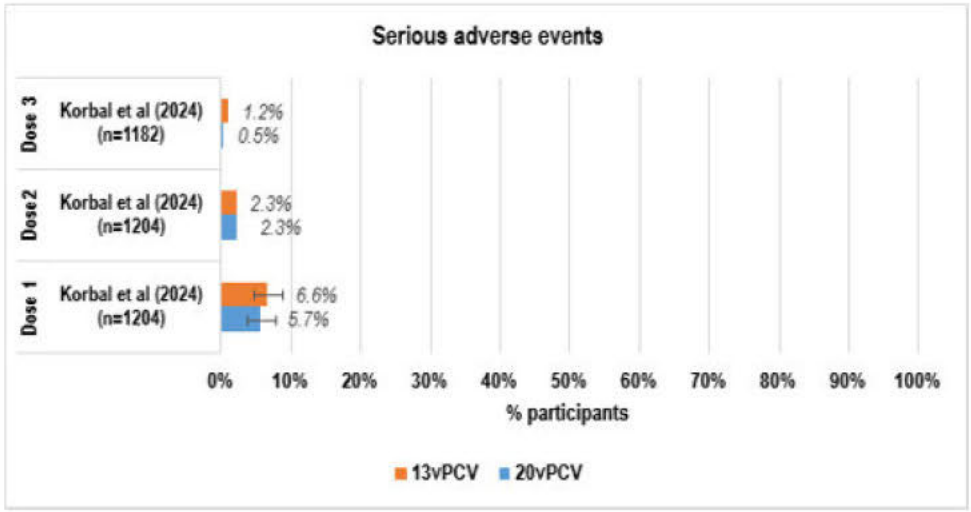
GRADE tables: Comparison of 20vPCV with 13vPCV in non-Indigenous infants without a risk condition

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 disease chapter.

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
CRITICAL OUTCOMES				
Any serious adverse events (SAE) post each dose follow-up: 1 month		1,204 (1 RCT)[1,2]	⊕⊕⊕⊕ High[a]	20vPCV results in little to no difference in SAE compared to 13vPCV

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
IMPORTANT OUTCOMES				
Difference in IgG response rate post dose 3 Assessed with: % participants with IgG ≥0.35ug/mL Follow-up: 30 days		996 (1 RCT)[1,3]	⊕⊕⊕◯ Moderate[b]	20vPCV likely results in no difference in IgG response rate for all shared ST post dose 3, except for ST 3 which did not meet the non-inferiority margin. 20vPCV likely results in higher IgG response rates for 20v-non-13v ST.

Study	**B7471012***	
PCV	20v	13v
N	497	504
Shared serotypes		
1	-3.1, 0.9	
3	-14.7, -6.7	
4	-1.4, 1.3	
5	-1.4, 2.2	
6A	-1.6, 1.5	
6B	-1.1, 2.7	
7F	-1.5, 0.4	
9V	-1.0, 1.9	
14	-3.7, 0.6	
18C	-0.5, 2.7	
19A	-1.1, 1.1	
19F	-0.9, 1.4	
23F	3.2, 1.4	

*Cells shaded red did not meet non-inferiority margin, yellow met the non-inferiority margin: LCI>-10 percentage points; blue met the superiority margin: LCI>10 percentage points

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
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>Interpretive statement</th></tr>
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continued
Difference in IgG response rate post dose 3

Assessed with:
% participants with IgG ≥0.35ug/mL

Follow-up: 30 days

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continued

<table>
<tr><td>Study</td><td colspan="2">B7471012*</td></tr>
<tr><td>PCV</td><td>20v</td><td>13v</td></tr>
<tr><td>N</td><td>497</td><td>504</td></tr>
<tr><td colspan="3">20v-non13v serotypes</td></tr>
<tr><td>8</td><td colspan="2">93.4, 97.1</td></tr>
<tr><td>10A</td><td colspan="2">94.1, 97.6</td></tr>
<tr><td>11A</td><td colspan="2">91.3, 95.6</td></tr>
<tr><td>12F</td><td colspan="2">94.3, 97.7</td></tr>
<tr><td>15B</td><td colspan="2">92.3, 96.3</td></tr>
<tr><td>22F</td><td colspan="2">96.1, 98.8</td></tr>
<tr><td>33F</td><td colspan="2">94.8, 98.0</td></tr>
</table>

