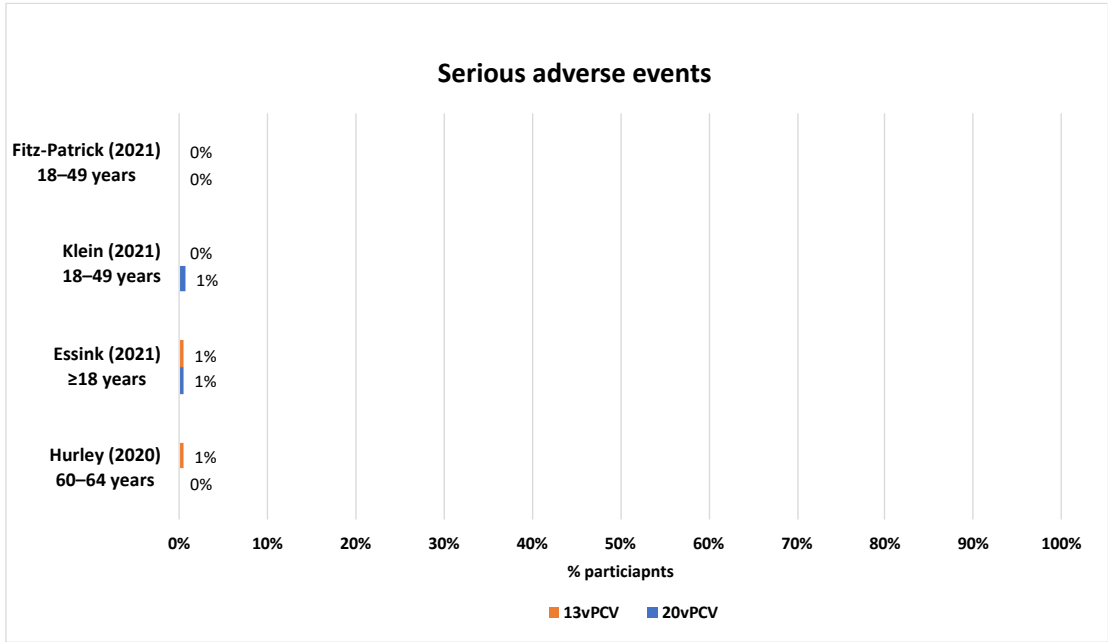
GRADE tables: Comparison of 20vPCV to 13vPCV in immunocompetent non-First Nations adults aged over 70 years without risk conditions

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

20vPCV compared to 13vPCV for immunocompetent non-First Nations adults aged ≥70 years without risk conditions				
Patient or population: Immunocompetent non-First Nations adults aged ≥70 years without risk conditions **Intervention:** 20vPCV **Comparison:** 13vPCV				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Serious adverse events (SAEs)		5,148 (4 RCTs)[1-4]	⨁⨁⨁⨁ High	20vPCV likely results in little to no difference in SAEs compared to 13vPCV.

OPA GMT ratios
follow-up: 27–49 days

Table 1a: 95% CI for OPA GMT ratios (20vPCV vs. 13vPCV) for shared serotypes at 1 month (27–49 days) post-vaccination shaded by non-inferiority (using 2 different thresholds) and superiority margins^

Study	**Essink (2021)**		**Klein (2021)***	
Population	**Aged ≥60 years**		**Aged 18–49**	
PCV	20	13	20	13
N	1,435	1,420	1,386	232
Serotype				
1	0.71, 0.90		0.58, 0.87	
3	0.78, 0.93		0.77, 1.03	
4	0.71, 0.93		0.66, 1.01	
5	0.74, 0.94		0.57, 0.85	
6A	0.66, 0.88		0.75, 1.12	
6B	0.73, 0.95		0.73, 1.09	
7F	0.77, 0.96		0.67, 0.99	
9V	0.82, 1.05		0.76, 1.10	
14	0.89, 1.13		0.83, 1.20	
18C	0.74, 0.97		0.70, 1.09	
19A	0.71, 0.90		0.73, 1.03	
19F	0.70, 0.91		0.54, 0.83	
23F	0.70, 0.97		0.74, 1.23	
8	NR		NR	
10A				
11A				
12F				
15B				
22F				
33F				

^Non-inferiority margins: orange=LCI>0.67[5]; yellow=LCI>0.5[6]

