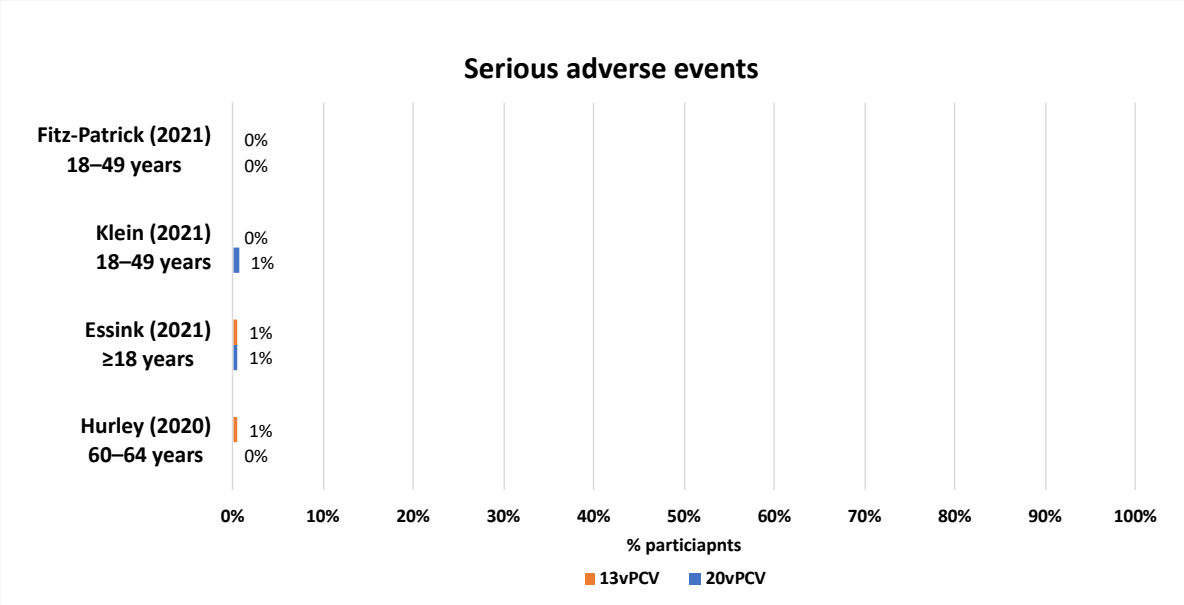
GRADE tables for 20vPCV + 23vPCV comparison to 13vPCV + 23vPCV in adults aged over 18 years with specific risk conditions

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 Australian adults aged ≥18 years with specific risk conditions

Patient or population: Australian adults aged ≥18 years with specific 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)		5,148 (4 RCTs)[1-4]	⨁⨁◯◯ Low[a,b]	20vPCV may result in little to no difference in SAEs compared to 13vPCV.

<table>
<tr>
<td>OPA GMT ratio for 7 serotypes shared with 20vPCV and 23vPPV follow-up: 27–49 days</td>
<td>
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^
<table>
<tr><td>Study</td><td colspan="2">Essink (2021)</td></tr>
<tr><td>Population</td><td colspan="2">Aged ≥60 years</td></tr>
<tr><td rowspan="2">PCV/PPV N</td><td>20
1,157–1,374</td><td>13+23
1,201–1,319</td></tr>
<tr><td>Serotype</td><td colspan="2"></td></tr>
<tr><td>8</td><td colspan="2">0.49, 0.62</td></tr>
<tr><td>10A</td><td colspan="2">1.63, 2.12</td></tr>
<tr><td>11A</td><td colspan="2">1.52, 2.01</td></tr>
<tr><td>12F</td><td colspan="2">1.27,1.72</td></tr>
<tr><td>15B</td><td colspan="2">2.62, 3.71</td></tr>
<tr><td>22F</td><td colspan="2">1.70, 2.32</td></tr>
<tr><td>33F</td><td colspan="2">1.21, 1.57</td></tr>
</table>
^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 on 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†
<table>
<tr><td>Study</td><td colspan="2">Essink (2021)</td></tr>
<tr><td>Population</td><td colspan="2">Aged ≥60 years</td></tr>
<tr><td rowspan="2">PCV/PPV N</td><td>20
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<tr><td>33F</td><td colspan="2">1.21, 1.57</td></tr>
</table>
†Green=LCI>1; red=UCI<1
</td>
<td>2,816
(1 RCT)[3]</td>
<td>⨁⨁◯◯
Low[a,c,e]</td>
<td>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.

