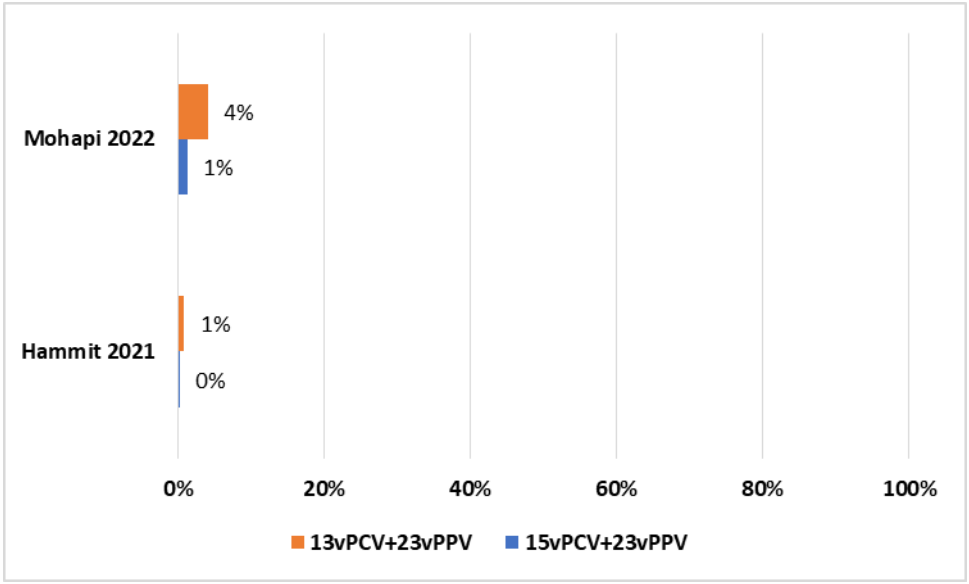
NCIRS is conducting GRADE in support of ATAGI and making pilot results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook Pneumococcal Chapter

15vPCV+23vPPV compared to 13vPCV+23vPPV for Adults ≥18 years with specific risk factors

Patient or population: Adults ≥18 years with specific risk factors
Intervention: 15vPCV+23vPPV
Comparison: 13vPCV+23vPPV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Serious adverse events (SAE)		1814 (2 RCTs)	⨁⨁◯◯ Low[a,b,c]	15vPCV+23vPPV may result in little to no difference in SAE compared to 13vPCV+23vPPV

OPA GMT ratios follow-up: 30 days

Table 1: 95% CI for OPA GMT ratios (15vPCV+23vPPV vs. 13vPCV+23vPPV) at Day 30 a) shaded by non-inferiority and superiority margins^ b) shaded by estimated that favour 15vPCV or 13vPCV†

a)

Study ID	**Hammit 2021***		**Mohapi 2022***	
Population	Age 18-49 years Pneumococcal vaccine naïve Immunocompetent with RFs (Non Native Americans) or without (Native American).		Age ≥18 years Pneumococcal vaccine naïve Adults living with HIV	
Interval between PPV and PCV	6 months		2 months	
PCV	15	13	15	13
N	1133	379	152	150
1	1.12, 1.58		0.94, 2.04	
3	0.85, 1.12		0.82, 1.39	
4	0.79, 1.01		0.72, 1.36	
5	0.86, 1.19		0.93, 1.95	
6A	0.87, 1.16		0.75, 1.49	
6B	1.06, 1.36		1.01, 1.95	
7F	0.89, 1.12		0.83, 1.41	
9V	0.84, 1.08		0.98, 1.61	
14	0.97, 1.26		1.12, 2.02	
18C	1.25, 1.57		1.17, 2.09	
19A	0.93, 1.2		0.82, 1.45	
19F	0.97, 1.22		0.91, 1.52	
23F	0.9, 1.21		0.9, 1.9	
22F	0.77, 1.05		0.81, 1.64	
33F	0.63, 0.85		0.67, 1.21	

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

*study not powered to detect a difference between 15vPCV and 13vPCV

b)