*Study not powered not to detect a difference between 20vPCV and 13vPCV but to demonstrate equivalence in immune response to the 3 20vPCV lots

Table 1b: 95% CI for OPA GMT ratios (20vPCV vs. 13vPCV) for shared and unique serotypes at 1 month (27–49 days) post-vaccination shaded by estimates that favour 20vPCV or 13vPCV†

Study	**Essink (2021)**		**Klein (2021)***	
Population	**Aged ≥60 years**		**Aged 18–49 years**	
PCV	20	13	20	13
N	1,435	1,420	1,386	232
Serotype				
1	0.71, 0.90		0.58, 0.87	
3	0.78, 0.93		0.77, 1.03	
4	0.71, 0.93		0.66, 1.01	
5	0.74, 0.94		0.57, 0.85	
6A	0.66, 0.88		0.75, 1.12	
6B	0.73, 0.95		0.73, 1.09	

4,473
(2 RCTs)[2,3]

⊕⊕⊕◯
Moderate[a]

20vPCV likely results in little difference in OPA GMT ratios for shared STs.

Note: OPA GMT ratios all met a non-inferiority margin of LCI>0.5.[6]

20vPCV compared to 13vPCV for immunocompetent non-First Nations adults aged ≥70 years without risk conditions					
Patient or population: Immunocompetent non-First Nations adults aged ≥70 years without risk conditions **Intervention:** 20vPCV **Comparison:** 13vPCV					
Outcomes	Impact			№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
	7F	0.77, 0.96	0.67, 0.99			
	9V	0.82, 1.05	0.76, 1.10			
	14	0.89, 1.13	0.83, 1.20			
	18C	0.74, 0.97	0.70, 1.09			
	19A	0.71, 0.90	0.73, 1.03			
	19F	0.70, 0.91	0.54, 0.83			
	23F	0.70, 0.97	0.74, 1.23			
	8	NR	NR			
	10A					
	11A					
	12F					
	15B					
	22F					
	33F					
	†Red=UCI<1 *Study powered not to detect a difference between 20vPCV and 13vPCV but to demonstrate equivalence in immune response to the 3 20vPCV lots					

