Supplementary File 1. Full search strategy

En	nbase Classic+Embase <1947 to 2020 June 10>	
Se	arch history sorted by search number ascending	
#	Searches	Туре
1	exp Human immunodeficiency virus/ or exp acquired immune deficiency syndrome/ or exp	Advanced
	Human immunodeficiency virus infection/ or (PLWH or HIV* or "Human immunodeficiency	
	virus" or AIDS or Acquired Immunodeficiency Syndrome or AIDS).ti,ab,kw.	
2	Pneumococcus vaccine/ or ("13-valent pneumococcal vaccine" or "23-valent pneumococcal	Advanced
	polysaccharide vaccine" or Prevenar* or PCV13 or PCV7 or PCV10 or pneumovax* or	
	PPSV23 or pneumococcal vaccin* or pneumococcal immune*).ti,ab,kw.	
3	1 and 2	Advanced
4	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or	Advanced
	piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or	
	monkeys or trout or marmoset\$1).ti. or (Animal experiment/ not (human experiment/ or	
	human/))	
5	3 not 4	Advanced
6	exp case report/	Advanced
7	5 not 6	Advanced
8	limit 7 to (conference abstracts or embase)	Advanced

0	Ovid MEDLINE(R) ALL <1946 to June 09, 2020>									
Se	arch history sorted by search number ascending									
#	Searches		Туре							

1	exp "HIV"/ or exp "Acquired Immunodeficiency Syndrome"/ or (PLWH or HIV* or		Advanced
	"Human immunodeficiency virus" or AIDS or Acquired Immunodeficiency		
	Syndrome or AIDS).ti,ab,kf.		
2	exp "Pneumococcal Vaccines"/ or ("13-valent pneumococcal vaccine" or "23-valent		Advanced
	pneumococcal polysaccharide vaccine" or Prevenar* or PCV13 or PCV7 or PCV10		
	or pneumovax* or PPSV23 or pneumococcal vaccin* or pneumococcal		
	immune*).ti,ab,kf.		
3	1 and 2		Advanced
4	case reports.pt.		Advanced
5	3 not 4		Advanced
6	exp animals/ not humans/		Advanced
7	5 not 6	5	Advanced

Supplementary File 2. Explanation of Newcastle Ottawa risk of bias assessment tool for cohort studies

Selection domain	
Representativeness of exposed cohort (max: •)	Awarded if HIV+ patients were representative for current HIV+ population: approximately 70% males; average age >40 years old; >75% on antiretroviral therapy; mean CD4>400
Selection of non-exposed cohort (max: ♥)	Awarded if study had a control group of HIV- negative individuals or unvaccinated HIV+ control group.
Ascertainment of exposure (max: •)	Awarded if vaccinations were administered during the study or vaccine administration was registered in the patient file/registry.
Outcome was not present at start of study (max: •)	Awarded if baseline IgG/OPA assessment was done
Comparability domain	
Comparability of cohorts on the basis of the design or analysis (max ♥♥)	Awarded if comparative analyses were adjusted/matched for age (1 star) and at least one other important factor such as cART use or CD4 count (2 stars).
Outcome domain	
Assessment of outcome (max: •)	Awarded if serological methods were sufficiently described, primary outcomes were predefined and reported and, when applicable if cut-offs for seroconversion/seroprotection were predefined and supported by previous literature.
Follow-up long enough(max: •)	Awarded if post-vaccination antibody assessment was done at least 4 weeks after vaccination.
Adequacy of follow-up of cohorts (max: •)	Awarded if loss to follow up or missing data was <10%

Thresholds for converting the NOS rating to Agency for Healthcare Research and Quality - AHRQ - standards (good, fair, and poor): Good quality: 3 or 4 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome domain Fair quality: 2 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome domain Poor quality: 0 or 1 star in Selection domain OR 0 stars in Comparability domain OR 0 or 1 stars in Outcome domain

