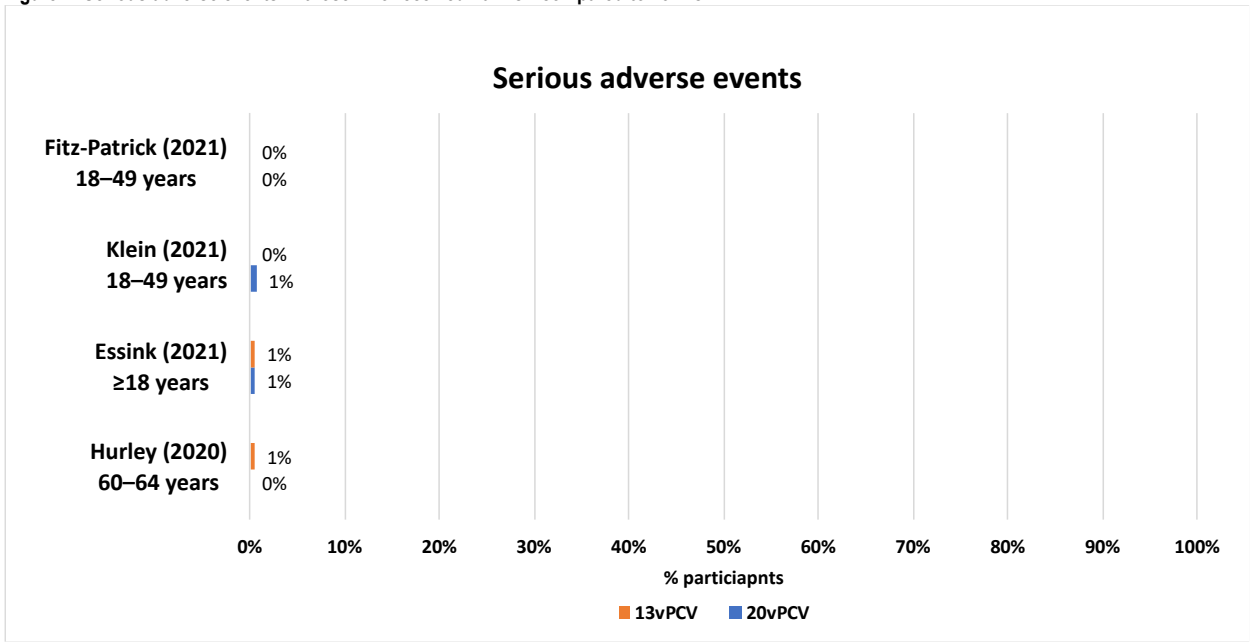
GRADE tables for 20vPCV + 23vPCV comparison to 13vPCV +23vPCV in First Nations adults aged over 50 years without specific risk conditions

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 Australian Immunisation Handbook pneumococcal chapter.

20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for immunocompetent First Nations adults aged ≥50 years without special risk conditions				
Patient or population: Immunocompetent First Nations adults aged ≥50 years without special risk conditions **Intervention:** 20vPCV followed by 23vPPV **Comparison:** 13vPCV followed by 23vPPV				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Serious adverse events(SAEs)	**Figure 1: Serious adverse events in those who received 20vPCV compared to 13vPCV** 	5,148 (4 RCTs)[1-4]	⨁⨁◯◯ Low[a,b]	20vPCV may result in little to no difference in SAEs compared to 13vPCV.

OPA GMT ratio 7 serotypes shared with 20vPCV and 23vPPV
follow-up: 27–49 days

Table 1a: 95% CI for OPA GMT ratios (20vPCV vs. 23vPPV) for 7 serotypes shared with 23vPPV at 1-month (28–49 days) post-vaccination shaded by non-inferiority (using 2 different thresholds) and superiority margins^

Study	**Essink (2021)**	
Population	**Aged ≥60 years**	
PCV/PPV	20	13+23
N	1,157–1,374	1,201–1,319
Serotype		
8	0.49, 0.62	
10A	1.63, 2.12	
11A	1.52, 2.01	
12F	1.27,1.72	
15B	2.62, 3.71	
22F	1.70, 2.32	
33F	1.21, 1.57	

^Non-inferiority margins: Orange=LCI>0.67[5]; yellow=LCI>0.5[6]; superiority margin blue=LCI>2[7] (no 20vPCV studies aimed to establish superiority – this margin is based of superiority criteria from trials for 15vPCV)