% of participants ≥ 4-fold rise of GMT pre- to 1 month (27–49 days) post-vaccination	Table 2: % of participants ≥ 4-fold rise of GMT pre- to 1-month (27–49 days) post-vaccination* **Study** **Essink (2021)** **Fitz-Patrick (2021)** **Hurley (2020)** **Population** **Aged ≥60 years** **Aged 18–49 years** **Aged 60–64 years** PCV 20 13 20 13 20 13 N 1,435 1,420 35 35 168–210 169–208 Serotype 1 72.1 (69.7 to 74.4) 74.8 (72.4 to 77.0) 94.1% (80.3, 99.3) 100% (89.7, 100.0) 81.4% (75.3, 86.5) 82.0% (76.0, 87.0) 3 56.1 (53.4 to 58.7) 61.7 (59.1 to 64.2) 64.7% (46.5, 80.3) 82.4% (65.5, 93.2) 64.4% (57.5, 70.9) 69.6% (62.8, 75.8) 4 75.5 (73.2 to 77.8) 79.6 (77.4 to 81.7) 83.3% (65.3, 94.4) 97.0 (84.2, 99.9) 75.9% (69.3, 81.7) 76.7% (70.1, 82.5) 5 55.6 (52.9 to 58.2) 60.6 (58.0 to 63.2) 70.6% (52.5, 84.9) 70.6% (52.5, 84.9) 63.7% (56.7, 70.3) 68.8% (61.9, 75.1) 6A 80.5 (78.3 to 82.5) 84.0 (82.0 to 85.9) 90.9% (75.7, 98.1) 96.7 (82.8, 99.9) 87.2% (81.7, 91.6) 85.9% (80.1, 90.5) 6B 75.7 (73.3 to 77.9) 77.6 (75.3 to 79.8) 92.9% (76.5, 99.1) 88.9% (70.8, 97.6) 80.8% (74.6, 86.1) 83.0% (76.8, 88.1) 7F 71.8 (69.3 to 74.1) 72.3 (69.8 to 74.6) 54.8% (36.0, 72.7) 83.% (65.3, 94.4) 70.3% (63.3, 76.6) 76.8% (70.2, 82.5) 9V 67.7 (65.1 to 70.3) 69.3 (66.7 to 71.8) 67.9% (47.6, 84.1) 55.2% (35.7, 73.6) 62.4% (55.3, 69.1) 69.9% (63.0, 76.2) 14 58.2 (55.5 to 60.8) 54.0 (51.3 to 56.6) 67.9% (47.6, 84.1) 55.2% (35.7, 73.6) 53.5% (46.3, 60.6) 55.1% (47.8, 62.1) 18C 77.7 (75.4 to 79.8) 79.6 (77.4 to 81.7) 76.7% (57.7, 90.1) 80.6% (62.5, 92.5) 76.5% (70.0, 82.2) 79.5% (73.1, 84.9) 19A 73.6 (71.3 to 75.9) 77.5 (75.2 to 79.7) 87.1% (70.2, 96.4) 96.7% (82.8, 99.9) 77.5% (71.1, 83.0) 82.2% (76.2, 87.2) 19F 63.6 (61.1 to 66.2) 66.9 (64.4 to 69.4) 85.3% (68.9, 95.0) 78.8% (61.1, 91.1) 65.2% (58.2, 71.7) 75.0% (68.5, 80.8) 23F 70.6 (68.2 to 73.0) 74.4 (72.0 to 76.7) 97.0% (84.2, 99.9) 97.1% (84.7, 99.9) 73.7% (67.1, 79.5) 77.3% (71.0, 82.9) 8 NR 96.4% (81.7, 99.9) 6.9% (0.8, 22.8) NR 10A 60.7% (40.6, 78.5) 0.0% (0.0, 11.6) 11A 56.3% (37.7, 73.6) 0.0% (0.0, 12.8) 12F 96.8% (83.3, 99.9) 0.0% (0.0, 11.6) 15B 81.3% (63.6, 92.8) 61.% (0.7, 20.2) 22F 72.4% (52.8, 87.3) 7.4% (0.9, 24.3) 33F 75.9% (56.5, 89.7) 0.0% (0.0, 10.6) *Green=a significantly higher (i.e. CIs do not overlap) proportion of participants in 20vPCV group had ≥4-fold rise of GMT pre- to post-vaccination compared with 13vPCV participants. Orange=borderline significantly lower proportion of participants in 20vPCV group had ≥4 fold rise of GMT pre- to post-vaccination compared with 13cPCV (upper CI of 20vPCV <1% above the lower CI of 13vPCV)							2,925 (3 RCTs)[1,3,4]	⊕⊕⊕◯ Moderate[b]	20vPCV results in little difference in % of participants with ≥ 4-fold rise of GMT pre- to 27–49 days post-vaccination for shared ST. 20vPCV likely increases % of participants with ≥ 4-fold rise of GMC pre- to 27–49 days post-vaccination for ST unique to 20vPCV. *Note:* CIs overlap, but point estimate for STs 3, 4, 5, 6A and 19A for 20vPCV does not appear in the CI for 13vPCV.