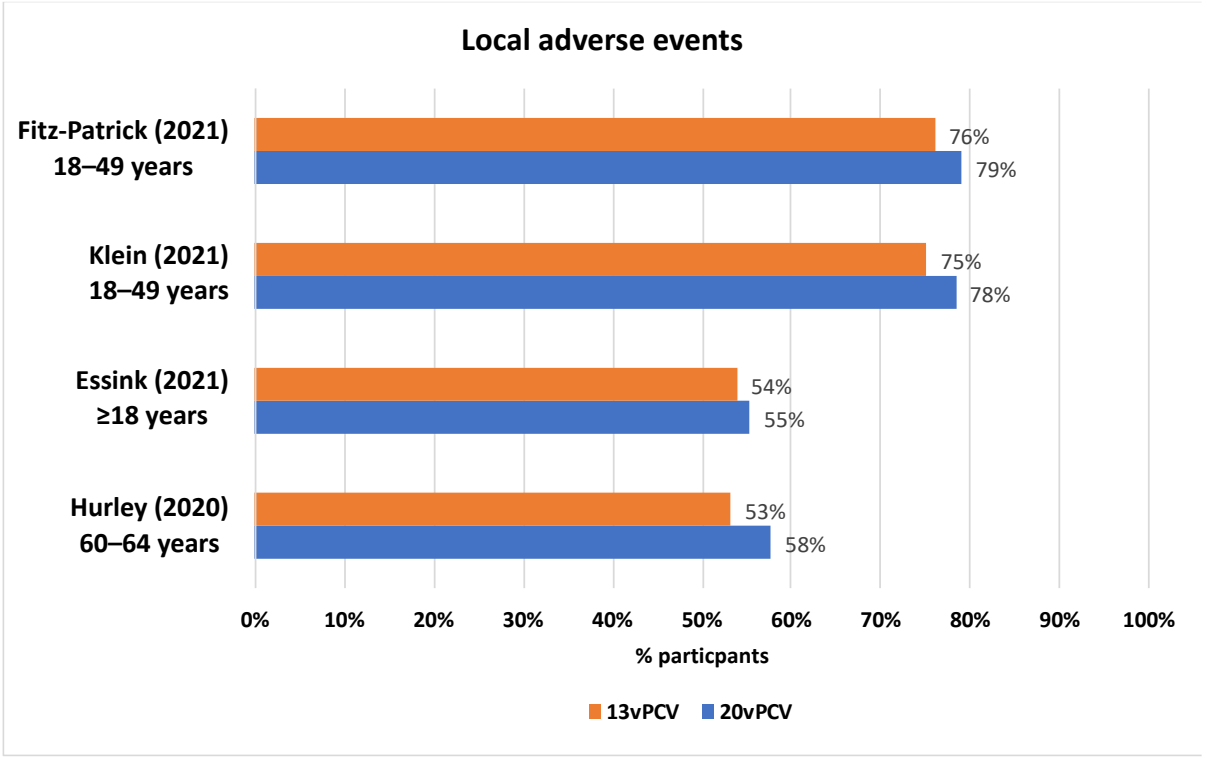
Note: OPA GMT ratios all met a non-inferiority margin of LCI>0.67,[5] except ST 8, which did not meet either non-inferiority margin.</td>
</tr>
</table>