Table 1b: 95% CI for OPA GMT ratios (20vPCV vs. 23vPPV) for 7 serotypes shared with 23vPPV at 1-month (27–49 days) post-vaccination shaded by estimates that favour 20vPCV or 23vPPV†

Serotype	**Essink (2021)**	
Population	**Aged ≥60 years**	
PCV/PPV	20	13+23
N	1,157–1,374	1,201–1,319
8	0.49, 0.62	
10A	1.63, 2.12	
11A	1.52, 2.01	
12F	1.27,1.72	
15B	2.62, 3.71	
22F	1.70, 2.32	
33F	1.21, 1.57	

†Green=LCI>1; red=UCI<1

2,816
(1 RCT)[2]

⊕⊕◯◯
Low[a,c,e]

20vPCV may result in little difference in OPA GMT ratios for shared STs, except for ST 15B, for which 20vPCV may result in an increase in OPA GMT.

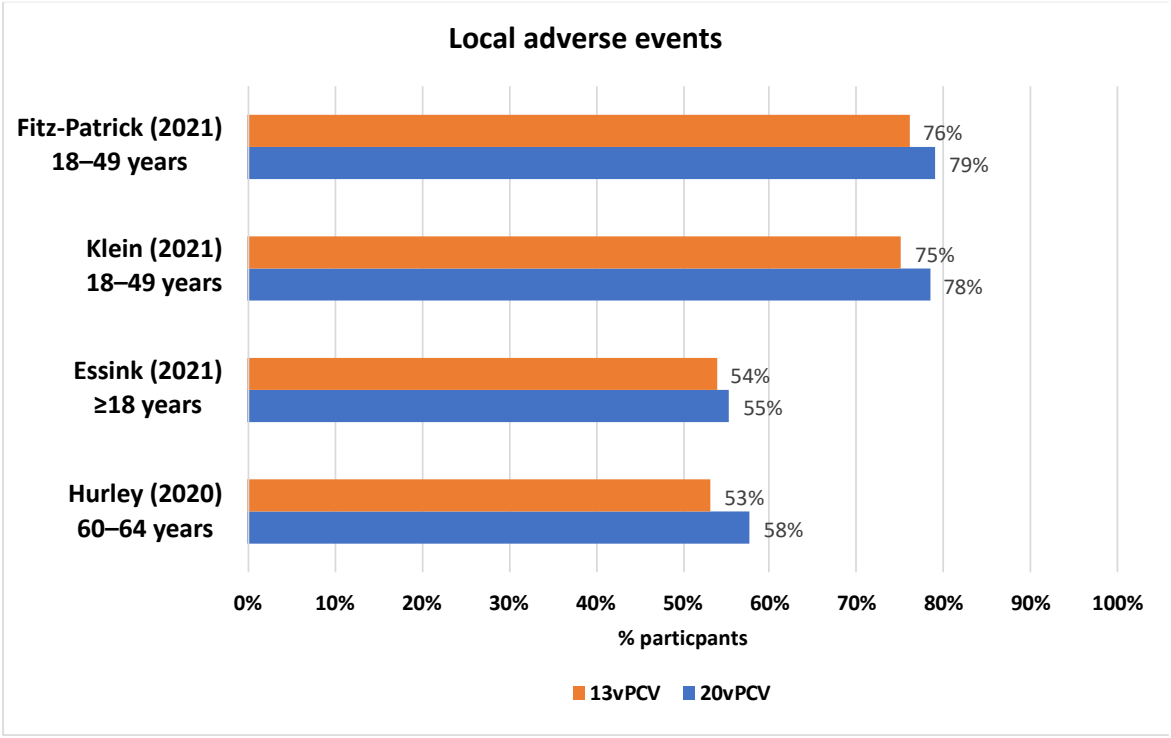
Note: OPA GMT ratios all met a non-inferiority margin of LCI>0.67, except ST 8, which did not meet the non-inferiority margin.

