PRIME: Immunogenicity Randomized Controlled Trial Risk of Bias Tool

	Question	Answers
1	Is the study randomized?	a. Yes b. Control group but not randomized c. No control arm/group d. Unclear e. Not stated/Full text not available (ie. Poster or abstract) f. Not applicable
2	Blinding of participants and personnel	a. Double-blind b. Single-blind (either participants or study personnel) c. Open label d. Unclear e. Not stated/Full text not available (ie. Poster or abstract)
3	Blinding of outcome assessment (e.g., specimens were tested without knowledge of pre/post PCV status or study arm)	a. Yes b. No (.e., not blinded or no control arm for the relevant outcome of interest) c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
4	Incomplete outcome data (e.g., the percent of those randomized to those analyzed)	a. 90% or more of those randomized were included in the analysis of the relevant outcome of interest b. Fewer than 90% were analyzed c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
5	Was industry (i.e., GSK or Pfizer) involved in this study?	a. No b. Yes, funded all or in part by Industry but conducted entirely by independent investigators (e.g., no co-authors from industry; lab work not performed by Industry) c. Yes, conducted all or in part by industry (e.g., analyses or lab work performed by Industry) d. Unclear e. Not stated/Full text not available (ie. Poster or abstract)
6	Other Risk of Bias	Please comment on other factors that may introduce bias

Immunogenicity Randomized Controlled Trial Risk of Bias Assessments

RefID	Reference (Author,Year)	Q1rand_ans	Q1rand_comments	Q2blindpart_ans	Q2blindpart_comments	Q3blindout_ans	Q3blindout_comments	Q4incomp_ans	Q4incomp_comments	Q5Industry_Ans	Q5industry_comments	Q6othbias_comments	Overall_Assessment: PICO1/PICO2	Overall_Assessment: PICO 3
1412	Esposito, 2010	a	"Subjects were randomly assigned in a 1:1 ratio to one of the two vaccine groups"	a	"This was a phase 3.... double-blind, multicenter trial... Treatment allocation was concealed from all subjects, study staff, and those assessing the outcomes."	a	"Treatment allocation was concealed from all subjects, study staff, and those assessing the outcomes."	c	Of the 606 randomized children (n=303 in each of the 2 arms), "285 (94.1% subjects in the PCV13 group and 281 (92.7% in the PCV7 group completed the entire study". However, as seen in Tables 4 and 5, the % of infants assessed varied by vaccine serotype and often was <90% of randomized children.	b, c	Study was funded by a grant from Wyeth and several of the author affiliations listed are for Wyeth.		LOW	
444	Lalwani, 2014	a	"This was a phase III randomized study"	c	Study only assessed 1 vaccine product, and "The study was conducted in an open manner, as the participants from the different groups received the study vaccine according to different vaccination schedules."	d	No mention of study personnel being masked.	b	According to Figure 2, between 74.7% - 93.1% of enrolled children were analyzed.	b,c	Study was conducted and funded by GSK.	74-95 children enrolled per arm so not a big study	UNCLEAR: not sure if lab analysis was blinded, varied completeness of outcome data	UNCLEAR:
263	Lim, 2014	a	"Infants were sub-randomized (1:1) to two subsets"	a	"The primary vaccination phase was double-blinded", while the phase that assessed the impact of a booster dose was "conducted in an open-label manner".	d	Not stated	b	According to Figure 1, only around ~50% of enrolled children completed the booster phase for analysis." Booster could only be done in Singapore setting.	b, c	Study was conducted and funded by GSK.		LOW	
88	Van Westen, 2015	c	Infants born in the Netherlands during September-December 2011 were enrolled in a controlled parallel group intervention study comparing immuno before and after a booster dose with PCV10 or PCV13. Children were randomly assigned to groups in which an intravenous blood sample was collected before and after the booster dose at different times.	c	staff members and parents were aware of the intervention	a	Lab staff were blinded	b	According to Figure 1, roughly 61-67 were randomized and included in the analysis	a	Study was funded by the Dutch Ministry of Health; however one author has received unrestricted research support from Pfizer, grant support for vaccine studies from Pfizer and GSK, and fes paid to her institution for advisory boards or participants in independent data monitoring committees for both companies.		LOW	
108	Hamaluba, 2015	a	Study staff allocated participants with a participant number and randomly assigned (4:4:5 ratio) them to receive PCV10 at either 6 and 14 weeks with a 9 month booster (2+1 group); age 6, 10, and 14 weeks (3+0 group), or no vaccine until age 10 and 11 months.	c	Open label study	a	Laboratory staff were masked to intervention group assignment	a	According to Figure 1, greater than 90% of children enrolled had blood draws at 10 months	b	GSK funded the study through and investigator originated grant, but had no role in the design or management of the study, data analysis and interpretation, or the final decision to submit to publication		LOW	
116	Gadzinowski, 2015	a	Health infants were randomized 1:1 to receive PCV13+P80 or PCV13 without P80 given at ages 2,3,4 and 12 months with concomitant vaccines	a	Double-blind multicenter trial	a	Laboratory personnel remained blinded at all times	a	According to Supplemental Digital Content 2, roughly 93% of participants were in the evaluable immunogenicity population	c	Study was sponsored by Wyeth, which was acquired by Pfizer; assays were preformed in clinical trail assay testing laboratories owned by Pfizer		LOW	
151	Martinón, 2015	c	Phase IV, open-label 2-arm, multicenter, parallel-group study with 2 groups: pre-term and term infants	c	Open label study	d	Not stated	a,b	According to Fig. 1, roughly 98% were included in the infant series analysis and roughly 88% were included in the toddler dose analysis	c	IgG and OPA testing was performed by Pfizer's Vaccine Research clinical testing laboratory		UNCLEAR	
600	Spijkerman, 2013	a	"400 infants were randomly assigned (1:1:1:1) to receive PCV13... Randomization was performed by a random number generator 13 using block randomization with randomly varying block size"	c	Since this study assessed different vaccine schedules, by nature, it was open label	a	"Study staff members and parents were aware of the child's allocated immunization schedule, but laboratory staff was not"	a	According to Figure 1, 90.5% of randomized children were included for analysis in the Per Protocol analysis (92% for ITT analysis).	a	Some author reported having received grants & fees from industry. Pfizer provided 1400 vaccines for the study.		LOW	
761	Kim, 2013	a	"Subjects were randomly assigned in a 1:1 ratio to receive either PCV13 or PCV7 based on a random assignment schedule prepared by the sponsor."	a	"This was a parallel-group, randomized, double-blind trial "	d	Not stated	a	According to Figure 1, 91.1% of randomized children were included for analysis.	c	Study was partially conducted and funded by Pfizer.	Small sample size	UNCLEAR	
828	Weckx, 2012	a	"Subjects were randomly assigned in a 1:1 ratio"	a	"This phase 3, randomized, active-controlled, double-blind, parallel-group, multicenter trial..."	d	Not stated	b	According to Figure 1, 85.8% of the n=354 randomized children were included for analysis.	c	Some authors are affiliated with Wyeth, Wyeth sponsored the study, and contributed to the study's design, data collection, analysis, etc.		LOW	