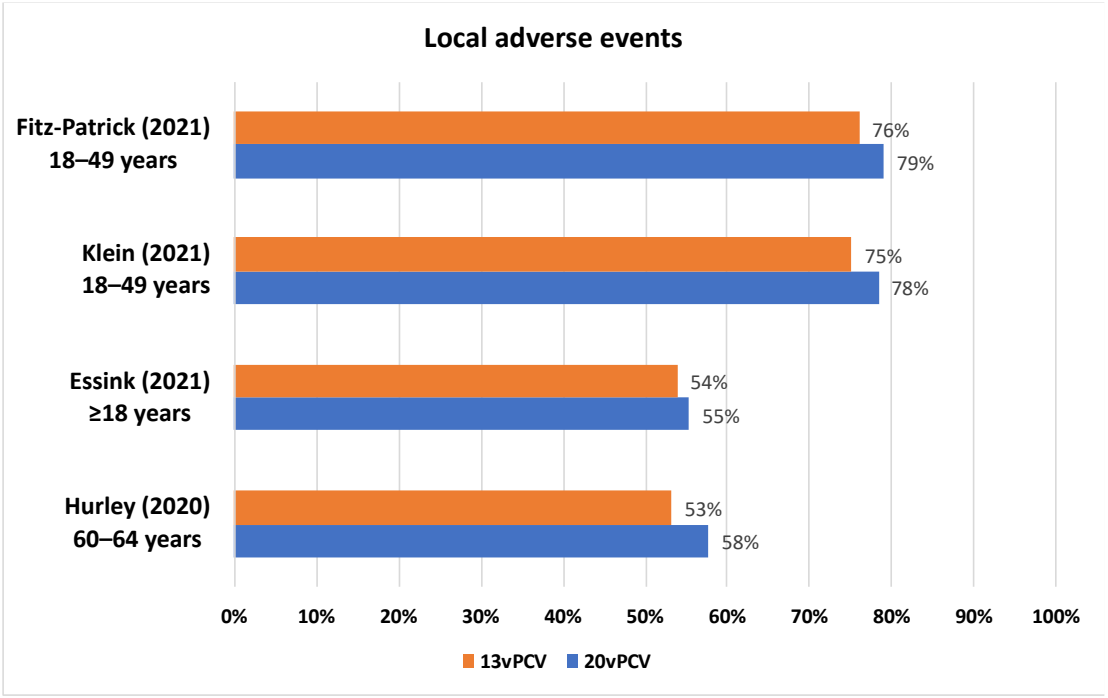
20vPCV compared to 13vPCV for immunocompetent non-First Nations adults aged ≥70 years without risk conditions

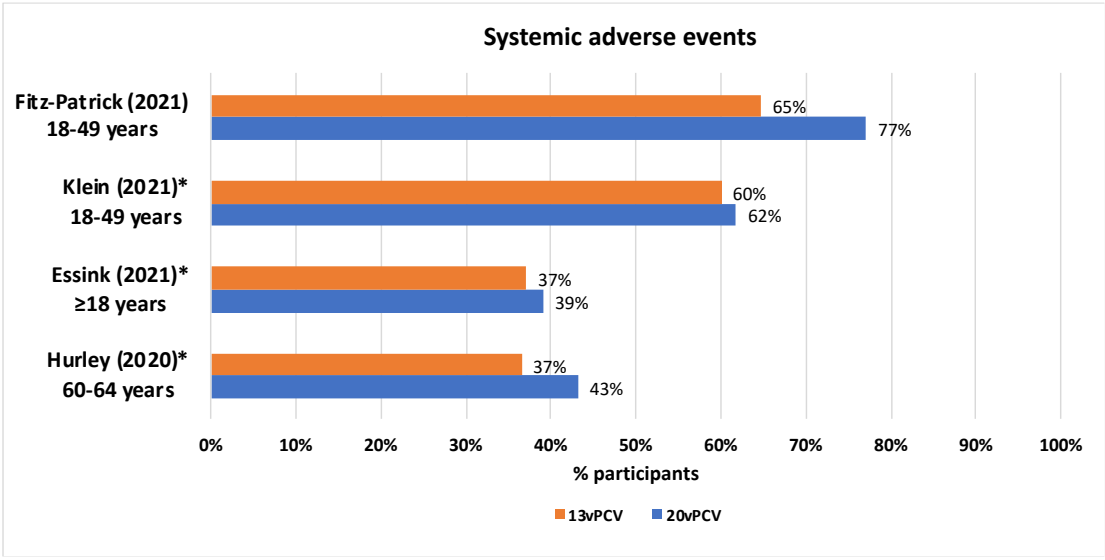
Patient or population: Immunocompetent non-First Nations adults aged ≥70 years without risk conditions
Intervention: 20vPCV
Comparison: 13vPCV