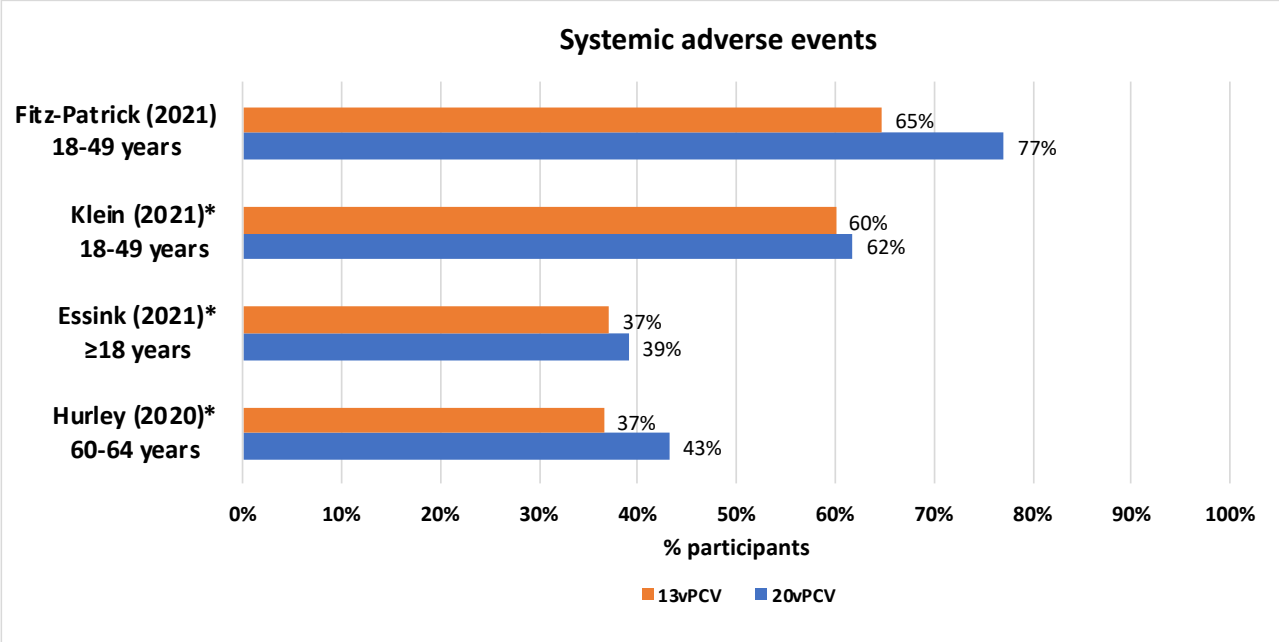
20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for immunocompetent First Nations adults aged ≥50 years without special risk conditions

Patient or population: Immunocompetent First Nations adults aged ≥50 years without special risk conditions
Intervention: 20vPCV followed by 23vPPV
Comparison: 13vPCV followed by 23vPPV

<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>% participants ≥4-fold rise in GMT for 7 serotypes shared by 20vPCV and 23vPPV</td>
<td>
Table 2: % participants with ≥4-fold rise in GMT for 7 serotypes shared by 20vPCV and 23vPPV†
<table>
<tr><td>Study</td><td colspan="2">Essink (2021)</td><td colspan="2">Hurley (2021)</td></tr>
<tr><td>Population</td><td>Aged ≥65 years</td><td></td><td>Aged 60–64 years</td><td></td></tr>
<tr><td>PCV/PPV</td><td>20</td><td>13+23</td><td>20</td><td>13+23</td></tr>
<tr><td>N</td><td>1,433</td><td>1,383</td><td>168–210</td><td>169–208</td></tr>
<tr><td>Serotype</td><td></td><td></td><td></td><td></td></tr>
<tr><td>8</td><td>77.8% (75.5, 80.0)</td><td>86.8% (84.8, 88.6)</td><td>80.3% (74.1, 85.5)</td><td>85.2% (79.4, 89.9)</td></tr>
<tr><td>10A</td><td>75.5% (73.0, 77.9)</td><td>65.6% (62.8, 68.4)</td><td>82.3% (76.1, 87.4)</td><td>67.6% (60.4, 74.2)</td></tr>
<tr><td>11A</td><td>59.2% (56.0, 62.3)</td><td>51.9% (48.7, 55.0)</td><td>63.2% (55.9, 70.0)</td><td>62.3% (54.7, 69.5)</td></tr>
<tr><td>12F</td><td>87.4% (85.5, 89.2)</td><td>80.6% (78.1, 82.8)</td><td>90.2% (84.9, 94.1)</td><td>86.9% (81.1, 91.4)</td></tr>
<tr><td>15B</td><td>77.8% (75.3, 80.1)</td><td>63.8% (61.0, 66.6)</td><td>84.1% (78.3, 88.8)</td><td>69.7% (62.8, 76.1)</td></tr>
<tr><td>22F</td><td>82.7% (80.4, 84.8)</td><td>76.8% (74.3, 79.2)</td><td>84.2% (78.2, 89.2)</td><td>74.2% (67.1, 80.4)</td></tr>
<tr><td>33F</td><td>60.1% (57.0, 63.1)</td><td>55.5% (52.4, 58.5)</td><td>67.3% (59.6, 74.3)</td><td>63.9% (56.2, 71.1)</td></tr>
</table>
†Green=Statistically significantly higher % of participants in 20vPCV group had a ≥4 fold-rise in GMT for the 7 shared ST. Red=Statistically significantly lower % of participants in 20vPCV group had a ≥4 fold-rise in GMT for the 7 shared ST
</td>
<td>3,234 (2 RCTs)[2,4]</td>
<td>⨁⨁◯◯ Low[a,c]</td>
<td>20vPCV may increase % of participants with ≥ 4-fold rise of GMT pre- to 27–49 days post-vaccination for shared STs, except ST 8.

