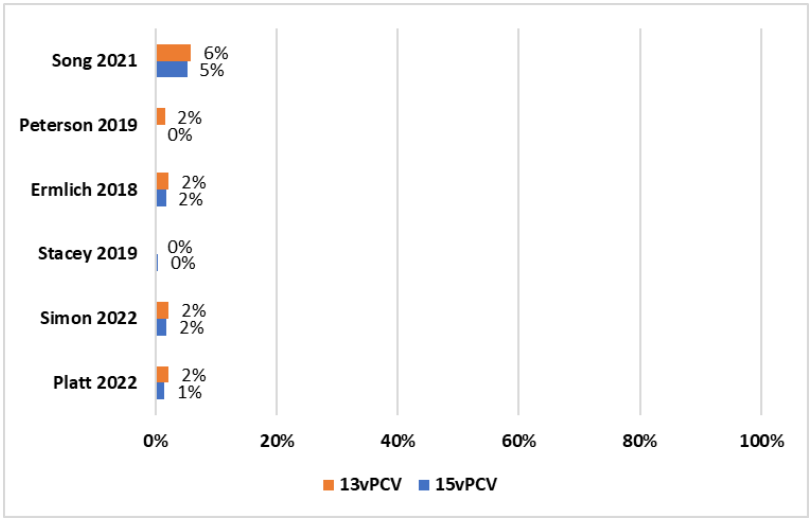
NCIRS is conducting GRADE in support of ATAGI and making pilot results available on the NCIRS website. Please read this material as a supplement to the [Australian Immunisation Handbook Pneumococcal Chapter]

Summary of findings: 15vPCV compared to 13vPCV for non-Indigenous adults ≥70 years old without special risk factors

Patient or population: Non-Indigenous Adults ≥70 years old
Intervention: 15vPCV
Comparison: 13vPCV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Serious adverse events (SAE)		5356 (6 RCTs)	⨁⨁⨁◯ Moderate[a]	15vPCV likely results in little to no difference in SAE compared to 13vPCV

OPA GMT ratios follow-up: 30 days

Table 1: 95% CI for OPA GMT ratios (15vPCV vs. 13vPCV) for shared and unique serotypes at Day 30. a) shaded by non-inferiority (using 3 different thresholds) and superiority margins^ b) shaded by estimates that favour 15vPCV or 13vPCV†

a)

Serotype	Platt 2022		Simon 2022*		Stacey 2019		Ermlich 2018*		Song 2021*		Peterson 2019*	
Population	≥50 years Immunocompetent (stable risk conditions) Pneumococcal vaccine naïve										≥65 years 23vPPV 1 year prior	
N	15	13	15	13	15	13	15	13	15	13	15	13
	602	600	2103	230	231	227	229	230	326	325	127	126
1	0.66, 0.96		0.81, 1.28		1.13, 2.56		1.21, 2.65		0.94, 1.58		0.9, 2.9	
3	1.38, 1.85		1.43, 2.01		2.28, 4.41		1.77, 2.93		1.56, 2.3		1.11, 2.96	
4	0.57, 0.8		0.57, 0.87		0.8, 1.56		0.68, 1.43		0.6, 0.97		0.64, 1.32	
5	0.64, 0.98		0.69, 1.14		0.69, 1.55		1.23, 2.6		0.81, 1.4		0.56, 1.21	
6A	0.84, 1.19		0.94, 1.41		0.58, 1.18		0.51, 1.23		0.92, 1.53		0.49, 1.21	
6B	1.02, 1.48		1.16, 1.74		0.85, 1.65		1.13, 2.42		1.31, 2.06		0.61, 1.41	
7F	0.68, 0.9		0.74, 1.04		0.56, 0.94		0.47, 0.89		0.8, 1.14		0.49, 1.02	
9V	0.7, 0.94		0.77, 1.09		0.88, 1.64		0.92, 1.86		0.83, 1.24		0.84, 1.77	
14	0.64, 0.89		0.79, 1.25		0.86, 1.5		0.68, 1.3		0.87, 1.37		1.01, 1.88	
18C	0.91, 1.26		1.16, 1.68		0.92, 1.7		0.95, 1.8		1.2, 1.84		1.12, 2.34	
19A	0.7, 0.93		0.87, 1.2		0.74, 1.25		0.57, 0.99		1.06, 1.55		0.85, 1.47	
19F	0.76, 1.02		0.85, 1.19		0.75, 1.41		0.42, 0.81		0.92, 1.32		0.82, 1.57	
23F	0.96, 1.44		1.13, 1.77		0.53, 1.1		1.11, 2.68		1.18, 2		0.83, 2.1	
22F	25.25, 39.97		25.59, 40.69		NR		NR		26.13, 46.5		NR	
33F	6.07, 8.32		7.46, 11.15						7.48, 11.2			

