Draft report

Haemophilus influenzae type b conjugate vaccines: a systematic review of schedule related RCTs

(Subject to change)

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1.1 Objectives

The objectives of the systematic review were to collect evidence on *Haemophilus influenzae* type b (Hib) conjugate vaccine schedules, to summarize the available data and to identify gaps in evidence that might shape future research in this area.

1.2 Review methods

A search was conducted in 21 electronic databases of published articles, trial registers, industry databases and other documents from the earliest citation until May 2010. The search was updated in June 2012.

Randomized controlled trials and quasi-randomized controlled trials (e.g. those with allocation strategies based on alternation, date of birth or case record number) were eligible for inclusion. Primary courses of Hib conjugate vaccine given to children up to 5.99 months of age or booster doses given between 6.00 months and 1.99 years of age were eligible. Additionally, studies where "catch-up campaign" doses (doses given to unvaccinated children after the recommended age for a primary vaccination) are given were also eligible for inclusion.

Hib conjugate vaccines of the following types were eligible for inclusion:

- PRP-HbOC (diphtheria CRM $_{197}$ protein conjugate)
- PRP-OMP (outer membrane protein (*Neisseria meningitidis*) conjugate)
- PRP-T (tetanus toxoid conjugate)

The following outcomes were eligible for inclusion:

Clinical efficacy

i) Invasive Hib disease (bacteremia/septicemia, meningitis etc)

ii) All-cause pneumonia (radiologically confirmed pneumonia where possible)

iii) Definitive Hib pneumonia (radiologically confirmed pneumonia and positive blood, lung tissue or empyema fluid culture for Hib)

iv) Death

Each clinical outcome had to be collected as a specific clinical outcome within the trial in order to be eligible for inclusion. Clinical outcomes other than mortality that are collected as adverse events and serious adverse events were not eligible for inclusion.

Nasopharyngeal carriage

a. percentage carriage of *Haemophilus influenzae* type b (Hib) before and after vaccination

Immunogenicity (ELISA or Farr-type immune-radioassay)

a. seropositivity after vaccination (e.g. PRP antibody concentration of > 0.15 μg/ml, or > 1.0 μg/ml)
b. geometric mean concentration (or titer)

Comparisons between groups receiving different schedules of Hib conjugate vaccine were eligible for analyses of clinical, carriage and immunological data and comparisons between groups receiving and not receiving Hib conjugate vaccine were additionally eligible for analyses of clinical and carriage data

Structured piloted forms were used to extract data on: the schedule; clinical disease outcomes (invasive Hib disease, pneumonia); mortality; nasopharyngeal carriage of Hib; seropositivity (%); geometric mean concentrations (GMC); study characteristics; and potential sources of bias and heterogeneity.

Where appropriate, random effects meta-analyses were used to combine results statistically. Between-trial heterogeneity was described using the I^2 statistic, where values below 25% represent low heterogeneity, up to 50% moderate heterogeneity, up to 75% severe heterogeneity and more than 75%, very severe heterogeneity.

Vaccine schedules are described using the following abbreviated style:

3p 3 doses in the primary (p) vaccination schedule with all doses given before 12 months of age;
+1 a booster dose.

All doses are Hib conjugate vaccine unless otherwise noted. Protective effects of Hib conjugate vaccine against clinical disease are reported as vaccine efficacy (VE).

1.3 Results

A total of 4337 items were identified in searches. Of these, 98 items comprising 39 RCTs were eligible for this review.

Nineteen different types of schedule comparison were examined among these RCTs, including those which compared a Hib conjugate vaccine schedule to no Hib vaccine.

1.3.1 Hib conjugate vaccine schedule–schedule comparisons

1.3.1.1 2p vs 1p schedules

There were no RCTs that directly compared these schedules and reported invasive disease, pneumonia or carriage data. Clinical data from trials comparing 2p to no Hib vaccine and 1p to no Hib vaccine are presented in figures 32-35. Carriage data from a single trial comparing 2p to no Hib vaccine and 1p to no Hib vaccine are presented in figure 36.

Seropositivity results are presented in figure 1, stratified by conjugate type.

1.3.1.2 3p vs 1p schedules

There were no RCTs that directly compared these schedules and reported invasive disease, pneumonia, carriage or immunological data. Clinical data from trials comparing 3p to no Hib vaccine and 1p to no Hib vaccine are presented in figures 32-35. Carriage data from a single trial comparing 3p to no Hib vaccine and 1p to no Hib vaccine are presented in figure 36.

1.3.1.3 3p vs 2p schedules

There were no RCTs that directly compared these schedules and reported invasive disease, pneumonia or carriage data. Clinical data from trials comparing 3p to no Hib vaccine and 2p to no Hib vaccine are presented in figures 32-35. Carriage data from a single trial comparing 3p to no Hib vaccine and 2p to no Hib vaccine are presented in figure 36.

Seropositivity results are presented in figures 2-5, stratified by conjugate type.

1.3.1.4 2p+1 vs 2p schedules

There were no RCTs that compared these schedules and reported invasive disease, pneumonia, carriage or immunological data.

1.3.1.5 3p vs 2p+1 schedules

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

Seropositivity results are presented in figures 6-9, stratified by conjugate type.

1.3.1.6 3p+1 vs 2p+1 schedules

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

Seropositivity results are presented in figures 10-13, stratified by conjugate type.

1.3.1.7 3p+1 vs 3p schedules

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

Seropositivity results are presented in figures 14-15, stratified by conjugate type.

1.3.1.8 Late vs early start schedules

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

Seropositivity results are presented in figures 16-21, stratified by conjugate type.

1.3.1.9 2-month vs 1-month interval schedules

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

Seropositivity results are presented in figures 22-27, stratified by conjugate type.

1.3.1.10 4-month vs 1-month interval schedules

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

Seropositivity results are presented in figures 28-29, stratified by conjugate type.

1.3.1.11 Long vs short interval between primary and booster schedules

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

Seropositivity results are presented in figures 30-31, stratified by conjugate type.

1.3.2 Comparisons of Hib conjugate vaccine schedule vs no Hib conjugate vaccine

Clinical results for all comparisons are presented in figures 32-35. Both intention-to-treat and per-protocol analyses are presented. For the purposes of this report, intention-to-treat refers to analyses where no randomized individuals are excluded from the analysis, and per-protocol to those where some individuals are excluded. Cluster-randomized trials are analyzed separately from individually randomized trials as the former measure direct- and indirect-effects of vaccination and the latter direct-effects. For completeness, the results of meta-analyses including both cluster- and individually-randomized trials are reported in the text, but not in figures.

Invasive Hib disease, intention-to-treat analyses

Results of this analysis are presented in figure 32. The analysis is stratified by schedule comparison and by randomization type (individual or cluster). Additionally, in an analysis where the four trials reporting invasive Hib disease for 3p schedules (Gambia4, USA2, USA3- individually randomized; Chile3 - cluster randomized) were analyzed together, the combined estimate was VE 83% (95%CI 72, 89) with low between trial heterogeneity (I^2 0.0%).

Invasive Hib disease, per-protocol analyses

Results of this analysis are presented in figure 33. The analysis is stratified by schedule comparison and by randomization type (individual or cluster). Additionally, in an analysis where the two trials reporting invasive Hib disease for 3p schedules (Gambia4 - individually randomized; Chile3 - cluster randomized) were analyzed together, the combined estimate was VE 93% (95%CI 78, 98) with low between trial heterogeneity (I^2 0.0%).

Pneumonia, intention-to-treat analyses

Results of this analysis are presented in figure 34. The analysis is stratified by schedule comparison, by randomization type (individual or cluster) and by diagnostic method (clinical or radiological). Additionally, in an analysis where the two trials reporting clinical pneumonia for 3p schedules (Gambia4 - individually randomized; Indonesia2 -cluster randomized) were analyzed together, the combined estimate was VE 4% (95%CI 1, 7) with low between trial heterogeneity (I^2 0.0%).

Pneumonia, per-protocol analyses

Results of this analysis are presented in figure 35. The analysis is stratified by schedule comparison, by randomization type (individual or cluster) and by diagnostic method (clinical, radiological or by percutaneous lung aspirate).

Carriage

Results from a single trial reporting this outcome are presented in figure 36. The analysis is stratified by schedule comparison.

1.4 Discussion

1.4.1 Strengths and limitations

To be added

1.4.2 Main findings and interpretation

To be added

1.4.3 Implications for future research

To be added

1.5 Conclusions

To be added

Tables

Figures

Tables

Table 1: Summary of included studies

Study name	Conjugate vaccine	Schedules, age at administration in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual, mean (SD)			
Belgium1 [1]	PRP-T	3, 4, 5 +b14	13.4 (0.6)		85	Seropositivity
		14	13.5 (0.6)	Placebo[1]	83	GMC
			Primary: NR			
Belgium2 [2]	PRP-T	3, 4, 5 +b12-14 (DTaP mixed)	3.0 (0.1) 4.0 (0.1) 5.0 (0.2) 14.0 (0.7)		54[3]	Seropositivity GMC
		3, 4, 5 +b12-14 (DTaP separate)	3.0 (0.1) 4.0 (0.1) 5.0 (0.2) 13.8 (0.6)		49[3]	
		2, 4, 6 (DTaP separate)	2.1 (0.2) 4.0 (0.2) 5.9 (0.2)		54[3]	
Canada1 [3]	PRP-T	2, 4, 6 + b18	NR[2]		82	Seropositivity
		2, 4, 6 + b15			85	GMC
		2, 4, 6 + b12			86	
Canada2 [4]	PRP-T	2, 4, 6 +b18 +b48-60	NR		106[3]	Seropositivity GMC
		2, 4, 6 +b18		DTwP-IPV or DTaP-IPV[1]	106[3]	
Canada3 [5]	PRP-T	3p+ b18	18.3 (0.26)		438	Seropositivity
		3p+ b17	17.4 (0.26)		450	GMC
		3p+ b16	16.4 (0.26)		449	
		3p+ b15	15.4 (0.27)		445	
			Primary: NR			
Canada4 [6]	PRP-T	2, 4, 6 +b18	18.33 (0.26)		167	Seropositivity
		2, 4, 6 +b15	15.33 (0.26)		168	GMC
Chile1 [7]	PRP-T	2, 4, 6 (DTP mixed)	2.1 (0.11)		94	Mortality Seropositivity
		2, 4, 6 (DTP separate)	2.1 (0.12)		93	GMC
		No doses		DTP or Placebo	93	
			Other doses:NR			

Study name	Conjugate vaccine	Schedules, age at administration in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual, mean (SD)			
Chile2	PRP-T	2,4,6	NR		186	Mortality[4]
[8]		No doses			91	Seropositivity
				DTP and Placebo or Placebo		GMC
Chile3	PRP-T	2, 4, 6	NR		38829	Invasive Hib disease
[9]		No doses		DTP + OPV	37704	Meningitis
						Pneumonia[5]
Chile4	PRP-T	2, 4, 6	NR		78	Seropositivity
[10]		4, 6			79	GMC
	PRP-HBOC	2, 4, 6			78	
		4, 6			78	
Chile5	PRP-T	3, 5, 7 + b12[6]	NR		710[3]	Mortality
[11]		3, 5, 7 + b12[6]				Seropositivity
		3, 5, 7 + b12[6]				GMC
		2, 4, 6 + b12 (mixed)				
		2, 4, 6 + b12 (separate)				
China1	PRP-T	3, 4, 5 +b18-20 (DTaP- IPV mixed)	NR		264	Mortality
[12]						Seropositivity
		3, 4, 5 +b18-20 (DTaP-IPV separate)			264	GMC
		2, 3, 4 +b18-20			264	
China2	PRP-T	3, 4, 5 (DTaP-IPV mixed)	3.33 (0.27)		324	Mortality
[13]						Seropositivity
		2, 3, 4 (DTaP-IPV mixed)	2.31 (0.26)		330	GMC
		2, 3, 4 (DTaP mixed, IPV separate)	2.31 (0.27)		330	
			dose 2-3:NR			
Europe	Hib conjugate (primary)	3p +b13[7]	NR		220	Mortality
[14]		3p +b12	14.9 (3.17)		224	Seropositivity
(Austria, Germany, Greece)	PRP-T (booster)	3p +b12 (MenACWY-TT separate)	14.6 (3.01)		222	GMC
			NR		127	
		3p		MenC conjugate[1]		
			primary NR			
France	PRP-T	2, 4, 6 + b15-17	NR		258	Seropositivity
[15]		2, 3, 4 + b15-17			258	GMC

Study name	Conjugate vaccine	Schedules, age at administration in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual, mean (SD)			
Gambia1	PRP-OMP	2, 4	NR[8]	NR	95	Seropositivity
[16]		1, 3			99	GMC
		No doses			90	
Gambia2	PRP-T	2, 4	NR	NR	43	Seropositivity
[17]		1, 3			45	GMC
		No doses			40	
Gambia3[18]	PRP-HbOC	2, 3, 4	NR		29	Mortality[9]
		No doses		PCV5 + DTP	60	Invasive Hib disease[10]
						Meningitis
						Seropositivity
						GMC
Gambia4	PRP-T	2, 3, 4	Median (IQR)		21490	Mortality
[19]			1st: 2.60 (2.23-3.13)			Invasive Hib
						Meningitis[10]
			2nd: 4.13 (3.53-5.03)			Pneumonia[5]
						Carriage (approx. at 16)
			3rd: 5.63 (4.83-6.93)			Seropositivity
		No doses		DTP + Placebo	21358	GMC
Guatemala	PRP-T	2, 4, 6	NR		414	Seropositivity
[20]		7, 9		DTwP[1]	106	GMC
Indonesia1	PRP-T	2, 4, 6 + b15-18 (DTaP mixed)	Over all groups:		357[3]	Seropositivity
[21]						GMC
		2, 4, 6 + b15-18 (DTwP mixed)[11]	1st: 3.30		360[3]	
			2nd:4.90			
		15-18 (DTaP mixed)	3rd: 6.70	DTaP[1]	172[3]	
Indonesia2	PRP-T	1.5, 2.5, 3.5	1st: 2.57		28147[3]	Mortality[12]
[22]			2nd:3.50			Meningitis
			3rd:4.67			Pneumonia
		No doses		DTP	26926[3]	Seropositivity
						GMC
Lithuania [23]	PRP-OMP/HbOC/T	3, 4.5, 6 (PRP-T)	NR		329	Seropositivity
		3, 4.5, 6 (PRP-HbOC)			110	GMC
		3, 6 (PRP-OMP)			110	
Mali	PRP-T	24-36	NR		120	Mortality
[24]		No doses		Malaria vaccine	120	

Study name	Conjugate vaccine	Schedules, age at administration in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual, mean (SD)			
Netherlands [25]	PRP-T	3, 4, 5 + b11 (DTwP-IPV mixed)	NR		180	Seropositivity GMC
		3, 4, 5 + b11 (DTwP-IPV separate)			181	
		6, 7 + b13			182	
Niger1 [26]	PRP-T	1.5, 2.5, 3.5	Over all groups, mean (range): 1.5m visit: 1.87 (0.93-2.80) 2.5m visit: 3.03 (2.10-5.13) 3.5m visit: 4.20 (3.03-6.77)		59	Seropositivity GMC
		2.5, 3.5			62	
		No doses		Men A and C polysaccharide vaccine	59	
Niger2 [27]	PRP-T	1.5, 2.5, 3.5	Over all groups: 1st: 1.46 (0.19)[13] 2nd and 3rd: NR		37	Mortality
		No doses		Combinations of placebo, Men A and C vaccines	83	
Spain [28]	PRP-HbOC	2, 4, 6 +b13-14 (MMR at booster)	13.4 (0.5)		102	Mortality Seropositivity GMC
		2, 4, 6 +b13-14 (no MMR at booster)	13.4 (0.5)		104	
		2, 4, 6	Primary: NR	MMR[1]	91	
Sweden [29]	PRP-T	2, 4, 6 +b13	NR[14]		118	Mortality
		3, 5 +b12			118	Seropositivity GMC
Thailand [30]	PRP-T	2, 4, 6	NR		140	Seropositivity GMC
	PRP-OMP	2, 4			66	
		No doses		DTP	62	
Turkey [2]	PRP-T	3, 4, 5 +b12-14 (DTaP mixed)	3.00 (0.15) 4.06 (0.27) 5.08 (0.31) 13.39 (1.07)		74[3]	Seropositivity GMC
		3, 4, 5 +b12-14 (DTaP separate)	2.99 (0.12) 4.03 (0.18) 5.06 (0.32) 13.51 (1.10)		78[3]	
		2, 4, 6 (DTaP separate)	2.06 (0.20) 4.00 (0.26) 5.93 (0.33)		81[3]	