1034	Martinón-Torres, 2012	a	"Subjects were randomly allocated in a 1:1: ratio"	a	"This was a double-blind study, and all participants and studypersonnel were blind to treatment allocation."	d	Not stated	b	According to the text, 74.8 % of the n=449 randomized children were included for analysis afer the toddler dose.	c	Some authors are affiliated with Wyeth, Wyeth sponsored the study, and contributed to the study's design, data collection, analysis, etc.		LOW	
4477	Odutola, 2016	a	8-10 week old infants were 1:1:1:1:1:1 - randomized	b	observer-blind study	d	Not stated (poster)	d	Not stated (poster)	c	Funded by GSK; some co-authors GSK affiliated		UNCLEAR: GSK study, blinding of lab personnel and completeness of outcome data not stated	
4475	Mulholland, 2016	e	Not stated/Full text not available (ie. Poster or abstract)	e	Not stated (presentation from SAGE WG)	d	Not stated (presentation from SAGE WG)	d	Not stated (presentation from SAGE WG)	e	Not stated (presentation from SAGE WG)		UNCLEAR: Not enough information to evaluate	
4468	Moisi, unpublished	a	Infants and toddlers randomized using random number generator function based on uniform probability distribution; performed in blocks of 20, after stratification by clinic for infant group	c	Open label study	b		a		b	No author affiliations listed, so not certain that co-authors were not industry-affiliated		LOW	LOW
4323	Falup-Pecurarui, 2016	a	infants were randomized 3:3:3:1:1:1	c	Open label study	b	all study staff were aware of treatment allocation	a		c			LOW	
3933	Verhagen, 2016	c	pre-vaccine time point the comparator for post-vaccine GMT	e	Not applicable since only 1 intervention	d	Not stated	d	Not stated	b	Funded partially by Pfizer Venezuela, but no co-authors affiliated with industry	High burden of IPD in SA indigenous population, natural history of pneumo disease & colonization affecting change in antibody response over time	HIGH: no control group except for pre-vaccine time point	
1052	Huang, 2011	a	"Subjects were randomly assigned in a 1:1 ratio"	a	"This randomized, double-blind, multicenter trial"	d	Not stated	a	According to Figure 1, 97.0% of the 168 randomized children were included for analysis.	c	One co-author has Pfizer affiliation, study was sponsored by Wyeth, and Wyeth contributed to the study's conduct.	Small sample size	LOW	
1088	Knuf, 2012	a	" Infants were subsequently randomized (1:1) to a PHiD-CV or 7vCRM study group"	b	The phase of the study which involved receipt of either PCV7 or PCV10 was single blind	a	"Serum aliquots were stored at -20°C until blinded analysis at GSK Biologicals' laboratory in Rixensart, Belgium."	b	According to Figure 1, 79.1% of the 134 randomized children were included for analysis.	c	One co-author has GSK affiliation, study was partially sponsored by GSK, and GSK was involved in all stages of conduct and analysis.		LOW	
1101	Grimprel, 2011	a	"Eligible subjects were randomly allocated in a 2:1:1 ratio... using a per-muted block randomization schedule"	a	"All participants, study staff, and those assessing the outcomes were blinded to the group assignment."	a	"All participants, study staff, and those assessing the outcomes were blinded to the group assignment."	b	According to Figure 1, 80.7% of the 613 randomized children were included for analysis.	c	Some authors are affiliated with Wyeth, Wyeth sponsored the study.		LOW	
1008	Lalwani, 2012	a	"Healthy infants wererandomized (2:1 treatment allocation ratio) "	b	"The study was conducted in a single-blinded manner meaning that the investigator was aware of the treatment assignment but the infant's parents/guardians were not"	b	"A potential limitation of this study was the absence of investi-gator blinding"	a	According to Figure 1, 95.8% of the 360 randomized children were included for analysis.	c	Some authors are affiliated with GSK, and GSK sponsored the study and was involved in all stages of conduct and analysis.		LOW	
1105	Kim, 2011	a	"Infants were randomized (3:1 treatment allocation ratio)"	b	"single-blind, randomized, controlled trial"	d	Not stated	b	According to Figure 1, 83.3% of the 503 randomized children were included for analysis.	c	Some authors are affiliated with GSK, and GSK sponsored the study and was involved in all stages of conduct and analysis.		UNCLEAR: not stated if lab personnel blinded, somewhat lower completeness of data	
1192	Vesikari, 2011	f	Infants were assigned a vaccine schedule based on age, and only 1 vaccine product was used. The reference group was children who had received the vaccine through the normal childhood vaccine schedule.	c	open label	d	Not stated	b	According to Figure 1, 88% of the 600 randomized children were included for analysis.	c	Some authors are affiliated with GSK, and GSK sponsored the study and was involved in all stages of conduct and analysis.		LOW	LOW
548	Odusanya, 2013	a	" A randomisation blocking scheme (2:1 ratio)... was used to ensure that balance between treatments was maintained"	c	"In this open, randomised, controlled study".	d	Not stated	a	According to the Trial Profile figure, 90% of the 120 randomized children were included for analysis.	c	Some authors are affiliated with GSK, and GSK sponsored the study and was involved in all stages of conduct and analysis.	Small sample size	LOW	
1142	Ruiz-Palacios, 2011	c	No control group present- "The objectives of this phase III, single-arm, open-labeled study..."	c	"The objectives of this phase III, single-arm, open-labeled study..."	d	Not stated	a	According to Figure 1, 95.2% of the 230 randomized children were included for analysis.	c	Some authors are affiliated with GSK, and GSK sponsored the study and was involved in all stages of conduct and analysis.	Comparison to European cohort	HIGH: Mexican group compared to European group	
443	Juergens, 2014	a	"In brief, eligible subjects were randomly assigned at a 1:1 ratio to receive PCV13 or PCV7."	a	"This randomized double-blind trial was conducted in Israel..."	d	Not stated	c	Authors present n=354 total children randomized, but then focus on the n=200 children subset (100 PCV7, 100 PCV13) selected for this analysis. Unclear.	c	Some authors are affiliated with Pfizer & Wyeth sponsored the study.		LOW	
452	Odusanya, 2014	a	This is a follow-up to an earlier study that randomized children to PCV10 primary series vaccination or to a control group. Previously vaccinated and control group children were then invited to participate in this booster phase study.	c	Since this study assessed different vaccine schedules, by nature, it was open label	d	Not stated	b	According to Figure 1, 86.5% of the 119 randomized children were included for analysis.	c	Some authors are affiliated with GSK, and GSK sponsored the study and was involved in all stages of conduct and analysis.	Small sample size	LOW	LOW

538	Togashi, 2013	c	"This was an open-label study that had only 1 treatment arm"	c	This was an open-label study that had only 1 treatment arm	d	Not stated	a	According to Figure 1, 95.3% of the 193 randomized children were included for analysis.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		UNCLEAR: 1 arm, so fold-rise compared pre and post vaccination. No definition of GMFR comparison. No mention of burden of Spn in community so potential for natural boosting.	
558	Diez-Domingo, 2013	a	"Subjects were randomized in a 1:1 ratio"	a	"Phase 3, parallel-group, randomized, active-controlled, double-blind, multicenter trial"	d	Not stated	a	According to Figure 1, 94.0% of the 619 randomized children were included for analysis.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		LOW	
593	Dagan, 2013	a	"Healthy infants were randomized (1:1) to receive PCV7 or PCV13"	a	"This randomized double-blind trial..."	d	Not stated	a	According to Figure 1, 93.9% of the 1,866 randomized children were included for analysis.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		LOW	
602	Grant, 2013	f	Study had an observational design, where blood samples were taken from children who had already received PCV as part of their routine vaccine schedule	d	Not applicable: Study had an observational design, where blood samples were taken from children who had already received PCV as part of their routine vaccine schedule. Study personnel therefore did not adminster vaccines to participants	d	Not stated	c	Supplementary figure 1 provides information on how many sera were collected at the beginning verus sera ultimately analyzed. According to Suppl Figure 1, 72.5% of the 561 sera collected were included for analysis. Suppl Figure 1 available here: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0074906#s5	b	Study was partially funded by Pfizer but conducted by authors with no industry affiliations.		UNCLEAR: changing epidemiology of circulating STs may also impact immunogencity by natural exposure	
647	Payton, 2013	a	"Subjects were randomly assigned in a 2:2:2:1 ratio to receive 1 of 3 lots of PCV13or PCV7 using a web based randomization system."	a	"This was a phase 3, randomized, double-blind, multicenter study"	d	Not stated	b	According to Figure 1, 72.6% of the 1,712 randomized children were included for analysis.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		LOW	
757	Singleton, 2013	f	Study had an observational design- "children were offered PCV13 as appropriate for age and prior PCV7 history"". No randomization occurred.	c	"This was a phase 3, open-label trial"	d	Not stated	b	According to the text, 48.8% of the 373 enrolled children (no randomization occurred) completed the full vaccination series per protocol. Even fewer had blood drawn within the protocol-specified time period	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.	Very small sample size	HIGH: small sample size, missing outcome data	
800	Dicko, 2013	c	Study had no control group	c	"This phase III, open-label, single-center study"	b	Only 1 intervention group	a	According to the text, 95.2% of the 147 enrolled children completed the study.	c	Some authors are affiliated with GSK and GSK sponsored the study.		LOW	
815	Brito, 2013	c	"This phase 3, open-label, single-arm, multicenter trial"	c	"This phase 3, open-label, single-arm, multicenter trial"	b	Only 1 intervention group	b	According to Figure 1, 81.3% of the 225 enrolled children completed the toddler dose.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		LOW	
838	Amdekar, 2013	a	"This was a phase 3, randomized, active-controlled, double-blind trial"	a	"This was a phase 3, randomized, active-controlled, double-blind trial"	d	Not stated	b	According to Figure 1, 54.8% of the 709 enrolled children were included for analysis after the toddler dose.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.	Clinical hold on PCV trials in India because of some adverse events	UNCLEAR: incomplete outcome assessment	
922	Lin, 2012	c	"This was a single-arm, open study"	c	"This was a single-arm, open study"	b	Single arm study	a	According to Figure 2, 95.2% of the 230 enrolled children were included in the according-to-protocol immunogenicity cohort.	c	Some authors are affiliated with GSK and GSK sponsored the study.		LOW	
3824	Zhu, 2016	a	phase 3, randomized trial; infants randomized 2:2:2:1 to PCV7 or PCV13 and different schedules	a and c	vaccines were administered	c	not specified in text	a and b	92% of randomized subjects analyzed for infant series; 82% after toddler dose	c	funded by Pfizer, some coauthors from Pfizer		LOW: one study arm not blinded probably because difference in schedule	
3832	Truck, 2016	a	randomized, controlled trial	c	open label for participants and clinical trial staff	a	blinded for laboratory staff	b	79%-85% of included subjects available at follow up time points	b	GSK support but did not have a role in study design and analysis		LOW: slightly lower outcome follow up %	
3878	Martinon-Torres, 2015	c	no control group, just preterm infants and full term infants who both received PCV13	c	open-label	b	assays done in Pfizer lab	b	88% part of evaluable immunogenicity population	c	Pfizer coauthors involved in study		LOW:: Pfizer lab conducted assays	
3916	Truck, 2016	a	randomized to either PCV13 or PCV10 booster	c	open label for participants and clinical trial staff	a	blinded for laboratory staff	b	87% available for memory B cell and antibody analysis	b	GSK support but did not have a role in study design and analysis		LOW	
3924	Martinon-Torres, 2017	c	no control group, just preterm infants and full term infants who both received PCV13	c	open-label	b	assays done in Pfizer lab	b	80% follow up at 1 year, 71% at 2 years	c	Pfizer coauthors involved in study		LOW: Pfizer lab conducted assays and lower follow: up at 2 years post	
3675	Pomat, 2016	a	infants randomized to either PCV10 or PCV13 arms, no control group	e	not stated in text	d	not stated in text	b	81% of infants available for post-primary analysis	a	no mention of industry in poster		LOW	
3696	Balloch, 2016	a	infants randomized to receive one of two schedules, no control group	e	not stated but unlikely as different ages for receipt of doses and blood draw	d	not stated	d	total N enrolled not stated, but study arm 2m/4m had 235 infants and 2m/6m only had 149 and not explained why	a	vaccine donated by GSK		LOW: though different n of arms, the findings are consistent with what we would expect and so likely reliable results	
3721	Silfverdal, 2009	a	infants randomized to receive one of two schedules, no control group	c	open label	d	not stated in text	a	89% of subjects included in analysis	c	funded by GSK and one of the co-authors employed at GSK, assays done at GSK lab		LOW	
3722	Vesikari, 2009	a	primary schedule: infants randomized, booster schedule: partially randomized based on what vaccines received as primary	e	not stated	a	blinded analyses conducted at GSK labs	a	90% for primary phase and 95% for booster phase	c	funded by GSK, assays done in GSK labs and GSK involved in study design & conduct		LOW	