^non-inferiority margins: orange=LCI>0.67[8]; yellow=LCI>0.5[5]; white=LCI>0.33[4]

^superiority margin: blue=LCI>2[5]

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

b)

Serotype	Platt 2022		Simon 2022*		Stacey 2019		Ermlich 2018*		Song 2021*		Peterson 2019*	
Population	≥50 years Immunocompetent (stable risk conditions) Pneumococcal vaccine naïve										≥65 years 23vPPV 1 year prior	
PCV	15	13	15	13	15	13	15	13	15	13	15	13
N	602	600	2103	230	231	227	229	230	326	325	127	126
1	0.66, 0.96		0.81, 1.28		1.13, 2.56		1.21, 2.65		0.94, 1.58		0.9, 2.9	
3	1.38, 1.85		1.43, 2.01		2.28, 4.41		1.77, 2.93		1.56, 2.3		1.11, 2.96	
4	0.57, 0.8		0.57, 0.87		0.8, 1.56		0.68, 1.43		0.6, 0.97		0.64, 1.32	
5	0.64, 0.98		0.69, 1.14		0.69, 1.55		1.23, 2.6		0.81, 1.4		0.56, 1.21	
6A	0.84, 1.19		0.94, 1.41		0.58, 1.18		0.51, 1.23		0.92, 1.53		0.49, 1.21	
6B	1.02, 1.48		1.16, 1.74		0.85, 1.65		1.13, 2.42		1.31, 2.06		0.61, 1.41	
7F	0.68, 0.9		0.74, 1.04		0.56, 0.94		0.47, 0.89		0.8, 1.14		0.49, 1.02	

5356 (6 RCTs)

⊕⊕⊕◻ Moderate[b,c]

15vPCV likely results in little difference in OPA GMT ratios for shared STs
15vPCV likely increases OPA GMTs for STs unique to 15vPCV

Note: OPA GMT ratios all met a non-inferiority margin of LCI>0.33. Across all studies 15vPCV is statistically significantly higher than 13vPCV for ST 3, 22F, 33F.

Summary of findings: 15vPCV compared to 13vPCV for non-Indigenous adults ≥70 years old without special risk factors

Patient or population: Non-Indigenous Adults ≥70 years old
Intervention: 15vPCV
Comparison: 13vPCV

	9V	0.7, 0.94	0.77, 1.09	0.88, 1.64	0.92, 1.86	0.83, 1.24	0.84, 1.77			
	14	0.64, 0.89	0.79, 1.25	0.86, 1.5	0.68, 1.3	0.87, 1.37	1.01, 1.88			
	18C	0.91, 1.26	1.16, 1.68	0.92, 1.7	0.95, 1.8	1.2, 1.84	1.12, 2.34			
	19A	0.7, 0.93	0.87, 1.2	0.74, 1.25	0.57, 0.99	1.06, 1.55	0.85, 1.47			
	19F	0.76, 1.02	0.85, 1.19	0.75, 1.41	0.42, 0.81	0.92, 1.32	0.82, 1.57			
	23F	0.96, 1.44	1.13, 1.77	0.53, 1.1	1.11, 2.68	1.18, 2	0.83, 2.1			
	22F	25.25, 39.97	25.59, 40.69	NR	NR	26.13, 46.5	NR			
	33F	6.07, 8.32	7.46, 11.15			7.48, 11.2				
	†Green=LCI>1; red=UCI<1 *Study not powered to detect a difference between 15vPCV and 13vPCV									
OPA GMT ratio follow-up: 12 months	Table 2: 95% CI for OPA GMT ratios (15vPCV vs. 13vPCV) for shared and unique serotypes at Month 12 in the Song 2021 study*							651 (1 RCT)	⨁⨁⨁◯ Moderate[c,d]	15vPCV likely results in little difference in OPA GMT ratios for shared ST 12 months post vaccination 15vPCV likely increases OPA GMTs for ST unique to 15vPCV 12 months post vaccination Note: OPA GMT ratios all met a non-inferiority margin of LCI>0.5

Serotype	Non-inferiority / superiority margins^	Favouring 15vPCV or 13vPCV†
1	0.92, 1.53	0.92, 1.53
3	1.29, 1.9	1.29, 1.9
4	0.57, 0.9	0.57, 0.9
5	0.78, 1.33	0.78, 1.33
6A	0.93, 1.41	0.93, 1.41
6B	1.16, 1.77	1.16, 1.77
7F	0.8, 1.11	0.8, 1.11
9V	0.81, 1.18	0.81, 1.18
14	0.9, 1.36	0.9, 1.36
18C	1.05, 1.55	1.05, 1.55
19A	0.91, 1.31	0.91, 1.31
19F	0.91, 1.29	0.91, 1.29
23F	1.06, 1.76	1.06, 1.76
22F	9.44, 17.34	9.44, 17.34
33F	2.73, 3.84	2.73, 3.84