Study ID	**Hammit 2021***		**Mohapi 2022***	
PCV	15	13	15	13
N	1133	379	152	150
1	1.12, 1.58		0.94, 2.04	
3	0.85, 1.12		0.82, 1.39	
4	0.79, 1.01		0.72, 1.36	
5	0.86, 1.19		0.93, 1.95	
6A	0.87, 1.16		0.75, 1.49	
6B	1.06, 1.36		1.01, 1.95	
7F	0.89, 1.12		0.83, 1.41	
9V	0.84, 1.08		0.98, 1.61	

1814 (2 RCTs)

⨁⨁◯◯ Low[b,c,d]

15vPCV+23vPPV may result in little difference in OPA GMT ratios

Note: OPA GMT ratios all met a non-inferiority margin of LCI>0.5. Across all studies, 15vPCV is statistically significantly higher than 13vPCV for ST 6B and 18C

15vPCV+23vPPV compared to 13vPCV+23vPPV for Adults ≥18 years with specific risk factors

	14	0.97, 1.26	1.12, 2.02		
	18C	1.25, 1.57	1.17, 2.09		
	19A	0.93, 1.2	0.82, 1.45		
	19F	0.97, 1.22	0.91, 1.52		
	23F	0.9, 1.21	0.9, 1.9		
	22F	0.77, 1.05	0.81, 1.64		
	33F	0.63, 0.85	0.67, 1.21		

†Green=LCI>1; red=UCI<1
*study not powered to detect a difference between 15vPCV and 13vPCV

% of participants ≥ 4-fold rise of GMT pre PCV to post PPV23 vaccination

Table 2: Proportion of participants with a ≥ 4-fold rise of GMT pre PCV to post PPV vaccination*

Study ID	Hammit 2021		Mohapi 2022	
PCV	15+23	13+23	15+23	13+23
N	839	280	152	150
1	88% (85,90)	84% (79,88)	84% (76,90)	73% (63,81)
3	67% (63,70)	67% (61,72)	50% (41,60)	52% (43,62)
4	84% (82,87)	86% (82,90)	85% (77,91)	81% (73,88)
5	87% (84,89)	87% (83,91)	82% (74,89)	70% (61,78)
6A	74% (70,77)	80% (75,85)	76% (67,84)	69% (59,78)
6B	76% (73,79)	74% (69,79)	83% (74,89)	79% (71,86)
7F	60% (56,63)	60% (54,66)	71% (62,79)	71% (62,79)
9V	51% (47,54)	52% (46,58)	44% (35,54)	45% (36,55)
14	65% (62,68)	59% (53,65)	68% (59,76)	57% (48,67)
18C	78% (75,80)	76% (71,81)	76% (67,83)	69% (59,77)
19A	68% (65,71)	71% (65,76)	80% (72,87)	69% (59,77)
19F	61% (58,64)	63% (57,69)	72% (62,80)	57% (48,67)
23F	74% (70,77)	72% (66,77)	84% (75,90)	70% (60,78)
22F	59% (55,63)	65% (59,71)	74% (64,82)	75% (66,83)
33F	53% (50,57)	61% (55,67)	61% (51,70)	68% (58,76)

*Hammit 2022: Proportion of participants with ≥4-fold rise in OPA antibodies from Day 1 (pre PCV) to Month 7 (post PPV23); Mohapi 2022: Proportion of participants with ≥4-fold rise in OPA antibodies from Day 1 (pre PCV) to Week 12 (post PPV23)

1814 (2 RCTs)

⊕⊕⊕◯ Moderate[b,c]

15vPCV+23vPPV likely results in little difference in ≥ 4-fold rise of GMT pre to post vaccination compared to 13vPCV+23vPPV

IgG GMC ratios follow-up: 30 days

Table 3: 95% CI for IgG GMC ratios (15vPCV+23vPPV vs. 13vPCV+23vPPV) for shared and unique serotypes at Day 30 a) shaded by non-inferiority and superiority margins^ b) shaded by estimates that favour 15vPCV or 13vPCV†

a)