3723	Wysocki, 2009	a	randomized but no control	c	open label	a	blinded analyses conducted at GSK labs	b	assessment for immunogenicity a secondary outcome (after safety) and prespecified as only n=180 per group			Study of safety and immunogenicity with different coadministered vaccines	LOW: GSK study, primary objective safety	
1090	Vanderkooi, 2012	a	"Subjects were randomized 1:1"	a	"This was a phase III, parallel-group, double-blind, multi-center trial"	d	Not stated	a	According to Figure 1, 94.3% of the 603 randomized children completed the toddler series for analysis.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		LOW	
1126	Dicko, 2011	a	"The objectives of this phase III, randomized, open, controlled study"	c	"The objectives of this phase III, randomized, open, controlled study"	d	Not stated	a	According to Figure 1, 91.9% of the 358 randomized children were included for in the ATP immunogenicity cohort.	c	Some authors are affiliated with GSK and GSK sponsored the study.		LOW	
798, 3724, 3725	Ruiz-Palacios, 2013	a	toddlers randomized to 1 of 3 dosing schedules	c	open label	a	"Laboratory personnel responsible for immunogenicity testing were blinded to the treatment group."	a	93% of subjects completed protocol for immunogenicity analysis	c	GSK funded study and involved in design, coauthors employed at GSK, GSK labs		LOW	
3754	van den Bergh, 2016	a	randomized to PCV10 or PCV7 arms	b	staff members aware of study arm allocation but parents were not	a	laboratory technicians not aware of study arm allocations	a	93% of subjects completed protocol for immunogenicity analysis	c	GSK funded study and involved in design, coauthors employed at GSK, GSK labs		LOW	
2226	Tregnaghi, 2014	a	RCT	a	Double-blind multicenter trial	a	"personnel involved in data gathering, processing, and analysis and safety assessment were blind to vaccine allocation"	b	67% for PP analysis of primary series, 45% for PP analysis of booster	c	GSK funded study and involved in design, coauthors employed at GSK, GSK labs	about 264 infants excluded from immunogenicity arms because of incorrect consent form. High rate of attrition between primary and booster time points.	LOW: GSK study, still large numbers in immunogenicity analysis	
2367, 3718	Bermal, 2011	a	infants randomized to receive either PCV10 or PCV7	a	double-blind	a	"sera were analyzed in a blinded manner"	a	93% of subjects completed protocol for immunogenicity analysis	c	GSK funded study and involved in design, coauthors employed at GSK, GSK labs	booster phase continued from primary phase of comparison RCT between PCV10 and PCV7	LOW	
3363	Vesikari, 2016	a	randomized, controlled cluster trial	a	double-blind	d	not stated	b	82% of infant group available for analysis; 74% of catch up group included in analysis	c	GSK funded study and involved in design, coauthors employed at GSK, GSK labs		UNCLEAR: not sure if lab analysis was blinded	
1424	Bryant, 2010	a	Infants (n 249) were randomly as- signed to receive PCV13 (n 122) or PCV7 (n 127)	e	not stated	d	not stated in text	a	91.6% of the infants (228 of 249) completed the primary vaccination series.	c	Dr Bryant has been an investigator on clinical trials funded by Wyeth Pharmaceuticals, GlaxoSmithKline, Novartis, MedImmune, Astellas, and Johnson and Johnson and has served as a consultant to Wyeth and Astellas, received honoraria from Sanofi Pasteur and Abbott for lectures and from GlaxoSmithKline for service on an advisory board; Dr Block has been an investigator on clinical trials funded by Wyeth, has served as an advisor to Wyeth, has served as a clinical investigator on trials funded by GlaxoSmithKline and Merck, and has served on an advisory board for Merck; Dr Baker was an employee of Wyeth at the time the study was conducted; and Drs		LOW	
1491	Timo, 2010	d	A total of 1650 subjects (1235 in the three PHiD-CV groups and 415 in the 7vCRM group) were enrolled for the primary vaccination phase and 1112 subjects for the booster phase (737 in the PHiD-CV primed and booster group, 92 in the 7vCRM primed and booster group and 283 in the 7vCRM primed and PHiD-CV booster group).	e	not stated	a	Blind analyses were conducted at GSK laboratories, Rixensart, Belgium. A	d	not stated	e	not stated		UNCLEAR: a lot of missing info	
1546	Ladhani 2015	b	only 1 intervention and historical control	c	This was an open, non-randomized study conducted by the same investigators in 2 of the same geographical areas (Gloucestershire/Hertfordshire) in 2011–2012 that assessed antibody responses in infants 1 month after primary immunization with the same vaccines and sched- ule and with samples tested by the same laboratories and assays as in this evaluation	d	not stated in text	a	95% completeness	a	This report is independent research commissioned and funded by the Department of Health Policy Research Programme (Na- tional Vaccine Evaluation Consortium, 039/0031). The Immunization, Hep- atitis and Blood Safety Department has provided vaccine manufactures with post-marketing surveillance reports (not pertussis-containing vaccines to date), which the companies are required to submit to the UK Licensing Au- thority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.	Historical control 2011-2012, study 2012-2014	LOW: historical controls also from PCV13 era	

1573	Iwata, 2015	a	This phase III, randomized, open-label, multicenter study (NCT01027845) conducted in Japan assessed the immunogenicity, safety, and reactogenicity of 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV, given intramuscularly) co-administered with diphtheria-tetanus-acellular pertussis vaccine (DTPa, given subcutaneously).	c	This phase III, randomized, open-label, multicenter study (NCT01027845) conducted in Japan assessed the immunogenicity, safety, and reactogenicity of 10-valent pneumococcal nontypeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV, given intramuscularly) co-administered with diphtheria-tetanus-acellular pertussis vaccine (DTPa, given subcutaneously)	d	no, also not stated in the article	a	according to figure 1, originally there were 360 individuals who could be randomized and after the whole series there were 216 in the PHID-CV group and 115 in the conrol group after booster phase so .919 or 92%	c	GlaxoSmithKline Biologicals SA was the funding source and was involved in all stages of the study conduct and analysis. Glax- oSmithKline Biologicals SA also took responsibility for all costs associated with the development and publishing of the present manuscript.		LOW	
1926	van den Bergh, 2012	a	780 health dutch children were randomly assigned	b	in this single blind study	d	abstract, not stated	b	>70% enrolled subjects evaluated for booster dose	b	GlaxoSmithKline Biologicals provided the funding		LOW	
1957	Prymula, 2014	a	health infants were randomized (1:1:1:1)	d	partially blinded study	d	abstract, not stated	d	abstract, not stated	b	GlaxoSmithKline Biologicals provided the funding		UNCLEAR: not much info to evaluate	
2089	Horn, 2014	a	randomized (1:1)	a	double blind	d	abstract, not stated	d	abstract, not stated	b	GlaxoSmithKline Biologicals provided the funding		UNCLEAR: not much info to evaluate	
2167	Wana, 2014	a	260 infants randomized	c	in an open randomized controlled trial	d	abstract, not stated	d	abstract, not stated	a	no conflicts of interest		LOW	
1181	van den Bergh, 2011	a	"In a single-blind, single-center, randomized controlled trial in the Netherlands"	b	"In a single-blind, single-center, randomized controlled trial in the Netherlands"	d	Not stated	b	According to Figure 1, 72.6% of the 797 randomized children were included in the ATP cohort for immunogenicity.	c	Some authors are affiliated with GSK and GSK sponsored the study.		LOW	
1229	Lagos, 2011	a	"children randomized to receive three doses of pHiD-cV (pHiD-cV group) or hepatitis avaccine"	b	"There were 2 study stages: an observer-blind, randomized, controlled primary vaccination stage (106208/NCT00338351) and an observer-blind booster/catch-up vaccination stage"	d	Not stated	b	According to Figure 1, 65.4% of the 240 enrolled children were included in the ATP immunogenicity cohort.	c	Some authors are affiliated with GSK and GSK sponsored the study.		LOW	LOW
1262	Gadzinowski, 2011	c	"healthy infants were randomly assigned in a 1:1 ratio" to receive 1 of 2 lots of PCV13	a	"This was a phase 3, parallel-group, randomized, double-blind, multi center (9 centers in Poland) trial"	d	Not stated	a	According to Figure 1, 96.3% of the 269 randomized children were included in the final analysis.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		LOW	
1335	Snape, 2010	a	"This phase III, randomized, double-blind, active-controlled study"	a	"All study sites, participants and relevant sponsor staff remained blinded to the vaccines received during the study."	a	" laboratory staff remained blinded to the study groups at both these stages."	b	According to Figure 1, 68.8% of the 286 randomized children were included in the toddler per-protocol analysis after completing the toddler stage.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		LOW	
1379	Yeh, 2010	a	"This phase 3, randomized, double-blind, active-controlled, multi center trial"	a	"This phase 3, randomized, double-blind, active-controlled, multi centertrial"	a	"Participants, study staff, and those who assessed outcomes were blinded to the group assignment"	b	According to Figure 1, 69.3% of the 666 randomized children were included in the toddler evaluable immunogenicity population.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.		LOW	
1406	Kieninger, 2010	a	"This was a parallel-group, randomized, active-controlled, double-blind, multicenter trial"	a	"This was a parallel-group, randomized, active-controlled, double-blind, multicenter trial"	a	"All participants, study staff, and those assessing theoutcomes were blinded to the group assignment"	a	According to Figure 1, 90.4% of the 605 randomized children were included in the toddler evaluable immunogenicity population.	c	Some authors are affiliated with Pfizer, and Pfizer conducted the pneumococcal immunogenicity assays.		LOW	
1407	Vesikari, 2010	a	"In this open, controlled study, 325 healthy children aged 12to 14 months were randomized to 1 of 3 groups"	c	"In this open, controlled study, 325 healthy children aged 12to 14 months were randomized to 1 of 3 groups"	b	"Potential limitations of this study include the relatively small sample size and the lack of investigator blinding"	a	According to Figure 1, 96.3% of the 325 randomized children were included in the ATP immunogenicity cohort.	c	Some authors are affiliated with GSK and GSK sponsored the study.		LOW	
2202	Wijmenga, 2015	e. Not stated/Full text not available (ie. Poster or abstract)	A single-centre, parallel-group intervention study with two groups (PCV10 recipients and PCV13 recipients) was conducted in the Netherlands among infants eligible for the routine National Immunization Program (NIP): vaccinations at 2, 3, 4 and 11 months of age, or the 3 +1 (primary plus booster) schedule	c	This was an open-label study for parents and study staff, but immunogenicity analysis was performed blinded.	a	This was an open-label study for parents and study staff, but immunogenicity analysis was performed blinded.	c	unclear, did not state this number	a	Funding: The authors have no funding or support to report.	however it should be noted that "The laboratory of DG and MZ receives grant support from GSK and DG acts as an occasional consultant to GSK. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials. All other authors declare to have no conflicts of interests."	UNCLEAR: not enough info to evaluate	