Study name	Conjugate vaccine	Schedules, age at administration in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual, mean (SD)			
USA1 [31]	PRP-OMP	1.5-3, 2.5-5	mean (range)		2588	Mortality[15]
		No doses	1st: 1.82 (1.17-3.50)	Placebo	2602	Invasive Hib
			2nd: NR			Meningitis
						Pneumonia[5]
						Seropositivity
						GMC
USA2 [32]	PRP-HbOC	2, 4, 6	NR		30400[3]	Invasive Hib[16]
		No doses		DTP + OPV	30680[3]	Meningitis
						Pneumonia[17]
						Seropositivity
						GMC
USA3 [33]	PRP-T	2, 4, 6	1st: 2.21		5208	Mortality
			2nd: 4.61			Invasive Hib
			3rd: 6.94			Seropositivity
		No doses		HepB + DTP	5109	GMC
USA4 [34]	PRP-OMP/HbOC	2, 4, 6 (dose 1 PRP-OMP, 2-3 PRP-HbOC)[19]	NR		36[18]	Seropositivity
						GMC
		2, 4, 6 (dose 1 PRP-HbOC, 2-3 PRP-OMP)[19]			35	
		2, 4, 6 (HbOC)[19]			96	
		2, 6 (PRP-OMP)[19]			36	
		2, 4 (PRP-OMP)[19]			39	
USA5 [35]	PRP-T	2, 4, 6 (PRP-T)	NR[20]		150[21]	Seropositivity
	HbOC	2, 4, 6 (PRP-HbOC)				GMC
		0, 2, 4, 6 (PRP-HbOC)				
USA6 [36]	PRP-T	2, 4, 6 (dose 1 PRP-OMP, 2-3 PRP-T)	Over all groups:		34	Seropositivity
	PRP-OMP		1st: 2.08 (0.28)			GMC
		2, 4, 6 (PRP-T)	2nd: 4.22 (0.30)		35	
		2, 4 (PRP-OMP)	3rd: 6.37 (0.37)		35	
USA7 [36]	PRP-T	2, 4, 6 (PRP-T)	Over all groups:		58	Seropositivity
	PRP-OMP	2, 4 (PRP-OMP, PRP-T)	1st: 2.17 (0.28)		62	GMC
		2, 4 (PRP-OMP)	2nd: 4.43 (0.42)		61	
			3rd: 6.51 (0.51)			

Study name	Conjugate vaccine	Schedules, age at administration in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual, mean (SD)			
West Africa [37] (The Gambia, Mali)	PRP-T	3p + b12-23 + b22-34	Median (range): 18 (12-23), 28 (20-32)		66[3]	Mortality
		3p + b22-34	25 (20-32)		134[3]	
		3p + b12-23	18 (12-23)		129[3]	
		3p	Primary NR		260[3]	

Legend

All times are in months of age unless otherwise stated. Clinical outcomes (e.g. Mortality, Pneumonia and Meningitis) are all-cause and not Hib specific unless specified.

3p – 3-dose primary schedule, etc.; +b – booster dose given at number of months indicated; c-u: catch up dose

Hib – Haemophilus influenzae type b vaccine; IQR - inter-quartile range; Men A and C vaccines - conjugate or polysaccharide meningococcal A and C vaccines; NR not reported; p - primary course; mixed - in same syringe as co-administered vaccines; PRP - polyribosylribitol phosphate; PRP-HbOC - PRP conjugated to diphtheria toxin CRM 197; PRP-OMP - PRP conjugated to outer membrane protein of Neisseria meningitidis; PRP-T - PRP conjugated to tetanus toxoid; SD - standard deviation; separate- in different syringe to co-administered vaccines.

1 No intervention groups received no doses of Hib conjugate vaccine, but a control intervention what used in some/all groups which received fewer doses of Hib conjugate vaccine.
2 Ages not stated but the following information is given for the booster doses: “The intended schedule of immunization was met for each child with single exceptions at 15 months (one week late) and 18 months (2 weeks late)”
3 N children who received vaccine; number of randomized children not reported
4 Mortality all-cause and due to pneumonia
5 Hib pneumonia and all-cause pneumonia
6 Each group has different vaccines (DTaP with OPV, or DTaP with IPV either mixed or separate) administered at 2, 4, 6m
7 Type of conjugate vaccines (3p) was not specified in this study.
8 Ages not stated but the following information is given:” “Full compliance with the vaccination schedule and blood sampling was achieved by 85 infants in group A (immunized with two doses of vaccine at 1 and 3 months) and by 56 in group B (immunized at 2 and 4 months).”
9 All-cause but probably septicemia
10 Hib meningitis
11 Some also received DTaP with booster
12 Mortality all-cause; mortality due to pneumonia, mortality due to meningitis, mortality due to Hib infection and due to meningitis and due to pneumonia and due to Hib infection
13 if assume first dose is at recruitment
14 Ages not stated but most doses were given on time:”805 injections were administered. Seven injections were given 1 to 6 days out of time range, 2 injections were given >1 month out of time range”
15 Mortality all-cause and due to Hib infection
16 Invasive Hib with bacteremia or sepsis, with meningitis, and with pneumonia
17 Pneumonia (presumptive Hib)
18 N children who were followed up; number of randomized or immunized children not reported
19 All groups received unconjugated-PRP booster at 15m. Comparisons after unconjugated-PRP booster not shown.
20 Group receiving 2, 4, 6 HbOC received 3rd dose at 6.7m. Other groups and doses not reported.
21 Total recruited, randomized and immunized; numbers per group not reported

Table 2: Available comparisons of vaccination schedules

Comparison	Study	Schedules, months[1]	Vaccine	Time at which outcomes measured[2]			
					Immunological data		
				Clinical	Age at which 0.15µg/ml available, months	Age at which 1.0µg/ml available, months	Age at which GMC available, months
Schedule vs schedule (comparisons A–T)							
Comparison A 2p vs 1p	Niger1	1.5, 2.5 2.5	PRP-T	NR	3.5	3.5	3.5
	USA4	2, 4 2	PRP-OMP	NR	NR	6	6
	USA5	0, 2 2	PRP-HbOC	NR	NR	NR	4
Comparison B 3p vs 1p	No RCTs						
Comparison C 3p vs 2p	Chile4	2, 4, 6 4, 6	PRP-T	NR	8, 12	8, 12	8, 12
	Chile4	2, 4, 6 4, 6	PRP-HbOC	NR	8, 12	8, 12	8, 12
	Chile5	2, 4, 6[3] 3, 5[3]	PRP-T	NR	7	7	7
	Guatemala	2, 4, 6 7, 9	PRP-T	NR	12	12	12
	Netherlands	3, 4, 5[4] 6, 7[4]	PRP-T	NR	11	11	11
	Niger1	1.5, 2.5, 3.5 2.5, 3.5	PRP-T	NR	4.5, 9	4.5, 9	4.5, 9
	Sweden	2, 4, 6 3, 5	PRP-T	NR	7, 13 6, 12	7, 13 6, 12	7, 13 6, 12
	USA5	0, 2, 4 2, 4	PRP-HbOC	NR	NR	NR	6
Comparison E 2p+1 vs 2p	No RCTs						
Comparison G 3p vs 2p+1	Sweden	2, 4, 6 3, 5 + b12	PRP-T	NR	7, 13 13	7, 13 13	7, 13 13
Comparison L 3p+1 vs 2p+1	Netherlands	3, 4, 5 +b11[4] 6, 7 + b13[4]	PRP-T	NR	12 14	12 14	12 14
	Sweden	2, 4, 6 + b13 3, 5 + b12	PRP-T	14[5]	14, 5.5y 13, 5.5y	14, 5.5y 13, 5.5y	14, 5.5y 13, 5.5y
Comparison M 3p+1 vs 3p	Canada3	3p + b15[6] 3p[6]	PRP-T	NR	NR	NR	16

Comparison	Study	Schedules, months[1]	Vaccine	Time at which outcomes measured[2]			
					Immunological data		
				Clinical	Age at which 0.15µg/ml available, months	Age at which 1.0µg/ml available, months	Age at which GMC available, months
	Europe	3p + b12[7] 3p[7]	PRP-T	NR	13	13	13
	Spain	2, 4, 6 + b13-14 2, 4, 6	PRP-HbOC	42 days after 13-14m	NR	NR	NR
	West Africa	3p + b12-23[8] 3p[8]	PRP-T[8]	9 months after 12-23m	NR	NR	NR
	West Africa	3p + b22-34[8] 3p[8]	PRP-T[8]	15 months after 22-34m	NR	NR	NR
Comparison M1 3p+2 vs 3p+1	Canada2	2, 4, 6, + b18 + b48-60 2, 4, 6 + b18	PRP-T	NR	49-61	49-61	49-61
Comparison M2 3p+2 vs 3p	West Africa	3p + b12-23 + b22-34[8] 3p[8]	PRP-T[8]	15 months after 22-34m	NR	NR	NR
Comparison N Birth dose vs no birth dose	USA5	0, 2 2	PRP-HbOC	NR	NR	NR	4
	USA5	0 2	PRP-HbOC	NR	NR	NR	2 4
	USA5	0, 2, 4 2, 4	PRP-HbOC	NR	NR	NR	6
	USA5	0, 2 2, 4	PRP-HbOC	NR	NR	NR	4 6
	USA5	0, 2, 4, 6 2, 4, 6	PRP-HbOC	NR	NR	NR	7
Comparison O Late start vs early start	Belgium2	3, 4, 5[11] 2, 4, 6	PRP-T	NR	6 7	6 7	6, 12-14 7, 12-14
	Chile5	3, 5, 7[3] 2, 4, 6[3]	PRP-T	NR	NR	NR	12
	Chile5	3, 5, 7 + b12[3] 2, 4, 6 + b12[3]	PRP-T	Until 14m	13	13	13
	China1	3, 4, 5[9] 2, 3, 4[9]	PRP-T	Until 18-20m[5]	6, 18-20 5, 18-20	18-20 18-20	6, 18-20 5, 18-20
	China1	3, 4, 5 + b18-20[9] 2, 3, 4 + b18-20[9]	PRP-T	Until 19-21m[5]	19-21	19-21	19-21

Comparison	Study	Schedules, months[1]	Vaccine	Time at which outcomes measured[2]			
					Immunological data		
				Clinical	Age at which 0.15µg/ml available, months	Age at which 1.0µg/ml available, months	Age at which GMC available, months
	China2	3, 4, 5[10]	PRP-T	Until 6m	6	NR	6
		2, 3, 4[10]		Until 5m	5		5
	Gambia1	2	PRP-OMP	NR	3	3	3
		1			2	2	2
	Gambia1	2, 4	PRP-OMP	NR	5, 18	5, 18	5, 18
		1, 3			4, 18	4, 18	4, 18
	Gambia2	2	PRP-OMP	NR	NR	NR	3
		1					2
	Gambia2	2, 4	PRP-OMP	NR	NR	NR	5
		1, 3					4
	Netherlands	6, 7 [4]	PRP-T	NR	11	11	11
		3, 4, 5 [4]			11	11	11
	Netherlands	6, 7 + b13[4]	PRP-T	NR	14	14	14
		3, 4, 5 +b11[4]			12	12	12
	Turkey	3, 4, 5[11]	PRP-T	NR	6	6	6, 12-14
		2, 4, 6[11]			7	7	7, 12-14
Comparison P	Belgium2	2, 4, 6[11]	PRP-T	NR	7	7	7, 12-14
2 month vs 1 month interval		3, 4, 5[11]			6	6	6, 12-14
	France	2, 4, 6	PRP-T	NR	7, 15-17	7, 15-17	7, 15-17
		2, 3, 4			5, 15-17	5, 15-17	5, 15-17
	France	2, 4, 6 + b15-17	PRP-T	NR	16-18	16-18	16-18
		2, 3, 4 + b15-17					
	Turkey	2, 4, 6[11]	PRP-T	NR	7	7	7, 12-14
		3, 4, 5[11]			6	6	6, 12-14
Comparison P1	USA4	2, 6	PRP-OMP	NR	NR	7, 15	7, 15
4 month vs 2 month interval		2, 4					
Comparison Q	Canada1	2, 4, 6 + b15	PRP-T	NR	16.5	16.5	16.5
longer vs shorter interval between primary and booster		2, 4, 6 + b12			13.5	13.5	13.5
	Canada1	2, 4, 6 + b18	PRP-T	NR	19.5	19.5	19.5
		2, 4, 6 + b12			13.5	13.5	13.5
	Canada1	2, 4, 6 + b18	PRP-T	NR	19.5	19.5	19.5
		2, 4, 6 + b15			16.5	16.5	16.5

Comparison	Study	Schedules, months[1]	Vaccine	Time at which outcomes measured[2]			
				Clinical	Immunological data		
					Age at which 0.15µg/ml available, months	Age at which 1.0µg/ml available, months	Age at which GMC available, months
	Canada3	3p + b17/18[6] 3p + b15/16[6]	PRP-T	NR	NR	18/19 16/17	18/19 16/17
	Canada3	3p + b18[6] 3p + b17[6]	PRP-T	NR	NR	NR	19 18
	Canada3	3p + b18[6] 3p + b16[6]	PRP-T	NR	NR	NR	19 17
	Canada3	3p + b18[6] 3p + b15[6]	PRP-T	NR	NR	NR	19 16
	Canada3	3p + b17[6] 3p + b16[6]	PRP-T	NR	NR	NR	18 17
	Canada3	3p + b17[6] 3p + b15[6]	PRP-T	NR	NR	NR	18 16
	Canada3	3p + b16[6] 3p + b15[6]	PRP-T	NR	NR	NR	17 16
	Canada4	2, 4, 6 + b18 2, 4, 6 + b15	PRP-T	NR	19 16	NR	19 16
	Chile5	2, 4, 6 + b12[3] 3, 5, 7 + b12[3]	PRP-T	Until 14m	13	13	13
	China1	2, 3, 4 + b18-20[9] 3, 4, 5 + b18-20[9]	PRP-T	Until 19-21m[5]	19-21	19-21	19-21
	Europe	3p + b13[7] 3p + b12[7]	PRP-T	NR	14 13, 14	14 13, 14	14 13, 14
	France	2, 3, 4 + b15-17m 2, 4, 6 + b15-17m	PRP-T	NR	16-18	16-18	16-18
	West Africa	3p + b22-34[8] 3p + b12-23[8]	PRP-T[8]	15 months after 22-34m	NR	NR	NR
Comparison T Primary (+/- booster) vs catch-up	Belgium1	3, 4, 5 + b14 14	PRP-T	NR	15, 48-72	15, 48-72	15, 48-72
	Indonesia1	2, 4, 6 + b15-18[12] 15-18	PRP-T	NR	16.5-19.5	16.5-19.5	16.5-19.5
Schedule vs no Hib vaccine (comparisons U−Z)							
Comparison U1 1p vs 0	Gambia4	2 No doses	PRP-T	Unclear	NA	NA	NA

Comparison	Study	Schedules, months[1]	Vaccine	Time at which outcomes measured[2]			
					Immunological data		
				Clinical	Age at which 0.15µg/ml available, months	Age at which 1.0µg/ml available, months	Age at which GMC available, months
	USA1	1.5-3 No dose	PRP-OMP	Until 2 months after dose 1	NA	NA	NA
Comparison U2 2p vs 0	USA1	1.5-3, 2.5-5 No dose	PRP-OMP	Until 15m Until 18m	NA	NA	NA
Comparison U3 3p vs 0	Chile1	2, 4, 6[13] No doses	PRP-T	Until 60 days after the third dose[5]	NA	NA	NA
	Chile2	2, 4, 6[13] No doses	PRP-T	Until 60 days after the third dose[5]	NA	NA	NA
	Chile3 (cluster)	2, 4, 6 No doses	PRP-T	Until April 1995 (18-30 months of follow up)	NR	NR	NR
	Indonesia2	1.5, 2.5, 3.5 No doses	PRP-T	Until 24m	NA	NA	NA
	Gambia3	2, 3, 4[14] No doses	PRP-HbOC	Until 8m Until 12m	NR	NR	NR
	Gambia4	2, 3, 4 No doses	PRP-T	Until March 1996 (5 months to 3 years of follow up) Carriage at approx. 16m	NA	NA	NA
	Niger2	1.5, 2.5, 3.5[15] No doses	PRP-T	During study, approx. until 12m	NR	NR	NR
	USA2[16]	2, 4, 6 No doses	PRP-HbOC	Until June 1990 or second birthday (0-22m follow up)%	NA	NA	NA
	USA3	2, 4, 6 No doses	PRP-T	Until Oct 1990 (1-16 months of follow up)	NA	NA	NA
Comparison W6 2p or 3p vs 0	Gambia4	2, 3, 4 No doses	PRP-T	Until March 1996 (5 months to 3 years of follow up)	NA	NA	NA

Comparison	Study	Schedules, months[1]	Vaccine	Time at which outcomes measured[2]			
					Immunological data		
				Clinical	Age at which 0.15µg/ml available, months	Age at which 1.0µg/ml available, months	Age at which GMC available, months
Comparison W2 2p+1 vs 0	No RCTs						
Comparison W3 3p+1 vs 0	No RCTs						
Comparison X1 1 catch-up dose vs 0	No RCTs						
Comparison X2 2 catch-up doses vs 0	Mali	24-36, 25-37 No doses	PRP-T	Until 41-56m	NR	NR	NR

Legend

3p – 3-dose primary schedule, etc.; +1 – booster dose; +b – booster dose given at number of months indicated.

b – booster; Hib – *Haemophilus influenzae* type b vaccine; DTaP - diphtheria, tetanus, acellular pertussis vaccine; DTwP - diphtheria, tetanus, whole cell pertussis vaccine; eIPV - enhanced inactivated poliovirus vaccine; MMR - measles, mumps and rubella vaccine; NA - not applicable, outcome reported in study but not eligible for inclusion ; NR - not reported, outcome not reported in the study; p - primary course; PCV - pneumococcal conjugate vaccine; PRP - polyribosylribitol phosphate; PRP-HbOC - PRP conjugated to diphtheria toxin CRM 197; PRP-OMP - PRP conjugated to outer membrane protein of *Neisseria meningitidis*; PRP-T - PRP conjugated to tetanus toxoid; y - years

Shaded grey rows are comparisons that are reported in main text.