^non-inferiority margin: orange=LCI>0.67[8]; yellow=LCI>0.5[5]; superiority margin: blue=LCI>2[5]
†Green=LCI>1; red=UCI<1
*Study not powered to detect a difference between 15vPCV and 13vPCV

Summary of findings: 15vPCV compared to 13vPCV for non-Indigenous adults ≥70 years old without special risk factors

Patient or population: Non-Indigenous Adults ≥70 years old
Intervention: 15vPCV
Comparison: 13vPCV

% of participant ≥ 4-fold rise of GMT pre to 30 days post vaccination*	**Serotype**	**Platt 2022**		**Stacey 2019**		**Ermlich 2018**		**Song 2021**		**Peterson 2019**		3023 (5 RCTs)	⊕⊕⊕⊕ High	15vPCV results in little difference in % of participant with ≥ 4-fold rise of GMT pre to 30 days post vaccination for shared ST. 15vPCV likely increases % of participant with ≥ 4-fold rise of GMT pre to 30 days post vaccination for ST unique to 15vPCV. Note: a statistically significantly higher (I.e., CI do not overlap) proportion of participants in 15vPCV group had ≥4-fold rise of GMT pre to 30 days post vaccination compared with 13vPCV participants across all studies for ST 22F and 33F (vaccine serotypes for PCV15 but not PCV13).
	N	PCV13	15	15	13	15	13	15	13	15	13			
		602	600	231	227	229	230	326	325	127	126			
	1	75% (71, 79)	78% (74, 81)	71% (64,77)	62% (55,68)	87% (82,91)	78% (72,84)	83% (79, 87)	76% (71, 81)	41% (32,50)	34% (25,43)			
	3	70% (66, 74)	59% (55, 63)	72% (65,78)	44% (37,51)	86% (80,90)	76% (69,81)	72% (67, 77)	51% (45, 57)	54% (44,63)	39% (30,49)			
	4	80% (76, 83)	85% (82, 88)	85% (79,90)	82% (75,87)	89% (84,93)	86% (80,90)	79% (74, 84)	85% (80, 88)	44% (35,54)	55% (45,64)			
	5	72% (68, 75)	75% (72, 79)	68% (61,75)	67% (60,74)	89% (84,93)	84% (79,89)	77% (72, 81)	79% (74, 83)	45% (36,54)	50% (41,60)			
	6A	77% (73, 80)	75% (71, 79)	85% (79,90)	83% (77,88)	79% (73,85)	74% (67,80)	79% (74, 84)	78% (73, 83)	72% (63,80)	77% (68,84)			
	6B	81% (78, 84)	79% (76, 82)	87% (81,92)	84% (78,89)	69% (62,75)	79% (73,84)	83% (79, 88)	76% (71, 81)	63% (53,71)	67% (57,76)			
	7F	66% (62, 70)	72% (69, 76)	68% (61,75)	75% (68,81)	69% (62,75)	59% (52,66)	67% (62, 73)	66% (60, 71)	41% (32,51)	50% (40,60)			
	9V	54% (50, 58)	60% (56, 64)	65% (58,71)	61% (53,68)	59% (52,66)	57% (50,64)	61% (55, 67)	57% (51, 62)	48% (39,57)	45% (35,54)			
	14	52% (48, 56)	61% (57, 65)	62% (55,68)	48% (41,55)	79% (72,84)	78% (72,83)	53% (47, 59)	53% (48, 59)	19% (12,27)	16% (10,24)			
	18C	71% (67, 75)	69% (65, 73)	75% (68,81)	64% (57,71)	72% (66,78)	73% (66,78)	83% (79, 87)	74% (69, 79)	54% (45,63)	43% (34,53)			
	19A	71% (67, 74)	71% (67, 75)	75% (68,81)	71% (64,77)	62% (55,69)	72% (65,78)	70% (65, 76)	70% (64, 75)	37% (29,47)	37% (28,47)			
	19F	62% (58, 66)	65% (61, 69)	74% (68,80)	76% (69,81)	82% (76,87)	82% (76,87)	63% (58, 69)	56% (50, 62)	40% (31,50)	38% (29,48)			
	23F	75% (71, 79)	71% (67, 75)	76% (70,82)	79% (73,85)	82% (76,87)	90% (86,94)	79% (74, 84)	71% (65, 76)	61% (52,70)	52% (43,62)			
	22F	71% (67, 75)	14% (11, 18)	77% (69,83)	15% (10,21)	76% (70,82)	12% (8,17)	73% (67, 78)	17% (12, 22)	50% (41,60)	10% (5,17)			
	33F	57% (53, 61)	6% (4, 9)	54% (46,61)	9% (5,14)	64% (57,70)	10% (6,14)	61% (56, 67)	3% (1, 6)	38% (29,48)	6% (3,13)			

