116) **Comparison**: 20vPCV				
Outcomes	**Impact**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
	3 [redacted] 6A [redacted] 7F [redacted] 8 [redacted] 10A [redacted] 11A [redacted] 12F [redacted] 19A [redacted] 22F [redacted] 33F [redacted]			

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact		No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	Unique STs: 20v-non-21v				
	1	NR			
	4	NR			
	5	NR			
	6B	NR			
	9V	NR			
	14	NR			
	18C	NR			
	19F	NR			
	23F	NR			
	15B*	NR			
	Unique STs: 21v-non-20v				
	9N	[redacted]			
	15A	[redacted]			
	15C	[redacted]			
	16F	[redacted]			
	17F	[redacted]			
	20A	[redacted]			
	23A	[redacted]			
	23B	[redacted]			
	24F	[redacted]			

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	31 [redacted] 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.			
% of participants with ≥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^*	2,300 (1 RCT)[1-3]	⊕⊕⊕◯ Moderate[a,b]	21vPCV results in an increase in the % of participants with ≥4-fold rise in OPA GMT for 4/10 shared serotypes (3, 8, 11A and 33F).

Study	**Platt et al (2024; STRIDE-3) ≥50 years**	
PCV	21vPCV	20vPCV
N	1179	1177
Shared STs		
3	71% (68.4–74.2)	59% (55.9–62.3)
6A	77% (74.0–79.5)	80% (77.2–82.4)
7F	71% (68.1–73.9)	66% (62.8–68.9)
8	76% (73.0 – 78.4)	67% (64.3–70.3)
10A	72% (69.1–74.6)	74% (71.3–76.9)
11A	70% (66.9–73.0)	62% (58.2–64.7)
12F	89% (87.0–90.9)	87% (84.9–89.1)
19A	64% (61.3–67.3)	70% (67.2–73.0)
22F	71% (67.5–73.4)	74% (71.5–77.2)

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact			No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	33F	68% (64.6–70.7)	62% (58.3–64.6)			
	Unique STs: 20v-non-21v					
	1	NR	NR			
	4	NR	NR			
	5	NR	NR			
	6B	NR	NR			
	9V	NR	NR			
	14	NR	NR			
	18C	NR	NR			
	19F	NR	NR			
	23F	NR	NR			
	15B*	[redacted]	[redacted]			
	Unique STs: 21v-non-20v					
	9N	65% (61.5–67.8)	20% (17.5–22.6)			
	15A	67% (63.0–70.2)	36% (32.3–39.5)			
	15C	83% (80.9–85.7)	74% (71.2–76.9)			
	16F	72% (68.8–74.8)	21% (18.3–23.5)			
	17F	76% (72.7–78.6)	10% (7.7–11.5)			
	20A	67% (64.3–70.2)	10% (7.8–11.6)			
	23A	79% (75.8–81.7)	37% (33.3–40.4)			
	23B	86% (83.2–87.6)	50% (46.4–52.7)			

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	24F: 81% (77.8–83.0); 6% (4.8–8.1) 31: 77% (73.6–79.3); 18% (15.5 – 20.5) 35B: 60% (56.7–63.2); 7% (5.3 – 8.5) Green = 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 20vPCV or 21vPCV. There was no statistically significant difference in the response for 6C in the P003 study 21vPCV = [redacted] (95%CI: [redacted] vs 20vPCV [redacted] (95%CI: [redacted]			
% of participants with ≥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 P003 (2023); **PCV**: 21vPCV / 20vPCV; **N**: 1179 / 1177 **Shared STs** 3: 57% (53.5–59.4); 41% (38.0–44.0) 6A: 73% (70.1–75.7); 80% (77.2–82.1) 7F: 76% (73.8–78.9); 76% (73.2–78.4) 8: 76% (73.1–78.3); 68% (64.9–70.6) 10A: 80% (77.8–82.6); 82% (79.5–84.2) 11A: 71% (68.1–73.8); 63% (59.8–65.6) 12F: 74% (71.5–76.7); 71% (68.6–74.1) 19A: 56% (52.6–58.5); 65% (62.0–67.8) 22F: 77% (74.2–79.3); 79% (76.0–81.0) 33F: 72% (68.8–74.2); 67% (63.8–69.6)	2,300 (1 RCT)[1]	⊕⊕⊕⊕ High[a]	21vPCV results in an increase in the % of participants with ≥4-fold rise in IgG GMC for 4/10 shared serotypes (3, 6A, 8, and 11A). It results in little to no difference for serotypes 5/10 shared serotypes (7F, 10A, 12F, 22F and 33F). 21vPCV results in a decrease in % participants with ≥4-fold rise in IgG GMC for 19A.