Study ID	Hammit 2021*		Mohapi 2022*	
PCV	15	13	15	13
N	1133	379	152	150
1	0.81, 1.01		0.59, 0.98	
3	0.85, 1.04		0.83, 1.21	
4	0.65, 0.82		0.63, 0.99	
5	0.84, 1.08		0.85, 1.36	
6A	0.78, 1.04		0.81, 1.45	
6B	0.96, 1.27		0.9, 1.6	
7F	0.8, 1		0.7, 1.12	
9V	0.81, 1.01		0.78, 1.21	
14	0.91, 1.17		0.76, 1.35	
18C	1.15, 1.46		0.86, 1.39	
19A	0.8, 1.01		0.73, 1.17	
19F	0.89, 1.12		0.79, 1.28	
23F	0.94, 1.21		0.67, 1.23	
22F	0.93, 1.23		0.79, 1.44	
33F	0.6, 0.77		0.6, 0.99	

^yellow= orange=LCI>0.67[5]; yellow=LCI>0.5[6]; blue=LCI>1.0 [6]

*study not powered to detect a difference between 15vPCV and 13vPCV

b)

Study ID	Hammit 2021*		Mohapi 2022*	
PCV	15	13	15	13
N	1133	379	152	150
1	0.81, 1.01		0.59, 0.98	
3	0.85, 1.04		0.83, 1.21	
4	0.65, 0.82		0.63, 0.99	
5	0.84, 1.08		0.85, 1.36	
6A	0.78, 1.04		0.81, 1.45	
6B	0.96, 1.27		0.9, 1.6	
7F	0.8, 1		0.7, 1.12	
9V	0.81, 1.01		0.78, 1.21	
14	0.91, 1.17		0.76, 1.35	
18C	1.15, 1.46		0.86, 1.39	
19A	0.8, 1.01		0.73, 1.17	

1814 (2 RCTs)

⨁⨁◯◯ Low[b,c,d]

15vPCV+23vPPV may result in little difference in IgG GMC ratios

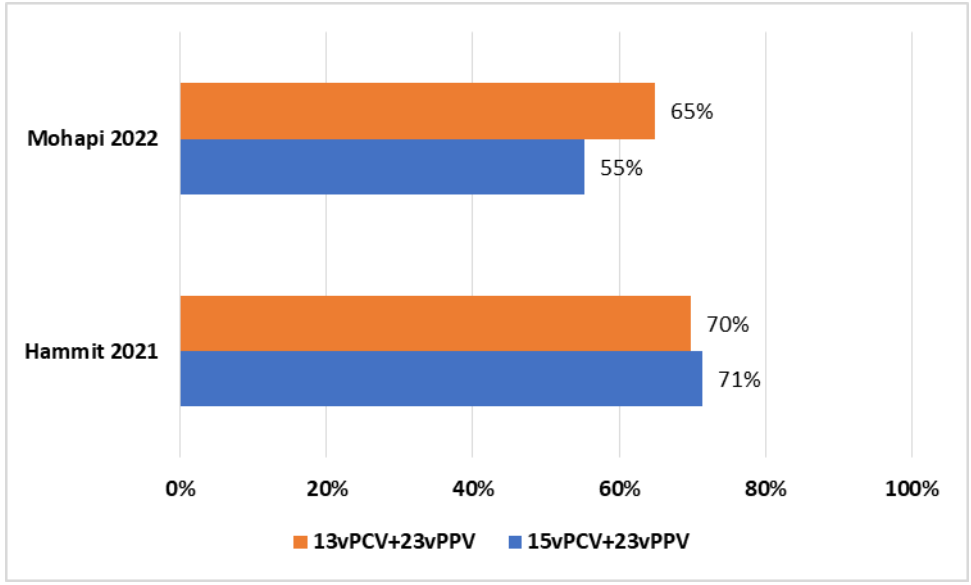
Note: All ST across all studies met a non-inferiority margin (LCI>0.5). This is consistent with OPA GMT ratio