*Cells shaded in green: a significantly higher (I.e., CI do not overlap) proportion of participants in 15vPCV group had ≥4-fold rise of GMT pre to post vaccination compared with 13vPCV participants. The proportion of participants with ≥4-fold rise of GMT pre to post vaccination was not statistically significantly higher for 13vPCV compared to 15vPCV in any ST

IgG GMC ratios follow-up: 30 days

Table 3: 95% CI for IgG GMC ratios (15vPCV vs. 13vPCV) 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)

Serotype	Platt 2022		Simon 2022*		Stacey 2019		Ermlich 2018*		Song 2021*		Peterson 2019*	
Population	≥50 years Immunocompetent (stable risk conditions) Pneumococcal vaccine naïve										≥65 years 23vPPV 1 year prior	
PCV	15	13	15	13	15	13	15	13	15	13	15	13
N	602	600	2103	230	231	227	229	230	326	325	127	126
1	0.62, 0.83		0.62, 0.91		1.07, 1.77		0.98, 1.64		0.72, 1.09		0.8, 1.37	
3	1.33, 1.71		1.2, 1.61		1.65, 2.62		1.58, 2.42		1.46, 2.07		1.24, 2.06	
4	0.62, 0.83		0.66, 0.94		0.82, 1.36		0.75, 1.23		0.64, 0.99		0.76, 1.33	
5	0.7, 0.96		0.74, 1.07		0.9, 1.6		1.04, 1.68		0.84, 1.3		0.68, 1.11	
6A	0.87, 1.21		0.95, 1.43		0.63, 1.2		0.68, 1.14		1.1, 1.77		0.66, 1.28	
6B	1.17, 1.64		1.21, 1.86		0.81, 1.53		1.38, 2.41		1.28, 2.1		0.81, 1.51	
7F	0.66, 0.89		0.73, 1.04		0.7, 1.17		0.6, 0.98		0.74, 1.13		0.82, 1.35	
9V	0.75, 1		0.72, 1.04		0.95, 1.6		0.93, 1.5		0.91, 1.41		0.96, 1.57	
14	0.65, 0.89		0.82, 1.2		1.08, 1.87		0.79, 1.35		0.87, 1.38		0.93, 1.47	
18C	0.77, 1.05		1.05, 1.51		0.79, 1.36		0.89, 1.43		1.27, 1.92		1.02, 1.8	
19A	0.73, 0.97		0.82, 1.15		0.67, 1.11		0.64, 1.02		0.91, 1.39		0.8, 1.27	
19F	0.78, 1.05		0.86, 1.23		0.69, 1.18		0.51, 0.84		0.92, 1.41		0.9, 1.56	
23F	0.92, 1.28		1.03, 1.54		0.67, 1.25		1.08, 1.88		1.27, 2.04		0.92, 1.76	
22F	9.37, 12.03		10.11, 14.74		NR		NR		13.78, 19.86		NR	
33F	8, 10.07		7.96, 11.13						10.82, 15.19			

^non-inferiority margin: orange=LCI>0.67[8]; yellow=LCI>0.5[4]; superiority margin: blue=LCI>1.0[4]

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

b)

Serotype	Platt 2022		Simon 2022*		Stacey 2019		Ermlich 2018*		Song 2021*		Peterson 2019*	
Population	≥50 years Immunocompetent (stable risk conditions) Pneumococcal vaccine naïve										≥65 years 23vPPV 1 year prior	
PCV	15	13	15	13	15	13	15	13	15	13	15	13
N	602	600	2103	230	231	227	229	230	326	325	127	126
1	0.62, 0.83		0.62, 0.91		1.07, 1.77		0.98, 1.64		0.72, 1.09		0.8, 1.37	
3	1.33, 1.71		1.2, 1.61		1.65, 2.62		1.58, 2.42		1.46, 2.07		1.24, 2.06	
4	0.62, 0.83		0.66, 0.94		0.82, 1.36		0.75, 1.23		0.64, 0.99		0.76, 1.33	
5	0.7, 0.96		0.74, 1.07		0.9, 1.6		1.04, 1.68		0.84, 1.3		0.68, 1.11	
6A	0.87, 1.21		0.95, 1.43		0.63, 1.2		0.68, 1.14		1.1, 1.77		0.66, 1.28	

5356 (6 RCTs)

⊕⊕⊕◯ Moderate[c,e]

15vPCV likely results in little difference in IgG GMC ratios for shared ST.
15vPCV likely increases IgG GMC ratios for ST unique to 15vPCV.