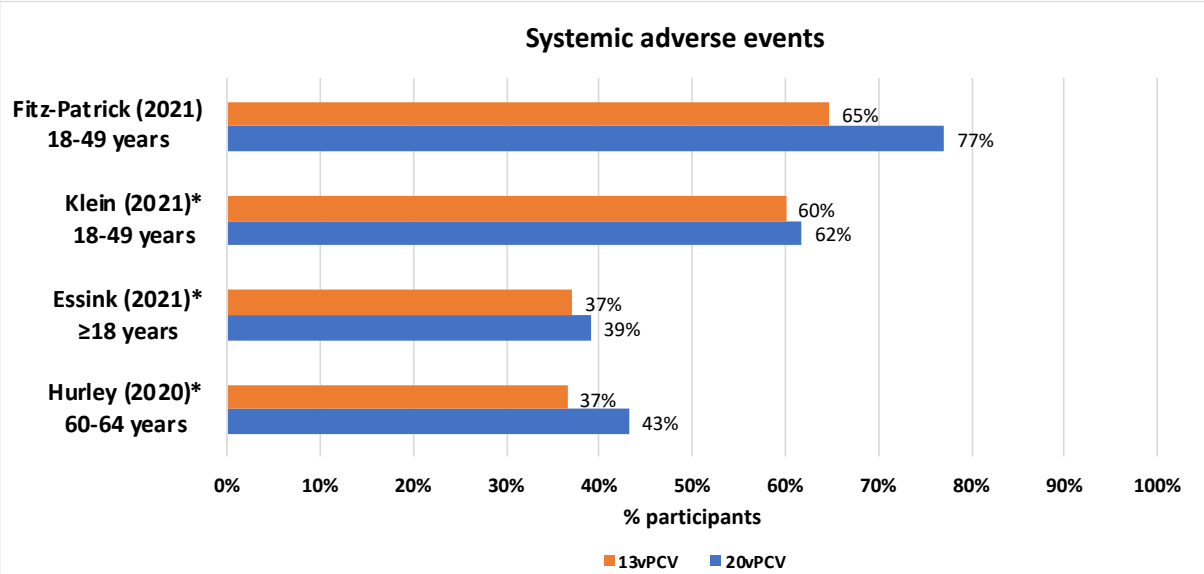
20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for Australian adults aged ≥18 years with specific risk conditions

Patient or population: Australian adults aged ≥18 years with specific 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 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>Hurley (2021)</td><td></td></tr>
<tr><td>Population</td><td colspan="2">Aged ≥65 years</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>1433</td><td>1383</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)[3,4]</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 Australian adults aged ≥18 years with specific risk conditions				
Patient or population: Australian adults aged ≥18 years with specific 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 within 7 days		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 Australian adults aged ≥18 years with specific risk conditions				
Patient or population: Australian adults aged ≥18 years with specific 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	 *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 Australian adults aged ≥18 years with specific risk conditions

Patient or population: Australian adults aged ≥18 years with specific risk conditions
Intervention: 20vPCV followed by 23vPPV
Comparison: 13vPCV followed by 23vPPV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
IgG GMFR	Table 3: IgG GMFR for 7 serotypes shared by 20vPCV and 23vPPV†	444 (1 RCT)[4]	⊕◯◯◯ Very low[a,c,d,e]	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).