Note: ST 8 is statistically significantly lower for 20vPCV compared to 13vPCV+23vPPV.</td>
</tr>
</table>

20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for immunocompetent First Nations adults aged ≥50 years without special risk conditions				
Patient or population: Immunocompetent First Nations adults aged ≥50 years without special risk conditions **Intervention:** 20vPCV followed by 23vPPV **Comparison:** 13vPCV followed by 23vPPV				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Local adverse events (follow up: 7 days)	**Figure 2: Injection site pain in those who received 20vPCV compared to 13vPCV** 	5,148 (4 RCTs)[1-4]	⨁⨁◯◯ Low[a,b]	20vPCV may result in a slight increase in injection site adverse events compared to 13vPCV.

20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for immunocompetent First Nations adults aged ≥50 years without special risk conditions				
Patient or population: Immunocompetent First Nations adults aged ≥50 years without special risk conditions **Intervention:** 20vPCV followed by 23vPPV **Comparison:** 13vPCV followed by 23vPPV				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Systemic adverse events	**Figure 3: systemic adverse events in those who received 20vPCV compared to 13vPCV**  *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]	⨁⨁◯◯ Low[a,b]	20vPCV may result in a slight increase in systemic adverse events compared to 13vPCV.

20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for immunocompetent First Nations adults aged ≥50 years without special risk conditions

Patient or population: Immunocompetent First Nations adults aged ≥50 years without special risk conditions
Intervention: 20vPCV followed by 23vPPV
Comparison: 13vPCV followed by 23vPPV

<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>IgG GMFR</td>
<td>
Table 3: IgG GMFR for 7 serotypes shared by 20vPCV and 23vPPV†
<table>
<tr><td>Study</td><td colspan="2">Hurley (2021)</td></tr>
<tr><td>Population</td><td colspan="2">Aged 60–64 years</td></tr>
<tr><td>PCV/PPV</td><td>20</td><td>13+23</td></tr>
<tr><td>N</td><td>208</td><td>203</td></tr>
<tr><td>Serotype</td><td></td><td></td></tr>
<tr><td>8</td><td>23.42 (18.19, 30.16)</td><td>32.51 (25.14, 42.03)</td></tr>
<tr><td>10A</td><td>38.94 (30.22, 50.18)</td><td>19.94 (16.17, 24.59)</td></tr>
<tr><td>11A</td><td>17.55 (14.21, 21.68)</td><td>13.48 (10.87, 16.73)</td></tr>
<tr><td>12F</td><td>15.22 (11.71, 19.78)</td><td>17.37 (13.59, 22.21)</td></tr>
<tr><td>15B</td><td>27.73 (21.60, 35.61)</td><td>15.75 (12.68, 19.57)</td></tr>
<tr><td>22F</td><td>76.45 (57.32, 101.95)</td><td>30.94 (23.68, 40.43)</td></tr>
<tr><td>33F</td><td>11.93 (9.59, 14.84)</td><td>14.21 (11.32, 17.85)</td></tr>
</table>
†Green=Statistically significantly higher IgG GMFR for 7 serotypes shared by 20vPCV and 23vPPV
</td>
<td>444
(1 RCT)[4]</td>
<td>⊕◯◯
◯
Very low[a,c,d,e]</td>
<td>The evidence is very uncertain about the effect of 20vPCV on IgG GMFR compared to 23vPPV. It may increase for ST 10A, 11A, 15B and 22F for 20vPCV compared to 23vPPV, but the evidence is very uncertain.