<table>
<tr><th>Outcomes</th><th>Impact</th><th>№ of participants (studies)</th><th>Certainty of the evidence (GRADE)</th><th>Interpretation</th></tr>
<tr>
<td>% of participants ≥ 4-fold rise of GMC pre- to 1 month (27–49 days) post-vaccination</td>
<td>Table 3: % of participants ≥ 4-fold rise of GMC pre- to 1 month (27–49 days) post-vaccination*
<table>
<tr><td>Study</td><td colspan="2">Fitz-Patrick 2021</td></tr>
<tr><td>Population</td><td colspan="2">Aged 18–49 years</td></tr>
<tr><td>PCV</td><td>20</td><td>13</td></tr>
<tr><td>N</td><td>35</td><td>35</td></tr>
<tr><td>Serotype</td><td></td><td></td></tr>
<tr><td>1</td><td>94.1% (80.3, 99.3)</td><td>97.1 (84.7, 99.9)</td></tr>
<tr><td>3</td><td>38.2% (22.2,56.4)</td><td>70.6% (52.5, 84.9)</td></tr>
<tr><td>4</td><td>91.2% (76.3, 98.1)</td><td>94.1 (80.3, 99.3)</td></tr>
<tr><td>5</td><td>97.1 (84.7, 99.9)</td><td>97.1 (84.7, 99.9)</td></tr>
<tr><td>6A</td><td>94.1 (80.3, 99.3)</td><td>88.2 (72.5, 96.7)</td></tr>
<tr><td>6B</td><td>91.2 (76.3, 98.1)</td><td>100.0 (89.7, 100.0)</td></tr>
<tr><td>7F</td><td>82.4 (65.5, 93.2)</td><td>97.1 (84.7, 99.9)</td></tr>
<tr><td>9V</td><td>91.2 (76.3, 98.1)</td><td>97.1 (84.7, 99.9)</td></tr>
<tr><td>14</td><td>76.5 (58.8, 89.3)</td><td>82.4 (65.5, 93.2)</td></tr>
<tr><td>18C</td><td>88.2 (72.5, 96.7)</td><td>94.1 (80.3, 99.3)</td></tr>
<tr><td>19A</td><td>85.3 (68.9, 95.0)</td><td>97.1 (84.7, 99.9)</td></tr>
<tr><td>19F</td><td>88.2 (72.5, 96.7)</td><td>91.2 (76.3, 98.1)</td></tr>
<tr><td>23F</td><td>100.0 (89.7, 100.0)</td><td>100.0 (89.7, 100.0)</td></tr>
<tr><td>8</td><td>97.1 (84.7, 99.9)</td><td>8.8 (1.9, 23.7)</td></tr>
<tr><td>10A</td><td>85.3 (68.9, 95.0)</td><td>0.0 (0.0, 10.3)</td></tr>
<tr><td>11A</td><td>73.5 (55.6, 87.1)</td><td>0.0 (0.0, 10.3)</td></tr>
<tr><td>12F</td><td>85.3 (68.9, 95.0)</td><td>5.9 (0.7, 19.7)</td></tr>
<tr><td>15B</td><td>79.4 (62.1, 91.3)</td><td>2.9 (0.1, 15.3)</td></tr>
<tr><td>22F</td><td>85.3 (68.9, 95.0)</td><td>0.0 (0.0, 10.3)</td></tr>
<tr><td>33F</td><td>67.6 (49.5, 82.6)</td><td>0.0 (0.0, 10.3)</td></tr>
</table>
*Green=a higher proportion of participants in 20vPCV group had ≥4-fold rise of GMC pre- to post-vaccination compared with 13vPCV participants. Orange=point estimate is almost halved for 20vPCV compared to 13vPCV. The proportion of participants with ≥4-fold rise of GMC pre- to post-vaccination was not statistically significantly higher or lower (i.e. CIs were overlapping) for 13vPCV compared to 20vPCV in any of the shared serotypes.</td>
<td>70
(1 RCT)[1]</td>
<td>⨁◯◯◯
Very low[a,c,d,e]</td>
<td>The evidence is very uncertain about the effect of 20vPCV on % of participants with ≥ 4-fold rise of GMC pre- to 2—49 days post-vaccination.

It may result in little to no difference for shared STs and may increase for unique STs, but the evidence is very uncertain.

Note: Point estimate for ST 3 is almost half for 20vPCV compared to 13vPCV. CIs overlap, but point estimate for 20vPCV does not appear in the CI for 13vPCV.</td>
</tr>
</table>

20vPCV compared to 13vPCV for immunocompetent non-First Nations adults aged ≥70 years without risk conditions				
Patient or population: Immunocompetent non-First Nations adults aged ≥70 years without risk conditions **Intervention:** 20vPCV **Comparison:** 13vPCV				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Local adverse events within 7 days		5,148 (4 RCTs)[1-4]	⨁⨁⨁⨁ High	20vPCV results in a slight increase in local adverse events compared to 13vPCV.