2203	Block, 2015	a	Overall, 751 healthy infants (age: 55–89 days) were rand- omized to receive 3 or 4 doses of MenACWY-CRM (2/4/12 or 2/4/6/12 months of age, respectively) with PCV13 + routine vaccinations (ACWY3 and ACWY4 groups, respectively) or PCV13 + routine vaccinations only (routine group)	c	Results of a Phase 3b, Randomized, Open-label Trial	a	All serological analyses were performed by staff blinded to vaccine group assignment.	b	Overall, 571 (75%) enrolled subjects completed the study.	b	Novartis Vaccines and Diagnostics, Inc. provided financial support for the conduct of the research, including study design as well as data collection, analysis and interpretation, and paid all costs associated with the manuscript development. L.H. and I.S. were employees of Novartis group companies and held stock ownership from the sponsoring company at the time of the study but are now employees of GlaxoSmithKline group companies. F.X. was a contractor associate at Novartis Vaccines and Diagnostics, Inc. but is now a contractor associate at GlaxoSmithKline LLC, United States. P.M.D. was a permanent employee of Novartis Vaccines and		LOW	
456	Andrews, 2014	e	reference for PCV13 not available	e	reference for PCV13 not available	d	reference for PCV13 study not available	d	reference for PCV13 study not available	b	some of the authors and institutions have received funding from industry		UNCLEAR: not enough data on source of immunogenicity results on PCV13	
734	Prymula, 2013	d	This is a follow-up to an earlier study that randomized children to PCV10 primary series vaccination or to a control group. However, children in the control group were not randomized.	c	This phase III, open-label, controlled study (NCT00950833) was conducted in 9 health centres	d	Not stated	b	According to Figure 2, only 62.5% of the total vaccinated cohort from the previous study that were eligible to participate in this study were included in the ATP immunogenicity cohort.	c	Some authors are affiliated with GSK and GSK sponsored and conducted parts of the study.			LOW
1581	Wysocki, 2015	f	While the study had 3 groups given different vaccine schedules, childrens' assignment into a group was based on their age, not randomization.	c	"This was a phase 3, open-label, multicenter study"	d	Not stated	a	According to Figure 1, 99.1% of the 355 enrolled children were included for analysis.	c	Some authors are affiliated with Pfizer, and Wyeth sponsored the study.			LOW
2816	Silfverdal, 2011	f	Of the 351 children vaccinated in the previous primary/ booster study, 110 (from 2 of the 4 countries in that study) were enrolled in the present follow-up study, that is, 51 in the PHiD-CV 2 1 and 59 in the PHiD-CV 3 1 group. A total of 62 unprimed, age-matched controls were also enrolled in this fol- low-up study. Figure 1 shows reasons for exclusion and the number of children included in the ATP immunogenicity cohort per group. The study groups in the ATP immunogenicity cohort were comparable with respect to demographic characteristics (Table 2); that is, age at the time of administration of the PHiD-CV dose ranged from 38 to 40 months across groups, gender distribu- tion (40%–52% girls across groups), and ethnicity (95%–100% white Caucasian or European heritage across groups).	c	This long-term follow-up (111736/NCT00792909) of a pre- vious primary/booster vaccination study12 had an open controlled design and included children from 2 Swedish and 5 Slovakian primary care centers in the period December 2008 to July 2009.	d	not stated	a	97% of children enrolled in study included in analysis	c	GSK involved in study conduct and design			LOW
1972	Odutola, 2014	a	"120 children… wre randomized (1:1) to receive…"	b	"In ths phase II, observer-blinded study"	d	ISPPD abstract does not state	c	120 children were randomized, but the tables presenting results are too blurry to make out. This abstract could not be found through an online search.	c	One author is affiliated with GSK, and GSK provided funding.			UNCLEAR: cannot evaluate completeness of data, limited info from abstract
2419	Dicko, 2015	f	Children were not truly randomized in this study- "The study population consisted of PHiD-CV unprimed Malian children previously enrolled in the control group of study NCT00678301 receiving a 2-dose catch-up vaccination with PHiD-CV in the second year of life."	c	"This phase III, open-label study"	d	Not stated	b	According to Figure 1, 75.6% of the 78 children in the cohort of unprimed subjects were included for analysis.	c	Some authors are affiliated with GSK and GSK sponsored and conducted parts of the study.	Small sample size n=59		LOW

PRIME: IPD Case Control Risk of Bias Tool

	Question	Answer Choice
1	Representativeness of cases	a) consecutive or obviously representative series of cases b) potential for selection biases or not stated c) Unclear d) Not stated/Full text not available (ie. Post or abstract)
2	Selection of Controls	a) community controls b) hospital controls c) test-negative controls (e.g. non-vaccine type cases) d) no description e) Unclear f) Not stated/Full text not available (ie. Post or abstract)
3	Definition of Controls	a) no history of disease (endpoint) b) no description of source c) Unclear d) Not stated/Full text not available (ie. Post or abstract)
4	Potential confounders measured and adjusted for in the analysis	Please list out factors that were controlled for in the analysis
5	Ascertainment of exposure	a) secure record (eg provider history; immunization registry) b) parent/guardian written record c) parent/guardian verbal record d) no description e) Unclear f) Not stated/Full text not available (ie. Post or abstract)
6	Same method of ascertainment for cases and controls?	a) yes b) no c) Unclear d) Not stated/Full text not available (ie. Post or abstract)
7	Other Risk of Bias	Please comment on other factors that may introduce bias

RefID		Reference (Country, Author, Year)	Q1rep_ans	Q1rep_Comments	Q2selcon_ans	Q2selcont_comments	Q3defcont_ans	Q3defcon_comments	Q4conf_ans	Q4conf_comments	Q5ascerexp_ans	Q5ascerexp_comments	Q6samemeth_ans	Q6samemeth_comments	Q7othbias_comments	PICO I & PICO II Assessment of Bias
3545		South Africa, von Gottberg, 2016	a	cases identified through national laboratory-based surveillance	b	matched hospital controls sought	d	one can infer that the controls are those with no history of the diseease, but it does not state it explicitly		This is a poster, so detailed information is not available. However, the tables state that models were adjusted for whether the patient had received 3 doses of dpt vaccine at 16 weeks and presence of crowding in the home for HIV-uninfected children. Models were also adjusted for receipt of antiretroviral treatment and presence of severe immunosuppression on CD4+ T cell count for HIV-infected children. Other models were adjusted for malnutrition and maternal education as well for HIV-uninfected children. Other models for HIV-infected children were adjusted for receipt of trimethoprim-sulfamethoxazole prophalaxis.	a	laboratory-based surveillance	a	matched hospital controls sought		HIGH
96		Quebec Canada, Deceuninck, 2015	b	Parents of children with laboratory-confirmed cases were contacted and invited to participate.	c	Table 1 illustrates that the controls did not have the IPD serotypes	a	Table 1 illustrates that the controls did not have the IPD serotypes		adjusted for age, year, season, and underlying medical condition (any indication for a 4th dose, including severe prematurity, or asthma)	a	laboratory-confirmed IPD cases	a	Telephone contact for voluntary participation until the number of necessry controls was reached		LOW
436		Brazil, Domingues, 2014	a		a	controls obtained from national birth registry	d	one can infer that the controls are those with no history of the diseease, but it does not state it explicitly		Some models adjusted for receipt of at least one dose of tetravalent diphtheria-tetanus-pertussis-Haemophilus influenza type B vaccine and any chronic illness.	a	laboratory-based surveillance	b	cases were identified from active laboratory-based surveillanceat participating hospitals and reference laboratories. Controls were identified from a national birth registry.		HIGH
456		UK, Andrews, 2014 **(indirect cohort study)**	c	"To assess vaccine effectiveness, we used all cases of invasive pneumococcal disease in the cohort eligible forPCV13 vaccination in England, Wales, and Northern Ireland identified up to Oct 31, 2013, through enhanced national surveillance by Public Health England"."	c	Indirect cohort study design- "... controls are individuals with invasive pneumococcal disease caused by the non-PCV13 serotypes"	a	Indirect cohort study design- "... controls are individuals with invasive pneumococcal disease caused by the non-PCV13 serotypes"		age, year of infection, clinical risk group/comorbidities, number & timing of doses	a	"We obtained vaccination history... from general practitioners through a postal questionnaire and telephone calls."	a	Indirect cohort study design- "... case-control design wherein the cases are individuals with vaccine-type invasive pneumococcal disease and controls are individuals with invasive pneumococcal disease caused by the non-PCV13 serotypes"		LOW
2199		Verani et al. 2015	a	cases were identified through laboratory-based surveillance in 10 states in Brazil from March 2010 to December 2012. Cases were defined as S. pneumoniae detected from a normally sterile site (e.g., blood or cerebrospinal fluid) in a child age-eligible to receive ≥1 PCV10 dose. Initially cases were identified by culture only; however starting in December 2010, some study sites detected cases using polymerase chain reac- tion (PCR). Pneumococcal isolates submitted to Brazil's national reference laboratory were serotyped using the Quellung reac- tion; cases detected by non-culture methods were serotyped by PCR	a	For each enrolled case, we aimed to enrol four age-matched and neighbourhood-matched controls. Potential controls were sought through the Information System for Live Births, a national birth registry (with >95% of all births registered)12 that also included all the cases. A list was generated of children born up to 1 month before or after the date of birth of the case and registered in the same neighbourhood in which the case resided at the time of illness.	c	because the choice of the controls using the national registry which also included those who could later on become cases, the definition of what they determined a control is unclear.		according to table 2 the following are the confounders adjusted for: Adjusted for date of admission/medical attention, age at illness, day care attendance and receipt of at least one diphtheria–tetanus–pertussis vaccine dose.	a	Vaccination histories were abstracted from case-patients' immunization cards	a	Cases and controls were enrolled in the study irrespective of whether vaccine records were available. The primary source of vaccination history data was the child's immunisation card, obtained from the parent or guardian. If these cards were not available, the vaccination history was sought at the immunisation post where the child was vaccinated.		LOW: It should be noted for this paper the methods were mentioned in another paper: here is the informaiton for that paper Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched case-control study. Lancet Respir Med 2014
2034		Auranen et al. 2014	d	not stated as this is an abstract	f	abstract thus the selection of controls not stated	d	abstract thus the definition of controls not stated	N/A	N/A	a	culture confirmed serotype specific ipd cases retrived from national infectious disease register	d	abstract thus the method of ascertainment for cases and controls		UNCLEAR
3624		Pakistan, Ali, 2016	d	poster, not stated	e	Controls are matched on age, catchment, and season, no mention of where they were recruited	d	poster, definition not stated		comparitive analysis is done yet, study is ongoing	f	not stated	d	poster, not stated		UNCLEAR
3646		Dominican Republic, Tomczyk, 2016	d	poster, not stated	e	controls are mathed on age and neaighborhood, no mention of where they were recruited	a	no history of disease in the prior month		weight-for-age z score and home built of wood	d	source of immunization status not provided	d	poster, not stated		UNCLEAR