*Cells shaded red did not meet non-inferiority margin, yellow met the non-inferiority margin: LCI>-10 percentage points; blue met the superiority margin: LCI>10 percentage points

</td>
<td>996 (1 RCT)[1,3]</td>
<td>⊕⊕⊕◯ Moderate[b]</td>
<td>20vPCV likely results in no difference in IgG response rate for all shared ST post dose 3, except for ST 3 which did not meet the non-inferiority margin.

20vPCV likely results in higher IgG response rates for 20v-non-13v ST.</td>
</tr>
</table>

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
Difference in IgG response rate post dose 2 Assessed with: % participants with IgG ≥0.35ug/mL Follow-up: 30 days	**Study** B7471012* **PCV** 20v 13v **N** 567 562 **Shared serotypes** 1 -18.3,-8.7 3 -23.2, -12.4 4 -16.0, -5.9 5 -17.8, -7.2 6A -19.5, -8.6 6B -21.0, -10.6 7F -6.3, 1.1 9V -19.7, -8.9 14 -7.9, 1.4 18C -10.6, -0.4 19A -4.8, 1.3 19F -4.0, 1.2 23F -23.6, -12.9 *Cells shaded red did not meet non-inferiority margin, yellow met the non-inferiority margin: LCI>-10 percentage points; blue met the superiority margin: LCI>10 percentage points.	1,128 (1 RCT)[1,3]	⊕⊕⊕◯ Moderate[b]	20vPCV likely results in no difference in IgG response rate for shared ST 7F, 14, 19A and 19F post dose 2. For all other shared ST 20vPCV likely results in a small reduction in IgG response rate as they did not meet the non-inferiority margin. 20vPCV likely results in higher IgG response rates for 20v-non-13v ST.

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
continued Difference in IgG response rate post dose 2 Assessed with: % participants with IgG ≥0.35ug/mL Follow-up: 30 days	***continued***	1,128 (1 RCT)[1,3]	⊕⊕⊕◯ Moderate[b]	20vPCV likely results in no difference in IgG response rate for shared ST 7F, 14, 19A and 19F post dose 2. For all other shared ST 20vPCV likely results in a small reduction in IgG response rate as they did not meet the non-inferiority margin. 20vPCV likely results in higher IgG response rates for 20v-non-13v ST.

Study	**B7471012***	
PCV	20v	13v
N	567	562
20v-non13v serotypes		
8	91.2, 95.4	
10A	22.4, 30.3	
11A	89.7, 94.2	
12F	26.5, 34.1	
15B	82.5, 88.5	
22F	89.9, 94.3	
33F	39.8, 48.5	

*Cells shaded red did not meet non-inferiority margin, yellow met the non-inferiority margin: LCI>-10 percentage points; blue met the superiority margin: LCI>10 percentage points.

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
IgG Geometric Mean Concentration (GMC) ratio post dose 3 Follow-up: 30 days	See table below	996 (1 RCT)[1,4]	⊕⊕⊕◯ Moderate[b]	20vPCV likely results in no difference in IgG GMC ratios for all shared ST post dose 3 except for 6B which did not meet the non-inferiority margin. 20vPCV increases IgG GMC ratios for 20v-non-13v ST.

Study	B7471012*	
PCV	20v	13v
N	497	504
Shared serotypes		
1	0.60, 0.75	
3	0.59, 0.73	
4	0.68, 0.87	
5	0.64, 0.81	
6A	0.57, 0.75	
6B	0.48, 0.67	
7F	0.67, 0.80	
9V	0.66, 0.81	
14	0.69, 0.92	
18C	0.67, 0.84	
19A	0.72, 0.93	
19F	0.68, 0.87	
23F	0.52, 0.69	

*Cells shaded red did not meet non-inferiority margin, yellow met the non-inferiority margin: LCI>0.5; cells shaded blue met the superiority margin: LCI>2.0

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
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>Interpretive statement</th></tr>
<tr>
<td>continued