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact			No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	Unique STs: 20v-non-21v					21vPCV results in an increase in % participants with ≥4-fold rise in IgG for 11/11 serotypes unique to 21vPCV. For the two serotypes the sponsor claims cross protection* for 21vPCV results in little to no difference in % participants with ≥4-fold rise in IgG GMC for 6C but results in a decrease for 15B.
	1	NR	NR			
	4	NR	NR			
	5	NR	NR			
	6B	NR	NR			
	9V	NR	NR			
	14	NR	NR			
	18C	NR	NR			
	19F	NR	NR			
	23F	NR	NR			
	15B*	[redacted]	[redacted]			
	Unique STs: 21v-non-20v					
	9N	78% (75.3–80.3)	29% (26.7–32.2)			
	15A	86% (83.5–87.8)	38% (34.8–40.7)			
	15C	81% (78.9–83.6)	63% (60.2–66.1)			
	16F	81% (78.9–83.6)	12% (10.0–13.9)			
	17F	85% (82.2–86.6)	43% (3.1–5.7)			
	20A	75% (72.1–77.3)	13% (0.7–2.2)			
	23A	86% (83.3–87.6)	29% (26.7–32.2)			
	23B	76% (73.4–78.6)	42% (39.3–45.2)			
	24F	84% (81.7–86.1)	2% (1.5–3.4)			
	31	81% (78.6–83.4)	4% (2.8–5.2)			

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	35B | 83% (80.8–85.3) | 3% (2.3–4.5) ^Green = point estimate favours intervention and CIs do not overlap; Red = point estimate favours comparator 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 20vPCV or 21vPCV. There was no statistically significant difference in the response for 6C in the P003 study 21vPCV = [redacted] (95%CI: [redacted]) and 20vPCV = [redacted] (95%CI: [redacted]).			
Any systemic adverse events (Any systemic AEs) Follow-up: 5 days	There was no difference in proportion of any systemic AEs between 21vPCV or 20vPCV groups among those 50 years and over. Platt et al 2024 (STRIDE-3): n=334/1177, 28.4% (95%CI: NR) in 21vPCV group; n= 323/1175, 27.5% (95%CI: NR) in 20vPCV group.	2,329 (1 RCT)[1,2]	⊕⊕⊕⊕ High[a]	21vPCV results in little to no difference in any systemic AEs compared to 20vPCV
Any local adverse event (Any local AE) Follow-up: 5 days	There was a slight decrease in the proportion of any local AEs between 21vPCV or 20vPCV groups among those 50 years and over. Platt et al 2024 (STRIDE-3): n=487/1177, 41.4% (95%CI: NR) in 21vPCV group; n= 630/1175, 53.6% (95%CI: NR) in 20vPCV group.	2,329 (1 RCT)[1,2]	⊕⊕⊕⊕ High[a]	21vPCV results in a slight decrease in any local AEs compared to 20vPCV

Comparison of 21vPCV (V116) to 20vPCV in non-indigenous adults aged ≥70 years without risk conditions

Patient or population: Non-Indigenous adults aged ≥70 years without risk conditions
Intervention: 21vPCV (V116)
Comparison: 20vPCV

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

Explanations

a. Inconsistency not assessed, as only 1 study included
b. Some concerns in missing outcome domain

Abbreviations: 21vPCV=21-valent pneumococcal conjugate vaccine; 20vPCV=20-valent pneumococcal conjugate 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; OP= 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)									
1	Randomised trials	Not serious	N/A[a]	Not serious	Not serious	None	The rates of SAEs ranged between 1.6% (No CI reported) for 21vPCV and 2.0% (No CI reported) for 20vPCV. No SAEs were considered by study investigators to be related to the vaccine.[1,2]	⨁⨁⨁⨁ High	CRITICAL
OPA GMT ratio (follow-up: 30 days)									
1	Randomised trials	Not serious	N/A[a]	Not serious	Not serious	None	The OPA GMT ratio 30 days following vaccination for shared serotypes ranges from 0.76 to 1.55. All serotypes across studies met a non-inferiority margin of a lower CI of >0.67. For 21v-non20v serotypes (9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, 31B), the OPA GMT ratio 30 days following vaccination range from 2.03 to 38.71. All serotypes, except 15C met a superiority margin of a upper 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			
IgG GMC ratio (follow-up: 30 days)									
1	Randomised trials	Not serious	N/A[a]	Not serious	Not serious	None	The IgG GMC ratio 30 days following vaccination for shared serotypes ranges from [redacted]. All serotypes across studies met a non-inferiority margin of a lower CI of >0.67 except 19A which met a non-inferiority margin of a lower CI of >0.50. For 21v-non20v serotypes (9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, 31B), the IgG GMC ratio 30 days following vaccination range [redacted]. All serotypes met a superiority margin of an upper 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]	⊕⊕⊕⊕ High	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
% of participants with ≥4-fold rise in OPA GMT (follow-up: 30 days)									
1	Randomised trials	Serious[b]	N/A[a]	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 64.4% to 89.0% for 21vPCV recipients and from 61.5% to 87.1% for 20vPCV recipients. For 21v-non20v serotypes (9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, 31B), the proportion of participants with ≥4-fold rise of OPA GMT pre- to post-vaccination ranged from 60.0% to 85.5% for 21vPCV and from 6.3% TO 49.6% for 20vPCV. 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 were [redacted] for 21vPCV and [redacted] for 20vPCV (15B), and [redacted] for 21vPCV and [redacted] for 20vPCV (6C).[1,2]	⨁⨁⨁◯ Moderate	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
% of participants with ≥4-fold rise in IgG GMC (follow-up: 30 days)									
1	Randomised trials	Not serious	N/A[a]	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 55.6% to 80.3% for 21vPCV recipients and from 41.0% to 82.0% for 20vPCV recipients. For 21v-non20v serotypes (9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, 31B), the proportion of participants with ≥4-fold rise of IgG GMC pre- to postvaccination ranged from 76.1% to 85.7% for 21vPCV and from 2.3% to 63.2% for 20vPCV. 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 GMT pre- to post-vaccination were [redacted] for 21vPCV and [redacted] for 20vPCV (15B), and [redacted] for 21vPCV and [redacted] for 20vPCV (6C).[1,3]	⊕⊕⊕⊕ High	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Any systemic adverse event (follow-up: 5 days)									
1	Randomised trials	Not serious	N/A[a]	Not serious	Not serious	None	The rate of systemic adverse events was 28.4% (no CI reported) for 21vPCV recipients and 27.5% (no CI reported) for 20vPCV recipients. Fatigue and headache were most common.[1,2]	⨁⨁⨁⨁ High	IMPORTANT
Any local adverse event (follow-up: 5 days)									
1	Randomised trials	Not serious	N/A[a]	Not serious	Not serious	None	The rate of local adverse events was 41.4% (no CI reported) for 21vPCV recipients and 53.6% (no CI reported) for 20vPCV recipients. Injection site pain was most common.[1,2]	⨁⨁⨁⨁ High	IMPORTANT