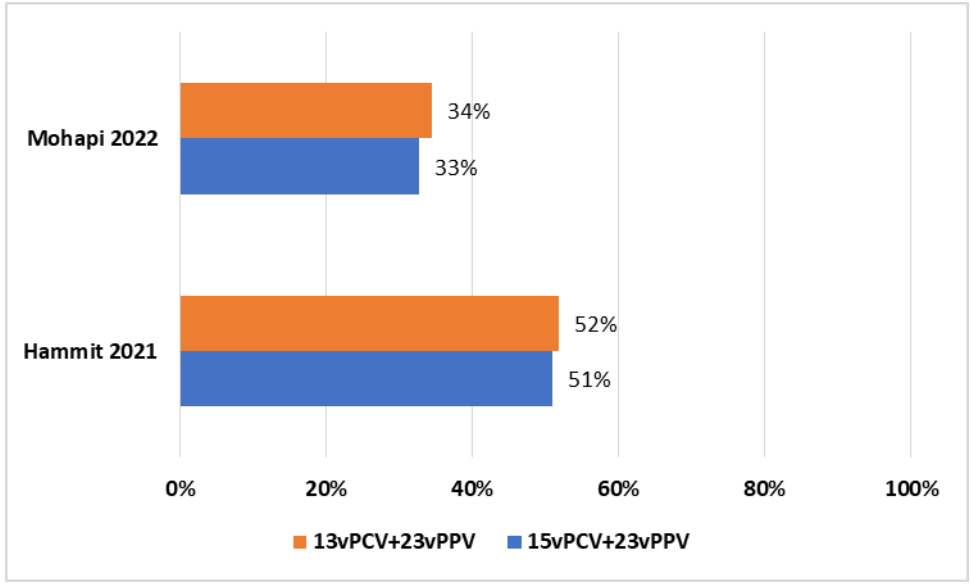
15vPCV+23vPPV compared to 13vPCV+23vPPV for Adults ≥18 years with specific risk factors

	19F	0.89, 1.12	0.79, 1.28			
	23F	0.94, 1.21	0.67, 1.23			
	22F	0.93, 1.23	0.79, 1.44			
	33F	0.6, 0.77	0.6, 0.99			
	†Green=LCI>1; red=UCI<1 *study not powered to detect a difference between 15vPCV and 13vPCV					
% of participants ≥ 4-fold rise of GMC pre PCV to post PPV23 vaccination	Table 4: Proportion of participants with a ≥ 4-fold rise of GMC pre to post vaccination*				1814 (2 RCTs)	⨁⨁⨁◯ Moderate[b,c]	15vPCV+23vPPV likely results in little difference in ≥ 4-fold rise of GMC pre to post vaccination compared to 13vPCV+23vPPV

Study ID	**Hammit 2021***		**Mohapi 2022**	
PCV	15	15+23	15+23	13
N	843	152	152	274
1	81% (79,84)	84% (79,88)	81% (73,87)	89% (82,94)
3	41% (37,44)	46% (40,52)	50% (42,59)	45% (36,54)
4	71% (68,74)	82% (77,86)	71% (63,79)	84% (76,90)
5	49% (45,52)	52% (46,58)	44% (36,53)	44% (35,53)
6A	82% (79,84)	82% (77,86)	83% (75,89)	80% (72,86)
6B	86% (84,89)	85% (81,89)	81% (74,88)	81% (73,87)
7F	77% (74,80)	84% (80,88)	81% (73,87)	86% (79,91)
9V	72% (69,75)	77% (72,80)	76% (68,83)	78% (70,85)
14	77% (74,80)	71% (65,76)	67% (58,75)	70% (62,78)
18C	83% (80,85)	80% (75,85)	82% (75,88)	84% (76,90)
19A	66% (63,69)	75% (69,80)	68% (59,76)	73% (65,81)
19F	75% (71,78)	79% (74,84)	78% (70,85)	84% (77,90)
23F	78% (75,81)	78% (73,83)	75% (67,82)	78% (70,85)
22F	69% (66,72)	66% (60,71)	84% (76,90)	86% (79,91)
33F	68% (65,71)	76% (70,81)	77% (69,84)	86% (79,91)

*Hammit 2022: Proportion of participants with ≥4-fold rise in IgG antibodies from Day 1 (pre PCV) to Month 7 (post PPV23); Mohapi 2022: Proportion of participants with ≥4-fold rise in IgG antibodies from Day 1 (pre PCV) to Week 12 (post PPV23)

15vPCV+23vPPV compared to 13vPCV+23vPPV for Adults ≥18 years with specific risk factors				
Injection site adverse event		1814 (2 RCTs)	⨁⨁⨁◯ Moderate[b,c]	15vPCV+23vPPV likely results in little difference in injection site adverse events compared to 13vPCV+23vPPV

15vPCV+23vPPV compared to 13vPCV+23vPPV for Adults ≥18 years with specific risk factors				
Systemic Adverse Events		1814 (2 RCTs)	⊕⊕⊕◯ Moderate[b,c]	15vPCV+23vPPV likely results in little difference in systemic adverse events compared to 13vPCV+23vPPV

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.