IgG Geometric Mean Concentration (GMC) ratio post dose 3

Follow-up: 30 days</td>
<td>continued
<table>
<tr><td>Study</td><td colspan="2">B7471012*</td></tr>
<tr><td>PCV</td><td>20v</td><td>13v</td></tr>
<tr><td>N</td><td>497</td><td>504</td></tr>
<tr><td colspan="3">20v-non13v serotypes</td></tr>
<tr><td>8</td><td colspan="2">100.05, 128.46</td></tr>
<tr><td>10A</td><td colspan="2">372.25, 480.73</td></tr>
<tr><td>11A</td><td colspan="2">199.06, 264.96</td></tr>
<tr><td>12F</td><td colspan="2">204.73, 245.76</td></tr>
<tr><td>15B</td><td colspan="2">465.44, 597.77</td></tr>
<tr><td>22F</td><td colspan="2">1908.27, 2520.41</td></tr>
<tr><td>33F</td><td colspan="2">470.15, 598.66</td></tr>
</table>
*Cells shaded red did not meet non-inferiority margin, yellow met the non-inferiority margin: LCI>0.5; cells shaded blue met the superiority margin: LCI>2.0</td>
<td>996
(1 RCT)[1,4]</td>
<td>⊕⊕⊕◯
Moderate[b]</td>
<td>20vPCV likely results in no difference in IgG GMC ratios for all shared ST post dose 3 except for 6B which did not meet the non-inferiority margin.

20vPCV increases IgG GMC ratios for 20v-non-13v ST.</td>
</tr>
</table>

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
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>Interpretive statement</th></tr>
<tr>
<td>IgG Geometric Mean Concentration (GMC) ratio post dose 2

Follow-up: 30 days</td>
<td>
<table>
<tr><td>Study</td><td colspan="2">B7471012*</td></tr>
<tr><td>PCV</td><td>20v</td><td>13v</td></tr>
<tr><td>N</td><td>567</td><td>562</td></tr>
<tr><td colspan="3">Shared serotypes</td></tr>
<tr><td>1</td><td colspan="2">0.54, 0.69</td></tr>
<tr><td>3</td><td colspan="2">0.64, 0.79</td></tr>
<tr><td>4</td><td colspan="2">0.52, 0.69</td></tr>
<tr><td>5</td><td colspan="2">0.52, 0.70</td></tr>
<tr><td>6A</td><td colspan="2">0.45, 0.65</td></tr>
<tr><td>6B</td><td colspan="2">0.43, 0.61</td></tr>
<tr><td>7F</td><td colspan="2">0.64, 0.80</td></tr>
<tr><td>9V</td><td colspan="2">0.50, 0.69</td></tr>
<tr><td>14</td><td colspan="2">0.70, 0.96</td></tr>
<tr><td>18C</td><td colspan="2">0.67, 0.92</td></tr>
<tr><td>19A</td><td colspan="2">0.51, 0.69</td></tr>
<tr><td>19F</td><td colspan="2">0.64, 0.82</td></tr>
<tr><td>23F</td><td colspan="2">0.44, 0.62</td></tr>
</table>
*Cells shaded yellow met the non-inferiority margin: LCI>0.5; cells shaded blue met the superiority margin: LCI>2.0
</td>
<td>1,118
(1 RCT)[1]</td>
<td>⊕⊕⊕◯
Moderate[b]</td>
<td>20vPCV likely results in no difference in IgG GMC ratios for most shared STs post dose 2, except for 6A, 6B and 23F which did not meet the non-inferiority margin.

20vPCV likely increases IgG GMC ratios for 20v-non-13v ST.</td>
</tr>
</table>

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
continued IgG Geometric Mean Concentration (GMC) ratio post dose 2 Follow-up: 30 days	***continued*** **Study** B7471012* **PCV** 20v 13v **N** 567 562 **20v-non13v serotypes** 8: 81.19, 102.43 10A: 7.20, 9.76 11A: 65.99, 84.17 12F: 15.66, 20.48 15B: 71.77, 97.28 22F: 287.86, 394.72 33F: 10.55, 14.09 *Cells shaded yellow met the non-inferiority margin: LCI>0.5; cells shaded blue met the superiority margin: LCI>2.0	1,118 (1 RCT)[1]	⊕⊕⊕◯ Moderate[b]	20vPCV likely results in no difference in IgG GMC ratios for most shared STs post dose 2, except for 6A, 6B and 23F which did not meet the non-inferiority margin. 20vPCV likely increases IgG GMC ratios for 20v-non-13v ST.