Study chara	acteristic	s							Patient characteristics Outcomes							
Study (year) *	Count ry	Design	Serologi c methods	Correlat e of protectio n	Sero-types assessed	Interval vaccinati on/ antibody assessme	Previous pneumoco ccal vaccinatio n	Vaccination schedule	Sub- jects at baseli ne (n)	Age (mean/med ian)	VL [§] un- dececta ble %	Seroprotec tion n/total (%)	Pre/Pos vaccina concent IgG (me	t- tion ration of cg/ml)	Authors contacte d for addition	
-						nt'							6B	14	al data	Response
Almeida (2009) ²³	Brazil	Prospectiv e cohort	ELISA	NR¶	1,3,5,6B, 9V,14	21-78 days (median 40)	0%	PPSV23 [#] (pregnant HIV ^Δ + women)	44	26	NR	NR	1.18/3. 05	3.20/9. 39	No, data available from publicati on.	NA
Amondolo	Italy	Prospectiv e cohort	ELISA		346B 10E		NR	PPSV23 CD4 <200	10	- 37	NR	NR	1.9/4.0	NR		
$(2002)^{22}$				NR	23F	30 days		CD4 200-500	23	-	NR	NR	2.6/8.5	NR	Yes	No
()								CD4 >500	24	ND	NR	NR	3.6/4.7	NR		
		Followup						PCV13 ⁰ +PCV13	20	NK	INK	INK	1.3/2.9	NK 5.75 /		
	Italy	Lombardi	ELISA	$IgG \ge 1.0$	1,3,4,5, 6A,		0%	(wk 0, 8)	50	44	92%	23/42 (55)	2.57	9.12		
Belmonti (2019) ²⁴		et al (2016); Prospectiv e cohort		for ≥ 9 serotypes (70%)	6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	5 years		PPSV23 (wk0)	50	46	84%	24/49 (49)	1.55 / 1.74	6.92 / 11.5	Yes	No
Bhorat (2015) ²⁵	South Africa, Roma nia	Prospectiv e cohort	ELISA + OPA↓	NR	1,3,4,5,6A,6 B, 7F, 9V, 14, 18C, 19A, 19F, 23F	1,2,3, 4 months	0%	3x PCV13 (mo 0,1,2) + PPSV23 (mo 3)	151 adults	41	71%	NR	3.13 /8.25	2.45 / 16.24	Yes	No
Chang	United States	Prospectiv e cohort	ELISA		Total PPSV23	20.1	0%	PPSV23 HIV+	12	41	50%	NR	Inverse 11.000 (graph)	IgG titer from	*7	Yes, but
(2000) ²⁶				NK	occal IgG (ELISA)	28 days		HIV- controls	10	35	NA	NR	Inverse 40.000 (graph)	IgG titer from	Yes	data not available.
Cheng	Taiwa	Prospectiv e cohort	EL IS A	IgG≥1.0	6B, 14, 19F,	2,3,4 5	0%	PCV7 (wk0)	109	36	44%	6B: 85/102 (83); 19F: 101/102 (99); 23F: 69/102 (68)	0.855/ 1.79	1.992 / 6.98	No, data available	NA
(2016) ⁴⁶	n	up Lu 2012)	ELISA	mcg/ml	23F	years	070	PCV7+PCV7 (wk0,4)	112	36	44%	6B: 82/103 (80) 19F: 97/103 (94) 23F: 76/103 (74)	0.774/ 1.73	1.91 / 8.22	publicati on.	INA

Supplentary file 3 – Table 1: Additional characteristics of included studies.

Crum- Cianflone (2010) ⁴⁸	United States	RCT⁵	ELISA	≥1.0 mcg/ml	4, 9V, 14, 19F	14 days, 2 , 6 months	100% of HIV+ 0% HIV-	PPSV23 HIV+ PCV7 HIV+ PCV HIV-	7313125	42 42 37	64% 70% NR	NR NR NR	NR NR NR	1.0/2.0 (from graph) 1.2/3.3 (from graph) 0.1/4.8 (from graph)	Yes	No
Deloria- Knoll (2006) ⁵⁰	United States	RCT (Vitamin A, Zinc, both or Placebo)	ELISA	NR	4, 6B, 9V, 14, 18C, 19F, 23F	1,6, 7 months	0%	PCV 7 + PPSV23 (mo 0, mo 6)	118	42	13%	NR	1.47- 3.21/ 2.96- 7.09	NR	Yes	Yes
Falco (2006)	Spain	Prospectiv e cohort	ELISA	NR	1, 6B, 14,	1, 12	0%	PPSV23 (HIV+)	113	39	79%	NR	5.99 / 7.64	3.6 /12.1	Yes	Yes
Vaccine 27					19F, 23F	monuis		PPSV23 (HIV-)	30	34			2.957 5.45	1.827 7.55		
Farmaki (2018) ⁵	Greece	Prospectiv e cohort	ELISA	NR	3,14	1, 13 months	70% between 1- 5 years earlier	PCV13+PPSV23 (0,12 mo)	40	51	100%	NR	NR	1.21 / 4.27	Yes	Yes
								PCV7+PCV7 (0,8wk)	15	45	NR	NR	0.99/ 2.0	5.0 / 10.3		
Feikin	United	DOT	ELISA +	ND	4, 6B, 9V,	8,9, 16, 17	0% in 5 _.	PCV7+PPSV23 (0,8wk)	18	42	NR	NR	1.2 / 2.2	5.0 / 11.4	V	N
(2001) ⁵¹	States	KUI	OPA	NK	14, 23F	,24 weeks	to study	Placebo+PPSV23 (0,8wk)	16	41	NR	NR	1.2 / 1.6	7.3 / 15.4	Yes	NO
								2 doses of placebo (0,8wk)	18	44	NR	NR	1.0/1.0	3.8/3.9		
Glesby (2015) ²⁸	United States	Prospectiv e cohort	ELISA + OPA	NR	1,3,4,5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	1,7 ,13 months	Yes 100% PPSV23	PCV13+PCV13+P CV13 (0,6,12 mo)	329	47	74%	NR	1.17 / 5.48	2.40 / 8.13	Yes	Yes, but data owned by Pfizer could not be provided uncondition ally
Hart (2007) ²⁹	United Kingd om	Prospectiv e cohort	ELISA	\geq 225	Total PPSV23 anti- pneumococca	1 , 3-6 months	NR	PPSV23 HIV+	33	46	100%	7/18 (39)	NR	NR	Yes	No
(2007)				C/111	l IgG and IgM	monuis		HIV- controls	NR	31	NR	7/8 (88)	NR			
Ho (2013)	Brazil	Randomis ed clinical trial	ELISA	\geq 1.00mcg /ml	6B, 9V, 14	2, 6 months	_	PPSV23+Placebo (mo 0, mo 2)	111	40	64%	6B: 47/89 (53) 14: 79/89 (89)	0.73/ 1.02	1.82 / 6.72	Yes	No