1 Schedules shown are intended schedules for Hib conjugate vaccine, without details of co-administered vaccines. Multiple groups within teach trial with the same Hib schedule are not shown in this table. Further detail about co-administered vaccines and groups which are compared in analyses are given in footnotes of this table.

2 All times are in months of age unless otherwise stated.

3 Multiple groups provide this comparison for this trial. Results presented compare a group receiving PRP-T at 3, 5, 7m and DTaP combined with eIPV at 2, 4, 6m to a group receiving PRP-T at 2, 4, 6m and DTaP combined with eIPV at 2, 4, 6m in the other leg. Other groups receiving PRP-T at 3, 5, 7m either received OPV instead of IPV, or had DTaP and eIPV given as separate injections. The other group receiving PRP-T at 2, 4, 6m received PRP-T mixed in the same syringe as DTaP and eIPV

4 Multiple groups provide this comparison for this trial. Results presented compare a group receiving PRP-T at 3, 4, 5 + b11m and DTwP combined with IPV as a separate injection from PRP-T at 3, 4, 5 + b11m to a group receiving PRP-T at 6, 7 + b13m and DTwP combined with IPV at 3, 4, 5 + b11m. The other group receiving PRP-T at 3, 4, 5 + b11m received PRP-T in the same syringe as DTwP and IPV

5 Observation period not reported. Assume followed up until last blood sample taken

6 Inclusion criteria state that children had received 3 primary doses of PRP-T (Pentacel) by 8 months of age. Randomized to booster at 15, 16, 17 or 18m. Data presented comparing 17 and 18m groups combined with15 and 16m groups combined as this is the main analysis presented in trial documents. If this comparison is not available for any outcome, the comparison of the 18m and 15m groups are presented to reflect the largest schedule difference. Other comparisons possible but not presented.

7 Inclusion criteria state that children had completed a three-dose primary vaccination with Haemophilus influenzae type b conjugate vaccine at least 180 days before administration of the first study vaccination. It is not specified which conjugate vaccines were in use at the time of the study. It is not certain that all children received PRP-T in the primary series. Multiple groups exist for the 3p + b12 schedule in this trial. Presented results compare a group receiving 3p then Meningococcal ACWY conjugate vaccine at 12m and PRP-T at 13m to a group receiving 3p then PRP-T co-administered with Meningococcal ACWY conjugate vaccine at 12m .

8 Study participants were recruited at 12-23m. Inclusion Criteria state that participants must be fully vaccinated according to local Expanded Program on Immunization (EPI) schedule. Although The Gambia and Mali had Hib vaccination schedules of 2, 3, 4m and 1.5, 2.5, 3.5m respectively in the years the study was conducted it is not explicitly stated that children in all areas of these countries received 3 primary doses of Hib vaccine. It is also not stated which Hib vaccines were in use at that time. It is not certain that all children received 3 primary doses of PRP-T. The 3p group used in all comparisons combines data from all groups which did not receive additional doses of Hib vaccine. All received some formulation of a meningococcal vaccine instead of Hib vaccine.

9 Multiple groups provide this comparison for this trial. Results presented compare a group receiving PRP-T, IPV and DTaP in the same syringe at 3, 4, 5m to a group receiving PRP-T, IPV and DTaP in the same syringe at 2, 3, 4m. Another group receiving PRP-T at 3, 4, 5m received DTaP and IPV separately at the same time (i.e. 3 separate syringes).

10 Multiple groups provide this comparison for this trial. Results presented compare a group receiving PRP-T, IPV and DTaP in the same syringes at 3, 4, 5m to a group receiving PRP-T, IPV and DTaP in the same syringes at 2, 3, 4m. Another group receiving PRP-T at 2, 3, 4m received DTaP in the same syringe and IPV at the same time but in a separate syringe.

11 Multiple groups provide this comparison for this trial. Results presented compare a group receiving PRP-T and DTaP in separate syringes at 3, 4, 5m to a group receiving PRP-T and DTaP in separate syringes at 2, 4, 6m. Another group receiving PRP-T at 3, 4, 5m in the same syringe as DTaP.

12 Multiple groups provide this comparison for this trial. Results presented compare a group receiving PRP-T-DTaP at 2, 4, 6 +b15-18m to a group receiving DTaP at 2, 4, 6m and receiving PRP-T-DTaP at 15-18m. Other groups receiving PRP-T at 2, 4, 6 +b15-18m received whole cell pertussis vaccine instead of acellular pertussis vaccine for at least one dose

13 Chile1 and Chile2 have identical schedules in the primary phase. Multiple groups provide this comparison for these trials. Results presented compare a group receiving PRP-T and DTP in separate syringes at 2, 4, 6m to a group receiving DTP at 2, 4, 6m. Another group receiving PRP-T at 2, 4, 6m received DTP in the same syringe.

14 Multiple groups provide this comparison for this trial. Results presented compare a group receiving PRP-T at 2, 3, 4m to a combined group receiving PCV at either 2, 4m or 2, 3, 4m. If data could not be combined for these groups, results are reported for a comparison of a group receiving PRP-T at 2, 3, 4m to a group receiving PCV at 2, 3, 4m.

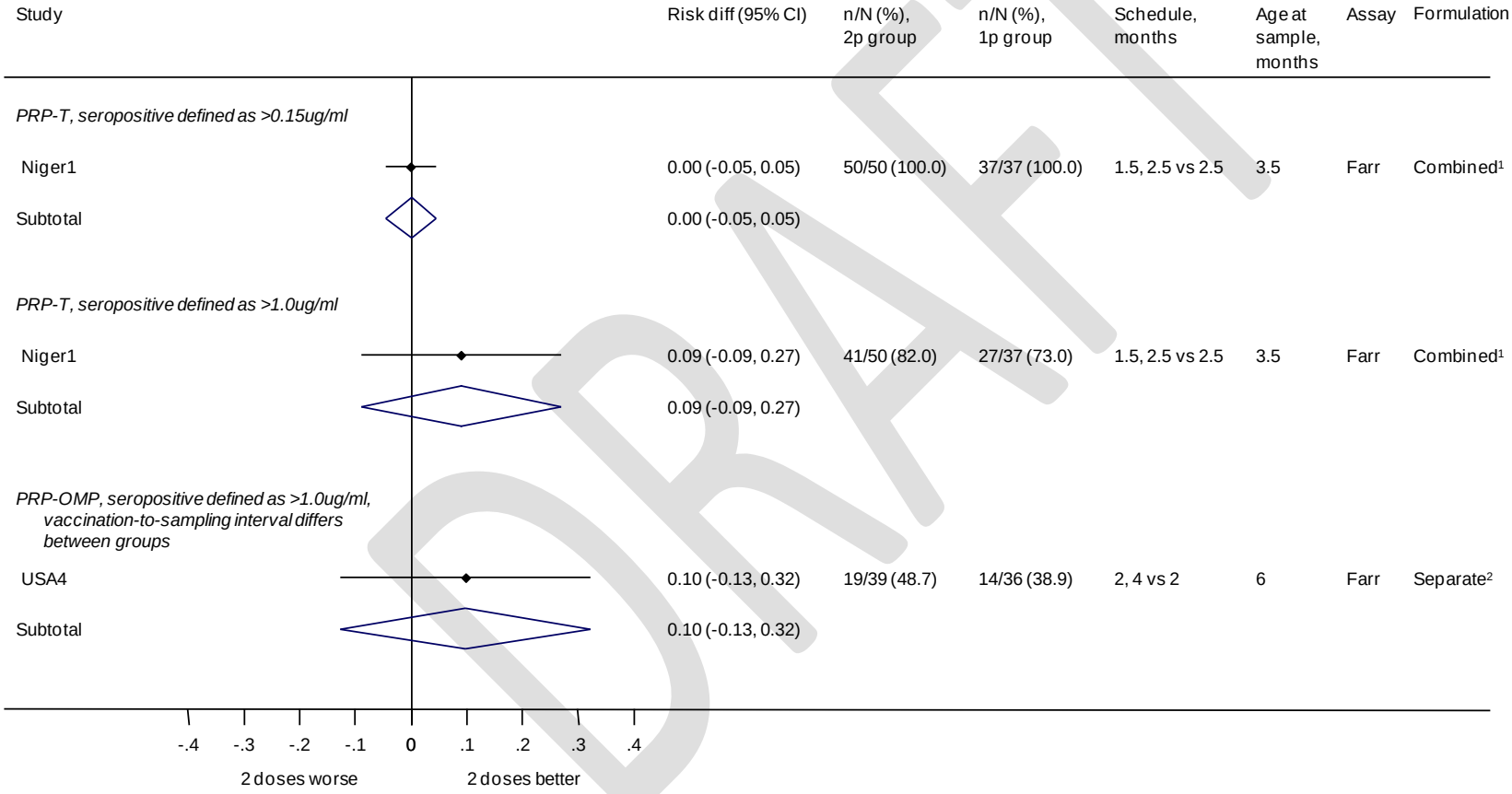
15 Multiple groups provide this comparison for this trial. Results presented compare a group receiving PRP-T at 1.5, 2.5, 3.5m to a combined group receiving meningococcal A and C conjugate (diphtheria toxoid) at 1.5, 2.5, 3.5m (several dosages in different groups) or polysaccharide vaccine at 2.5, 3.5m. If data could not be combined over groups results for a comparison of a group receiving PRP-T at 1.5, 2.5, 3.5m to a group receiving the lowest dosage of meningococcal A and C conjugate (diphtheria toxoid) at 1.5, 2.5, 3.5m.

16 Quasi-randomized study. Allocation based on birth date. Children born in the first 5 or 6 days of each month were not offered vaccine. Parents of children born later in each month could accept or refuse Hib conjugate vaccine. Results from analyses where those offered vaccine are compared to those not offered vaccine are shown in forest plots. Results from analyses where unvaccinated group includes vaccine refusers are not shown in forest plots but are reported in text.

Figures

Immunological data

Figure 1: 2p vs 1p, 1m post primary, 0.15µg/ml and 1.0µg/ml

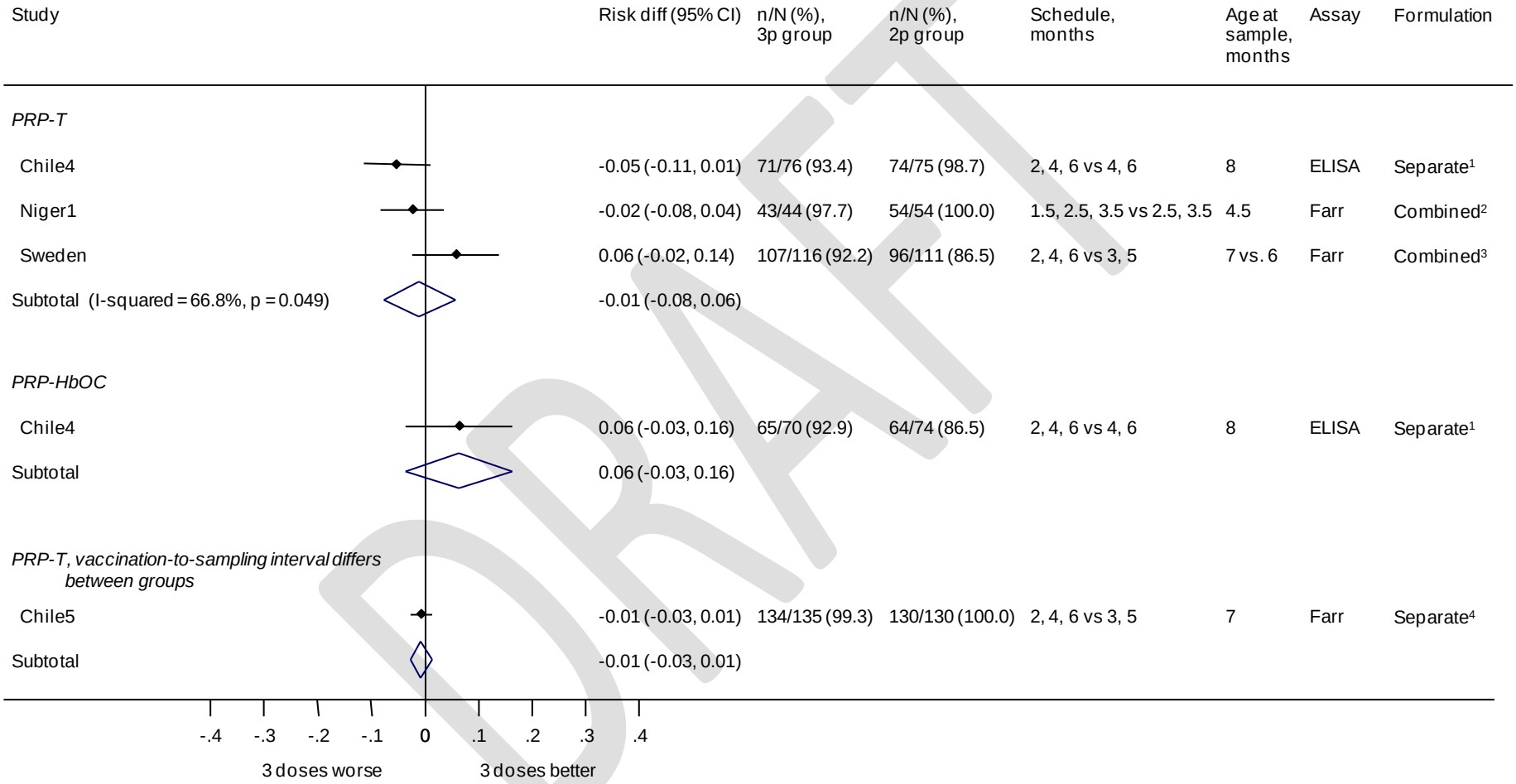


Combined – Hib vaccine mixed in same syringe as other vaccines; separate– Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTP both groups at 1.5, 2.5, 3.5 . Unclear if aP or wP. In one syringe with Hib vaccine when Hib given;2 DTP, OPV, MMR given to both groups "according to published guidelines"