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

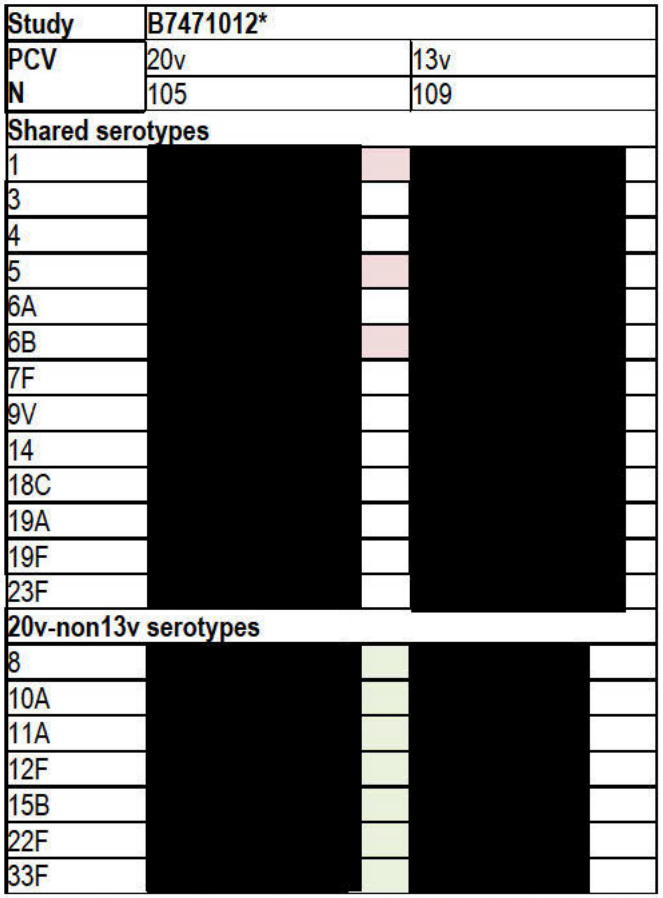
Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
OPA response rate post dose 3 Assessed with: % ≥LLOQ Follow-up: 30 days	**Study** B7471012* **PCV** 20v 13v **N** 105 109 **Shared serotypes** 1 [redacted] 3 4 5 6A 6B 7F 9V 14 18C 19A 19F 23F *Cells shaded red have a lower point estimate for 20vPCV and non-overlapping confidence intervals, green have higher point estimate for 20vPCV and non-overlapping confidence intervals	214 (1 RCT)[1,2]	⊕⊕◯◯ Low[b,c]	20vPCV may result in little to no difference in OPA response rate for shared ST except ST1 post dose 3, which was statistically significantly lower for 20vPCV. 20vPCV may increase OPA response rate for 20v-non-13v ST post dose 3.