							0%	PCV7/Placebo (mo 0, mo 2)	110	40	67%	6B: 45/91 (50) 14: 76/89 (84)	0.51 / 1.24	1.15 / 9.32		
								PCV7/PPSV23 (mo 0, mo 2)	110	42	73%	6B: 54/91 (59) 14: 77/91 (85)	0.57 / 1.76	1.40 / 6.35		
Horster (2010) ³⁰	Germa ny	Prospectiv e cohort	ELISA	NR	Total PPSV23 antipneumoc occal IgG (ELISA)	1-13 months (median 4)	Not in 5 years prior to study	PPSV23	100	40	NR	NR	NR	NR	No, data available from publicati on.	NA
Huang (2018) ³¹	China	Prospectiv e cohort	OPA	NR	6B, 19A, 19F, 23F	1 month	0%	PPSV23 (HIV+)	63	38	NR	NR	27/901	NR	No (method s not suitable for meta- analysis)	NA
								PPSV23 (HIV-)	56	64	NA		85/265 0	NR		
	Taiwa n		ELISA				0%	PPSV23 CD4 <100	35	39	77%	14: 30%; 23F: 10% (from graph)	NR			
Hung		Prospectiv e cohort,		≥0.35	14 105 225	5		CD4 100-199	36	41	91%	14: 60%; 23F: 30% (from graph)	NR			
(2010) 32		report of Lu 2013		mcg/ml	14, 19F, 23F	5 years		CD4 200-349	34	42	94%	14: 55%; 23F: 30% (from graph)	NR			Yes,
								CD4 ≥350	64	39	81%	14: 60%; 23F: 35%) (from graph)	NR		Yes	however requested data not available.
Kang (2016) ³³	United Kingd om	Retrospec tive cohort	NR	≥ 0.35 mcg/ml for ≥ 6 serotypes	NR	NR	NR	PPSV23	435	43	NR	258/435 (59)	NR		Yes	No
Leggat (2015) ³⁴	United States of Ameri ca	Prospectiv e cohort	ELISA + OPA	NR	14, 23F	1 month	0%	PPSV23 CD4>200 cART-	20	28	NR	NR	NR	5.2 / 27.8		Yes, but data could not be
							_	CD4<200 cART-	12	36	NR	NR	NR	6.9 / 26.0	Yes	provided timely

								CD4<200 cART+	11	45	NR	NR	NR	5.0/9.6		
								HIV- controls	22	26	NR	NR	NR	NR		
Lesprit	France	RCT	ELISA	≥1.00mcg	1,4,5 6B, 9V, 14, 18C, 19F,	8 weeks,	Not in 5 years prior to study	PCV7+PPSV23 (wk 0, wk 4)	105	44	66%	NR	0.47/ 2.18	1.68 / 9.34		
(2007) **				/ml	23F	24 weeks	-	PPSV23 (wk4)	103	45	58%	NR	0.47/ 1.55	1.07 / 5.88	Yes	Yes
Lombardi	Italy	Prospectiv e cohort		≥1.0	1,3,4,5,6A, 6B, 7F, 9V,	8, 24 ,48	0%	PCV13+PCV13 (wk 0, 8)	50	44	84%	6B 44/46 (96); 14 45/46 (98) 23F 43/46 (93)	1.41 / 4.05	5.59 / 15.11		
(2016) ¹³			ELISA	mcg/ml	14, 18C, 19A, 19F, 23F;	weeks		PPSV23 (wk0)	50	46	92%	6B 44/49 (90);14 49/49 (100); 23F 44/49 (90)	1.53 / 2.69	6.69/18 .69	Yes	Yes
L (2012)	Taiwa n	Prospectiv e cohort	ELISA		6D 14 10E	12 , 24,	0%	PCV7 (wk 0)	114	38	46%	NR	NR	NR		Yes, however
LU (2012) 36				≥1.00mcg /ml	0B, 14, 19F, 23F	36, 48 weeks		PCV7+PCV7 (wk 0 ,wk 4)	115	37	46%	NR	NR	NR	Yes	requested data not available.
	Taiwa n	Prospectiv	ELISA				Yes 100% received	PPSV23 (wk 0)	127	45	83%	NR	NR	NR		
Lu (2014)		e cohort			6B 14 19F	12, 24,	PPSV23 5	PCV7 (wk 0)	50	44	82%	NR	NR	NR		Yes,
35		(follow- up Hung 2010)		≥1.00mcg /ml	23F	36, 48 weeks	years earlier (Hung 2010)	PCV7+PCV7 (wk 0 ,wk 4)	44	43	84%	NR	NR	NR	Yes	however requested data not available.
	Taiwa n	Prospectiv e cohort (PPSV23 arm = same	ELISA				0%	PPSV23	169	39	84%	NR	NA	2.35/ 3.14	Yes	Yes, however requested data not available.
Lu (2013) ³⁷		cohort as Hung 2010; PCV7 arm = same cohort as Lu 2012)		NR	6B, 14, 19F, 23F	24, 48 weeks		PCV7	114	39	59%	NR	0.76 / 1.06	1.83/5. 00		
MacLenna n (2016) ³⁸	United Kingd om	Prospectiv e cohort	Multiple x fluoresce nce	\geq 1.3 mcg/ml for 8/12 serotypes (67%)	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	4-6 weeks	0%	PPSV23 (HIV+)	211	35	73%	6B: 44% 14: 75% 23F: 43% Overall: 33%	0.32 / 0.97	1.51 / 5.12	Yes	No