3p vs 2p schedules

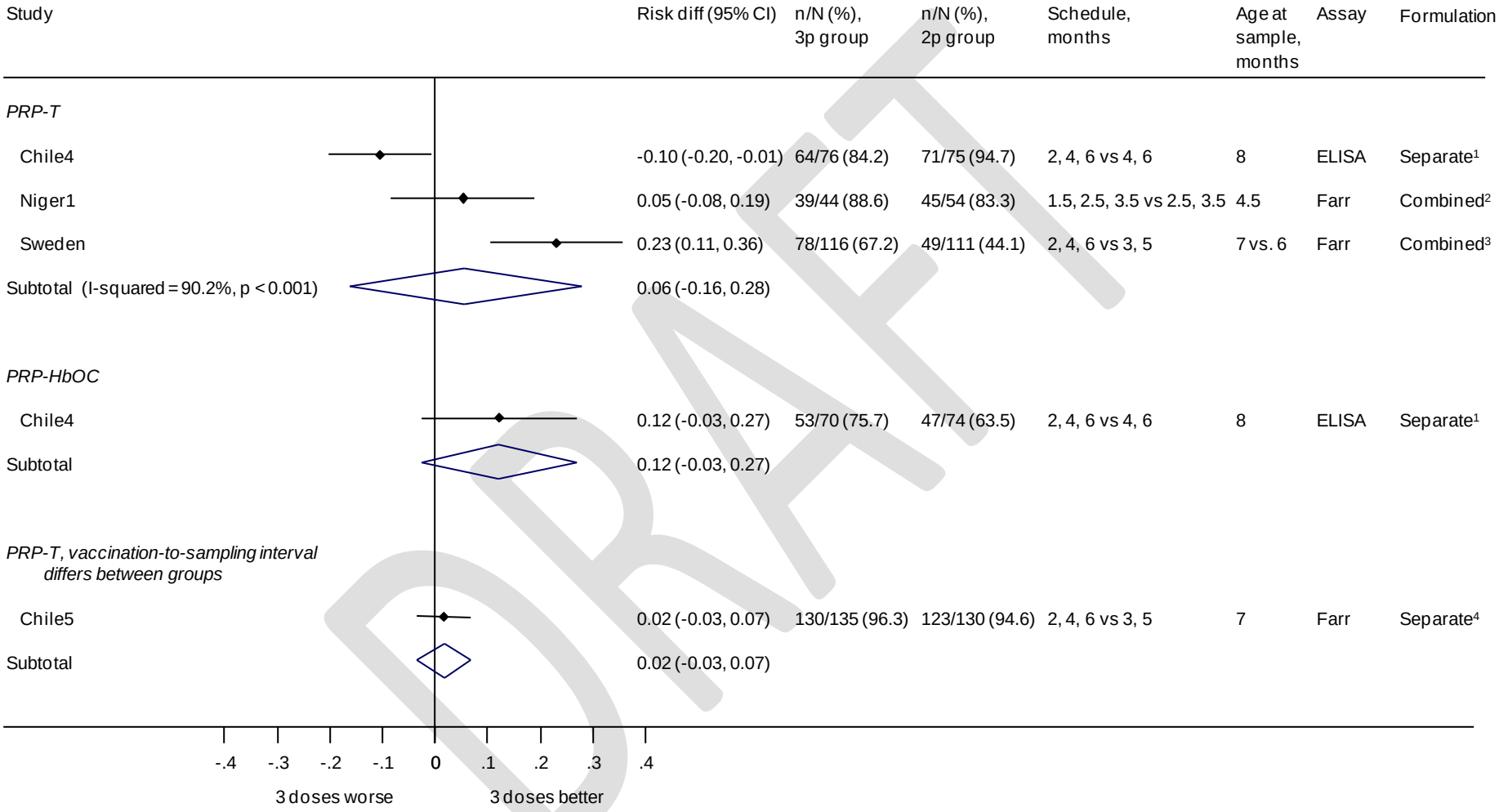
Figure 2:3p vs 2p, approx. 1m post primary, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTP both groups at 2, 4, 6. Unclear if aP or wP; 2 DTP both groups at 1.5, 2.5, 3.5 . Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTaP 2, 4, 6 both groups

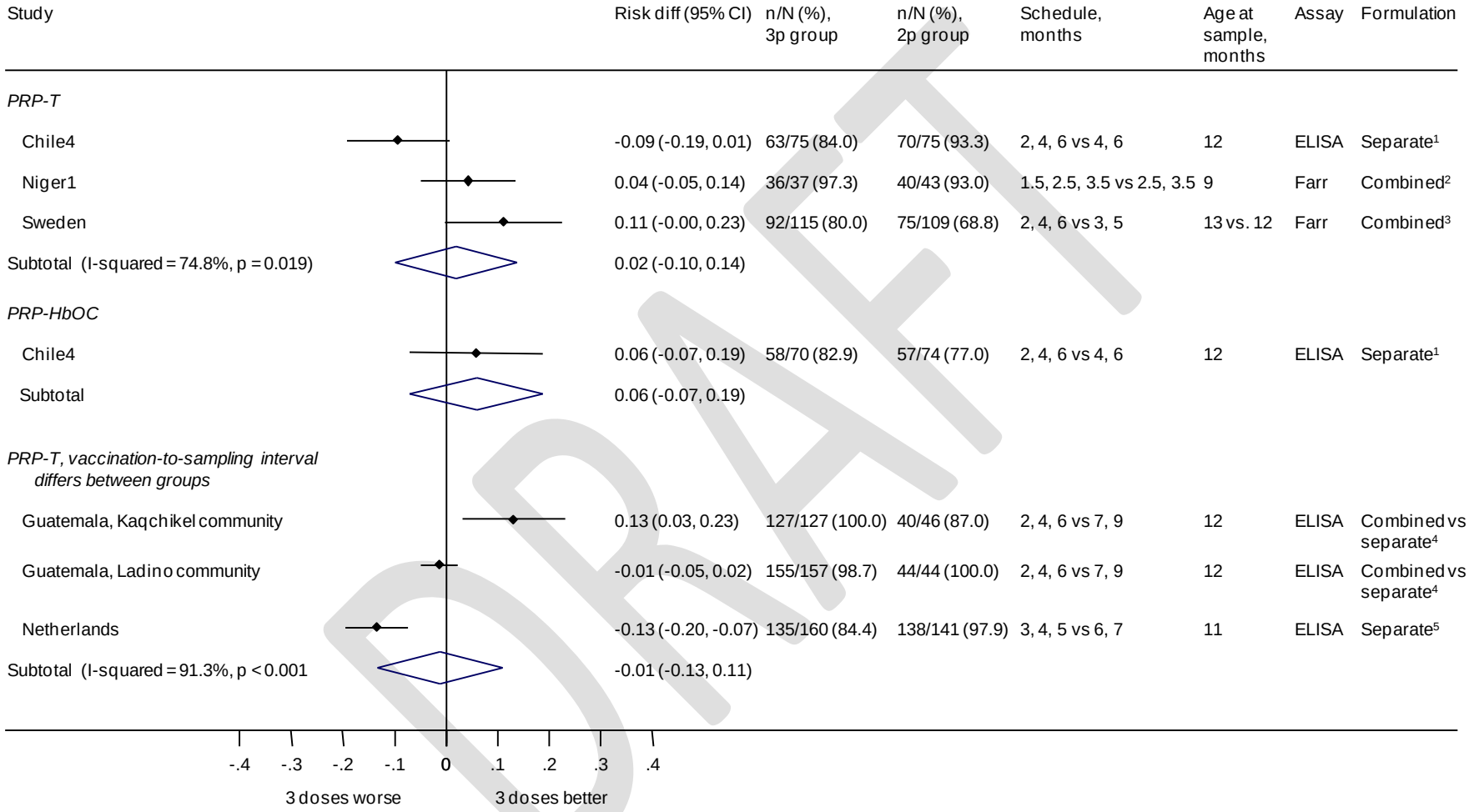
Figure 3:3p vs 2p, approx. 1m post primary, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTP both groups at 2, 4, 6. Unclear if aP or wP; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTaP 2, 4, 6 both groups

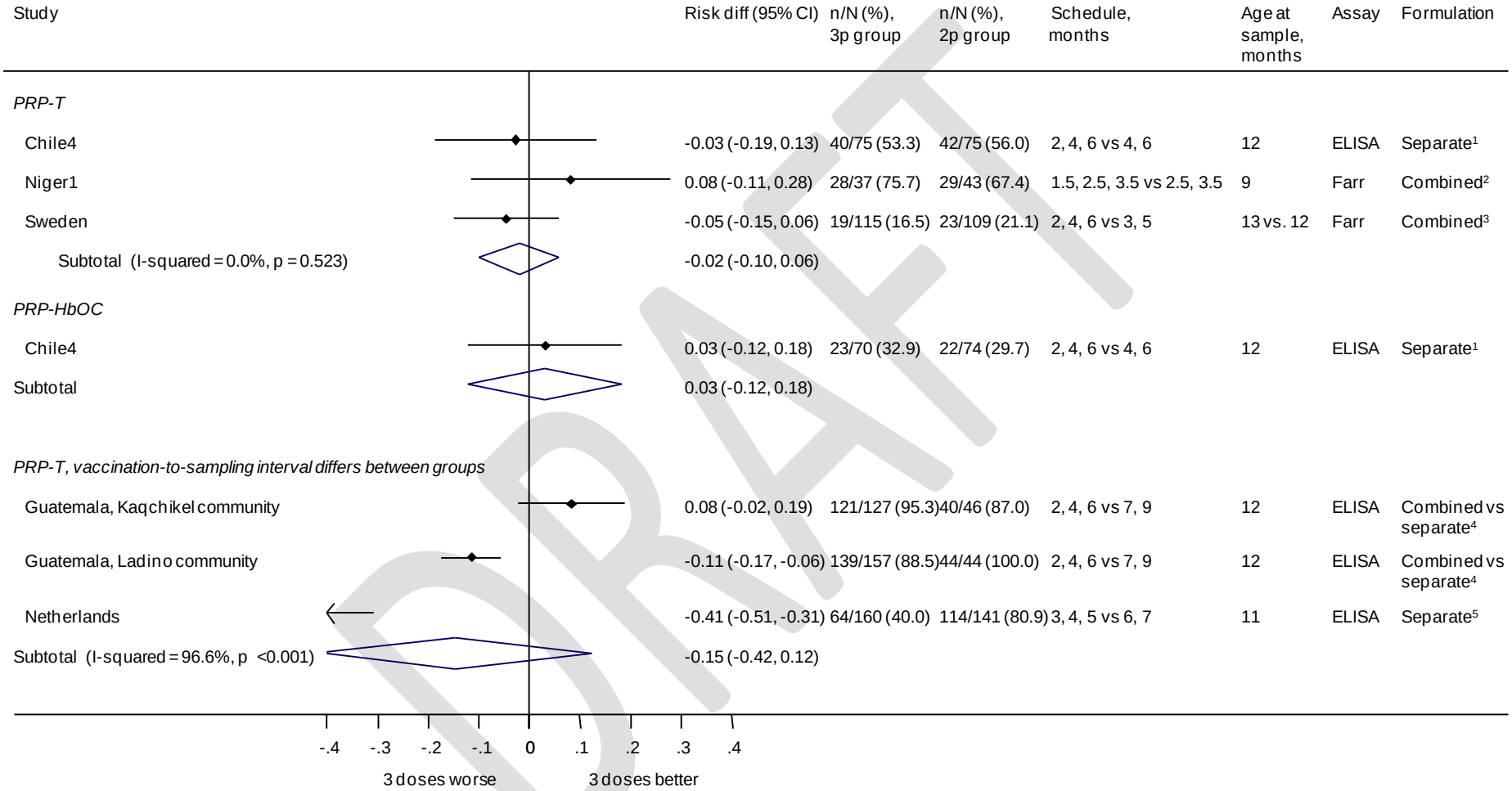
Figure 4: 3p vs 2p, approx. 6m post primary, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTP both groups at 2, 4, 6. Unclear if aP or wP; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 5 DTwP-IPV both groups at 3, 4, 5

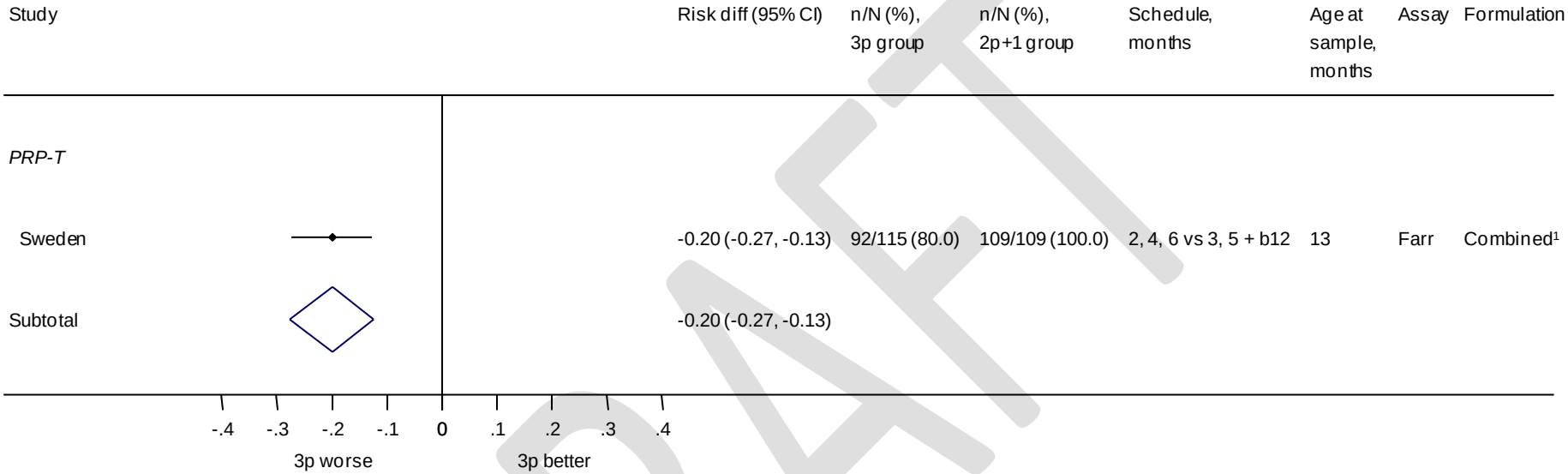
Figure 5: 3p vs 2p, approx. 6m post primary, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine. 1 DTP both groups at 2, 4, 6. Unclear if aP or wP ; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 5 DTwP-IPV both groups at 3, 4, 5