Note: IgG GMC ratios all met the non-inferiority margin of LCI>0.5. This is broadly consistent with OPA GMT ratios (except for ST 6A, 7F, and 19F, across some studies)

Summary of findings: 15vPCV compared to 13vPCV for non-Indigenous adults ≥70 years old without special risk factors

Patient or population: Non-Indigenous Adults ≥70 years old
Intervention: 15vPCV
Comparison: 13vPCV

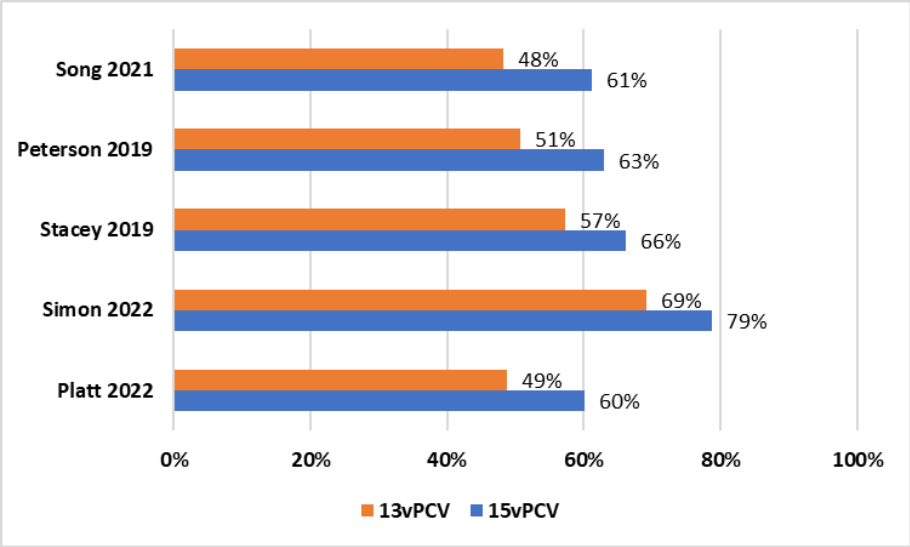
6B	1.17, 1.64	1.21, 1.86	0.81, 1.53	1.38, 2.41	1.28, 2.1	0.81, 1.51	
7F	0.66, 0.89	0.73, 1.04	0.7, 1.17	0.6, 0.98	0.74, 1.13	0.82, 1.35	
9V	0.75, 1	0.72, 1.04	0.95, 1.6	0.93, 1.5	0.91, 1.41	0.96, 1.57	
14	0.65, 0.89	0.82, 1.2	1.08, 1.87	0.79, 1.35	0.87, 1.38	0.93, 1.47	
18C	0.77, 1.05	1.05, 1.51	0.79, 1.36	0.89, 1.43	1.27, 1.92	1.02, 1.8	
19A	0.73, 0.97	0.82, 1.15	0.67, 1.11	0.64, 1.02	0.91, 1.39	0.8, 1.27	
19F	0.78, 1.05	0.86, 1.23	0.69, 1.18	0.51, 0.84	0.92, 1.41	0.9, 1.56	
23F	0.92, 1.28	1.03, 1.54	0.67, 1.25	1.08, 1.88	1.27, 2.04	0.92, 1.76	
22F	9.37, 12.03	10.11, 14.74	NR	NR	13.78, 19.86	NR	
33F	8, 10.07	7.96, 11.13			10.82, 15.19		

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

Summary of findings: 15vPCV compared to 13vPCV for non-Indigenous adults ≥70 years old without special risk factors

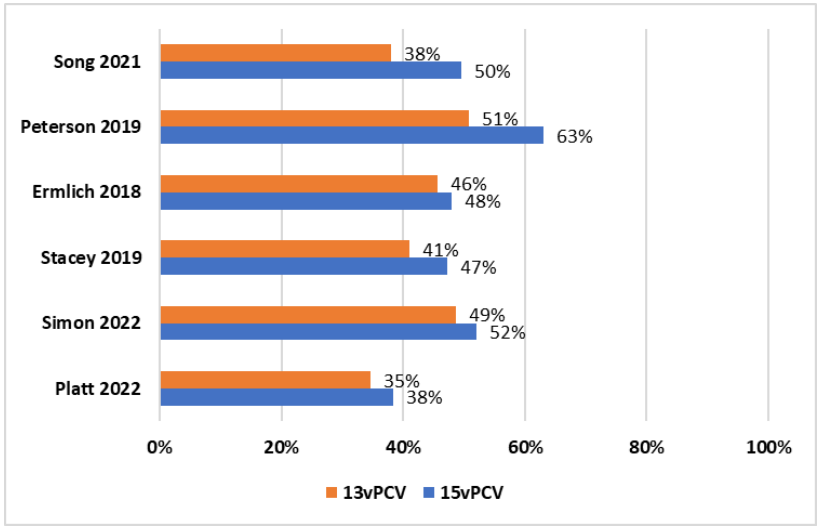
Patient or population: Non-Indigenous Adults ≥70 years old
Intervention: 15vPCV
Comparison: 13vPCV