20vPCV compared to 13vPCV for immunocompetent non-First Nations adults aged ≥70 years without risk conditions				
Patient or population: Immunocompetent non-First Nations adults aged ≥70 years without risk conditions **Intervention:** 20vPCV **Comparison:** 13vPCV				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Systemic adverse events within 7 days	 *Studies did not report overall values for systemic adverse events; muscle pain has been used as a proxy measure	5,148 (4 RCTs)[1-4]	⨁⨁⨁⨁ High	20vPCV results in a slight increase in systemic adverse events compared to 13vPCV.

OPA GMFR pre- to 1-month (27–49 days) post-vaccination	Table 4: OPA GMFR pre- to 1-month (27–49 days) post-vaccination* **Study** / **Hurley (2021)** / **Essink (2021)** / **Fitz-Patrick (2021)** **Population** / **Aged 60–64 years** / **Aged ≥60 years** / **Aged 18–49 years** PCV: 20 / 13 / 20 / 13 / 20 / 13 N: 168–210 / 169–208 / 1360–1425 / 1294–1418 / 35 / 35 Serotype 1: 21.2 (17.0, 26.6) / 33.5 (25.8, 43.7) / 12.6 (NR) / 4.8 (NR) / 29.1 (18.9, 44.8) / 31.8 (21.4, 47.2) 3: 6.0 (5.0, 7.2) / 7.1 (5.9, 8.6) / 15.4 (NR) / 5.8 (NR) / 6.1 (4.4, 8.5) / 9.2 (6.4, 13.3) 4: 37.8 (27.4, 52.1) / 51.0 (36.0, 72.3) / 31.2 (NR) / 39.3 (NR) / 96.3 (40.5, 228.9) / 177.6 (97.6, 323.3) 5: 8.3 (6.6, 10.5) / 11.6 (9.09, 14.7) / 6.1 (NR) / 7.2 (NR) / 11.0 (6.0, 20) / 15.7 (8.5, 28.7) 6A: 58.6 (44.2, 77.8) / 68.6 (49.5, 95.2) / 34.3 (NR) / 42.6 (NR) / 144.7 (70.7, 296.4) / 152.7 (77.0, 302.6) 6B: 29.6 (22.6, 38.7) / 38.8 (28.5, 52.7) / 23.8 (NR) / 26.5 (NR) / 65.1 (31.4, 134.2) / 46.7 (22.2, 98.2) 7F: 12.2 (9.9, 15.2) / 15.8 (12.6, 19.8) / 12.2 (NR) / 13.5 (NR) / 8.4 (4.4, 15.8) / 18.1 (10.6, 30.8) 9V: 7.7 (6.2, 9.6) / 10.1 (7.95, 12.7) / 11.0 (NR) / 12.5 (NR) / 7.5 (4.3, 13.1) / 11.3 (6.8, 18.9) 14: 8.5 (6.35, 11.26) / 9.6 (7.2, 12.9) / 9.3 (NR) / 8.3 (NR) / 11.9 (5.8, 24.3) / 11.2 (5.1, 24.5) 18C: 26.8 (19.7, 35.9) / 35.2 (26.0, 47.5) / 33.8 (NR) / 37.7 (NR) / 38.8 (19.1, 78.8) / 53.7 (24.0, 120.0) 19A: 23.3 (18.0, 30.2) / 30.9 (23.7, 40.4) / 21.0 (NR) / 25.9 (NR) / 46.3 (24.3, 88.3) / 98.9 (60.4, 162.1) 19F: 11.8 (8.9, 15.5) / 18.4 (14.2, 23.9) / 8.6 (NR) / 10.8 (NR) / 20.3 (11.6, 35.7) / 27.4 (14.5, 51.6) 23F: 33.6 (24.2, 46.5) / 39.8 (28.9, 54.9) / 24.9 (NR) / 30.7 (NR) / 136.9 (79.2, 236.6) / 90.9 (51.6, 160.1) 8: NR / NR / 150.7 (72.5, 313.3) / 0.9 (0.6, 1.4) 10A: 10.6 / 0.7	3,331 (3 RCTs)[1,3,4]	⊕⊕◯◯ Low[b,f]	20vPCV likely results in little difference GMFR pre- to 27–49 days post-vaccination for shared STs. 20vPCV likely increases GMFR pre- to 27–49 days post-vaccination for STs unique to 20vPCV. *Note:* Magnitude of difference for GMFR point estimate ST 4 for 20vPCV pre- to post-vaccination compared with 13vPCV participants is of potential concern.