Serotype	**Hurley 2021**	
Population	**Aged 60–64 years**	
PCV/PPV	20	13+23
N	208	203
8	23.42 (18.19, 30.16)	32.51 (25.14, 42.03)
10A	38.94 (30.22, 50.18)	19.94 (16.17, 24.59)
11A	17.55 (14.21, 21.68)	13.48 (10.87, 16.73)
12F	15.22 (11.71, 19.78)	17.37 (13.59, 22.21)
15B	27.73 (21.60, 35.61)	15.75 (12.68, 19.57)
22F	76.45 (57.32, 101.95)	30.94 (23.68, 40.43)
33F	11.93 (9.59, 14.84)	14.21 (11.32, 17.85)

†Green=Statistically significantly higher IgG GMFR for 7 serotypes shared by 20vPCV and 23vPPV

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 (13vPCV+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

20vPCV followed by 23vPPV compared to 13vPCV followed by 23vPPV for Australian adults aged ≥18 years with specific risk conditions				
Patient or population: Australian adults aged ≥18 years with specific risk conditions **Intervention:** 20vPCV followed by 23vPPV **Comparison:** 13vPCV followed by 23vPPV				
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
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 3: 20vPCV (followed by 23vPPV) in adults aged ≥18 years with specific risk conditions (as in the Handbook list) for the prevention of pneumococcal disease

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 ranged from 0.49 to 3.71. Serotype 8 did not meet the non-inferiority margin, 0.5, but all other serotypes (10A, 11A, 12F, 15B, 22F, 33F) did. No studies reported GMT ratios for 23v-non20v serotypes (2, 9N, 17F) or the additional serotypes shared between 20vPCV and 23vPPV.[3]	⊕⊕◯◯ 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 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 the additional serotypes shared between 20vPCV and 23vPPV.[3,4]	⊕⊕◯◯ Low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Injection site pain									
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 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 10.87 to 42.03 for 23vPPV. No studies reported IgG GMFR for 23v-non20v serotypes (2, 9N, 17F) or the additional serotypes shared between 20vPCV and 23vPPV.[4]	⊕◯◯◯ Very low	IMPORTANT

Explanations
a. Downgraded, as intervention in study (20vPCV) not intervention of interest for PICO (20vPCV+23vPPV)
b. Downgraded, as comparator in study (13vPCV) not intervention of interest for PICO (13vPVB+23vPPV)
c. Downgraded, as ethnicity of study population not reflective of population of interest (Indigenous Australians)
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) in adults aged ≥18 years with specific risk conditions (as in the Handbook list) for the prevention of pneumococcal disease

Should 20vPCV (followed by 23vPPV) be used in adults aged ≥18 years with specific risk conditions (as in the Handbook list) for the prevention of pneumococcal disease?					
Population	Adults aged ≥18 years with specific 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 GMC ratios (follow-up: 30 days) *Safety* 23vPPV after previous 15vPCV or 13vPCV delivery: - 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
• Individuals with certain underlying risk conditions have increased risk of pneumococcal disease. • Serotypes that cause pneumococcal disease in those with risk conditions are more diverse compared to others. • The use of PCVs over several years, combined with high coverage, has meant that certain non-PCV serotypes have emerged and there has been increasing incidence of invasive pneumococcal disease. This replacement disease is more pronounced in the population with risk conditions. • PCVs with extended valency would likely improve protection against pneumococcal disease in individuals with underlying risk conditions.					
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 either 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.[5] • No studies reported immunogenicity outcomes for 23v-non20v serotypes (2, 9N, 17F) or for the additional serotypes shared between 20vPCV and 23vPPV. • No evidence is available on clinical outcomes after 20vPCV or 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 serious adverse events 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; 3/6 outcomes were rated as moderate, 2/6 were rated as low and 1/6 were rated as very low. • Domains were downgraded due to indirectness, as the 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 people with risk conditions. 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 increases in 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, vaccination uptake of the 23vPPV vaccine in adults aged ≥65 years was estimated to be 52%.[8] 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 likely due more to lack of awareness[9] of pneumococcal vaccines and the program being relatively new than to a lack of acceptability of the intervention. The vaccination uptake in adults aged ≥18 years with risk conditions is likely to be lower.					
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. 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.
2. 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.
3. 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 18 years and older. *Clinical Infectious Diseases* 2021.
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5. World Health Organisation (WHO). Guidelines on clinical evaluation of vaccines: regulatory expectations. 2017.
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