			microbea d assay					PPSV23 (HIV-)	73	40		6B: 55% 14: 74% 23F: 63% Overall: 53%	0.36 / 1.67	1.03 / 7.76		
	United States	Prospectiv e cohort	ELISA + OPA		PCV13/PPS V23: 14, 23F		87%	PPSV23 (HIV+)	22	55	100%	NR	NR	NR (only in graph)		
Ohtola (2016) ³⁹				≥1.00mcg /ml		1 month after PPSV23	HIV+; 7% HIV- >5 years prior	PCV13+PPSV23 (wk 0, 8 HIV+)	15	55	100%	NR		NR (only in graph)		Yes, but data could
							to study	PCV13+PPSV23 (wk 0, 8 HIV-)	14	57	NA	NR		NR (only in graph)	Yes	not be provided timely
Pavaras	Spain	Prospectiv e cohort	ELISA + OPA		Total PPSV23 antipneumoc		0%	PPSV23 (HIV+ and recurrent bacterial infection)	33	35	NR	NR	874 U/I	nl		
$(2002)^{40}$				NR	occal IgG (ELISA);	4 weeks		PPSV23 (HIV+ controls)	33	37	NR	NR	1265 U	/ml		
					OPA for serotype 3			PPSV23 (HIV-)	NR	NR	NA	NR	2501 U	/ml	Yes	No
Peñarand a (2010) ⁵⁴	Spain	RCT	ELISA	≥1.00mcg	4, 6B, 9V, 14, 18C, 19F,	4, 8 weeks	0%	PCV7/PPSV23 (wk0, wk4)	110	44	100%	NR	NR	NR		
a (2010)	C 1	D (/ml	23F;	weeks		PPSV23 (wk 0)	110	44	100%	NR	NR	NR	Yes	No
Rash (2015) ⁴¹	a Canad	e cohort	NR	≥1.3 mcg/ml	NR	4 weeks	NR	PPSV23	23	NR	100%	NR	NR	NR	Yes	No
	United States	Prospectiv e cohort	ELISA			4-12 weeks		PPSV23 (cART+), first time	46	47	46%	NR	0.76 / 1.40	NR		
Rodriguez- Barradas (2003) ⁴²							n=41 (analysed seperately)	PPSV23 (cART+) second time	41	47	46%	NR	0.96 / 1.95	NR		Yes, but data could not be
								PPSV23 (cART-)	38	42	0	NR	0.88 / 3.12	NR	Yes	provided timely
	United States	RCT (immediat	ELISA + OPA			1 ,6,12	DDSV22 >	PPSV23/Placebo (mo 0, mo 9-12)	36	44	0%	NR	5.12 / 7.85	NR		
Rodriguez -Barradas (2015) ⁴⁹		e versus delayed PPSV23 vaccinatio n)		≥1.0 mcg/ml	1,3,4, 6B, 23F	months after each interventi on	3 years earlier 20%	Placebo/PPSV23 (mo 0, mo 9-12)	36	45	60%	NR	5.17 / 5.79		Yes	Yes, but data could not be provided timely
Rossheim	United States	Prospectiv e cohort	ELISA	ND	3, 6A, 7F,	1, 12	100% PPSV23	PCV13 (PPSV23 1-3 years earlier)	42	46	100%	NR	NR	NR		Yes, but data could
(2016) ⁴³				NK	19A	months	prior to study	PCV13 (PPSV23 >3 years earlier)	54	42	100%	NR	NR	NR	Yes	not be provided.
Sadlier (2016) 55	Ireland	RCT	ELISA + OPA	≥ 1.0 mcg/ml	1,3,4,5, 6B, 7F, 9V, 14,	8 , 28 weeks	0%	PCV13+PPSV23 (wk 0, 4)	28	37	NR	NR	0.18/ 1.56	0.44 / 4.61	Yes	No