% of participant ≥ 4-fold rise of GMC pre to 30 days post vaccination	**Serotype**	**Platt 2022**		**Stacey 2019**		**Ermlich 2018**		**Song 2021**		**Peterson 2019**		3023 (5 RCTs)	⊕⊕⊕⊕ High	15vPCV results in little difference in % of participant with ≥ 4-fold rise of GMC pre to 30 days post vaccination for shared ST. 15vPCV likely increases % of participant with ≥ 4-fold rise of GMC pre to 30 days post vaccination for ST unique to 15vPCV. Note: a statistically significantly higher proportion of participants in 15vPCV group had ≥4-fold rise of GMC pre to 30 days post vaccination compared with 13vPCV participants across all studies for ST 3 (shared with 15vPCV and 13vPCV), 22F and 33F (vaccine serotypes for PCV15 but not PCV13)
	PCV	15	13	15	13	15	13	15	13	15	13			
	N	602	600	2301	227	229	230	326	325	127	126			
	1	73% (69, 77)	78% (75, 82)	78% (72,84)	65% (59,72)	76% (70,82)	69% (62,75)	75% (70,80)	81% (76,85)	33% (24,42)	27% (19,35)			
	3	62% (58, 66)	51% (47, 56)	58% (52,65)	31% (25,38)	71% (65,77)	50% (43,57)	62% (57,68)	43% (37,48)	36% (28,45)	17% (11,25)			
	4	65% (61, 69)	76% (72, 79)	72% (65,78)	62% (55,69)	71% (65,77)	75% (69,81)	71% (66,76)	74% (69,79)	36% (28,45)	36% (27,45)			
	5	45% (41, 49)	53% (49, 56)	52% (45,59)	48% (41,55)	46% (39,53)	36% (30,43)	52% (47,58)	49% (44,55)	19% (13,28)	24% (17,33)			
	6A	84% (80, 86)	83% (80, 86)	74% (67,79)	77% (71,83)	76% (70,82)	65% (58,71)	88% (84,92)	84% (80,88)	65% (55,73)	65% (56,74)			
	6B	83% (80, 86)	78% (74, 81)	76% (69,81)	66% (60,73)	75% (68,80)	71% (65,77)	86% (81,89)	77% (72,82)	55% (45,64)	46% (37,56)			
	7F	74% (70, 77)	79% (75, 82)	69% (63,76)	70% (63,76)	73% (66,79)	67% (60,73)	77% (72,81)	76% (70,80)	31% (23,40)	33% (25,43)			
	9V	70% (66, 73)	76% (72, 79)	73% (65,77)	65% (58,71)	55% (48,61)	52% (45,59)	73% (68,78)	70% (65,75)	35% (27,45)	24% (17,33)			
	14	49% (45, 55)	60% (55, 64)	58% (51,65)	49% (42,56)	73% (67,79)	73% (66,79)	54% (48,60)	56% (50,62)	19% (12,27)	9% (5,16)			
	18C	73% (69, 77)	76% (73, 80)	72% (65,78)	71% (64,77)	61% (54,67)	62% (55,68)	84% (79,88)	76% (70,80)	46% (37,56)	31% (23,40)			
	19A	67% (63, 71)	71% (67, 75)	65% (58,72)	65% (58,71)	47% (40,54)	58% (51,64)	71% (66,76)	69% (64,74)	31% (23,40)	35% (26,44)			
	19F	70% (66, 73)	76% (72, 79)	60% (53,66)	63% (56,69)	75% (69,81)	73% (66,79)	78% (72,82)	76% (71,81)	35% (27,45)	33% (25,43)			
	23F	75% (71, 78)	74% (71, 78)	73% (66,79)	72% (65,77)	76% (70,82)	81% (75,86)	80% (75,84)	70% (65,75)	53% (44,62)	45% (36,55)			
	22F	71% (68, 75)	2% (1, 3)	72% (65,78)	2% (1,5)	79% (72,84)	1% (0,3)	77% (72,81)	1% (0,3)	32% (24,41)	0% (0,3)			
	33F	67% (63, 70)	2% (1, 3)	73% (66,79)	1% (0,3)	73% (67,79)	1% (0,3)	71% (66,76)	1% (0,2)	24% (17,33)	0% (0,3)			
	*Cells shaded in green: a higher proportion of participants in 15vPCV group had ≥4-fold rise of GMC pre to post vaccination compared with 13vPCV participants. The proportion of participants with ≥4-fold rise of GMC pre to post vaccination was not statistically significantly higher for 13vPCV compared to 15vPCV in any ST													