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

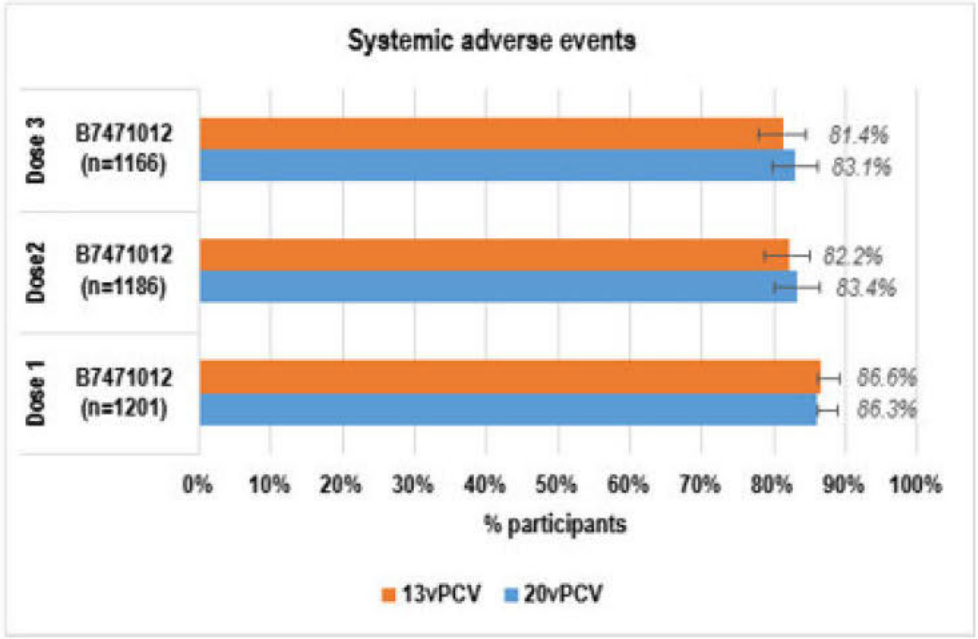
Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
continued OPA response rate post dose 3 Assessed with: % ≥LLOQ Follow-up: 30 days	***continued*** **Study** B7471012* **PCV** 20v 13v **N** 105 109 **20v-non13v serotypes** 8 [redacted] 10A 11A 12F 15B 22F 33F *Cells shaded red have a lower point estimate for 20vPCV and non-overlapping confidence intervals, green have higher point estimate for 20vPCV and non-overlapping confidence intervals	214 (1 RCT)[1,2]	⊕⊕◯◯ Low[b,c]	20vPCV may result in little to no difference in OPA response rate for shared ST except ST1 post dose 3, which was statistically significantly lower for 20vPCV. 20vPCV may increase OPA response rate for 20v-non-13v ST post dose 3.

OPA response rate post dose 2 Assessed with: % ≥LLOQ Follow-up: 30 days	 *Cells shaded red have a lower point estimate for 20vPCV and non-overlapping confidence intervals, green have higher point estimate for 20vPCV and non-overlapping confidence intervals	228 (1 RCT)[1,2]	⊕⊕◯◯ Low[b,c]	20vPCV may result in little to no difference in OPA response rate for shared ST except ST1, 5 and 6B post dose 2, which were statistically significantly lower for 20vPCV. 20vPCV may increase OPA response rate for 20v-non-13v ST post dose 2.

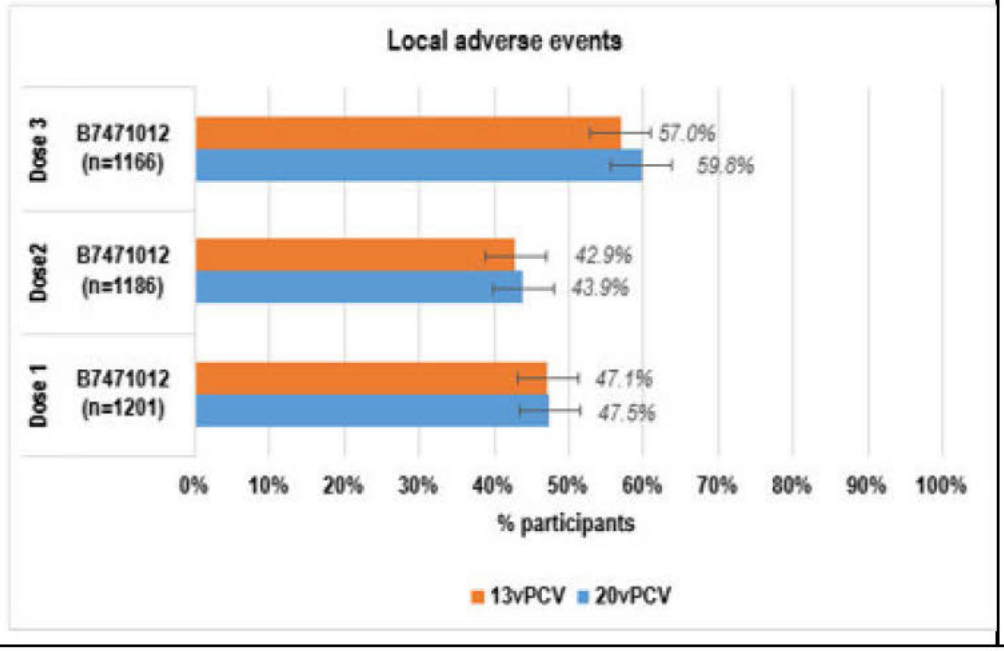
20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
Systemic adverse events post each dose Follow-up: 7 days		1201 (1 RCT)[1,4]	⊕⊕⊕⊕ High[a]	20vPCV results in little to no difference in systemic adverse events compared to 13vPCV