Abbreviations: 13vPCV, 13-Valent pneumococcal conjugate vaccine; 15vPCV, 15-Valent pneumococcal conjugate vaccine; 23vPPV, pneumococcal polysaccharide vaccine; CI, confidence interval; GMC, geometric mean concentrations; GMT, geometric mean titres; ID, identification; IgG, Immunoglobulin G; LCI, lower confidence interval; OPA, opsonophagocytic activity; RCTs, randomised controlled trials; SAE, serious adverse events; UCI, upper confidence interval

Explanations

a. Downgraded due to low number of events
b. Mohapi 2022 included people with HIV and Hammit 2021 included Non-native Americans with at least 1 RF aged 18-64 years. Results from these populations may not be generalisbale to all eligible Australians
c. Included studies had an interval of 2 and 6 months between PCV and PPV vaccines. This differs to the 12 months interval recommended in the Australian Immunisation Handbook
d. No studies were powered to detect a difference between 15vPCV+23vPPV and 13vPCV+23vPPV

Evidence Profile: Adults ≥18 years with specific risk factors

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Serious adverse events									
2	randomised trials	not serious	not serious	serious[b,c]	not serious[a]	none	The rates of serious adverse events ranged from 0% to 1% for 15vPCV+23vPPV recipients and 1% to 4% for 13vPCV+23vPPV recipients. None were considered by study investigators to be related to the vaccine.	⊕⊕◯◯ Low	CRITICAL
OPA GMT ratios (follow-up: 30 days)									
2	randomised trials	not serious	not serious	serious[b,c]	serious[d]	none	The OPA GMT ratio 30 days following vaccination for shared serotypes ranges from 0.89 to 1.57. For 15v-non13v serotypes (22F and 33F) OPA GMT ratios ranged from 0.73 to 1.63. Majority of serotypes across all studies met a non-inferiority margin of 0.67.[5]	⊕⊕◯◯ Low	IMPORTANT
% of participants ≥ 4-fold rise of GMT pre to post vaccination									
2	randomised trials	not serious	not serious	serious[b,c]	not serious	none	The proportion of participants with ≥4-fold rise of GMT pre PCV to post PPV vaccination for shared serotypes ranged from 44% to 88% for 15vPCV+23vPPV recipients and 45% to 87% for 13vPCV+23vPPV recipients. For 15v-non13v serotypes (22F and 33F) the proportion of participants with ≥4-fold rise of GMT pre PCV to post PPV ranged from 53% to 74% for 15vPCV+23vPPV recipients and 61% to 75% for 13vPCV+23vPPV recipients.	⊕⊕⊕◯ Moderate	IMPORTANT
IgG GMC ratios (follow-up: 30 days)									
2	randomised trials	not serious	not serious	serious[b,c]	serious[d]	none	The IgG GMC ratio 30 days following vaccination for shared serotypes ranges from 0.73 to 1.30. For 15v-non13v serotypes (22F and 33F) the IgG GMC ratio 30 days following vaccination ranged from 0.68 to 1.07. Majority of serotypes across all studies met a non-inferiority margin of 0.67.[5]	⊕⊕◯◯ Low	IMPORTANT
% of participants ≥ 4-fold rise of GMC pre to post vaccination									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2	randomised trials	not serious	not serious	serious[b,c]	not serious	none	The proportion of participants with ≥4-fold rise of GMC pre PCV to post PPV vaccination for shared serotypes ranged from 41% to 86% for 15vPCV+23vPPV recipients and 44% to 89% for 13vPCV+23vPPV recipients. For 15v-non13v serotypes (22F and 33F) the proportion of participants with ≥4-fold rise of GMC pre PCV to post PPV ranged from 68% to 84% for 15vPCV+23vPPV recipients and 66% to 86% for 13vPCV+23vPPV recipients.	⨁⨁⨁◯ Moderate	IMPORTANT
Solicited local adverse event									
2	randomised trials	not serious	not serious	serious[b,c]	not serious	none	The rate of injection site adverse events ranged from 55% to 71% for 15vPCV+23vPPV recipients and 70% to 65% for 13vPCV+23vPPV recipients	⨁⨁⨁◯ Moderate	IMPORTANT
Solicited Systemic Adverse Events									
2	randomised trials	not serious	not serious	serious[b,c]	not serious	none	The rates of systemic adverse events ranged from 33% to 51% for 15vPCV+23vPPV recipients and 34% to 52% for 13vPCV+23vPPV recipients	⨁⨁⨁◯ Moderate	IMPORTANT