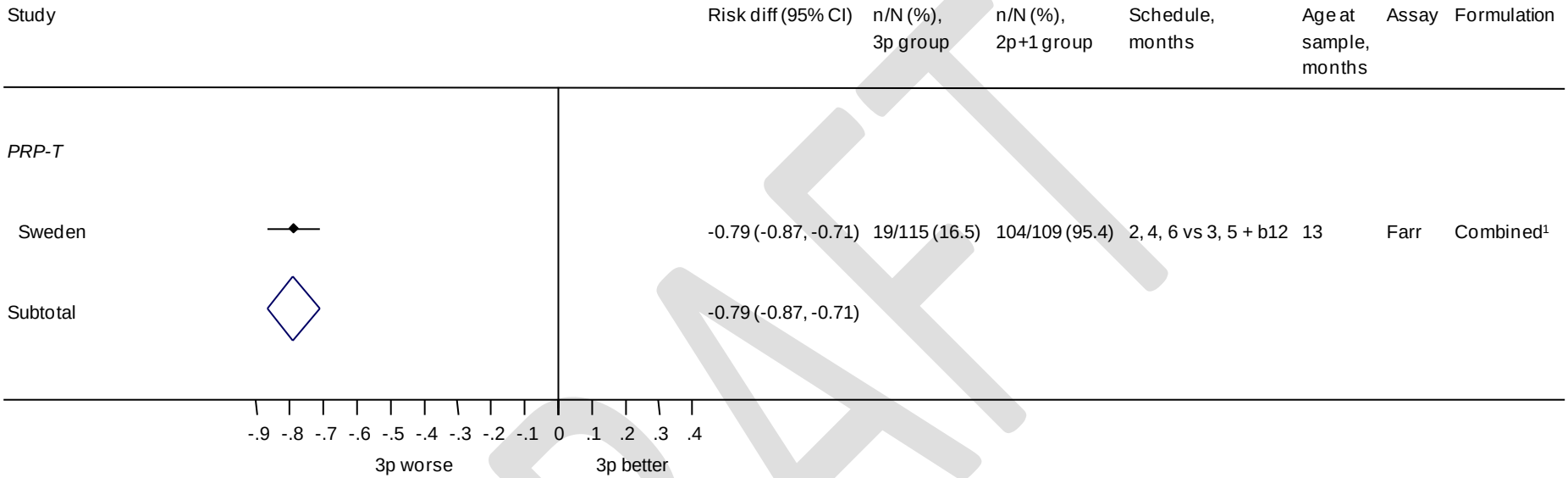
3p vs 2p+1 schedules

Figure 6: 3p vs 2p+1, 13 months of age, 0.15µg/ml



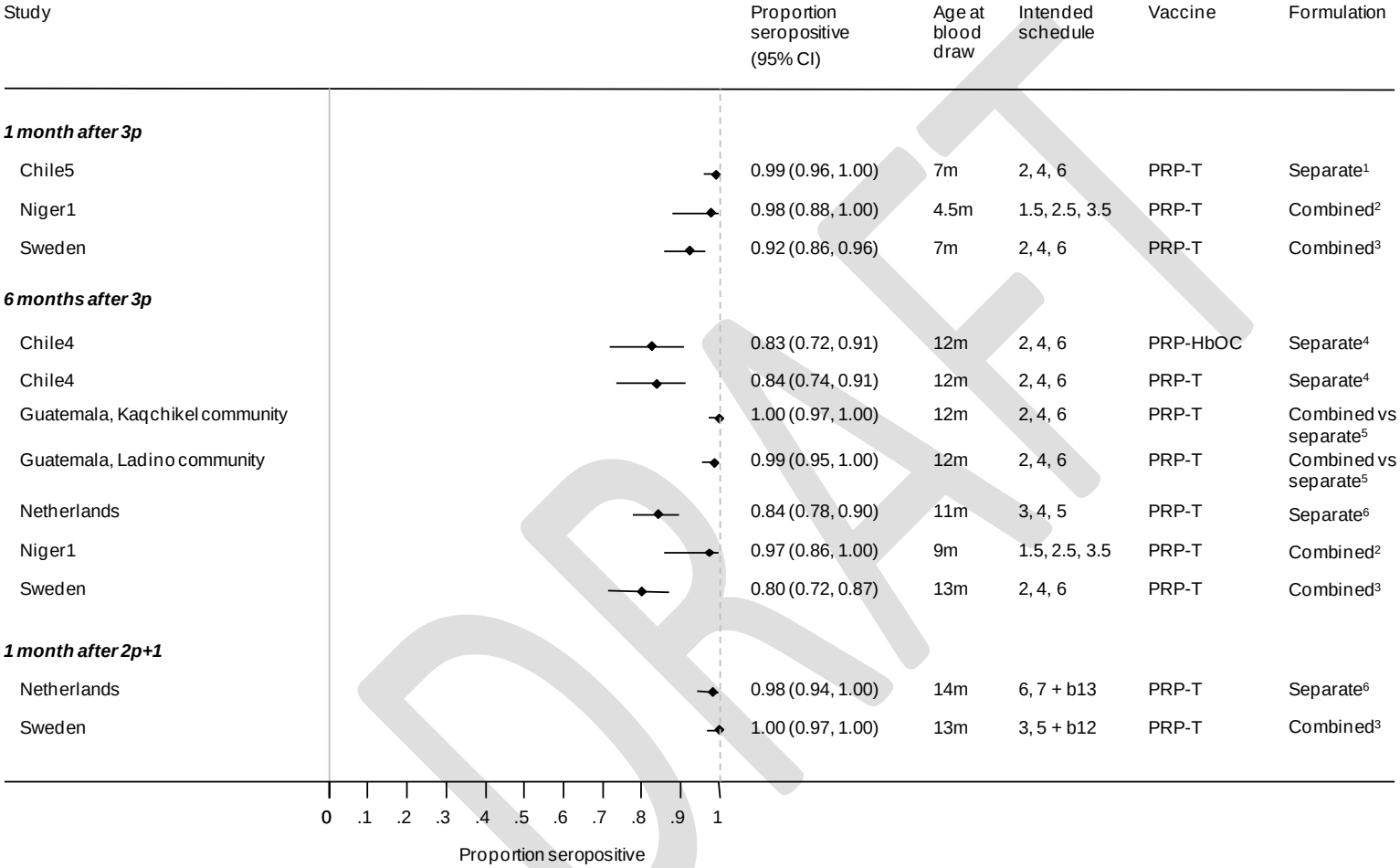
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-IPV/Hib both groups

Figure 7: 3p vs 2p+1, 13 months of age, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-IPV/Hib both groups

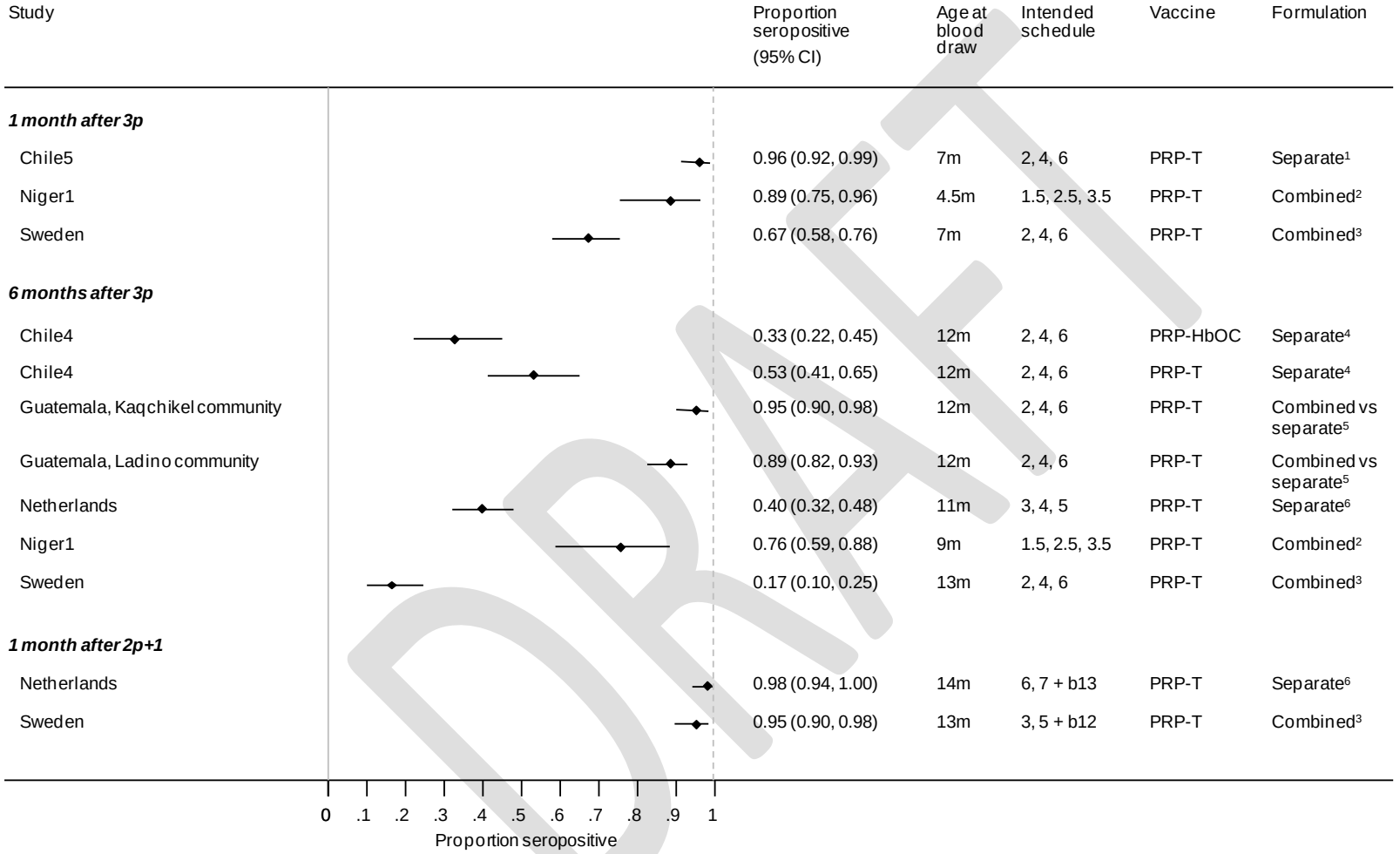
Figure 8: Seropositivity after 3p and 2p+1, 1 and 6 months after 3p and 1 month after 2p+1, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTaP 2, 4, 6 both groups; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTP both groups at 2, 4, 6. Unclear if aP or wP; 5 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 6 DTwP-IPV both groups at 3, 4, 5

Figure 9: Seropositivity after 3p and 2p+1, 1 and 6 months after 3p and 1 month after 2p+1, 1.0µg/ml

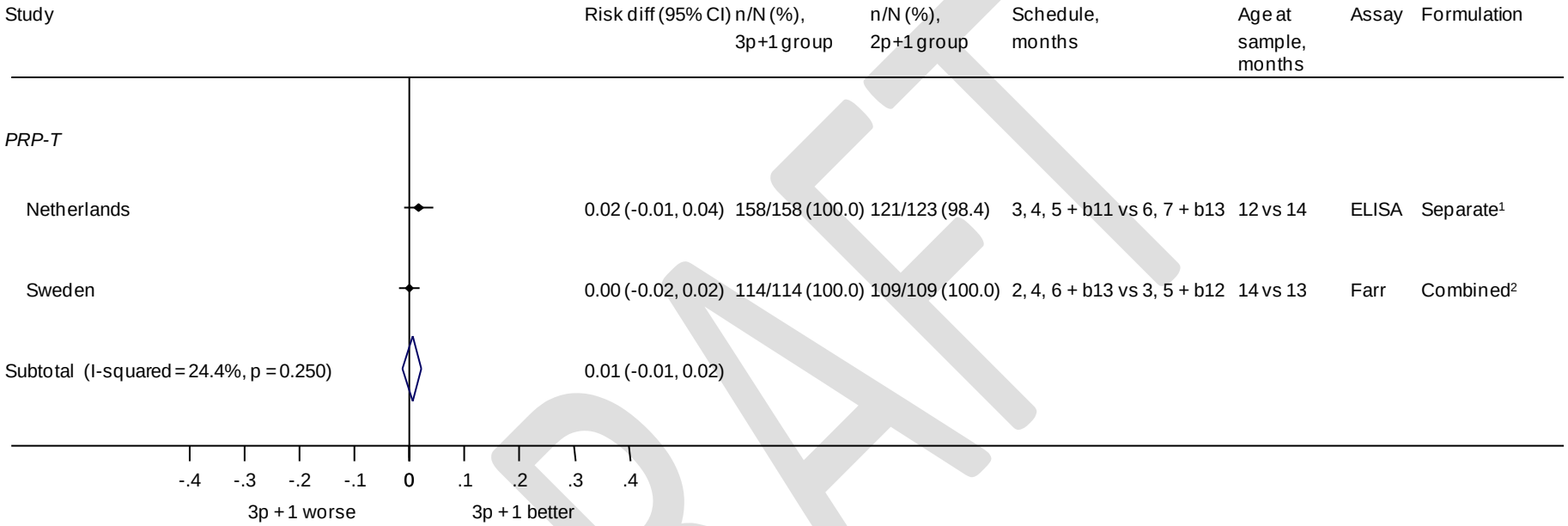


Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTaP 2, 4, 6 both groups; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTP both groups at 2, 4, 6. Unclear if aP or wP; 5 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 6 DTwP-IPV both groups at 3, 4, 5

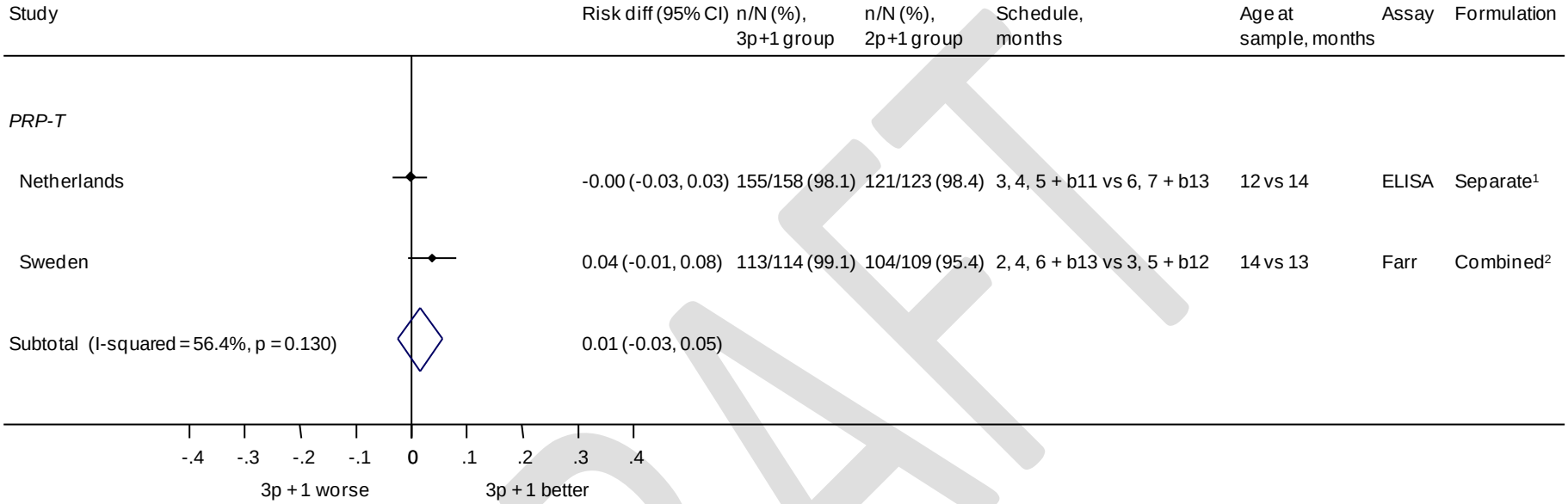
3p+1 vs 2p+1 schedules

Figure 10: 3p+1 vs 2p+1, 1m post booster, 0.15µg/ml



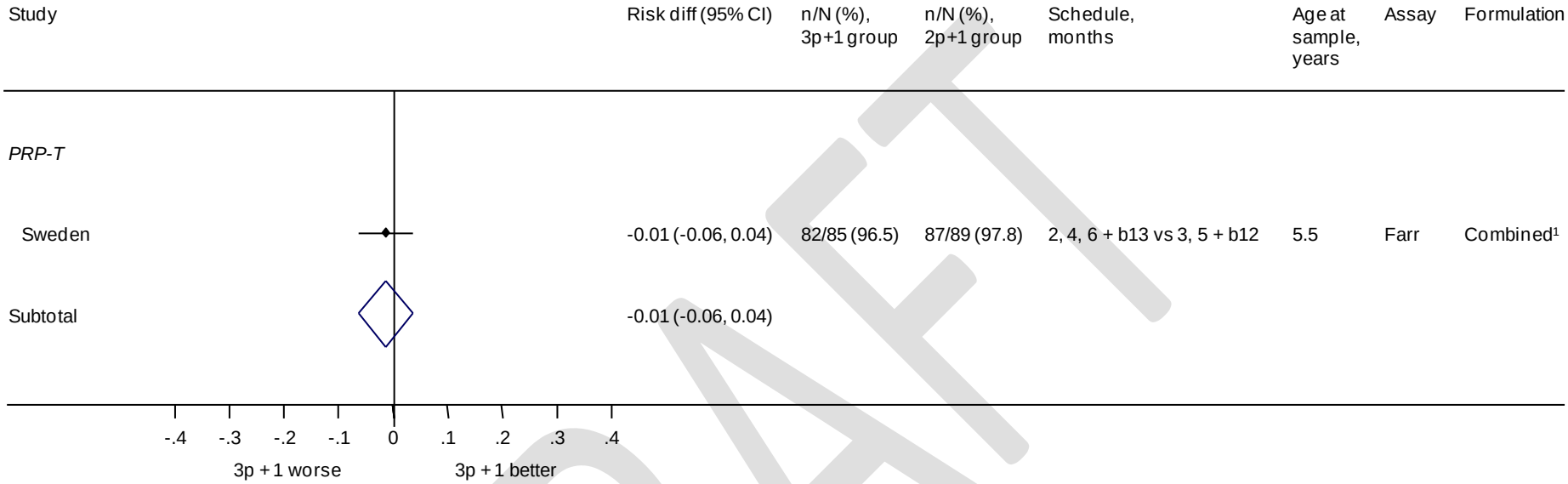
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTwP-IPV both groups at 3, 4, 5; 2 DTaP-IPV/Hib both groups

Figure 11: 3p+1 vs 2p+1, 1m post booster, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTwP-IPV both groups at 3, 4, 5; 2 DTaP-IPV/Hib both groups