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretive statement
Local adverse events post each dose Follow-up: 7 days		1201 (1 RCT)[1,4]	⊕⊕⊕⊕ High[a]	20vPCV results in little to no difference in local adverse events compared to 13vPCV

20vPCV compared to 13vPCV in non-Indigenous infants without a risk condition in a 2+1 schedule

Patient or population: Non-Indigenous infants without a risk condition in a 2+1 schedule
Intervention: 20vPCV
Comparison: 13vPCV

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

Explanations

a. Inconsistency not assessed as only single study
b. Some concerns in the domain of risk of bias in the selection of the reported results
c. Downgraded due to small sample size (n = <400)

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 20vPCV=20-valent pneumococcal conjugate vaccine; AE=adverse event; CI=confidence interval; GMC=geometric mean concentrations; GMT=geometric mean titres; IgG=Immunoglobulin G; LCI=lower confidence interval; LLOQ = lower limit of quantification; NR=not reported; OPA=opsonophagocytic activity; RCTs=randomised controlled trials; SAE=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

Evidence profile: 20vPCV compared to 13vPCV for non-Indigenous infants without a risk condition

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Any serious adverse event (SAE) following each dose (follow-up: 1 month)									
1	Randomised trials	Not serious	N/a[a]	Not serious	Not serious	None	The rate of SAEs from Dose 1 to the end of the study was 5.7% for 20vPCV recipients and 6.6% for 13vPCV recipients.[1,2] From dose 2 to 1 month of follow up the rate of SAE was 2.3% for both 13vPCV and 20vPCV. For dose 3 to 1 month of follow up the rates were 0.5% and 1.2% for 20vPCV and 13vPCV respectively.	⊕⊕⊕⊕ High	CRITICAL
Difference in IgG response rate post dose 3 (follow-up: 30 days; assessed with: % participants w/ IgG ≥0.35ug/mL)									
1	Randomised trials	Serious[b]	N/a[a]	Not serious	Not serious	None	The difference in the proportion of participants with IgG ≥0.35 ug/mL at 30 days post dose 3 for shared serotypes ranges from -14.7 percentage points to 2.7 percentage point. All shared serotypes except ST3 met a non-inferiority margin of LCI > -10 percentage points.[1,3] For 20v-non-13v serotypes the difference in proportion of participants with IgG ≥0.35 ug/mL at 30 days post dose 3 ranges from 91.3 percentage points to 98.8 percentage points.[1,3] All 20v-non-13v serotypes met the superiority margin of LCI>10 percentage points.	⊕⊕⊕◯ Moderate	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Difference in IgG response rate post dose 2 (follow-up: 30 days; assessed with: % participants with IgG ≥0.35ug/mL)									
1	Randomised trials	Serious[b]	N/a[a]	Not serious	Not serious	None	The difference in the proportion of participants with IgG ≥0.35 ug/mL at 30 days post dose 2 for shared serotypes ranged from -23.6 percentage points to 1.4 percentage points. Four out of the 13 shared STs (7F, 14, 19A and 19F) were the only shared serotypes that met a non-inferiority margin of LCI > -10 percentage points. The remaining nine STs did not meet this margin after dose 2.[1,3] For the 20v-non-13v serotypes, the difference in the proportion of participants with IgG ≥0.35 ug/mL at 30 days post dose 2 ranged from 22.4 percentage points to 95.5 percentage points.[1,3] All 20v-non-13v serotypes met the superiority margin of LCI>10 percentage points.	⊕⊕⊕◯ Moderate	IMPORTANT
IgG Geometric Mean Concentration (GMC) ratio post dose 3 (follow-up: 30 days)									