Note: For ST 10A, 11A, 15B and 22F 20vPCV is statistically significantly higher (CI does not overlap with 23vPPV).</td>
</tr>
</table>

20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for immunocompetent First Nations adults aged ≥50 years without special risk conditions				
Patient or population: Immunocompetent First Nations adults aged ≥50 years without special risk conditions **Intervention:** 20vPCV followed by 23vPPV **Comparison:** 13vPCV followed by 23vPPV				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Explanations a. Downgraded, as intervention in study (20vPCV) not intervention of interest in PICO (20vPCV+23vPPV) b. Downgraded, as comparator in study (13vPCV) was not the intervention of interest for this PICO (13vPVB+23vPPV) c. Downgraded, as ethnicity of study population not reflective of population of interest (First Nations people) d. Downgraded for serious risk of bias (reporting bias) e. Inconsistency not assessed, as only 1 study included **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 event; 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 2: 20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for immunocompetent First Nations adults aged ≥50 years without special risk conditions

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	Very serious[a,b]	Not serious	None	There were no safety data post-23vPPV. The rates of SAEs ranged from 0% to 1% for 20vPCV recipients and 0% to 1% for 13vPCV recipients. None were considered by study investigators to be related to the vaccine.[1-4]	⊕⊕◯◯ Low	CRITICAL
OPA GMT 7 serotypes shared with 20vPCV and 23vPPV (follow-up: 27–49 days)									
1	Randomised trials	Not serious	N/A[e]	Very serious[a,c]	Not serious	None	The OPA GMT ratio 30 days following vaccination with 20vPCV or 13vPCV+23vPPV, for the 7 additional 20v-non13v serotypes shared with 23vPCV ranges from 0.49 to 3.71. Serotype 8 did not meet the non-inferiority margin, 0.5[6], but all other serotypes (10A, 11A, 12F, 15B, 22F, 33F) did. 15B met the superiority margin of LCI≥2[7]. No studies reported GMT ratios for 23v-non20v serotypes (2, 9N, 17F) or for the additional serotypes shared between 20vPCV and 23vPPV.[2]	⊕⊕◯◯ Low	IMPORTANT
% participants ≥4-fold rise GMT for 7 serotypes shared by 20vPCV and 23vPPV									
2	Randomised trials	Not serious	Not serious	Very serious[a,c]	Not serious	None	The proportion of participants with ≥4-fold rise of GMT pre- to post-vaccination for the 7 additional 20v-non-13v serotypes shared with 23vPPV ranged from 56% to 94.1% for 20vPCV recipients and from 49% to 91% for 13vPCV+23vPPV recipients. No studies reported % participants with ≥4-fold rise in GMT for 23v-non20v serotypes (2, 9N, 17F) or for the additional serotypes shared between 20vPCV and 23vPPV.[2,4]	⊕⊕◯◯ Low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Local adverse events									
4	Randomised trials	Not serious	Not serious	Very serious[a,b]	Not serious	None	There were no safety data post-23vPPV. 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]	⊕⊕◯◯ Low	IMPORTANT
Systemic adverse events									
4	Randomised trials	Not serious	Not serious	Very serious[a,b]	Not serious	None	There were no safety data post-23vPPV. 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]	⊕⊕◯◯ Low	IMPORTANT
IgG GMFR									
1	Randomised trials	Serious[d]	N/A[e]	Very serious[a,c,d]	Not serious	None	The IgG GMFR 27–49 days following vaccination for the 7 additional 20v-non-13v serotypes shared with 23vPPV ranges from 9.59 to 101.95 for 20vPCV and from 10.87 to 42.03 for 23vPPV. No studies reported IgG GMFR for 23v-non20v serotypes (2, 9N, 17F) or for the additional serotypes shared between 20vPCV and 23vPPV.[4]	⊕◯◯◯ Very low	IMPORTANT

Explanations
a. Downgraded, as intervention in study (20vPCV) not intervention of interest in PICO (20vPCV+23vPPV)
b. Downgraded, as comparator in study (13vPCV) was not the intervention of interest for this PICO (13vPVB+23vPPV)
c. Downgraded, as ethnicity of study population not reflective of population of interest (First Nations people)
d. Downgraded for serious risk of bias (reporting bias)
e. Inconsistency not assessed, as only 1 study included

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 event; ST=serotype; UCI=upper confidence interval

Evidence to decision framework: 20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for immunocompetent First Nations adults aged ≥50 years without special risk conditions