	Guevara_2016.pdf	a	Cases of IPD were identified through the active labora- tory-based surveillance. IPD was defined as isolation, PCR or antigen detection of Streptococcus pneumoniae from a normally sterile body site.	a	eight controls were selected from children with no previous IPD, individually matched by paediatric practice, district of residence and date of birth (±2 months). Of all the children who met these eligibility criteria, the eight with dates of birth closest to that of the case were selected. Previous inclusion of a twin was an exclusion criterion. This study was done on a cohort of inhabitants of a region of Navarra	a	no previous IPD, individually matched by paediatric practice,	a	Cox regression adjusted for age as underlying time scale, sex and a variable that combines time periods and vaccination status in table 3. Conditional logistic regression adjusted for sex and parental income level in table 5	a	The Navarra Health Service provides healthcare, free at point of service, to 97% of the inhabitants of the region. Clinical records have been computerised since 2000 and include reports from primary care, hospital admissions, the regional vaccination register, and lab- oratory test results. Vaccination history was obtained from the regional vac- cination register [23], which includes all doses received by children, including those acquired in the private market.	a	"A case–control study, nested within the cohort" indicates that the underlying cohorts which is made up of the cases/ controls the information collection method is the same		LOW
	(IDC) Refid 17 Van der Linden et al 2016.pdf	a	The German National Reference Center for Streptococci (GNRCS) has conducted surveillance for IPD in Germany since 1992, using a laboratory-based approach. IPD cases were defined as Streptococcus pneumoniae isolates from blood, cerebrospinal fluid (CSF) or any other normally sterile body fluid. Microbiological diagnostic laboratories from all over Germany have been sending isolates of IPD cases to the GNRCS on a voluntary basis. In total, over 400 laboratories have participated, including large, nationally- operating commercial labs. Participating labora- tories are located in all German federal states, and the number of laboratories per federal state correlates to the different population densities of the states.	c	This study describes the effects of the introduction of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease among children and adults in Germany, focus- ing on the dynamics of serotype distributions in vaccinated and non-vaccinated age groups over a period of 22 years.	a	This study describes the effects of the introduction of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease among children and adults in Germany, focus- ing on the dynamics of serotype distributions in vaccinated and non-vaccinated age groups over a period of 22 years.	N/A	N/A	d	no description as to the method they got the vaccination history for the inidviduals just the following "Cases were grouped per pneumococcal season (from July to June of consecutive years) because of known infection clusters during winter. For the analysis of vaccination effects, we defined three time periods. The pre- vaccination period from 1997–2006 summarizes 9 pneumococcal seasons in which children were not vaccinated (for adults: 1992–2006, 14 seasons). The season 2006–2007 was considered a transition year in which pneumococcal conjugate vaccination was introduced, and was taken out of the analysis. The early vaccination period summarized the three seasons (2007–2008, 2008–2009 and 2009–2010) in which PCV7 was used, and the late vaccination period summarizes four seasons (2010–2011, 2011–2012,	d	not stated		UNCLEAR
1130	(ind_cohort)Miller-2011.pdf	a	Cases were categorised into those eligible to receive one or more priming doses of PCV13 at 2 or 4 months and aged between 2.5 and 13 months at time of infection and those eligible for the 13 month booster dose who had received doses of either PCV7 and /or PCV13 at 2 and 4 months and were aged between 13 and 23.9 months at time of infection. Only cases with serotype and known vaccination history were included in the analysis.	c	Also use of the indirect cohort method automatically controls for biases in ascertainment between cases (i.e. those with a vaccine serotype) and controls (i.e. those with a non- vaccine serotype) as the infect- ing serotype is unknown at the time of diagnostic investigation and subsequent reporting to our surveillance system	a	Also use of the indirect cohort method automatically controls for biases in ascertainment between cases (i.e. those with a vaccine serotype) and controls (i.e. those with a non-vaccine serotype) as the infect- ing serotype is unknown at the time of diagnostic investigation and subsequent reporting to our surveillance system	N/A	N/A	a	Vaccination histories were obtained for all cases by telephoning the General Practitioner and obtaining dates and batch numbers of any PCV7 or PCV13 doses given and, for vaccine- eligible children with no record of having received any PCV doses, requesting reasons for failure to vaccinate. Written confirmation of information provided by telephone was obtained.	a	Vaccination histories were obtained for all cases by telephoning the General Practitioner and obtaining dates and batch numbers of any PCV7 or PCV13 doses given and, for vaccine- eligible children with no record of having received any PCV doses, requesting reasons for failure to vaccinate. Written confirmation of information provided by telephone was obtained.		LOW
3360	(ind_cohort)Weinberger-2016.pdf	a	We used data from a nationwide surveillance program of IPD for children <16 years based on cases identified by the German pedi- atric surveillance unit (“Erhebungseinheit für seltene pädiatrische Erkrankungen [ESPED]”). Inclusion criteria were: IPD cases in chil- dren 2.5–56 months of age admitted to a German pediatric hospital from 01.01.2010 to 31.12.2014 with information on serotype and vaccination status available.	c	Among the cases with non PCV13 serotypes (control group, N = 115) uptake of at least one dose was 80%, of at least two doses was 74% and of three doses 60% by the age of 10 months. Among cases with serotypes included in PCV13, 38% had received at least one dose, 32% at least two doses and 30% three doses.	a	Among the cases with non PCV13 serotypes (control group, N = 115) uptake of at least one dose was 80%, of at least two doses was 74% and of three doses 60% by the age of 10 months. Among cases with serotypes included in PCV13, 38% had received at least one dose, 32% at least two doses and 30% three doses.		year of infection, age in months adjusted for year of infection (2010, 2011, 2012, 2013 and 2014) to account for potential herd effects and for age in months to account for age specific serotype variation in IPD risk.	a	We used data from a nationwide surveillance program of IPD for children <16 years based on cases identified by the German pedi- atric surveillance unit (“Erhebungseinheit für seltene pädiatrische Erkrankungen [ESPED]”). Inclusion criteria were: IPD cases in chil- dren 2.5–56 months of age admitted to a German pediatric hospital from 01.01.2010 to 31.12.2014 with information on serotype and vaccination status available. A child was considered as vaccinated 14 days after the first dose.	a	We used data from a nationwide surveillance program of IPD for children <16 years based on cases identified by the German pedi- atric surveillance unit (“Erhebungseinheit für seltene pädiatrische Erkrankungen [ESPED]”). Inclusion criteria were: IPD cases in chil- dren 2.5–56 months of age admitted to a German pediatric hospital from 01.01.2010 to 31.12.2014 with information on serotype and vaccination status available. A child was considered as vaccinated 14 days after the first dose.	RW and MI report no competing interests. ML has been a mem- ber of advisory boards for and has received speaker honoraria from Pfizer, GSK, Merck and SanofiPasteurMSD. Rvk was supported by a grant from Pfizer Pharma GmbH.	UNCLEAR

(IDC)Knol Netherlands EID 2015.pdf

PRIME: IPD Pre Post Risk of Bias Assessment Tool

	Question	Answers
1	Was the outcome measured consistently across the study period (e.g. surveillance methodology changes; was % all IPD cases serotyped consistent pre and post)	a. Yes b. No c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
2	Does the surveillance initiation predate the time period used as baseline (i.e. did the data collection start before the study baseline period?)	a. Yes b. No c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
3	Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre to post changes?	a. Yes b. No c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
4	Were the outcome measures of interest taken multiple times **before** the intervention? (ex. were multiple time points reported for the baseline period; was baseline averaged for more than one year?)	a. Yes b. No c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
5	Were the outcome measures of interest taken multiple times **after** the intervention (ex. were multiple time points reported for the post-intervention period; was post-intervention period averaged for more than one year?)	a. Yes b. No c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
6	Was industry (i.e., GSK or Pfizer) involved in this study?	a. Yes b. No c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
7	Other risk of bias	Comments