					18C, 19A, 19F, 23F			PPSV23 (wk 4)	33	36	NR	NR	0.18 / 0.81	1.04 /5.71		
Sögaard	Denm ark	RCT	ELISA + OPA	>1.0	PCV7/PPSV 23: 4,6B, 9V,	3 / 9 10	n=3 PPSV23	PCV7/PCV7/PPS V23 (mo 0, 3,9)+placebo	49	49	100%	NR	1.23 / 4.07	2.38 /10.1		
(2010) ⁴⁷				mcg/ml	23F; PPSV23 : 1, 7F, 19A	months	(>5 years earlier)	PCV7/PCV7/PPS V23 (mo 0, 3,9) + CPG7909 adjuvans	48	49	100%	NR	1.03 / 5.21	1.92 / 9.76	Yes	Yes
Slayter	Canad a	RCT Immediat e versus	ELISA + OPA	NR	PCV7/PPSV 23: 4, 6B,	1, 6,12	0%	PCV7 (immediate/delaye d)	(23 16)	(43 42)	NR	NR	0.20/ 0.55	0.25 / 0.92		
(2013) ¹⁴		delayed immuniza tion		NK	9V, 14, 18C, 19F, 23F	months		PPSV23 (immediate/delaye d)	(19 21)	(40 38)	NR	NR	0.14 / 0.43	0.25 /0.80	Yes	Yes
	Korea	Prospectiv e cohort					0%	PCV13 (CD4 >350)	34	41	62%	34/34 (100)	NR	NR	No (method	
Song (2019) ⁴⁴			Multiple x OPA	OPA titer >≥1:64	5,6B,18C, 19A	21-35 days		PCV13 (CD4<350)	33	42	52%	29/33 (88)	NR	NR	s not suitable for meta- analysis)	NA
	United States	RCT / Prospectiv						PPSV23 first time (cART-)	14	27	0%	NR	NR	NR		
Tasker (2002) ⁵⁷		e cohort study	ELISA	NR	4, 6B, 9V, 14	6 ,12 weeks	n= 85 (>5 years prior	PPSV23 second time (cART+)	56	26	NR		NR	NR		Yes, however
		(combine d)					to study)	Placebo (second time cART+)	29	37	NR		NR	NR	Yes	data not available
Tsachouri	Greece	Prospectiv	ELISA	NR	Total PPSV23	4 , 48 weeks	0%	PPSV23 (cART+)	35	33	NR	NR	NR	NR		
45		e cohort			antipneumoc occal IgG			PPSV23 (cART-)	31	30	NR		NR	NR	Yes	No
NCT02717	Brazil	RCT (pregnant HIV+ women)	ELISA	>0 35			0%	PCV10	115	27	NR	114/114 (100)	NR	NR		
494 (2020) 56		,		mcg/ml	NR	4 weeks		PPSV23	115	28		109/110 (99)	NR	NR	1	Yes, but data could
								Placebo	116	28		106/113 (94)	NR	NR	Yes	not be provided.

Legend supplementary table 1 * Studies printed in bold were included in the meta-analysis

† If multiple time-points were assessed, results are shown for the bold printed time-point

‡ cART= combination antiretroviral treatment, defined as a combination of at least antiretroviral drugs

§ VL= viral load, undetectable viral load was defined as a value below the lowest level of detection in individual studies

| ELISA= Enzyme-Linked Immuno Sorbent assay

 \P NR = not reported

PPSV23 = 23-valent pneumococcal polysaccharide vaccine

 Δ HIV= human Immunodeficiency virus

- ◊ PCV= pneumococcal conjugate vaccine
- \downarrow OPA= opsonophagocytic assay
- RCT = Randomized clinical trial

Supplementary figure 1: Forest plot of studies comparing seroconversion rates for the pneumococcal conjugated vaccine (PCV) versus the pneumococcal polysaccharide vaccine (PPSV) – fixed effects model (corresponding to figure 5)

A Serotype 6 B

	PCV	PPSV	23		Odds Ratio	Odds Ratio
Study or Subgroup	Events To	otal Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Lombardi 2016	27	46 20	49	50.6%	2.06 [0.91, 4.67]	⊢∎
Slayter 2013 (delayed)	7	10 6	17	8.4%	4.28 [0.80, 22.93]	+
Slayter 2013 (immediate)	7	19 10	18	41.0%	0.47 [0.13, 1.74]	
Total (95% CI)		75	84	100.0%	1.59 [0.86, 2.97]	►
Total events	41	36				
Heterogeneity: Chi² = 5.05, i	df = 2 (P = 0.1)	.08); I ² = 60%				
Test for overall effect: $Z = 1$.	47 (P = 0.14))				Favours PPSV23 Favours PCV13