20vPCV compared to 13vPCV for immunocompetent non-First Nations adults aged ≥70 years without risk conditions

Patient or population: Immunocompetent non-First Nations adults aged ≥70 years without risk conditions
Intervention: 20vPCV
Comparison: 13vPCV

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

				(4.5, 25.3)	(0.5, 1.1	
			11A	6.1 (3.2, 11.6)	0.7 (0.6, 1.0)	
			12F	149.1 (68.0, 327.2)	1.0 (0.6, 1.0)	
			15B	101.6 (35.5, 291.0)	1.3 (0.9, 1.0)	
			22F	19.6 (8.4, 45.7)	1.3 (0.8, 2.1)	
			33F	10.0 (6.3, 15.6)	0.9 (0.7, 1.1)	

*Green: GMFR point estimate for 20vPCV pre- to post-vaccination was higher compared with 13vPCV participants. Orange: magnitude of difference for GMFR point estimate for 20vPCV pre- to post-vaccination compared with 13vPCV participants is of potential concern

Explanations
a. Downgraded, as study population (aged 18–49 years) not reflective of population of interest (aged ≥70 years)
b. Downgraded for serious risk of bias (reporting bias)
c. Downgraded, as ethnicity of study population not reflective of population of interest
d. Downgraded due to small sample size (<400 people in each arm)
e. Inconsistency not assessed, as only 1 study included
f. Downgraded due to inconsistent results across studies that cannot be explained by variation in study populations alone

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 20vPCV=20-valent pneumococcal conjugate vaccine; CI=confidence interval; GMC=geometric mean concentrations; GMT=geometric mean titres; GMFR=geometric mean fold rise; 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

Table 1: Evidence profile PICO 1: 20vPCV compared to 13vPCV for non-First Nations adults aged ≥70 years without special risk factors

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Serious adverse events (SAEs)									
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	The rates of SAEs ranged from 0% to 1% for 20vPCV recipients and from 0% to 1% for 13vPCV recipients. No SAEs were considered by study investigators to be related to the vaccine.[1-4]	⊕⊕⊕⊕ High	CRITICAL
OPA GMT ratios (follow-up: 27–49 days)									
2	Randomised trials	Not serious	Not serious	Serious[a]	Not serious	None	The OPA GMT ratio 30 days following vaccination for shared serotypes ranges from 0.54 to 1.23. All serotypes across studies met a non-inferiority margin of a lower CI of 0.5[6]. No studies reported GMT ratios for 20v-non13v serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F).[2,3]	⊕⊕⊕◯ Moderate	IMPORTANT
% of participants ≥ 4-fold rise of GMT pre- to 1 month (27–49 days) post-vaccination									
3	Randomised trials	Serious[b]	Not serious	Not serious	Not serious	None	The proportion of participants with ≥4-fold rise of GMT pre- to post-vaccination for shared serotypes ranged from 36% to 100% for 20vPCV recipients and from 36% to 100% for 13vPCV recipients. For 20v-non13v serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F), the proportion of participants with ≥4-fold rise of GMT pre- to post-vaccination ranged from 38% to 100% for 20vPCV and from 0% to 24% for 13vPCV.[1,3,4]	⊕⊕⊕◯ Moderate	IMPORTANT
% of participants ≥ 4-fold rise of GMC pre- to 1 month (27–49 days) post-vaccination									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	Randomised trials	Not serious	N/A[e]	Very serious[a,c]	Serious[d]	None	The proportion of participants with ≥4-fold rise of GMC pre- to post-vaccination for shared serotypes ranged from 22% to 100% for 20vPCV recipients and from 53% to 100% for 13vPCV recipients. For 20v-non13v serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F), the proportion of participants with ≥4-fold rise of GMC ranged from 50% to 100% for 20vPCV and from 0% to 24% for 13vPCV.[1]	⊕◯◯◯ Very low	IMPORTANT
Injection site adverse events									
5	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	The rate of injection site adverse events ranged from 55% to 79% for 20vPCV recipients and from 53% to 76% for 13vPCV recipients.[1-4]	⊕⊕⊕⊕ High	IMPORTANT
Systemic adverse events									
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	3 out of 4 studies did not report overall values for systemic adverse events; muscle pain has been used as a proxy measure. The rates of systemic adverse events ranged from 39% to 77% for 20vPCV recipients and from 37% to 65% for 13vPCV recipients.[1-4]	⊕⊕⊕⊕ High	IMPORTANT
OPA GMFR pre- to 1 month (27–49 days) post-vaccination									
3	Randomised trials	Serious[b]	Serious[f]	Not serious	Not serious	None	The OPA GMFR 27–49 days following vaccination for shared serotypes ranged from 4.3 to 236.6 for 20vPCV and from 4.8 to 323.3 for 13vPCV. The GMFR for 20v-non13v serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) ranges from 3.2 to 327.2 for 20vPCV and from 0.5 to 2.1 for 13vPCV.[1,3,4]	⊕⊕◯◯ Low	IMPORTANT