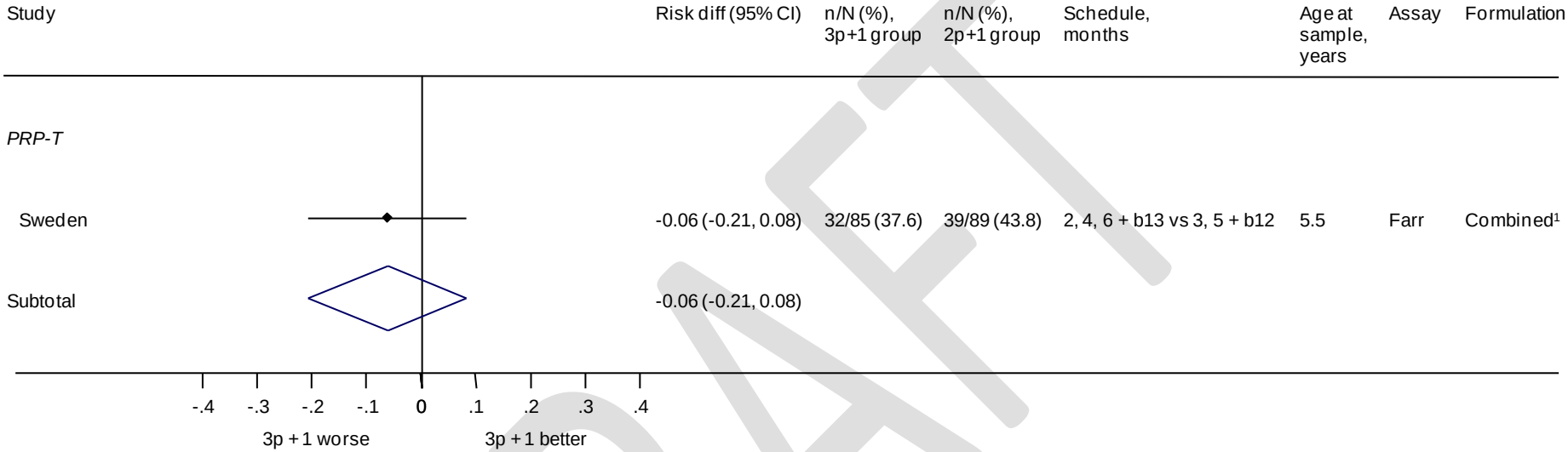
Figure 12: 3p+1 vs 2p+1, approx. 4.5y post booster, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate– Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTaP-IPV/Hib both groups

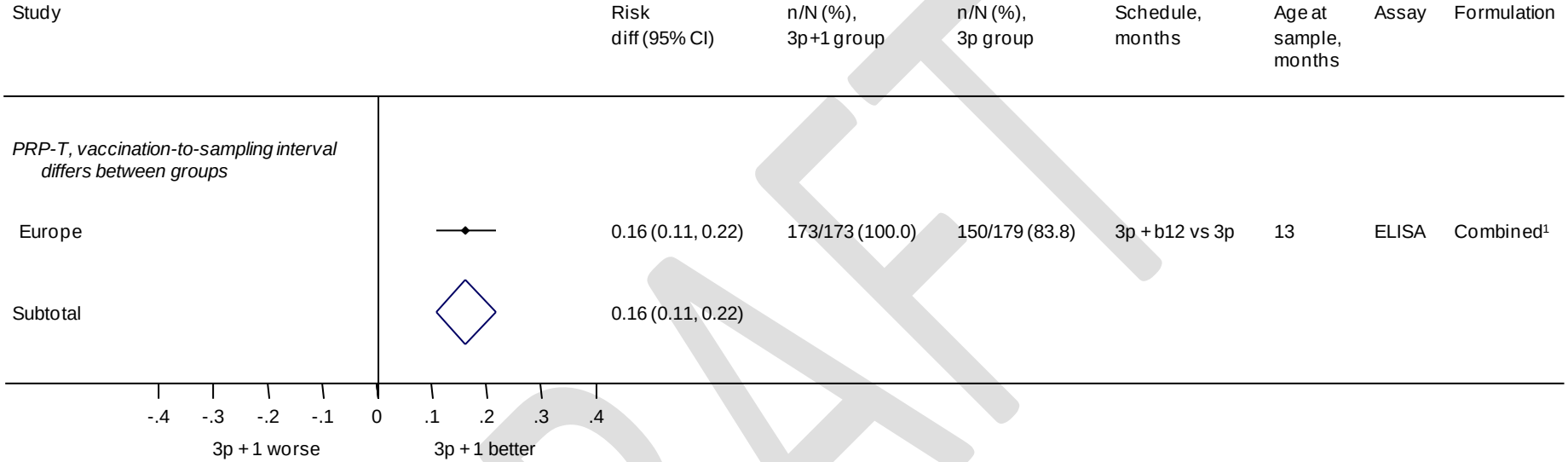
Figure 13: 3p+1 vs 2p+1, approx. 4.5y post booster, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate– Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-IPV/Hib both groups

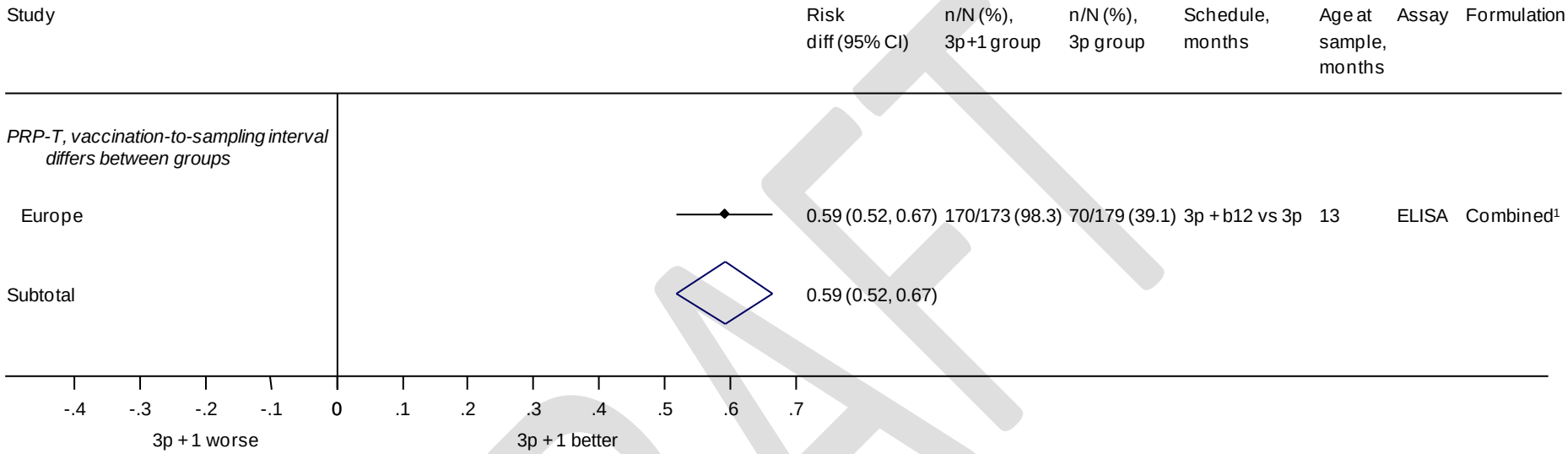
3p+1 vs 3p schedules

Figure 14: 3p+1 vs 3p, 1m post booster, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-hepB-IPV/Hib. Men ACWY given at 12m in both groups

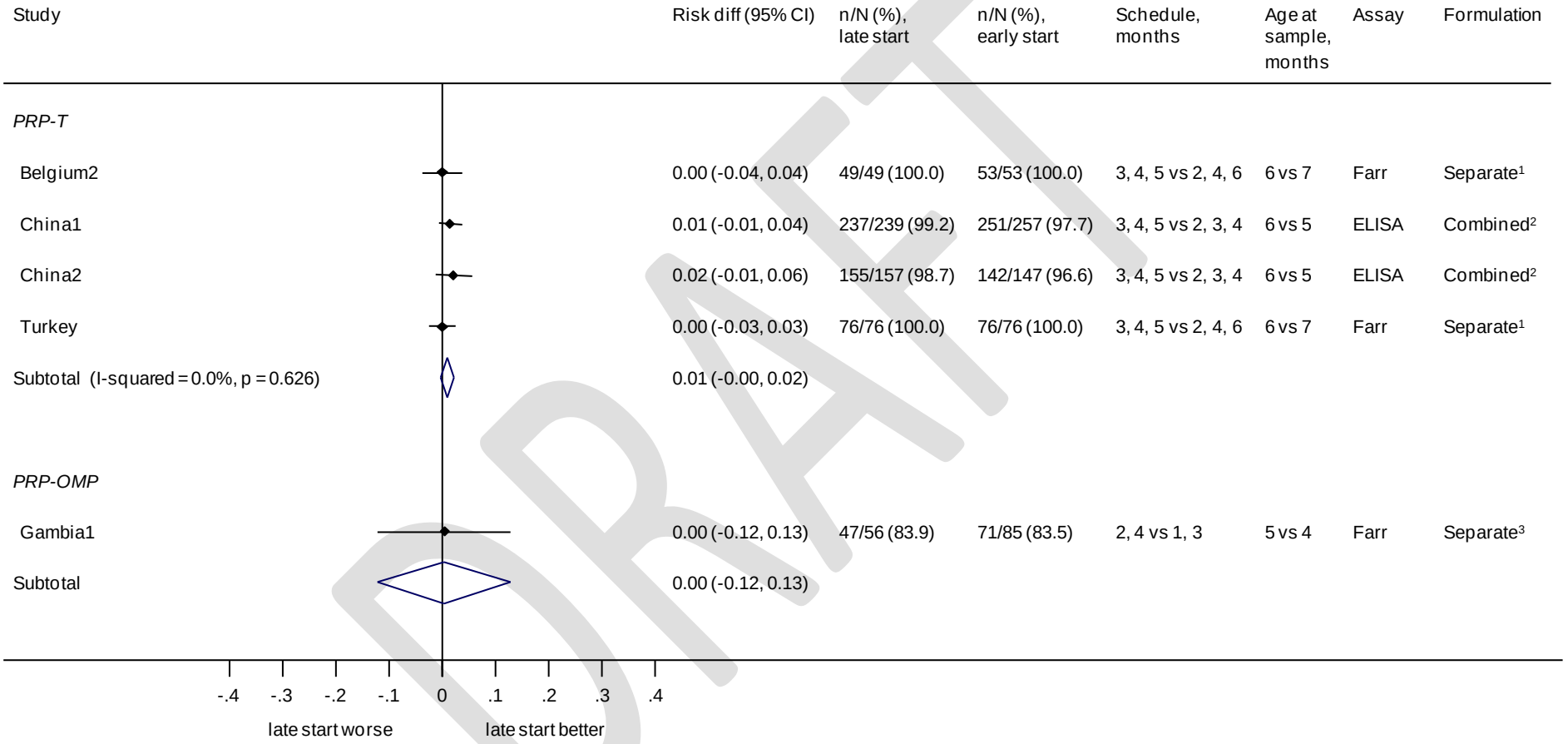
Figure 15: 3p+1 vs 3p, 1m post booster, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate– Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-hepB-IPV/Hib. Men ACWY given at 12m in both groups

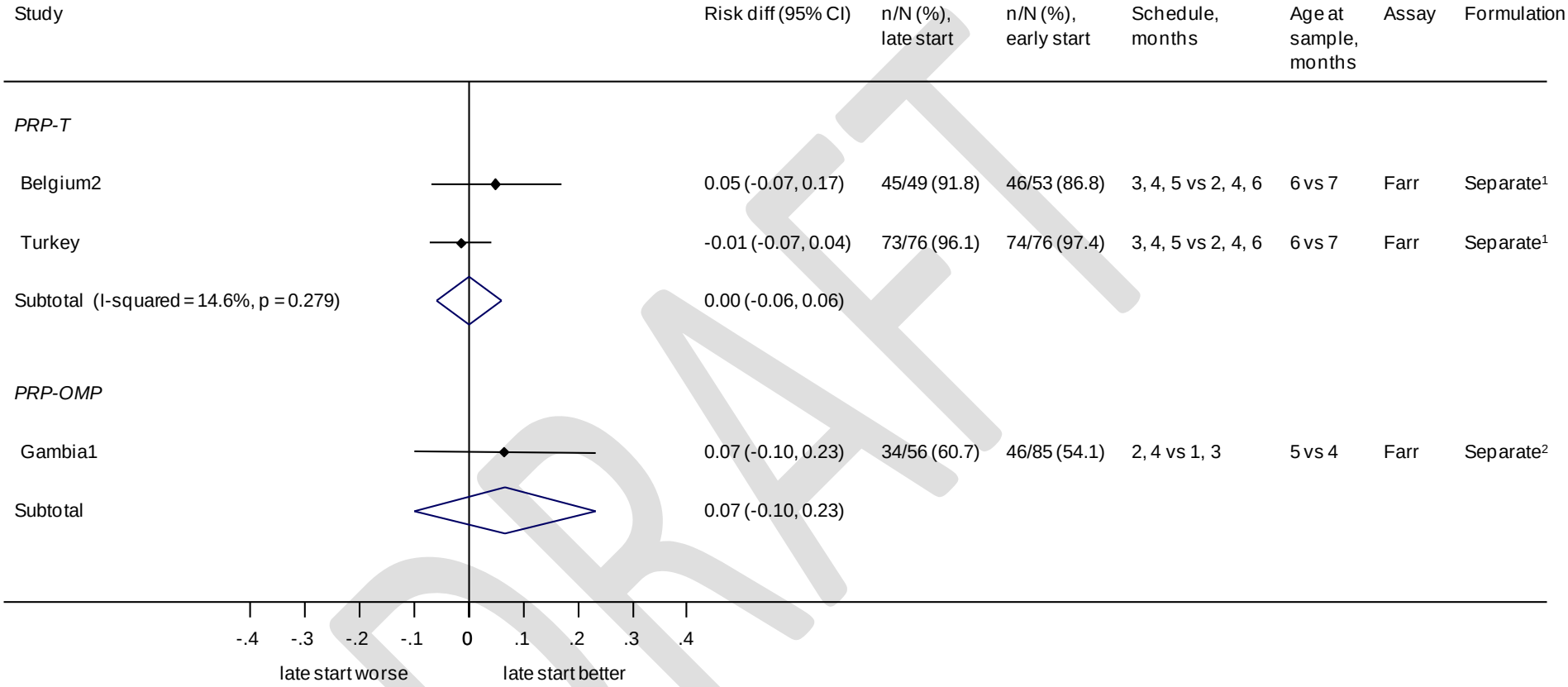
Late vs early start schedules

Figure 16: late vs early start, 1m post primary, 0.15µg/ml



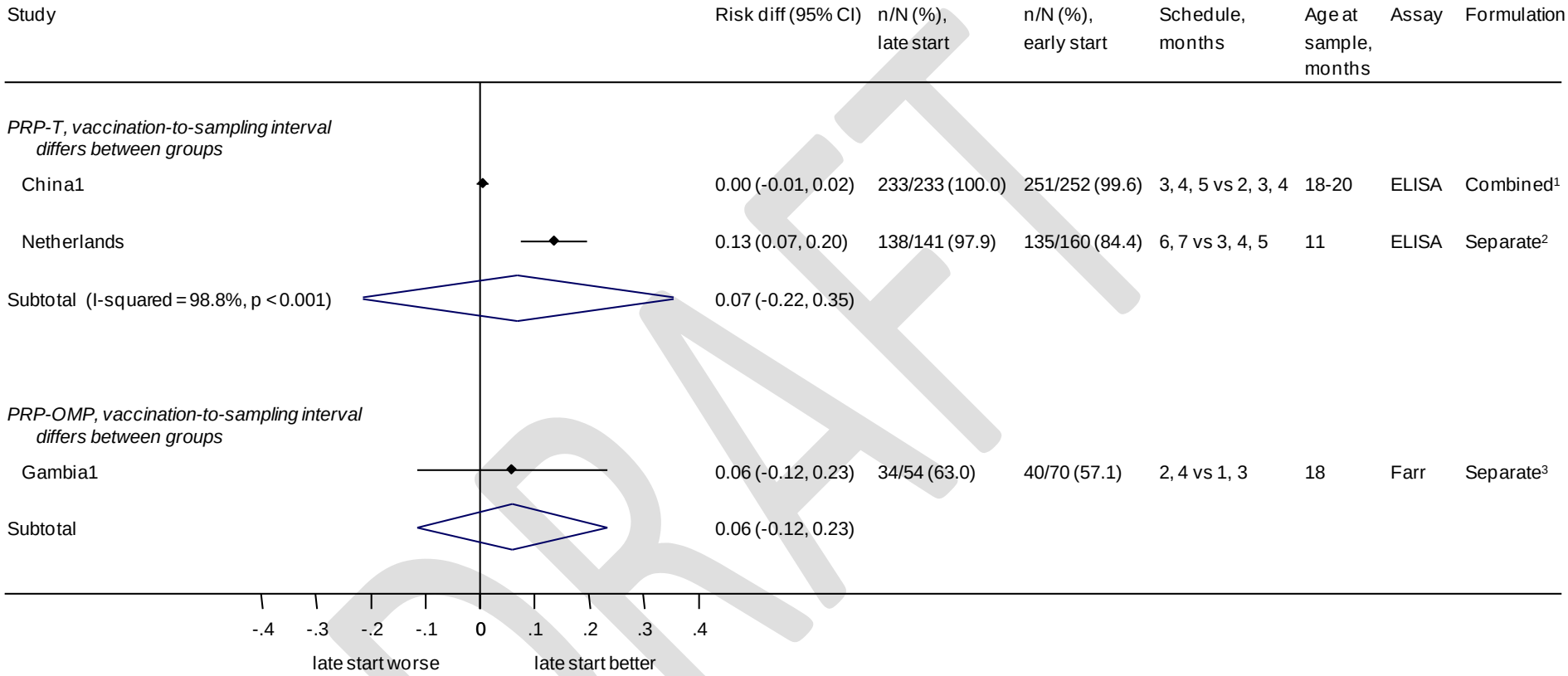
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP at same time as Hib in separate syringe; 2 DTaP-IPV/Hib; 3 OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