B Serotype 14

	PC\	/	PPSV	23		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Crum-Cianflone 2010	61	120	28	64	48.8%	1.33 [0.72, 2.45]	
Lombardi 2016	28	46	33	49	34.0%	0.75 [0.33, 1.75]	
Slayter 2013 (delayed)	7	10	11	17	6.6%	1.27 [0.24, 6.82]	
Slayter 2013 (immediate)	10	19	8	18	10.6%	1.39 [0.38, 5.07]	
Total (95% CI)		195		148	100.0%	1.14 [0.73, 1.77]	+
Total events	106		80				
Heterogeneity: Chi ² = 1.28,	df = 3 (P =	= 0.73);	l² = 0%				
Test for overall effect: $Z = 0$.	57 (P = 0.	57)					Favours PPSV Favours PCV

C Overall

	PCV PPSV					Odds Ratio		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI				
Crum-Cianflone 2010	68	120	23	64	39.2%	2.33 [1.25, 4.36]						
Lombardi 2016	10	46	14	49	32.0%	0.69 [0.27, 1.77]						
Slayter 2013 (delayed)	7	10	11	17	7.4%	1.27 [0.24, 6.82]						
Slayter 2013 (immediate)	7	19	11	18	21.5%	0.37 [0.10, 1.40]	-					
Total (95% CI)		195		148	100.0%	1.31 [0.83, 2.05]		•				
Total events	92		59									
Heterogeneity: Chi ² = 8.49, i	df = 3 (P =	: 0.04);	I ² = 65%						100			
Test for overall effect: Z = 1.1	17 (P = 0.	24)					Eavo	ours PPSV Favours PCV	100			

Supplementary figure 2: Forest plot of studies comparing seroconversion rates for the combined pneumococcal vaccination schedule (PCV+PPSV) versus the pneumococcal polysaccharide vaccine (PPSV) alone - fixed effects model (corresponding to figure 6)

Α Serotype 6B

		_										
		PCV+PI	PSV	PPS	v		Odds Ratio	Odds Ratio				
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI				
	Feikin 2001	8	18	3	16	3.8%	3.47 [0.73, 16.53]					
	Lesprit 2007	57	105	53	103	52.6%	1.12 [0.65, 1.93]					
	Peñaranda 2010	31	98	30	100	43.6%	1.08 [0.59, 1.97]					
	Total (95% CI)		221		219	100.0%	1.19 [0.81, 1.76]	•				
	Total events	96		86								
	Heterogeneity: Chi ² =	1.95, df =	2 (P = 1	0.38); I ² =	0%							
	Test for overall effect: .	Z = 0.88 (P = 0.3	8)				Eavours PPSV Eavours PCV+PPSV				
в	Serotype 14	Ļ										
		PCV+P	PSV	PPS	V		Odds Ratio	Odds Ratio				
_	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl				
	Feikin 2001	7	18	7	16	7.4%	0.82 [0.21, 3.22]					
	Lesprit 2007	57	105	70	103	52.9%	0.56 [0.32, 0.98]					
	Peñaranda 2010	49	98	49	100	39.7%	1.04 [0.60, 1.82]					
	Total (95% CI)		221		219	100.0%	0.77 [0.53, 1.12]	•				
	Total events	113		126								
	Heterogeneity: Chi ² =	2.36, df=	2 (P =	0.31); i² =	15%							
	To at fair an and all affects	7 - 4 35 4	n – o 4	0)				0.01 0.1 1 10 100				

Heterogeneity: Chi² = 2.36, df = 2 (P = 0.31); l² = 15% Test for overall effect: Z = 1.35 (P = 0.18)



С Overall

	PCV+P	PSV	PPSV	23		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lesprit 2007	62	105	41	103	71.8%	2.18 [1.25, 3.79]	
Ohtola 2016	11	15	12	22	11.0%	2.29 [0.55, 9.47]	
Sadlier 2016	16	26	11	28	17.2%	2.47 [0.83, 7.39]	
Total (95% CI)		146		153	100.0%	2.24 [1.41, 3.58]	◆
Total events	89		64				
Heterogeneity: Chi ² =	0.04, df=	2 (P = 1	0.98); I ^z =	:0%			
Test for overall effect:	Z = 3.39 (P = 0.0	007)				Favours PPSV23 Favours PCV+PPSV

Supplementary figure 3: Forest plot of studies showing comparison of log-transformed geometric mean concentrations of IgG of serotype 6B (A and B) and serotype 14 (B and C) for the pneumococcal conjugated vaccine (PCV) versus the pneumococcal polysaccharide vaccine (PPSV)