RefID	Reference (Country, Author,Year)	Q1consis_ans	Q1consis_comments	Q2base_ans	Q2base_comments	Q3prepost_ans	Q3prepost_comments	Q4before_ans	Q4before_comments	Q5after_ans	Q5after_comments	Q6industry_ans	Q6industry_comments	Q7othbias_comments	PICO I/ PICO II Overall Assessment
63	Finland, Jokinen, 2015	a	serotypes available on >96% of notified cases	a	surveillance system NIDR since 1995	a	95% Cis provided	a	2 reference cohorts, each spanning 3 years	a	1 target cohort spanning 3 years	a	National Institute for Health and Welfare received funding from GSK for FinIP trial	Participants in FinIP were excluded from the indirect effects group, reference cohorts did not overlap with FinIP trial years	Low
137	UK, Waight, 2015	b	50% missing serotype data in 2001/02 and only <10% missing serotype data after PCV13 intro. Also in 2010, reporting became mandatory, before then it was voluntary.	c	not stated in full text, but voluntary reporting system before 2010	a	95% Cis provided for PCV7-PCV13 comp	a	average of 7 years	b	1 year for PCV13 data, but 2 years for PCV7 data	b	Public Health England is funder	Authors attempted to correct for missing age and serotype data	High
262	Denmark, Harboe 2014	a	All IPD isolates routinely serotyped, national reference lab at SSI	a	Authors mention serotype specific data from 1993 onwards	a	IRR with 95% Cis provided	a	8 years pre-PCV data	a	3 years for PCV7 and 3 years for PCV13	b	study funded by SSI which does not produce PCVs	Authors modeled for cyclic variation in serotype prevalence	Low
3535	Netherlands, Knol, ISPPD10 2016	a	indirect population: sentinel surveillance covering 25% of population, direct population: national lab surveillance. All isolates were serotyped by the national reference lab	d	pediatric surveillance predates study by 1 year, not stated for adult sentinel surveillance	a	IRR with 95% Cis provided for serotype groups and 19A	a	2 years pre-PCV7 reported	a	2 years for PCV7 and PCV13 periods each, more years shown on graph	b	National Institute for Public Health and the Environment	Very low incidence of 6A and 6C disease, may not be powered to detect differences	Low
3636	Israel, Regev-Yochay, 2016	a	all labs performing blood cultures in country provided all isolates	d		b	IRR only given for overall IPD, not VT IPD	b	no pre-PCV7 data	a	2 years for PCV7 period and 4 years of PCV13	b	IAIPD Group	Capture-recapture method assured reporting of >95% cases	Low
3672	Finland, Nuorti, 2016	a	all clinical labs submit Spn isolates to THL for serotyping	a	NIDR in place since 1995	a	authors state that changes were significant but do not provide p-values or Cis	a	4 years pre-PCV	a	4 years of PCV10	b	THL and Univ of Tampere	Excluded years of FinIP trial and a transition year	Low
3677	Ireland, Corcoran, 2016	d	no information on the source of the isolates and completeness of reporting	b	surveillance commenced in April of 1st year	b	just IR reported	b	1 year of pre-PCV data	a	2 years of PCV7 and 5 years of PCV13	a	partly funded by Pfizer Ireland	unclear what % of all isolates this study represents	High
4454	Australia, Jayasinghe, 2017	c	% isolates serotypes not stated	b	"constant and consistent capture of isolates since 2002" the first year of study	a	IRR with 95% CI provided	a	3 years of pre-PCV data	a	5 years of PCV7 and 3 years of PCV13	b	NCIRS funded by govt dept of heatlh	Adjusted for missing serotype data	Low
127	Ben-Shimol(2015)	b	The proportion of isolates for which a serotype was determined increased from 40% to 70% in the period between July 2004 and June 2009 to >95% since July 2009 to December 2012. To evalute	a	surveillance initiated in 1989	a	IRR with 95% Cis provided	a	6 years pre-PCV7 data	a	2 year post PCV7, 1 year post PCV13	b	Israeli and Pediatric and Bacteremia and Meningitis Group		Low
326	Ben-Shimol et al. 2014	b. No	isolates for which a	a	from an ongoing	a	(IRR) and 95%	a	deviations are	b	information for	b	Bacteremia and		Low
428	Von Gottberg 2014	a	surveillance	a	surveillance for	a	rates and the	a	period 2005-2008	b	pneumococcal	c	reports receiving grant		Low

525	Steens 2013	a	observational-retrospective population study; routine collection of serotype specific data in MSIS started in 2006. For 2004, 2004, and 2006, serotype specific data was linked to notified data from MSIS retrospectively.	a	Surveillance started in Jan 2004 and PCV7 was introduced in July 2006	a	IRR with 05% Cis provided	a	2 years pre PCVC7 data	a	4 years for PCV7 data and 1 year post PCV13 data	b	Conducted by medical microbiological laboratoriesand clincians in Norway		
1536	Diawara et al. 2015	a	National lab surveillance	a	surveillance started in 2007 and PCV13 was introduced in 2010	a	absolute and relative risk reduction with 95% Cis	a	pre-PCV13 incidence averaged for 2007-2010	a	1 year post PCV13 before the transition to PCV10; 3 years post PCV10	a	This work was supported by an unrestricted, investigator initiated grant from Pfizer. The authors conceived the study and the study design was developed and agreed to by the authors without any input from the funding body.	incidence rate reductions in children of >2-5 years was no observed. The vaccination program was not fully implemented in all Moroccan children. In fact, in Oct 2010 only children less than or equal to 2 montsh were included in the vaccine program.	
3217	Porat et al. Vaccine 2016	a	and Sp6B was	a	started in July 1999	a	IRR with 95% Cis	a	for 1999-2007	a	and 3 years post	a	supported by a grant		
160	Lepoutre 2015	a	since 2001, pneumococcal strains isolated from CSF (meningitis) and from blood in children (0–15 years of age) are collected from hospital-laboratories and sent to the NRCP by 22 regional laborato- ries organized into a pneumococcal surveillance regional scheme (Observatoires Régionaux des Pneumocoques). In addition a system- atic 1/6 sample of pneumococcal isolates isolated from blood in adults (>15 years) are collected and sent to the NRCP by the	b	Three periods were defined according to the dates of the intro- duction of PCV7 and PCV13 in the French immunization schedule: pre PCV7 period (2001–2002), late PCV7 period (2008–2009) cor- responding to the last years of PCV7 exclusive use in France, and post PCV13 period (2012), two years after PCV13 introduction.	a	Incidence rate ratios (IRR) were computed for all types-, and spe- cific serotypes-groups IPD between periods, confidence intervals for incidence rate ratios were computed using the “cohort study risk calculator” command of Stata 12.1. Incidence rates were compared between the periods by Fisher exact test. The significance level was set at 0.05. Percent change in the incidence of IPD between periods was computed as (IRR-1) ×100. The analysis was done with STATA 12.1 (StataCorp®).	c	initially they do not mention that the IR are mean values, however in table 1 they mention that they have listed the mean number of cases/year for pre-pcv period and this is where they could have calculated the IR values from	c	since there is the same situaiton in Post PCV7 period, it is unclear as to whether it is mean numbers	a	A. Lepoutre declares no potential conflicts of interest, E. Varon received fees from Pfizer and GlaxoSmithKline for participation in working groups on pneumococcal vaccines, S. Georges, F. Dorléans, C. Janoir, L. Gutmann and D. Lévy-Bruhl declare no potential con- flicts of interest.		Low

137	Waight-2015.pdf	a	Public Health England manages the largest national invasive pneumococcal disease dataset in the world, with around 5000 annual reports of invasive pneumococcal disease from England and Wales, of which more than 90% are serotyped. Using this national dataset, we assessed the effect of the PCV13 programme on the serotype-specific incidence of invasive pneumococcal disease in vaccinated cohorts and older unvaccinated age	b	We calculated incidence rate ratio (IRR) for invasive pneumococcal disease by comparing incidence in the epidemiological year 2013/14 with the average incidence in the 2 years preceding PCV13 introduction (July, 2008, to June, 2010) and the average of the pre-PCV7 baseline years (July, 2000, to June, 2006) using Poisson regression.	a	We calculated incidence rate ratio (IRR) for invasive pneumococcal disease by comparing incidence in the epidemiological year 2013/14 with the average incidence in the 2 years preceding PCV13 introduction (July, 2008, to June, 2010) and the average of the pre-PCV7 baseline years (July, 2000, to June, 2006) using Poisson regression.Significance (for testing the null hypothesis of IRR=1) was set at 5% for serotype-grouped analyses and at 1% for serotype-specific analyses.	a	average incidence in the 2 years preceding PCV13 introduction (July, 2008, to June, 2010) and the average of the pre-PCV7 baseline years (July, 2000, to June, 2006) using Poisson regression	b	none, because they did the IRR for 1 year	b	Public Health England funds national surveillance of invasive pneumococcal disease.		
1829	1829_Jokinen_2012.pdf	d	abstract, not stated how the measured the outcome	d	abstract, thus it states that this information was from the National Infections Disease Registry from finland however never specific when this registry was started	d	its an abstract, only had incidence rates from pre post periods with out having p values or CIs stated might be a part of the full text	d	abstract not stated about baseline	d	abstract, not stated about this	d			
1908	1908_Scott_2012.pdf	d	abstract, specifically did not stated how the measured the outcome	d	abstract	a	althrough its an abstract reported on 1 IRR with CI	d	abstract not stated about baseline	d	abstract	b	Funding from Wellcome Trust, Gavi Alliance		
299	Denmark, Slotved 2014	b	culture techniques changed over the 60 years of surveillance; more recently only after 2007 has it been "mandatory for diagnositc laboratories to submit all isolates causing IPD to SSI for serotype identification"	a	Danish national lab surveillance since 1943	b	Cis given for a range of annual VT incidence rates; the range is wide and not specific to certain data points; Cis given for total IPD incidence	a	yearly incidence since 1943	a	3 years post PCV13	b	Funded by SSI	Low number of cases in neonates so Cis are very wide	Low: methods sound, mandatory reporting coincides with intro of PCV7, wide Cis so findings are not statistically sig
2177	Sweden, Galanis 2016	a	93% of all reported IPD cases were serotyped, not mentioned if this proportion changed over the period of study	c	not stated in full text	a	95% Ci for IRR	a	3 years of pre-PCV data	a	2 years of PCV7 and 4 years of PCV13	b	No mention of industry in text		Low
2197	Denmark, Slotved 2016	a	mandatory reporting to Danish reference laboratory initiated in 2007, but estimated 90-95% coverage of all IPD isolates in	a	another paper states NSR data goes back to 1943	a	95% CI for incidence and IRR provided	a	8 years pre-PCV data	a	multiples years of PCV7 and PCV13 data	b	Funded by SSI		Low