Abbreviations: 13vPCV, 13-Valent pneumococcal conjugate vaccine; 15vPCV, 15-Valent pneumococcal conjugate vaccine; 23vPPV, pneumococcal polysaccharide vaccine; CI, confidence interval; GMC, geometric mean concentrations; GMT, geometric mean titres; ID, identification; IgG, Immunoglobulin G; LCI, lower confidence interval; OPA, opsonophagocytic activity; RCTs, randomised controlled trials; SAE, serious adverse events; UCI, upper confidence interval

Explanations

a. Downgraded due to low number of events
b. Mohapi 2022 included people with HIV and Hammit 2021 included Non-native Americans with at least 1 RF aged 18-64 years. Results from these populations may not be generalisbale to all eligible Australians
c. Included studies had an interval of 2 and 6 months between PCV and PPV vaccines. This differs to the 12 months interval recommended in the Australian Immunisation Handbook
d. No studies were powered to detect a difference between 15vPCV+23vPPV and 13vPCV+23vPPV

Evidence to Decision Framework: individual perspective

Should 15vPCV (followed by 23vPPV) be used in adults ≥18 years old with specific risk conditions (as in HB list) for the prevention of pneumococcal disease?	
Population	Adults ≥18 years with specific risk factors
Intervention	15-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) - % of participants ≥ 4-fold rise of GMC pre to post vaccination Safety: with 23vPPV after previous 15vPCV or 13vPCV delivery - Severe adverse events (SAE) - Injection site adverse events - Systematic adverse events
Setting	USA, South Korea, Spain, Taiwan, Canada, Chile, Poland, Australia, New Zealand, France, Peru, South Africa, Thailand
Perspective	Individual
ASSESSMENT	

Problem
Is the problem a priority?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- In Australia about 800 cases of invasive pneumococcal disease (IPD, the severe form of pneumococcal disease) occurs annually.[11] The incidence of all community acquired pneumonia caused by pneumococcus is several fold higher than IPD.[12]
- Serotypes that cause pneumococcal disease in those with risk conditions is more diverse compared to others.
- With the use of PCVs over several years with high coverage certain non-PCV serotypes have emerged with increasing IPD incidence and 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

- There is variability in the evidence of immunogenicity outcomes of 15vPCV+23vPPV compared with 13vPCV+23vPPC. Although there are small effects at improving immunogenicity outcomes for 15v-non13v serotypes from the 15vPCV, these benefits are diminished following 23vPPV vaccine.
- There is no evidence available on clinical outcomes after 15vPCV and no evidence available on the persistence of 15vPCV+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 certainty of evidence is moderate due to imprecision as some studies were not powered to detect a different between 15vPCV and 13vPCV

Values
I*s 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

- 15vPCV+23vPPV was found to have similar desirable and undesirable effects compared to 13vPCV+23vPPV. Although there are small effects at improving immunogenicity outcomes in the 15v-non13v serotypes from the 15vPCV vaccine, these benefits are diminished following 23vPPV vaccine.
- Undesirable effects are minor

Acceptability
Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably No	Probably Yes	Yes

<table>
<tr><td colspan="6">• 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% [13]. The vaccination uptake in adults aged ≥18 years is likely to be lower.</td></tr>
<tr><td colspan="6">Feasibility
Is the intervention feasible to implement?</td></tr>
<tr><td>Don’t know</td><td>Varies</td><td>No</td><td>Probably No</td><td>Probably Yes</td><td>Yes</td></tr>
<tr><td colspan="6">• 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</td></tr>
</table>

References

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