Serotype 6B Baseline



Serotype 6B Post-vaccination

	F	PCV			PPSV Mean Difference Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Feikin 2001	0.693	1.25	18	0.47	1.35	16	9.9%	0.22 [-0.66, 1.10]		
Ho 2013	0.631	1.71	100	0.372	1.68	100	34.7%	0.26 [-0.21, 0.73]	- +	
Lombardi 2016	1.4	1.04	46	1.21	0.967	49	46.8%	0.19 [-0.21, 0.59]		
Slayter 2013	-0.59	1.83	29	-0.84	2.01	35	8.6%	0.25 [-0.69, 1.19]		
Total (95% CI)			193			200	100.0%	0.22 [-0.05, 0.50]	◆	
Heterogeneity: Tau² =	: 0.00; Ch	ni² = 0.	05, df=	= 3 (P =	1.00); P	²= 0%				
Test for overall effect:	Z=1.58	Favours PPSV Favours PCV								

Serotype 14 Baseline

		PCV		P	PSV23			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Feikin 2001	1.61	1.13	18	1.99	0.944	16	19.7%	-0.38 [-1.08, 0.32]	
Ho 2013	0.14	1.85	109	0.599	1.55	111	30.8%	-0.46 [-0.91, -0.01]	
Lombardi 2016	1.72	0.995	50	1.901	0.974	50	34.6%	-0.18 [-0.57, 0.20]	
Slayter 2013	-1.39	1.67	31	-0.04	1.97	38	14.9%	-1.35 [-2.21, -0.49]	←
Total (95% CI)			208			215	100.0%	-0.48 [-0.87, -0.09]	•
Heterogeneity: Tau² = Test for overall effect:	: 0.08; Cl Z = 2.39	hi ² = 6.0) (P = 0.	-2 -1 0 1 2 Favours PPSV Favours PCV						

Serotype 14 Post-Vaccination

	I	PCV		PF	SV23			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Feikin 2001	2.37	1.11	18	2.73	1.14	16	19.9%	-0.36 [-1.12, 0.40]	
Ho 2013	2.51	2.12	100	2.18	1.74	100	32.3%	0.33 [-0.21, 0.87]	
Lombardi 2016	2.85	1.21	46	3.23	1.21	49	36.5%	-0.38 [-0.87, 0.11]	
Slayter 2013	1.15	2.1	29	1.23	2.25	35	11.3%	-0.08 [-1.15, 0.99]	_
Total (95% CI)			193			200	100.0%	-0.11 [-0.50, 0.27]	•
Heterogeneity: Tau² =	0.04; Cl	hi² = 4							
Test for overall effect:	Z = 0.57	' (P = (Favours PPSV Favours PCV						

Supplementary figure 4: Forest plot showing comparison of log-transformed geometric mean concentrations of IgG of serotype 6B (A and B) and serotype 14 (B and C) for the combined vaccination schedule (PCV+PPSV) versus the pneumococcal polysaccharide vaccine (PPSV) alone.

A 6B Baseline

	PC	V+PPS	v	F	PSV			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Feikin 2001	0.182	1.05	18	0.182	0.99	16	27.7%	0.00 [-0.69, 0.69]	+
Lesprit 2007	-0.76	1.31	105	-0.76	1.29	103	60.2%	0.00 [-0.35, 0.35]	— —
Sadlier 2016	-0.71	2.76	27	-1.71	1.32	33	12.2%	1.00 [-0.13, 2.13]	
Total (95% CI)			150			152	100.0%	0.12 [-0.30, 0.54]	
Heterogeneity: Tau ^z = Test for overall effect:	0.04; C Z = 0.57	hi² = 2 7 (P = (-2 -1 0 1 2 Favours PPSV Favours PCV+PPSV						

B 6B Post-vaccination

	PCV+	+PPS	V	P	PSV			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Feikin 2001	0.788 1	1.13	18	0.47	1.35	16	26.2%	0.32 [-0.52, 1.16]	
Lesprit 2007	0.445 1	1.92	105	0.438	1.38	103	56.4%	0.01 [-0.45, 0.46]	#
Sadlier 2016	0.779 1	1.61	26	-0.211	2.42	28	17.4%	0.99 [-0.10, 2.08]	
Total (95% CI)			149			147	100.0%	0.26 [-0.24, 0.76]	-
Heterogeneity: Tau ² =	0.06; Chi	i ^z = 2.1	79, df=	: 2 (P = 0).25); I	~ = 28%	b b		-2 -1 0 1 2
Test for overall effect:	Z=1.02((P = 0	.31)						Favours PPSV Favours PCV+PPSV

C 14 Baseline

	PCV	+PPS	V		PPSV			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Feikin 2001	1.61	1.13	18	1.99	0.944	16	32.5%	-0.38 [-1.08, 0.32]	
Lesprit 2007	0.519	1.45	105	0.068	1.76	103	38.2%	0.45 [0.01, 0.89]	-∎-
Sadlier 2016	-0.82	1.82	27	0.039	1.42	33	29.3%	-0.86 [-1.70, -0.02]	
Total (95% CI)			150			152	100.0%	-0.20 [-1.00, 0.60]	-
Heterogeneity: Tau ² =	0.39; Ch	ii² = 9. ∕⊡ = 0	-4 -2 0 2 4						
restion overall ellect.	∠ = 0.50	(== 0	Favours PPSV Favours PCV+PPSV						