Figure 17: late vs early start, 1m post primary, 1.0µg/ml



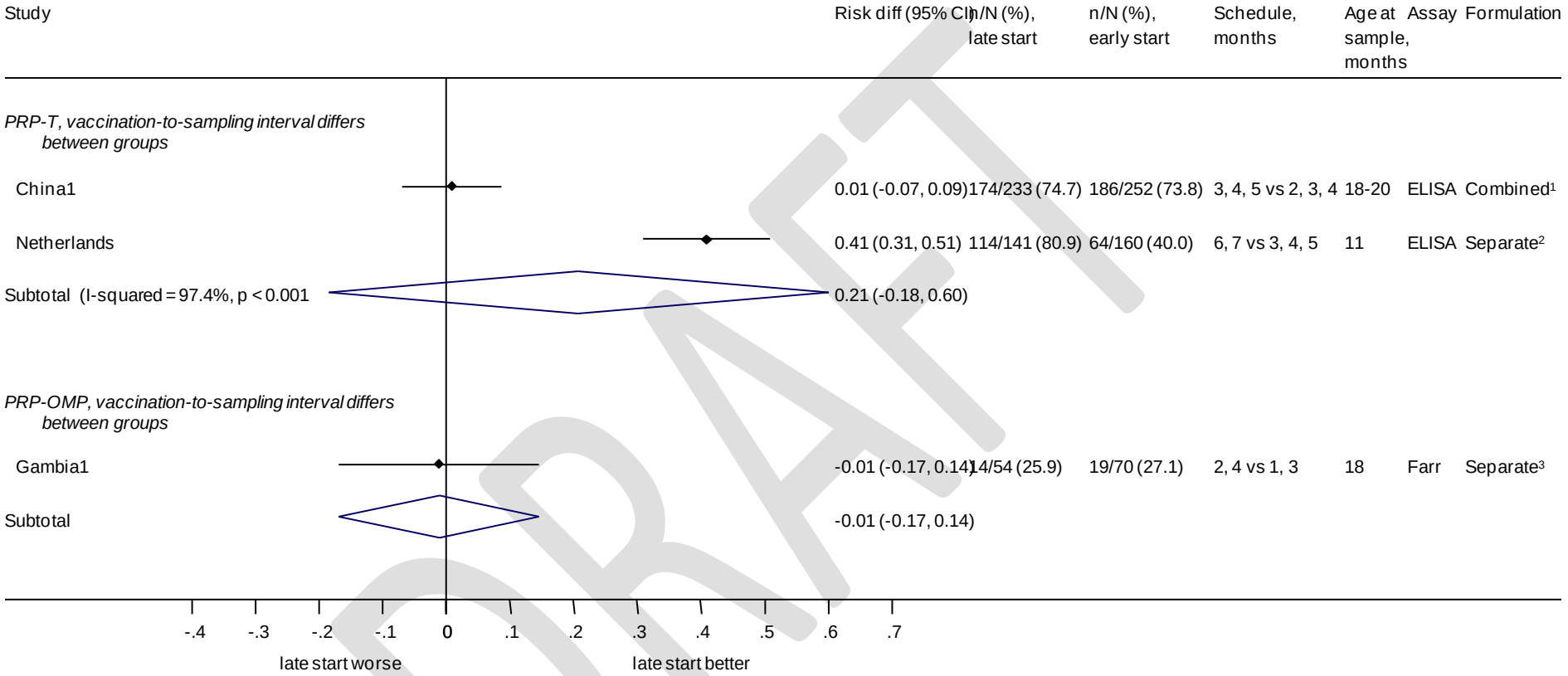
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP at same time as Hib in separate syringe; 2 OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

Figure 18: late vs early start, pre-booster, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate– Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time fromHib vaccine.
1 DTaP-IPV/Hib; 2 DTwP-IPV both groups at 3, 4, 5; 3 OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

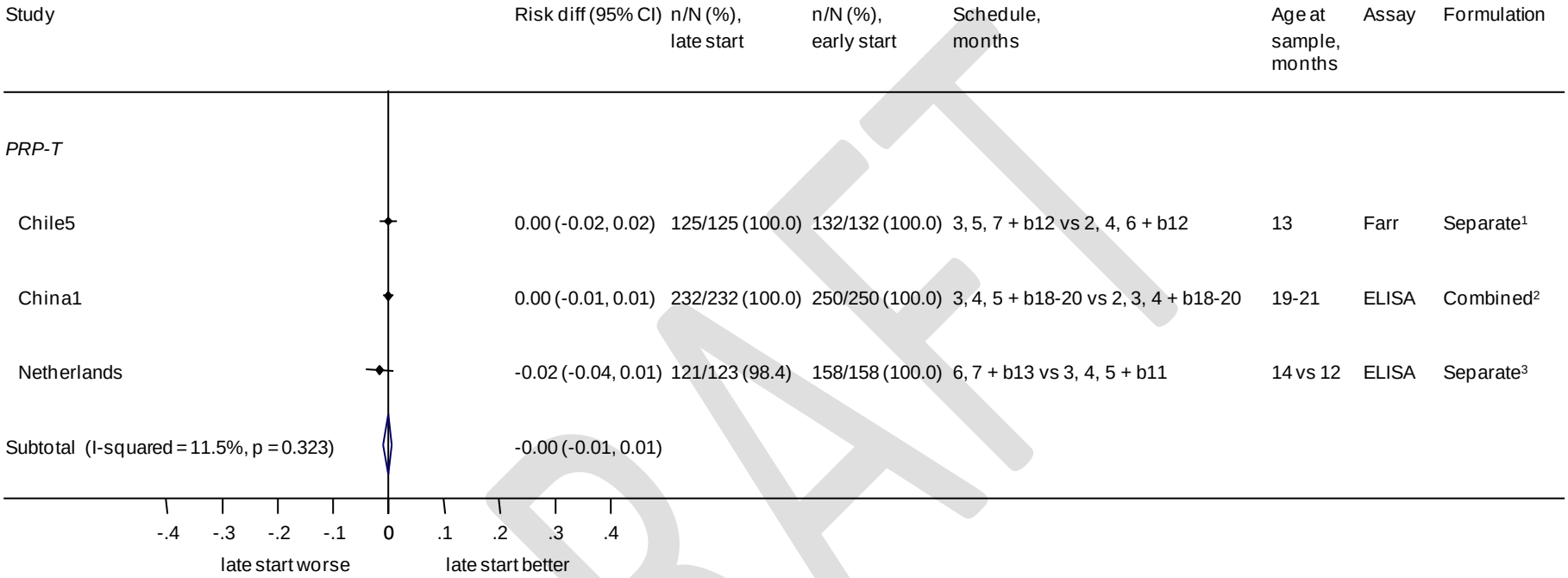
Figure 19: late vs early start, pre-booster, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

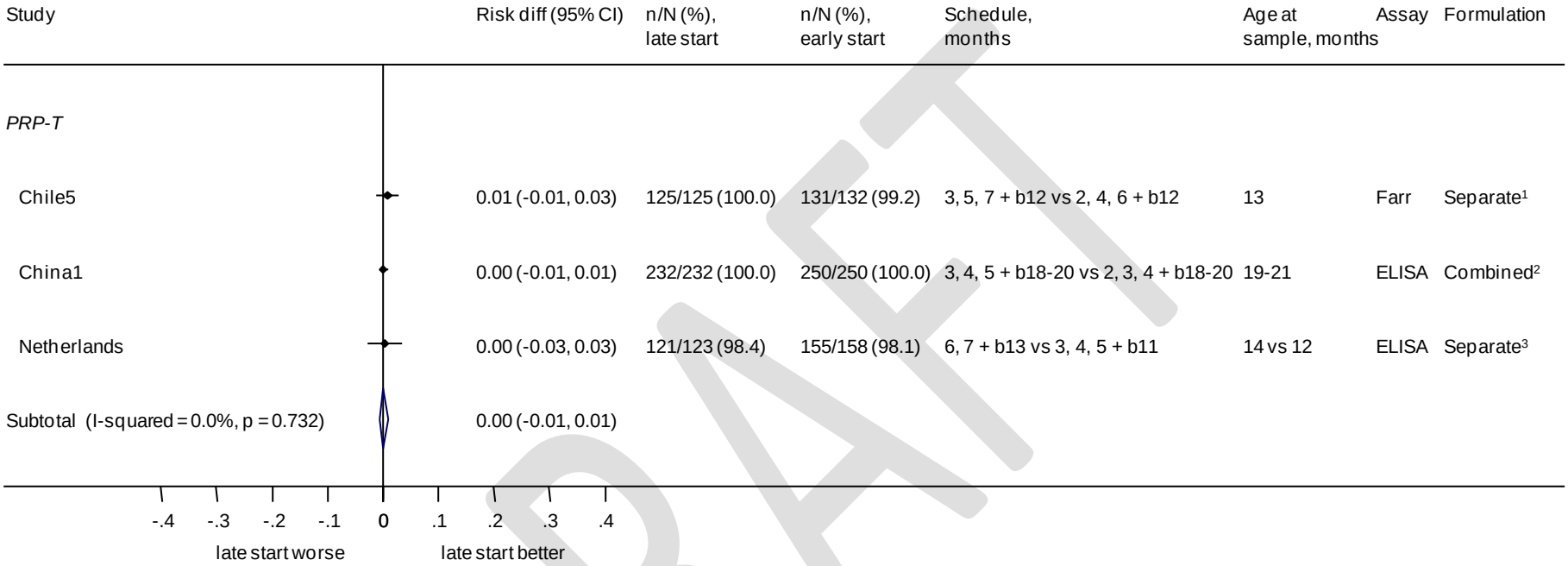
1 DTaP-IPV/Hib; 2 DTwP-IPV both groups at 3, 4, 5; 3 OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

Figure 20: late vs early start, 1m post booster, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP 2, 4, 6 both groups; 2 DTaP-IPV/Hib; 3 DTwP-IPV both groups at 3, 4, 5

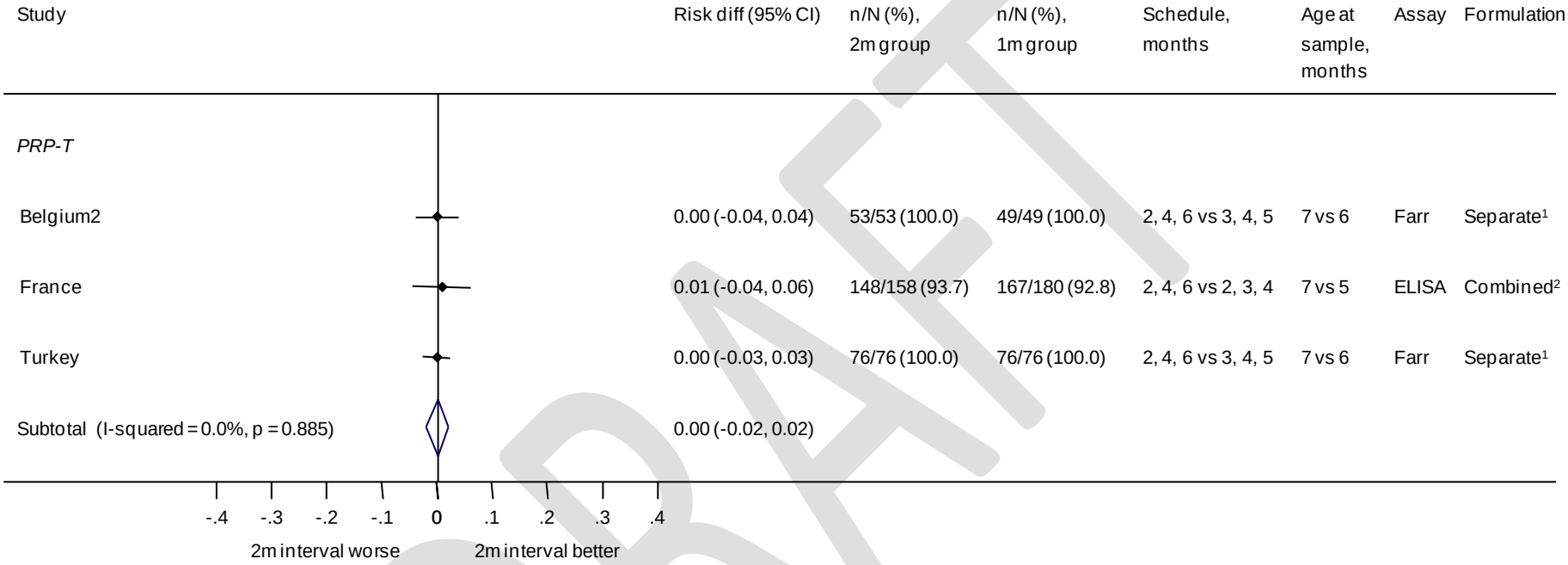
Figure 21: late vs early start, 1m post booster, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate– Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP 2, 4, 6 both groups; 2 DTaP-IPV/Hib; 3 DTwP-IPV both groups at 3, 4, 5