Explanations

a. Inconsistency not assessed, as only 1 study included
b. Some concerns in missing outcome domain

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 to 20vPCV for non-Indigenous adults aged ≥70 years without risk conditions

Should 21vPCV be recommended as an alternative for or preferred over 13vPCV use in non-indigenous adults ≥70 years for the prevention of pneumococcal disease?	
Population	Non-indigenous adults aged ≥70 years without risk conditions with or without a history of previous 23-valent pneumococcal polysaccharide vaccine (23vPPV) or 13-valent or 15-valent pneumococcal conjugate vaccine vaccination
Intervention	21-valent pneumococcal conjugate vaccine (21vPCV)
Comparison	20-valent pneumococcal conjugate vaccine (20vPCV)
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* With 20vPCV or 13vPCV delivery: • serious adverse events • local adverse events • systemic adverse events
Setting	Australia, Belgium, Chile, Germany, Republic of Korea, New Zealand, Puerto Rico, Sweden, Taiwan, Turkey, & USA.
Perspective	Individual

ASSESSMENT					
Problem *Is the problem a priority?*					
Don't know	Varies	No	Probably no	Probably yes	Yes
• Pneumococcal disease incidence is high in older adults. In Australia, over 2,200 cases of invasive pneumococcal disease (IPD, the severe form of pneumococcal disease) occurred in 2023. Rates of IPD were highest in children aged 0 to 4 years (24.7 per 100,000 population) and adults aged 65 years and over (17.8 per 100,000 population).[4] The incidence of all community-acquired pneumonia caused by pneumococcus is several-fold higher than IPD.[5] • 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 non-indigenous adults aged ≥70 years.[6] • 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-non20v serotypes based on the OPA and IgG GMR, and the % of participants with ≥4-fold rise in OPA GMT and IgG GMC. • Evidence for the shared serotypes between 21vPCV and 20vPCV suggests there is little to no difference in the immunogenicity. • No evidence is available on persistence of immunogenicity or effectiveness against clinical outcomes after 20vPCV.					
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 rate of local adverse events is slightly lower than those seen after 20vPCV and there was little to no difference in the rate of systemic adverse events compared to 20vPCV.
- The rate of serious adverse events was low and comparable to 20vPCV.

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 slightly favour 21vPCV compared to 20vPCV due to the slightly lower rate of local adverse events.
- The overall balance of desirable effects of 21vPCV are comparable to 20vPCV for the shared serotypes and slightly favour 21vPCV for undesirable effects

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.
- Six out of the seven outcomes the certainty of evidence was high.
- The evidence was downgraded to moderate for one outcome (% participants ≥4 fold-rise in OPA GMT) due to serious risk of bias due to missing outcome data.

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 ≥65 years was estimated to be 52%.[7]
- The 13vPCV program commenced in July 2020. 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 awareness[8] 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.

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 ≥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 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 20vPCV in those aged ≥70 years without risk conditions.
Justification and considerations
• Rates of any systemic and any serious adverse events were generally comparable between 20vPCV and 21vPCV. A lower rate of local adverse events is observed following 21vPCV compared to 20vPCV • The evidence suggests that 21vPCV likely results in little difference in the immunogenicity outcomes for the shared serotypes compared to 20vPCV. 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 20vPCV, 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 20vPCV 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 serotypes. 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 (20vPCV) 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.

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