3501	UK, Collins 2016	b	authors adjusted for proportion serotyped and in the pre-PCV period for improvements in surveillance. Public Health England surveillance system, % serotyped increased over time from 49% to 93%	a	authors refer to extracting data for the study period	b	% change reported but no p-values given	a	5 years of pre-PCV data	a	2 years of PCV7 and 4 years of PCV13	b	No mention of industry in poster		Low
3835	The Gambia, Mackenzie, 2016	a	99% of IPD cases identified have serotyping results. Serotyping repeated on 10% of samples in South Africa	b	surveillance began 12may2008, annual incidence reported for 2008 was extrapolated back to 1jan2008. using 2009 data. However, IRRs reporte only use the actual data from 12may2008 as the baseline comparison	a	p value set at 0.05, 95% CI for IRR reported with overdispersed poisson distribution taken into account for two age groups	a	prePCV baseline 2 years (May 12, 2008–May 11, 2010)	a	last 2 years post PCV13 (2013-2014)	b	Funded by Gavi, BMGF, UK MRC	authors extrapolated counts from 5 months before surveillance started and for a period of 1 month when flooding halted surveillance (2010). This only impacts the annual incidence estimates, these two extrapolated time pionts were not used in the pre/post	Low
2031	Iceland, Haraldsson, 2014	d	abstract, not stated. Surveillance part of Landspitali University Hospital	c	unclear if surveillance was already in place	c	p values provided, exact statistical methods are not described	a	prePCV annual average from 2008-2010	a	Post PCV was annual average from 2011-2013	d	not stated		
2132	2132_Nzenze_2014.pdf	d. Not stated/Full text not available (ie. Poster or abstract)	abstract, not stated how the measured the outcome	d	abstract thus unclear if the surviellence period predates the study periods	a	IRR stated with 95% CI	a	average of 2005-2008 (or pre vaccination period)	b	post pcv period was 2012	b	no conflict of interest stated		
2183	Knol-2015.pdf	a	We used data from a stable surveillance system with constant coverage over time; age and serotype data were nearly complete (99.9%).	b	study period is from 2004 to 2014, with the baseline starting at 2004	a	Incidence rate ratios (IRRs) with 95% CIs and p values were calculated. Dif- ferences between IRRs were tested by calculating p values for interaction between birth cohort and serotype; the IRR for serotypes not related to PCV10 was used as reference.	b	not averaged, a cumulative number	b	not averaged, a cumulative number	b	no conflict of interest stated		
247	247_Gabarrot_2014.pdf	a	As our laboratory is the National Public Health Reference Center for S. pneumoniae surveillance, we regularly receive isolates with enclosed relevant patient information. Our routine protocol assigns a laboratory number to identify each isolate. After that the patient records/information is anonymized and de- identified prior to analysis	a	Laboratory-based surveillance of IPD started in 1987 [12] and became nationwide in 1994, when a regional pneumococcal network called SIREVA, was organized. While the study period starts in 2003	a	Changes in incidence rates (IR) were presented as incidence rate ratio with 95% confidence intervals (CI) and percent changes. Proportions of pneumococcal isolates by clinical diagnosis were tested with Chi-square test or Fisher exact test, as required. A p,0.05 was considered to be significant	b	not averaged, a cumulative number	b	not averaged, a cumulative number	b	no conflict of interest stated		
3674	Israel, Regev-Yochay, 2016	a	all 27 labs part of nationwide active surveillance, all isolates were serotyped in central laboratory	b	surveillance began in 2009 with PCV7 intro	a	CI bars shown on annual incidence graph	b	first year of surveillance was 1st year of PCV7 use	a	1 year of PCV7 and 4 years of PCV13 use	b	No mention of industry in poster		Low

3546	South Africa, von Gottberg, 2016	d	no information describing surveillance system in poster	d	not stated in poster	a	95% Cis provided for change pre-post	a	4 years pre-PCV	a	4 years of post PCV13	b	No mention of industry in poster		Unclear: not enough info in poster to assess surveillance system
3773	Denmark, Slotved, 2016	b	mandatory reporting to Danish reference laboratory initiated in 2007, but estimated 90-95% coverage of all IPD isolates in	a	national surveillance system in place since the 1930's	a	95% CI for IRR reported	a	data from 1999	a	5.5 years post PCV13	b	No mention of industry support	2016 data was based on a projection extending from the first 6 months of the year	Low
4034	Canada, Waye, 2015	a	population-based surveillance since 2000 with IPD being a notifiable disease, all isolates are forward to the public health lab	b	surveillance system since 2000, 1st year of data reported in study	b	no Cis provided for incidence rates	a	2 years of pre-PCV data	a	3 years of post PCV13	b	no mention of industry in paper		Low: but no CI's for estimates
4285	Canada, Desai, 2016	c	IPD a notifiable disease, all isolates serotyped in central labs. 73% of cases had serotypes documented, but not sure if this proportion varied between early and later years.	b	routine reporting began in 2007 the 1st year of the study	a	p values reported for pre-post trends	b	PCV7 introduced in 2005 but routine reporting did not start until 2007	a	4 years of PCV13 data	a	1 author received research grant from Pfizer		High: 73% of cases with serotype information, not sure if this varied over time
	UK, Kandasamy, 2017 (unpublished)	d	surveillance system is Public Health England, no description provided in manuscript	d	not stated in text	a	95% CI's for IRR provided	b	study is only in PCV13 era	b	1.5 years of late PCV13 period data	b	no mention of industry support	NPC surveys from Thames valley region, but IPD incidence from national data so there may be some regional variation in carriage that could skew the case:carrier ratios	High: 1 year of early PCV13 data compared to 1 year of late PCV13 data so there may be secular trends that are impacting the changes
345	Chang-2014.pdf	d. Not stated/Full text not available (ie. Poster or abstract)	abstract, not stated how the measured the outcome	d	abstract	d	abstract	d	abstract not stated about baseline	d	abstract, not stated about this	d	no mention of industry, however this is the abstract and need the full text to make sure		
3504	ISPPD-22.pdf	d. Not stated/Full text not available (ie. Poster or abstract)	poster and the full text is not provided, only states that this comes from state based morbidity data and commonwealth data	d	not fully articulated when the data source began	a	IPD notification rates (in person-years) by vaccination status were compared using Cox proportional hazards models (with age as the time scale) adjusting for the following factors if they remained significant (p<0.05 or >10% change in log hazard ratio) in the multivariate model: Child: season & year of birth, sex, birthweight, gestational age, APGAR score, delivery mode , state (NSW or WA), hospitalisation <6 weeks of age or code associated with high IPD risk. Mother: remoteness & socioeconomic	d	poster not fully stated	d	poster, not stated about this	b	This work was funded by The Population Health Research Network and NHMRC. HG, HM and CB are funded by NHMRC Postdoctoral Research Fellowships. We thank the data linkage units, data custodians, Department Human Services, and the study reference groups (Aboriginal Immunisation Reference Group & Infectious Diseases Community Reference Group) for their support and advice.		

3515	ISPPD-100.pdf	d. Not stated/Full text not available (ie. Poster or abstract)	poster, only know that the outcome diagnosised is based on Clinical-radiological criteria (WHO) and Blood and pleural effusion culture (standard techniques).	d	poster and not fully stated if data collection predates study period	d	poster not fully stated	d	poster not fully stated	d	poster, not stated about this	d	poster not stated about funding sources or potential sources of conflicts		
3555	UK, Collins 2016_ISPPD	c	poster, limited discussion of methods	c	poster, surveillance system start not stated	b	p-values are not reported for the calculated % reduction	a	prePCV from 2000/2001 - 2005/2006	a	post PCV 7 period is 2 years (08/09-09/10)	d	poster, funding source not listed		
3562	Argentina, Papucci, 2016	d	poster, details of surveillance not reported	d	poster, not stated	a	p-value from fisher exact two-tailed test and confidence intervals	a	prePCV - 4 years averaged	a	post PCV is 3 years averaged	d	poster, no funding information		
458	Uruguay, Pirez, 2014	a	standarized government case definitions	a	data is from hospital records	a	p-value from fisher exact or chi square	a	prePCV (2003-2007)	a	post PCV (2009-2012)	c	study funding not listed, but several authors report recieing fund from industry as a conflict of interest		
508	UK, Moore, 2014	a	two hospitals were added partway through the study	a	this surveillance network began in 1996	a	p-values and confidence intervals	a	10 years of pre-pcv	a	3 years of post PCV13	a	Pfizer funds the surveillance network used		
3954	The Gambia, Levy, 2016													Paper is a commentary, no data presented	
888	888_De Wals_2012.pdf (post_inc)	a	IPD is in the list of notifiable diseases in Quebec and all microbiology laboratories are invited to transmit isolates from children <5 years to the provincial reference laboratory. Compli- ance is high (86% in 2006) as measured in a record linkage study [1]. Serotype identification was performed using the traditional capsular swelling method (Quellung reaction) and, for selected serogroups, by a monoclonal antibody technique. Polymerase chain reaction (PCR)	b	This is a population-based ecological study of children born in 2007–2010 in the province of Quebec, Canada, and followed up to December 31, 2010.	a	IPD rates in different cohorts were compared by two statistical methods using SAS 9.2 software (SAS Institute, Cary, NC). Firstly, a ?2 test was performed using the number of IPD cases and the number of persons at risk in each cohort. Secondly, Poisson regres- sion models were used to compute rate ratios, adjusting for age (in months), and the number of doses received (0, 1, 2, 3, not taking into account 3rd doses received before age 12 months). The vaccine coverage of each dose at a given	b	they did not take the average of the rates rather they provided rate numbers	b	did not take the average, provided rates	b	The study was supported by a research grant from the 'Ministère de la santé et des Services sociaux du Québec'. The funder had no role in the design and conduct of the study; collection, manage- ment, analysis and interpretation of data; and preparation of the manuscript.		