Summary of findings: 15vPCV compared to 13vPCV for non-Indigenous adults ≥70 years old without special risk factors				
Patient or population: Non-Indigenous Adults ≥70 years old **Intervention**: 15vPCV **Comparison**: 13vPCV				
Injection site adverse events		5356 (6 RCTs)	⊕⊕⊕⊕ High	15vPCV results in a slight increase in injection site adverse events compared to 13vPCV

Summary of findings: 15vPCV compared to 13vPCV for non-Indigenous adults ≥70 years old without special risk factors

Patient or population: Non-Indigenous Adults ≥70 years old
Intervention: 15vPCV
Comparison: 13vPCV

Systemic adverse events		5356 (6 RCTs)	⊕⊕⊕⊕ High	15vPCV results in a slight increase in systemic adverse events compared to 13vPCV

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; CI, confidence interval; GMC, geometric mean concentrations; GMT, geometric mean titres; ID, identification; IgG, Immunoglobulin G; LCI, lower confidence interval; NR, not reported; OPA, opsonophagocytic activity; RCTs, randomised controlled trials; SAE, serious adverse events; ST, serotype; UCI, upper confidence interval

Explanations

a. Downgraded due to low number of events
b. Inconsistency assessed as not serious as majority of serotypes across most studies met the WHO non-inferiority margin of LCI>0.67, all serotypes across all studies met a non-inferiority margin of LCI>0.33 as referenced in Stacey 2019
c. Some studies were not powered to detect a difference between 15vPCV and 13vPCV
d. Inconsistency not assessed as only 1 study included
e. Inconsistency assessed as not serious as all studies met a non-inferiority margin of LCI>0.5 as referenced in Stacey 2019[4]

Evidence Profile: 15vPCV compared to 13vPCV for Non-Indigenous Adults ≥70 years old without special risk factors

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Serious adverse events									
6	randomised trials	not serious	not serious	not serious	serious[a]	none	The rates of serious adverse events ranged from 0% to 5% for 15vPCV recipients and 0% to 6% for 13vPCV recipients. None were considered by study investigators to be related to the vaccine.	⨁⨁⨁◯ Moderate	CRITICAL
OPA GMT ratios (follow-up: 30 days)									
6	randomised trials	not serious	not serious[b]	not serious	serious[c]	none	The OPA GMT ratio 30 days following vaccination for shared serotypes ranges from 0.58 to 3.17. Majority of serotypes across studies met a non-inferiority margin of 0.67[8] For 15v-non13v serotypes (22F and 33F) OPA GMT ratios ranged from 7.11 to 34.68. All serotypes across all studies met a superiority margin (LCI >2)[5] Across all studies immune responses were higher for ST3, and the 2 15v-non13v serotypes (22F and 33F) post 15vPCV compared to 13vPCV	⨁⨁⨁◯ Moderate	IMPORTANT
OPA GMT ratio (follow-up: 12 months)									
1	randomised trials	not serious	NA[d]	not serious	serious[c]	none	The OPA GMT ratio 12 months following vaccination for shared serotypes ranged from 0.72 to 1.57. All but one serotype (4) met a non-inferiority margin of 0.67[8] For 15v-non13v serotypes (22F and 33F) OPA GMT ratios were 12.29 (22F) and 3.24 (33F). Both serotypes met a superiority margin (LCI>2[5])	⨁⨁⨁◯ Moderate	IMPORTANT
% of participants ≥ 4-fold rise of GMT pre to post vaccination									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
5	randomised trials	not serious	not serious	not serious	not serious	none	The proportion of participants with ≥4-fold rise of GMT pre to post vaccination for shared serotypes ranged from 19% to 89% for 15vPCV recipients and 10% to 90% for 13vPCV recipients For 15v-non13v serotypes (22F and 33F) the proportion of participants with ≥4-fold rise of GMT pre to post vaccination ranged from 38% to 77% for 15vPCV and 3% to 52% for 13vPCV	⨁⨁⨁⨁ High	IMPORTANT
IgG GMC ratios (follow-up: 30 days)									
6	randomised trials	not serious	not serious[e]	not serious	serious[c]	none	The IgG GMC ratio 30 days following vaccination for shared serotypes ranges from 0.65 to 2.08. Majority of serotypes across studies met a non-inferiority margin of 0.67.[8] This is broadly consistent with OPA GMT ratios For 15v-non13v serotypes (22F and 33F) the IgG GMCs ranged from 8.86 to 16.54. Across all studies immune responses were higher for serotype 3, 22F and 33F post 15vPCV compared to 13vPCV	⨁⨁⨁◯ Moderate	IMPORTANT
% of participants ≥ 4-fold rise of GMC pre to post vaccination									
5	randomised trials	not serious	not serious	not serious	not serious	none	The proportion of participants with ≥4-fold rise of GMC pre to post vaccination for shared serotypes ranged from 19% to 88% for 15vPCV recipients and 0% to 84% for 13vPCV recipients For 15v-non13v serotypes (22F and 33F) the proportion of participants with ≥4-fold rise of GMC ranged from 24% to 79% for 15vPCV and 0% to 45% for 13vPCV	⨁⨁⨁⨁ High	IMPORTANT
Solicited local adverse event									
6	randomised trials	not serious	not serious	not serious	not serious	none	The rate of injection site adverse events ranged from 60% to 79% for 15vPCV recipients and 48% to 69% for 13vPCV recipients	⨁⨁⨁⨁ High	IMPORTANT
Solicited Systemic Adverse Events									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
6	randomised trials	not serious	not serious	not serious	not serious	none	The rates of systemic adverse events ranged from 38% to 63% for 15vPCV recipients and 35% to 51% for 13vPCV recipients	⨁⨁⨁⨁ High	IMPORTANT