1	Randomised trials	Serious[b]	N/a[a]	Not serious	Not serious	None	The IgG GMC ratio 30 days post dose 3 for shared serotypes ranged from 0.48 to 0.93. Most serotypes met a non-inferiority margin of LCI>0.5 except for 6A, 6B and 23F.[1,4] For 20v-non-13v serotypes the IgG GMCs ranged from 100.05 to 2520.41. All 20v-non13v serotypes IgG GMCs met the superiority margin of LCI>2.0.[1,4]	⊕⊕⊕◯ Moderate	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
IgG Geometric Mean Concentration (GMC) ratio post dose 2 (follow-up: 30 days)									
1	Randomised trials	Serious[b]	N/a[a]	Not serious	Not serious	None	The IgG GMC ratio 30 days post dose 2 for shared serotypes ranged from 0.51 to 0.82. All serotypes met a non-inferiority margin of LCI>0.5 except for 6B.[1] For 20v-non-13v serotypes the IgG GMCs ranged from 8.38 to 337.08. All 20v-non13v serotypes IgG GMCs met the superiority margin of LCI>2.0.[1]	⊕⊕⊕◯ Moderate	IMPORTANT
OPA response rate post dose 3 (follow-up: 30 days; assessed with: % participants ≥LLOQ)									
1	Randomised trials	Serious[b]	N/a[a]	Not serious	Serious[c]	None	The OPA response rate 30 days post dose 3 for shared serotypes ranged from [redacted] to [redacted] for 20vPCV and [redacted] to [redacted] for 13vPCV. ST1 had a statistically significantly lower OPA response rate for 20vPCV compared to 13vPCV as it did not have overlapping confidence intervals.[1,2] For the 20v-non13v serotypes the OPA response rate ranged from [redacted] to [redacted] for 20vPCV and [redacted] to [redacted] for 13vPCV. All 20v-non-13 serotypes had statistically significantly higher response rates for 20vPCV compared to 13vPCV based on non-overlapping confidence intervals.[1,2]	⊕⊕◯◯ Low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
OPA response rate post dose 2 (follow-up: 30 days; assessed with: % participants ≥LLOQ)									
1	Randomised trials	Serious[b]	N/a[a]	Not serious	Serious[c]	None	The OPA response rate 30 days post dose 2 for shared serotypes ranged from [redacted] to [redacted] for 20vPCV and [redacted] to [redacted] for 13vPCV. STs 1, 5 and 6B had a statistically significantly lower OPA response rates for 20vPCV compared to 13vPCV as they did not have overlapping confidence intervals.[1,2] For the 20v-non13v serotypes the OPA response rate ranged from [redacted] to [redacted] for 20vPCV and [redacted] to [redacted] for 13vPCV. All 20v-non-13 serotypes had statistically significantly higher response rates for 20vPCV compared to 13vPCV based on non-overlapping confidence intervals.[1,2]	⊕⊕◯◯ Low	IMPORTANT
Systemic adverse events post each dose (follow-up: 7 days)									
1	Randomised trials	Not serious	N/a[a]	Not serious	Not serious	None	The rate of systemic adverse events ranged from 83.1% to 86.3% for 20vPCV recipients and 81.4% to 86.6% for 13vPCV recipients, depending on the dose, with the highest rate reported post dose 1.[1,4]	⊕⊕⊕⊕ High	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Local adverse events post each dose (follow-up: 7 days)									
1	Randomised trials	Not serious	N/a[a]	Not serious	Not serious	None	The rate of local adverse events ranged from 43.9% to 59.8% for 20vPCV recipients and 42.9% to 57.0% for 13vPCV recipients, depending on the dose, with the highest rate reported post dose 1.[1,4]	⊕⊕⊕⊕ High	IMPORTANT

Explanations

a. Inconsistency not assessed as only single study
b. Some concerns in the domain of risk of bias in the selection of the reported results
c. Downgraded due to small sample size n is <400

Abbreviations: 13vPCV=13-valent pneumococcal conjugate vaccine; 20vPCV=20-valent pneumococcal conjugate vaccine; CI=confidence interval; GMC=geometric mean concentrations; GMT=geometric mean titres; ID=identification; IgG=immunoglobulin G; LCI=lower confidence interval; LLOQ = lower limit of quantification; NR=not reported; OPA=opsonophagocytic activity; PD=post dose; RCTs=randomised controlled trials; SAE=serious adverse events; ST=serotype; UCI=upper confidence interval.