Explanations
a. Downgraded, as study population (aged 18–49 years) not reflective of population of interest (aged ≥70 years)
b. Downgraded for serious risk of bias (reporting bias)
c. Downgraded, as ethnicity of study population not reflective of population of interest
d. Downgraded due to small sample size (<400 people in each arm)
e. Inconsistency not assessed, as only 1 study included
f. Downgraded due to inconsistent results across studies that cannot be explained by variation in study populations alone

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 20vPCV=20-valent pneumococcal conjugate vaccine; CI=confidence interval; GMC=geometric mean concentrations; GMT=geometric mean titres; GMFR=geometric mean fold rise; 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

Evidence to Decision Framework: 20vPCV compared to 13vPCV for non-First Nations adults aged >70 years without special risk factors

Should 20vPCV be recommended as an alternative for or preferred over 13VPCV use in Australian adults ≥70 years for the prevention of pneumococcal disease?	
Population	Non-First Nations adults aged ≥70 years without special risk factors with or without a history of previous 23-valent pneumococcal polysaccharide vaccine (23vPPV) or 13-valent or 15-valent pneumococcal conjugate vaccine vaccination
Intervention	20-valent pneumococcal conjugate vaccine (20vPCV)
Comparison	13-valent pneumococcal conjugate vaccine (13vPCV)
Main outcomes	*Immunogenicity* OPA and IgG geometric mean titres: • OPA GMT ratios pre- to post-vaccination (follow-up: 27–49 days) • % of participants ≥ 4-fold rise of GMT pre- to post-vaccination (follow-up: 27–49 days) • % of participants ≥ 4-fold rise of GMC pre- to post-vaccination (follow-up: 27–49 days) • OPA GMFR pre- to post-vaccination (follow-up: 27–49 days) *Safety* With 20vPCV or 13vPCV delivery: - serious adverse events - local adverse events - systemic adverse events (in 3 out of 4 studies, muscle pain was used as a proxy for systemic adverse events)
Setting	US, Sweden
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, around 800 cases of invasive pneumococcal disease (IPD, the severe form of pneumococcal disease) occur annually.[7] The incidence of all community-acquired pneumonia caused by pneumococcus is several-fold higher than IPD.[8]
- 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 20vPCV cause a considerable amount of residual IPD in non-First Nations adults aged ≥70 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 20v-non13v serotypes based on the % of participants with ≥4-fold rise in OPA GMT and IgG GMC, and based on the OPA GMFR.
- Evidence for the shared serotypes between 20vPCV and 13vPCV 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 rates are slightly higher than those seen after 13vPCV.
- There were no vaccine-related serious adverse events reported in the included studies.

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, due to indirectness, as some studies did not include the population of interest in their study population. There was also serious risk of bias in one study. There was also inconsistency of the results for the immunogenicity outcome of OPA GMFR.

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.

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 improvement in immune response from 20vPCV for the 20v-non13v serotypes probably outweighs the additional frequency of non-serious adverse events/reactogenicity compared to 13vPCV.
- The overall balance of desirable and undesirable effects of 20vPCV are comparable to 13vPCV for the shared serotypes.
- Undesirable effects are minor yet slightly higher in 20vPCV compared to 13vPCV.

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%.[9] The 13vPCV program commenced in July 2020. While vaccine coverage for 13vPCV in adults aged over 70 years was around 20% in 2021, this is more likely due to lack of awareness[10] of pneumococcal vaccines and the program being relatively new than to a lack of acceptability of the intervention.					
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.					

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