Abbreviations: **Abbreviations:** 13vPCV, 13-Valent pneumococcal conjugate vaccine; 15vPCV, 15-Valent pneumococcal conjugate 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. Inconsistency assessed as not serious as majority of serotypes across most studies met the WHO non-inferiority margin of LCI>0.67, all serotypes across all studies met a non-inferiority margin of LCI>0.33 as referenced in Stacey 2019[4]
c. Some studies were not powered to detect a difference between 15vPCV and 13vPCV
d. Inconsistency not assessed as only 1 study included
e. Inconsistency assessed as not serious as all studies met a non-inferiority margin of LCI>0.5 as referenced in Stacey 2019[4]

Evidence to Decision Framework: individual perspective

Should 15vPCV be recommended as an alternative for or preferred over 13VPCV use in Australian adults ≥70 years for the prevention of pneumococcal disease?	
Population	Non-Indigenous Adults ≥70 years old without special risk factors with or without a history of previous 23 valent Pneumococcal Polysaccharide Vaccine (23vPPV)vaccination
Intervention	15-valent pneumococcal conjugate vaccine (15vPCV)
Comparison	13-valent pneumococcal conjugate vaccine (13vPCV)
Main outcomes	Immunogenicity: OPA and IgG geometric mean titres - OPA GMT ratios (follow-up: 30 days) - OPA GMT ratios (follow-up: 12 months) - % 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 15vPCV or 13vPCV delivery - Severe adverse events (SAE) - Injection site adverse events - Systemic adverse events
Setting	Canada, Denmark, Israel, Norway, Poland, Spain, Sweden, USA, Japan, Taiwan, Australia, Chile, Finland, UK, South Korea
Perspective	Individual

ASSESSMENT

Problem
Is the problem a priority?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Pneumococcal disease incidence is high in older adults. In Australia about 800 cases of invasive pneumococcal disease (IPD, the severe form of pneumococcal disease) occurs annually.[16] The incidence of all community acquired pneumonia caused by pneumococcus is several fold higher than IPD.[17]
- With the use of PCV over several years with high coverage certain non-vaccine serotypes have increased in Australia. In the current 13vPCV era the additional serotypes in 15vPCV (i.e.22F and 33F) cause a considerable amount of residual IPD in non-indigenous adults aged ≥70 years.
- Extended valency PCVs would likely improve pneumococcal disease prevention in adults.

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Overall, there is evidence of a small effect at improving immunogenicity outcomes for 15v-non13v serotypes.

- There is variability in the evidence for the shared serotypes between 15vPCV and 13vPCV
- Evidence of persistence is based on immunogenicity data and limited to 12 months following 15vPCV vaccination. There appears to be little to no waning across all vaccine serotypes at 12 months after 15vPCV vaccination
- There is no evidence available on effectiveness against clinical outcomes after 15vPCV.

Undesirable Effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Undesirable effects include frequent rates of injection site adverse events and systemic adverse events which are mostly of mild to moderate severity. In comparison the rates are slightly higher than those seen after 13vPCV.
- There were no vaccine-related serious adverse events reported in the included studies.

Certainty of evidence
What is the overall certainty of the evidence of effects?

No Included Studies	Very Low	Low	Moderate	High

- The certainty of evidence is moderate due to 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

- The overall improvement in immune response from 15vPCV for the 15v-non13v serotypes probably outweighs the additional frequency of non-serious adverse events/reactogenicity compared to 13vPCV.
- The overall balance of desirable and undesirable effects of 15vPCV are comparable to 13vPCV for the shared serotypes.
- Undesirable effects are minor yet slightly higher in 15vPCV compared to 13vPCV

Acceptability
Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Vaccination to prevent pneumococcal disease appears to be acceptable in the Australian setting. In 2016 the vaccination uptake of the 23vPPV vaccine in adults aged ≥65 years was estimated to be 52%[18]

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					

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