	Rinta Kokko et al ISPPD 2016 Abstract 200.pdf	a	National Infectious Disease Register data were used for calculating culture-confirmed serotype-specific IPD rates in the study cohorts. A population-based laboratory surveillance system in place since 1995, All clinical microbiology laboratories submit pneumococcal isolates to THL reference laboratories for serotyping and susceptibility testing: currently, over 97% of the case isolates are received. Case Definition: S. pneumoniae	a	A population-based laboratory surveillance system in place since 1995 and the study period is children born 06/2010-09/2015, age range 3 to 66 months	c	unclear because have relative rate reduction with 95%	b	they did not take the average of the rates rather they provided rate numbers	b	did not take the average, provided rates	d	not stated as this was a poster		Unclear

PRIME: NP Carriage Randomized Controlled Trial Risk of Bias Tool

1	Is the study randomized?	a. Yes b. Control group but not randomized c. No control arm/group d. Unclear e. Not stated/Full text not available (ie. Poster or abstract) f. Not applicable
2	Blinding of participants and personnel	a. Double-blind b. Single-blind (either participants or study personnel) c. Open label d. Unclear e. Not stated/Full text not available (ie. Poster or abstract)
3	Blinding of outcome assessment (e.g., specimens were tested without knowledge of pre/post PCV status or study arm)	a. Yes b. No (.e., not blinded or no control arm for the relevant outcome of interest) c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
4	Incomplete outcome data (e.g., the percent of those randomized to those analyzed)	a. 90% or more of those randomized were included in the analysis of the relevant outcome of interest b. Fewer than 90% were analyzed c. Unclear d. Not stated/Full text not available (ie. Poster or abstract)
5	Was industry (i.e., GSK or Pfizer) involved in this study?	a. No b. Yes, funded all or in part by Industry but for the relevant outcome was conducted entirely by independent investigators (e.g., no co-authors from industry; lab work not performed by Industry) c. Yes, evaluation of the relevant outcome was conducted all or in part by industry (e.g., analyses or lab work performed by Industry) d. Unclear e. Not stated/Full text not available (ie. Poster or abstract)
6	Other Risk of Bias	Please comment on other factors that may introduce bias

RefID	Reference (Author,Yea	Link	Q1rand	Q1rand_comments	Q2bli	Q2blindpart_comments	Q3bl	Q3blindout_comments	Q4in	Q4incomp_comments	Q5ind	Q5industry_comments	Q6othbias_comments	PICO I: Schedule	PICO II: Product	PICO III: Catch-up
108	Hamaluba, 2015		a	"Study staff allocated participants with a participant number and randomly assigned (4:4:5 ratio) them to receive PCV10 at either age 6 and 14 weeks with a 9-month booster (2+1 group); age 6, 10, and 14 weeks (3+0 group); or no vaccine until age 10 and 11 months (0+2 group)."	c	From abstract: " We did an open-label, randomised, parallel group, controlled trial ..."	a	labeled by ID which was not linked to study arm.	b	According to Figure, only 205/239 were sampled at 10 months (86%). But same in both groups and just 1-4 lost per visit so no likely bias.	b	"This study was supported by funding from... and GlaxoSmithKline Biologicals, Belgium" but NP specimens were tested by the Bacterial Microarray Group, St George's Hospital, University of London		LOW: no evidence of and low opportunity for bias	LOW: no evidence of and low opportunity for bias	
3656	Temple; Smith-Vaugha	3621 4	e	This study is a poster abstract that did not specify anything regarding randomization	d	This study is a poster abstract that did not specify anything regarding blinding.	d	This study is a poster abstract that did not specify anything regarding blinding.	d	This study is a poster abstract that did not specify anything regarding the percent of participants randomized vs. analyzed.	a	GSK provided the vaccines used in this study.	Says "see Poster ISPPD-0449 for details of the Vietnam Pneumococcal Project". Is this 3621_Smith-Vaughan_ISPPD-406? (If so, no more info on rand, blinding; nor in Kim's ppt). MDC: yes this is refering to Smith Vaughan and Mullholtands trial. I went into the ISPPD folder and the 449 Post is from south africa, i think any data we will find will be in these three posters	LOW: no evidence of and low opportunity for bias	LOW:no evidence of and low opportunity for bias	
777	Van Den Bergh, 2013		a	"Infants were randomly assigned (1:1:1)... resulting in a 2:1 ratio for immunization with either PHiD-CV or 7vCRM. A randomization list used to number the vaccines was generated using a standard SAS... Each participant was assigned to a group via a web-based central randomization system that determined the vaccine number to be used."	b	"Parents and study site staff were aware of the treatment assignment, but outcome assessors were not."	a	"Parents and study site staff were aware of the treatment assignment, but outcome assessors were not."	a	According to Figure 1, n=769 were sampled at the 24 month visit (98% of the original n=780 randomized).	b, c	"This study was sponsored by GlaxoSmithKline Biologicals SA. The sponsor was involved in all stages of this study, including the final analysis." GSK did not draft the manuscript but reviewed it. NP Swabs were tested at Regional Laboratory of Public Health (Haarlem, the Netherlands)		LOW: no evidence of and low opportunity for bias	LOW: no evidence of and low opportunity for bias	
3534	Jokinen 2016		a	randomized cluster trial to assess IPD but NPS was sampled in 1550 3-5 years after randomization - unclear how sampled.	a	double-blind	a	NP specimens were collected 3-5 years after vax in FinIP trial, no mention of unblinding - possibly this is part of trial follow-up (i.e., ongoing).	b	1550 were sampled for NPS 3-5y post-vacc but FinIP trial had over 47,000 children enrolled, so this assesment is in a small percentage. Not clear how sampled.	b	funded by GSK but unclear where NPC testing done. No authors are from industry.	Intro of PCV10 into NIP started right after enrollment ended and NPS collected 3-5yrs later so 3 yrs of indirect effects impact the control carriage.	LOW: Likely some indirect effects lowering carriage in control (and vacc) group so efficacy likely underestimated. But %VT carriage still relatively high in this age group so probably not a large effect (no catch-up).	LOW: Likely some indirect effects lowering carriage in control (and vacc) group so efficacy likely underestimated. But %VT carriage still relatively high in this age group so probably not a large effect (no catch-up).	
3363	Vesikari, 2016		a	"Clusters were randomized.... using a blocking scheme... For nested study participants, individual randomization codes were used." but "because of a randomization error,[16% of] infants did not receive the treatment assigned to their cluster. These mis-randomized infants were reallocated to the groups corresponding to the vaccination they actually received"	a	Abstract states study was double-blind	a	Authors did not specify in either the full-text or the supplemental document. However, the study was double-blinded	a	According to Figure 1, 92.1% and 90.0% of the enrolled children completed the carriage study in the infant cohort and catch-up cohort, respectively. However, there was a randomization error in 16% in they were analyzed in the group corresponding to the vaccination they actually received.	b, c	9 of 13 author affiliations are GSK. GSK was also listed as the funding source and "was involved in all stages of the study conduct and analysis." But NPS were tested at National Institute for Health and Welfare in Oulu,Finland.		LOW: There was a randomization error in 16% and the study was conducted by industry. But was double blind and NPS were tested at National Institute for Health lab.	LOW: There was a randomization error in 16% and the study was conducted by industry. But was double blind and NPS were tested at National Institute for Health lab.	LOW: There was a randomization error in 16% and the study was conducted by industry. But was double blind and NPS were tested at National Institute for Health lab.
1287	Prymula,,R		b	age-matched controls were recruited at time of swab	c	age-matched controls were recruited at time of swab	d	not stated; tested at a central microbiological laboratory in Hradec Kralove, Czech Republic within 8 hrs of sampling. Isolates under-went further testing for identification of serotypes at the NationalReference Laboratory of the National Institute of Public Health inPrague.	a	Although paper states controls were age-matched, there were 19% fewer controls than vaccinees assessed for NPC. But of those enrolled, compliance was >90%.	b, c	GSK Biologicals was the fundingsource and was involved in all stages of the study conduct andanalysis as well as the development of the manuscript and itsapproval for submission. GSK Biologicals also took in charge allcosts associated to the development and the publishing of thepresent manuscript. N365 of 11 authors are GSK		UNCLEAR: No pre-vaccination data to show that PCV and control groups were comparable (i.e., had similar carriage pre-vac). No other data to show comparability of controls to PCV group (e.g., age, sex, exposure risk, etc.).	UNCLEAR: No pre-vaccination data to show that PCV and control groups were comparable (i.e., had similar carriage pre-vac). No other data to show comparability of controls to PCV group (e.g., age, sex, exposure risk, etc.).	
1751	D. Borys, 2012		a	children were randomized	a	double-blind	a	double-blind and assessed during trial so assume yes	d	not stated	c	Part of COMPAS trial which was conducted by GSK (they co-authored the main paper)	no pre-vax data or other data to show comparability between sampled groups. NVT carriage was similar between groups, which is expected to be higher in the PCV-vaccinated group.	LOW: part of large double-blind rand trial that led to licensure for PCV10 against pneumonia so likely high quality trial despite limited info in abstract.	LOW: part of large double-blind rand trial that led to licensure for PCV10 against pneumonia so likely high quality trial despite limited info in abstract.	
2961	Prymula, 2011		a	This is a follow-up study of two randomized stu	e	This study is a poster abstract	d	This study is a poster abstract and did	d	This study is a poster abstract and	e	This study is a poster abstract and specified that no authors were affiliated with industry. However, no information on funding or conflicts of interest is provided.		EXCLUDE: this is a 3+1 evaluation and should be deleted	EXCLUDE: this is a 3+1 evaluation and should be deleted	
3649	Orami; Pomat 2016	3675	a	randomized to PCV10 (Synflorix) or PCV13"	e	This study is a poster abstract	d	This study is a poster abstract and did	b	80% were assessed 1 month post	a	No authors are affiliated with industry, and no mention is given of industry funding or conducting any portion of the analysis.			LOW: not affiliated with industry. PCV10 directly compared to PCV13 in head-to-head randomized trial. Losses to follow-up similar in both groups.	
	Verhagen		b	controls were older siblings and adults so not comparable to the vaccinated children, but there was pre-post immunization NPC in the vaccinated children for assessing effects	c	no comparable control group	c	unclear if pre-post specimen status was known to the lab	a	results were presented for all enrolled	b	This work was supported by Pfizer Venezuela. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.	Conducted in a high-risk population of indigenous people living in remote settings so not representative of national population but may reflect many developing country settings.			low: measured direct impact pre to post PCV on NPC; however, the change in NPC the time period (6wks) post-PCV is too short to measure impact on new acquisition.