Should 20vPCV+23vPPV vaccination be used in First Nations adults aged ≥50 years without risk conditions for pneumococcal disease for the prevention of pneumococcal disease?	
Population	First Nations adults aged ≥50 years without special risk factors
Intervention	20-valent pneumococcal conjugate vaccine with subsequent 23-valent pneumococcal polysaccharide vaccine
Comparison	13-valent pneumococcal conjugate vaccine with subsequent 23-valent pneumococcal polysaccharide vaccine
Main outcomes	*Immunogenicity* OPA and IgG geometric mean titres - OPA GMT ratios (follow-up: 30 days) - % of participants ≥ 4-fold rise of GMT pre- to post-vaccination - IgG GMFR *Safety* - serious adverse events - local adverse events - 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

- First Nations people have a disproportionately higher incidence of pneumococcal disease than others. A higher incidence of Invasive pneumococcal disease occurs at a much younger age in First Nations adults compared to non-First Nations adults.[8,9]
- The serotypes that cause pneumococcal disease in First Nations adults are more diverse than in others.
- Following several years of PCV use with high uptake, certain non-PCV serotypes have emerged to cause increased incidence of invasive pneumococcal disease. This serotype replacement disease is particularly marked among First Nations adults.
- New PCVs with extended valencies will likely improve the protection against pneumococcal disease in First Nations adults.

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- No studies reported immunogenicity outcomes of 20vPCV+23vPPV compared with 13vPCV+23vPPV. Data were only available for 20vPCV compared with 13vPCV+23vPPV. One serotype (8) did not meet the non-inferiority margin for GMT ratios. One serotype (15B) met the criteria for superiority. The 5 other additional 20v-non13v serotypes shared with 23vPPV all met the non-inferiority margin of 0.67.[10]

- No studies reported immunogenicity outcomes for 23v-non20v serotypes (2, 9N, 17F) or for the additional serotypes shared between 20vPCV and 23vPPV.
- There is no evidence available on clinical outcomes after 20vPCV and no evidence available on the persistence of 20vPCV or 20vPCV+23vPPV vaccination.

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. Rates are similar to those seen after 13vPCV+23vPPV.
- There were no vaccine-related SAEs 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 overall certainty of evidence is low as there were 5/6 outcomes rated as low and 1/6 as very low.
- Domains were downgraded due to indirectness as intervention and comparator in study populations (20vPCV vs 13vPCV+23vPCV) were not the intervention and comparator of the PICO (20vPCV+23vPCV vs 13vPCV+23vPCV). The study populations also did not include First Nations populations (<1%). One study also had serious risk of bias.

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

- It is unlikely that there will 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

- 20vPCV was found to have similar desirable and undesirable effects compared to 13vPCV+23vPPV. Although there are small effects at improving immunogenicity outcomes in the 20v-non13v serotypes from the 20vPCV vaccine, it is unknown if there are benefits following 23vPPV vaccine in those who receive 20vPCV.
- Undesirable effects are minor.

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%[11] The 13vPCV program commenced in July 2020. Whilst the vaccine coverage for 13vPCV in First Nations adults aged over 70 years was around 20% in 2021, this is likely more due to lack of awarenesstrent[12] of pneumococcal vaccines and the program being relatively new, rather than 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.

References

1. Klein NP, Peyrani P, Yacisin K, et al. A phase 3, randomized, double-blind study to evaluate the immunogenicity and safety of 3 lots of 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naive adults 18 through 49 years of age. *Vaccine* 2021;39:5428-35.
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3. Fitz-Patrick D, Young Jr M, Scott DA, et al. A randomized phase 1 study of the safety and immunogenicity of 2 novel pneumococcal conjugate vaccines in healthy Japanese adults in the United States. *Human Vaccines and Immunotherapeutics* 2021;17(7):2249-56.
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5. World Health Organisation (WHO). Guidelines on clinical evaluation of vaccines: regulatory expectations.2017. Available from: https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9.
6. Essink B, Sabharwal C, Cannon K, et al. Pivotal Phase 3 Randomized Clinical Trial of the Safety, Tolerability, and Immunogenicity of 20-Valent Pneumococcal Conjugate Vaccine in Adults Aged ≥18 Years. *Clinical infectious diseases* 2022;75:390-8.
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9. Australian Institute of Health and Welfare (AIHW). Vaccine preventable disease among Aboriginal and Torres Strait Islander people. 2018. Available from: https://www.aihw.gov.au/getmedia/2fca3ed6-d242-4454-a00f-e298dd120ccb/aihw-phe-236_atsi.pdf.aspx (Accessed 10 October 2023).
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12. Trent MJ, Salmon DA, MacIntyre CR. Predictors of pneumococcal vaccination among Australian adults at high risk of pneumococcal disease. *Vaccine* 2022;40:1152-61.