Evidence to Decision Framework: individual perspective

Should 20vPCV (2+1 schedule) be used in non-Indigenous children without a risk condition for the prevention of pneumococcal disease?	
Population	All non-Indigenous infants without a risk condition
Intervention	20-valent pneumococcal conjugate vaccine (20vPCV) in a 2+1 schedule
Comparison	13-valent pneumococcal conjugate vaccine (13vPCV) in a 2+1 schedule
Main outcomes	*Immunogenicity* • Difference in IgG response rate (30-days post dose 3) – Important • Difference in IgG response rate (30-days post dose 2) – Important • IgG GMC ratios (30-days post dose 3) – Important • IgG GMC ratios (30-days post dose 2) – Important • OPA response rate (30-days post dose 3) – Important • OPA response rate (30-days post dose 2) – Important *Safety* • Serious adverse events (SAE) – Critical • Local adverse events – Important • Systemic adverse events – Important
Setting	Multicentre (Australia, Belgium, Czechia, Denmark, Estonia, Finland, Italy, Netherlands, Norway, Russia, Slovakia)
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 younger children. In Australia in 2016 there were 1,666 IPD notifications of which 234 (14%) were in children under 5 years. Of the 2,434 hospitalisations for pneumonia in 2016, 5% were in children under 5 years.[5]
- Rates of IPD caused by most vaccine serotypes fell after vaccination with 13vPCV was introduced for infants, however non-13v serotypes cause a considerable amount of residual IPD.

- Extended valency PCVs would likely improve pneumococcal disease prevention in children.

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Overall, there is improved immunogenicity outcomes for 20v-non-13v serotypes.
- None of the shared serotypes between 20vPCV and 13vPCV have superior immunogenicity outcomes for 20vPCV. Serotype 3 did not meet the non-inferiority margin for IgG response rate post dose three.
- There is no evidence available on the effectiveness against clinical outcomes after 20vPCV in children.

Undesirable effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Undesirable effects include frequent rates of local adverse events and systemic adverse events which are mostly of mild to moderate severity. The rates were similar to those seen after 13vPCV.
- The rates of serious adverse events were low and comparable between 20vPCV and 13vPCV

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 was rated as moderate as 3/9 were high, 4/9 were moderate and 2/9 were low.
- Studies were downgraded due to some conerns in the risk of bias domain around the reported outcomes and imprecsion due to small sample size.

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

- 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-non-13v serotypes outweigh the potential reduction in some shared serotypes. • The undesirable effects of 20vPCV are comparable to 13vPCV						
Acceptability *Is the intervention acceptable to key stakeholders?*						
Don't know	Varies	No	Probably No	Probably Yes	Yes	
• Vaccination of infants against pneumococcal disease appears to be acceptable in the Australian setting. In 2023 the vaccination uptake of pneumococcal vaccination in infants aged one and two years was 96% and 95%, respectively.[6]						
Feasibility *Is the intervention feasible to implement?*						
Don't know	Varies	No	Probably No	Probably Yes	Yes	
• Minimal barriers in implementation, as vaccine delivery system already in use and this vaccine would likely replace the use of another vaccine for the individuals receiving it.						
ATAGI RECOMMENDATION						
20vPCV is recommended in preference to 13vPCV in non-Indigenous children without risk conditions for the prevention of pneumococcal disease.						
JUSTIFICATION AND CONSIDERATIONS						
For 20v-non13v serotypes (8, 10A, 11A, 12F, 15B, 22F and 33F), 20vPCV likely results in improved protection based on immunogenicity outcomes compared to 13vPCV. The evidence suggests that 20vPCV likely results in little difference in the immunogenicity outcomes for most of the shared serotypes compared to 13vPCV. All safety outcomes are comparable between 20vPCV and 13vPCV.						

References

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