D 14 Post- Vaccination

	PC	/+PPS	V		PPSV			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% Cl	
Feikin 2001	2.43	1.15	18	2.18	0.696	16	30.3%	0.25 [-0.38, 0.88]			
Lesprit 2007	2.23	1.61	105	1.77	1.61	103	63.0%	0.46 [0.02, 0.90]		₽	
Sadlier 2016	1.53	3.14	26	1.74	1.61	28	6.7%	-0.21 [-1.56, 1.14]			
Total (95% CI)			149			147	100.0%	0.35 [0.00, 0.70]		•	
Heterogeneity: Tau ² = Test for overall effect:	: 0.00; C Z = 1.98	hi ^z = 1 } (P = (-2	-1 0 1 Favours PPSV Favours PCV+PI	2 2 2						

Box 1: Research questions

The proposed systematic review sought to answer the following research questions:

• What is the immunologic response to pneumococcal vaccines (polysaccharide, conjugate or both) in adult PLWH, either expressed in seroconversion rate (SCR), or geometric mean concentration (GMC) of anti-pneumococcal IgG levels, or opsonophagocytic activity (OPA)?

• Does the response to vaccination differ between different pneumococcal vaccination schedules?

• Does the response to vaccination differ between subgroups of PLHW, based on CD4 count, viral load and/or cART use?

• Is the immunologic response to vaccination durable in PLWH?

Box 2: Eligibility criteria

The following studies were included in the systematic review:

o Randomized controlled trials (RCT), prospective, and retrospective cohort studies, in which at least one dose of pneumococcal vaccine (either conjugate, or polysaccharide or both) was administered to adult PLWH.

o Studies performed in the era of advanced antiretroviral therapy, which is after the year 2000, when combination antiretroviral therapy became universally recommended.

o Studies reporting vaccine immunogenicity outcomes, including seroconversion rate (SCR), geometric mean anti-pneumococcal IgG levels, or opsonophagocytic activity.

We excluded paediatric studies; animal studies; case reports; studies that did not reported serological outcomes, and vaccination studies published before 2000, because pre- or early cART eras do not adequately reflect the current situation for PLWH.

The following studies were also included in the meta-analysis:

o Studies reporting seroconversion rates (SCR) for serotype 6B, 14, and/or the overall seroconversion rate, 1-3 months after vaccination, following one or more of the following definitions:
1. The n/total (%) of patients reaching a ≥ 2-fold increase in IgG for serotype 6B, or the n/total

(%) of patients reaching a \geq 2-fold increase AND IgG level \geq 1.00 µg/ml for serotype 6B.

The n/total (%) of patients reaching a ≥ 2-fold increase in IgG for serotypes 14, or the n/total
 (%) of patients reaching a ≥ 2-fold increase AND IgG level ≥1.00 µg/ml for serotype 14.

3. The n/total (%) of patients reaching a \geq 2-fold increase for at least 50-70% of measured serotypes, or the n/total (%) of patients reaching a \geq 2-fold increase AND IgG level \geq 1.00 µg/ml for at least 50-70% of measured serotypes (overall SCR).

o Studies comparing PPSV23 to PCV, or to the combination of PCV/PPSV23, and which reported baseline and post-vaccination GMCs with 95% confidence intervals 1-3 months after vaccination, for serotype 6B and/or 14. Studies from which the GMCs had to be extracted from graphs were excluded from meta-analysis.

Box 3: Methods for meta-analysis

We obtained pooled SCRs for serotypes 6B, 14, and the overall SCR, and associated 95% confidence intervals (CI) in PLWH, after single PCV, multiple PCVs, PPSV23, and PCV/PPSV23 combined, using R version 3.5.0. package 'meta', command 'metaprop'. We used the I² test to indicate the level of statistical heterogeneity between studies. Odds ratios for SCR-differences between vaccination regimens were calculated in RevMan version 5.3. GMCs for serotype 6B and 14, and their 95% confidence intervals, were log transformed, and the standard error was calculated from the log-transformed 95% confidence interval. Log transformed data were entered in RevMan 5.3, using the inverse variance method, to calculate the GMC differences between vaccination schedules (PCV versus PPSV23, and PCV/PPSV23 combined versus PPSV23).

In view of the sample size and considerable statistical heterogeneity we used the random-effects model for all meta-analyses. We depicted the results of our meta-analysis in Forest plots. Where appropriate, we used the 95% confidence interval (CI) to indicate statistical significance. In addition, prediction intervals were calculated for all Odds ratios from the comparative meta-analysis, because a CI

provides an incomplete summary of the underlying heterogeneity in meta-analysis, whereas prediction intervals show the range of true effects as can be expected from future studies. Last, subgroup analyses were performed to investigate the influence of study quality, cART use, and CD4-cell counts on effect estimates and heterogeneity.