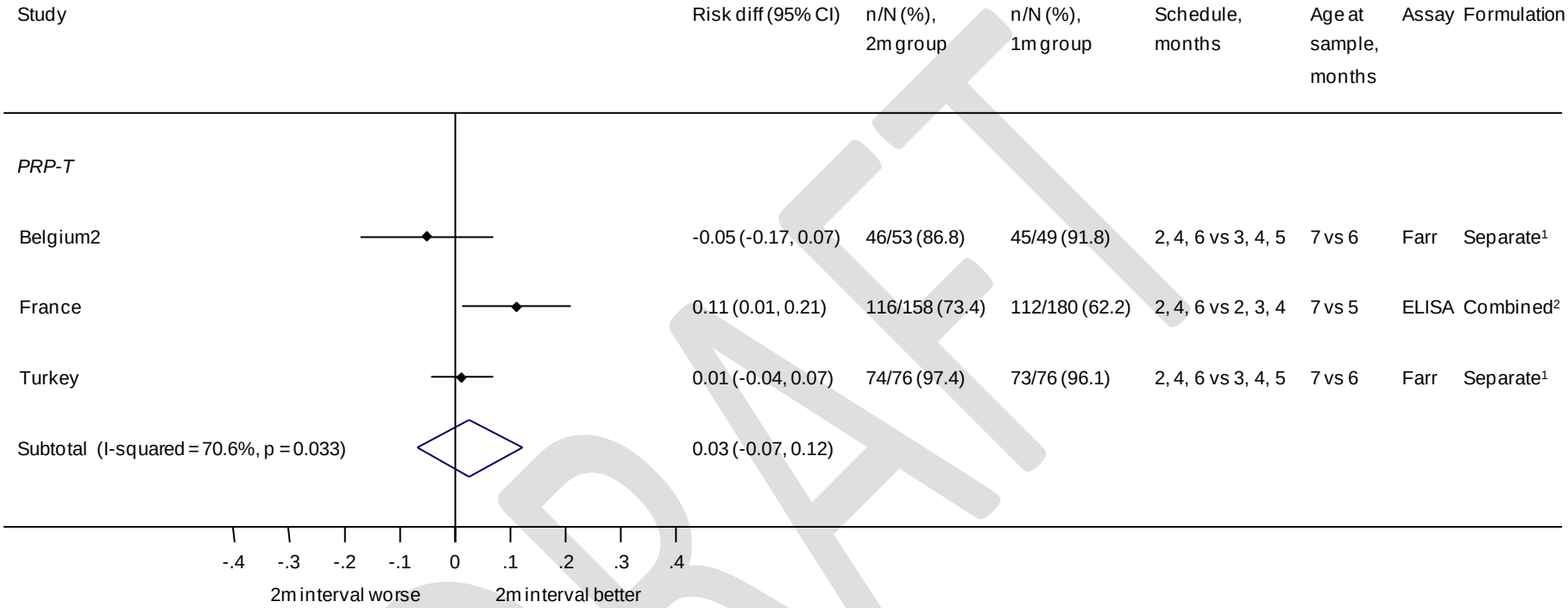
2-month vs 1-month interval schedules

Figure 22: 2m vs 1m interval in primary course, 1m post primary, 0.15µg/ml



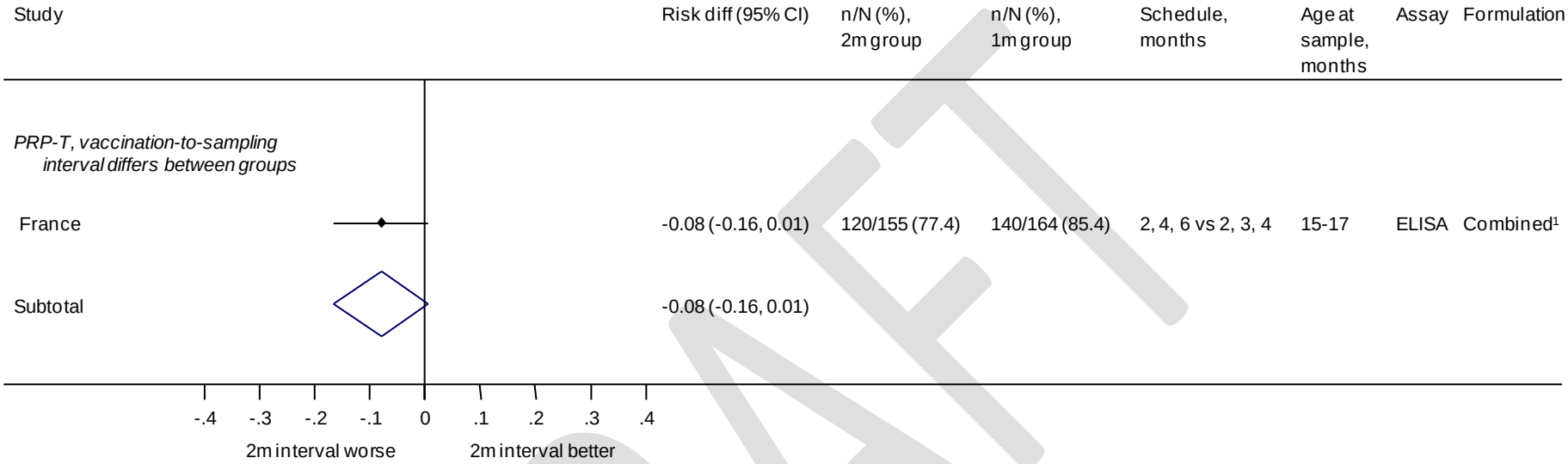
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP at same time as Hib in separate syringe; 2 DTaP-hepB-IPV/Hib

Figure 23: 2m vs 1m interval in primary course, 1m post primary, 1.0µg/ml



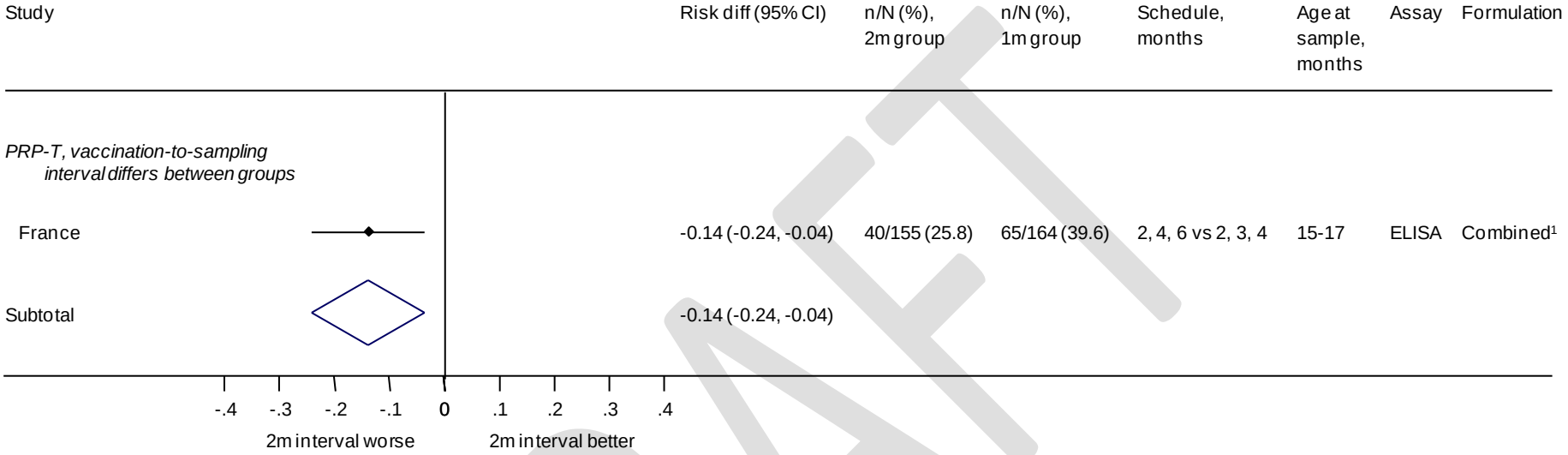
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP at same time as Hib in separate syringe; 2 DTaP-hepB-IPV/Hib

Figure 24: 2m vs 1m interval in primary course, pre-booster, 0.15µg/ml



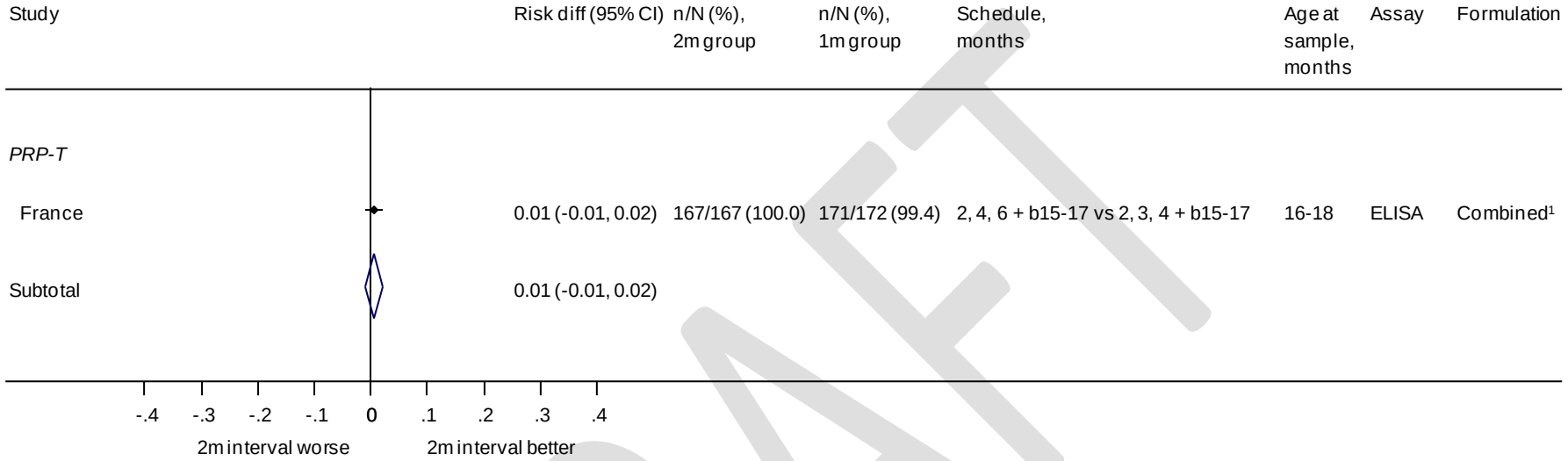
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-hepB-IPV/Hib

Figure 25: 2m vs 1m interval in primary course, pre-booster, 1.0µg/ml



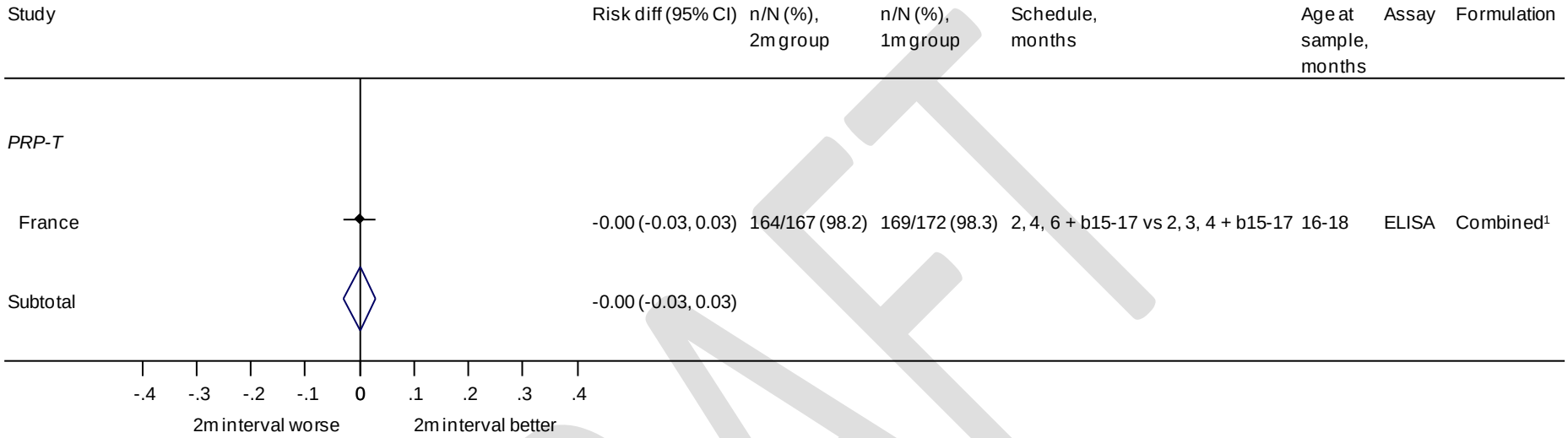
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-hepB-IPV/Hib

Figure 26: 2m vs 1m interval in primary course, 1m post booster, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-hepB-IPV/Hib

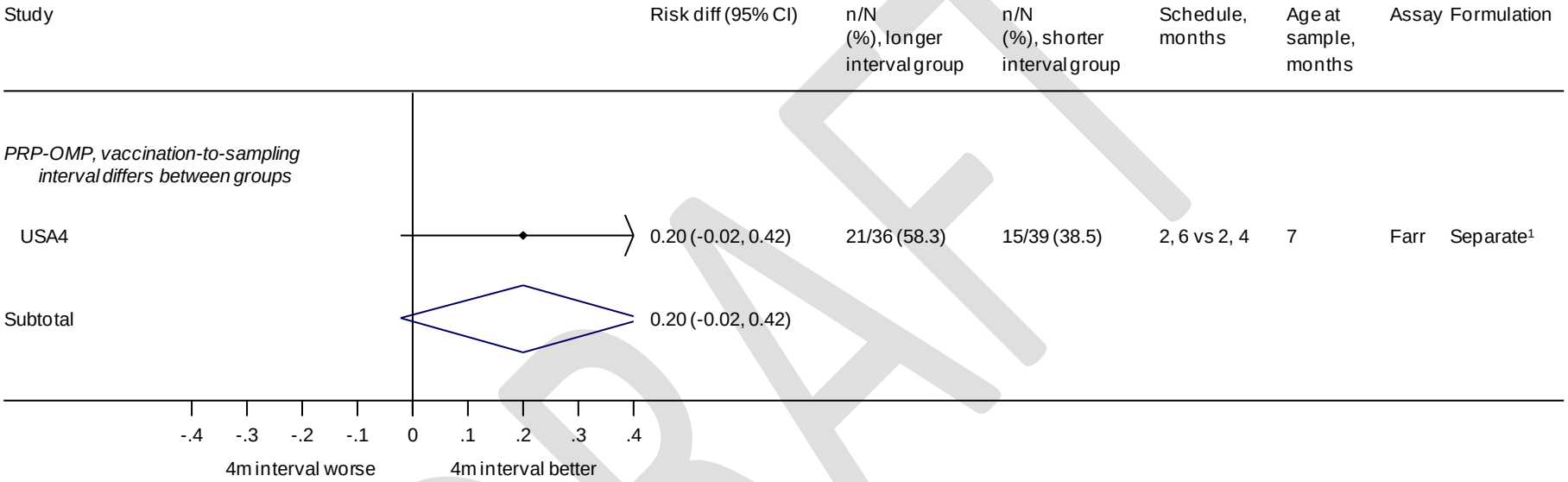
Figure 27: 2m vs 1m interval in primary course, 1m post booster, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1 DTaP-hepB-IPV/Hib

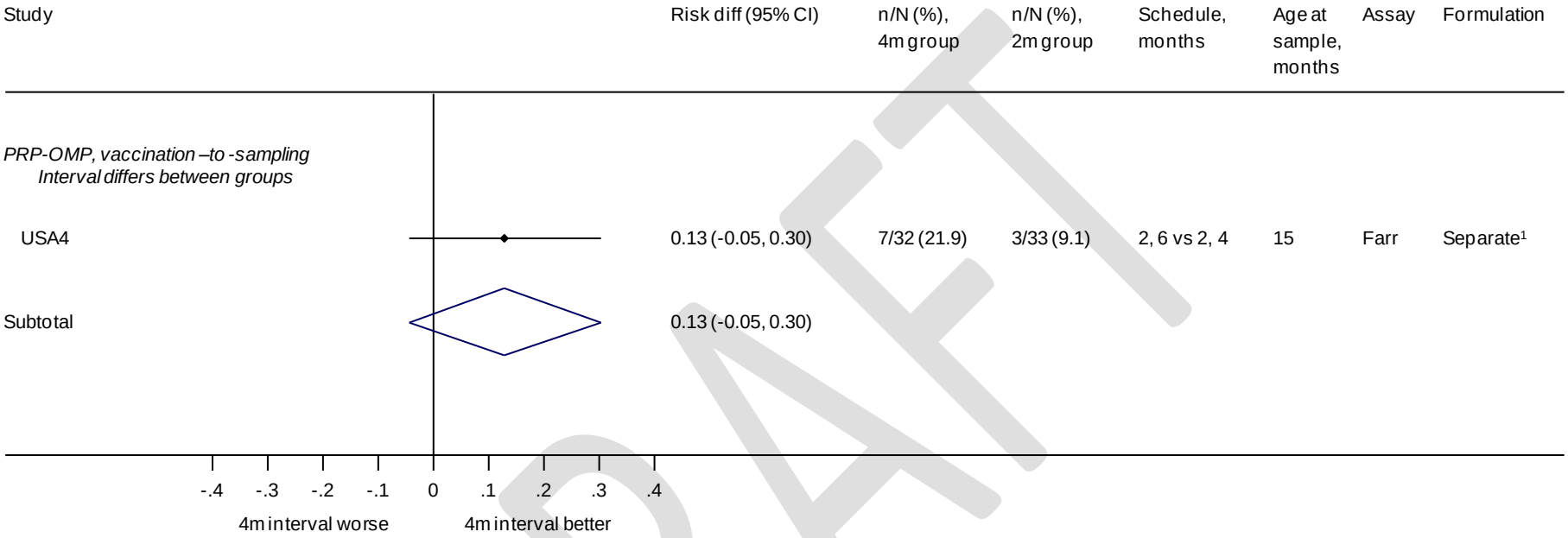
4-month vs 2-month interval schedules

Figure 28: 4-month vs 2-month interval, 1m post primary, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1DTP, OPV, MMR given to both groups "according to published guidelines"

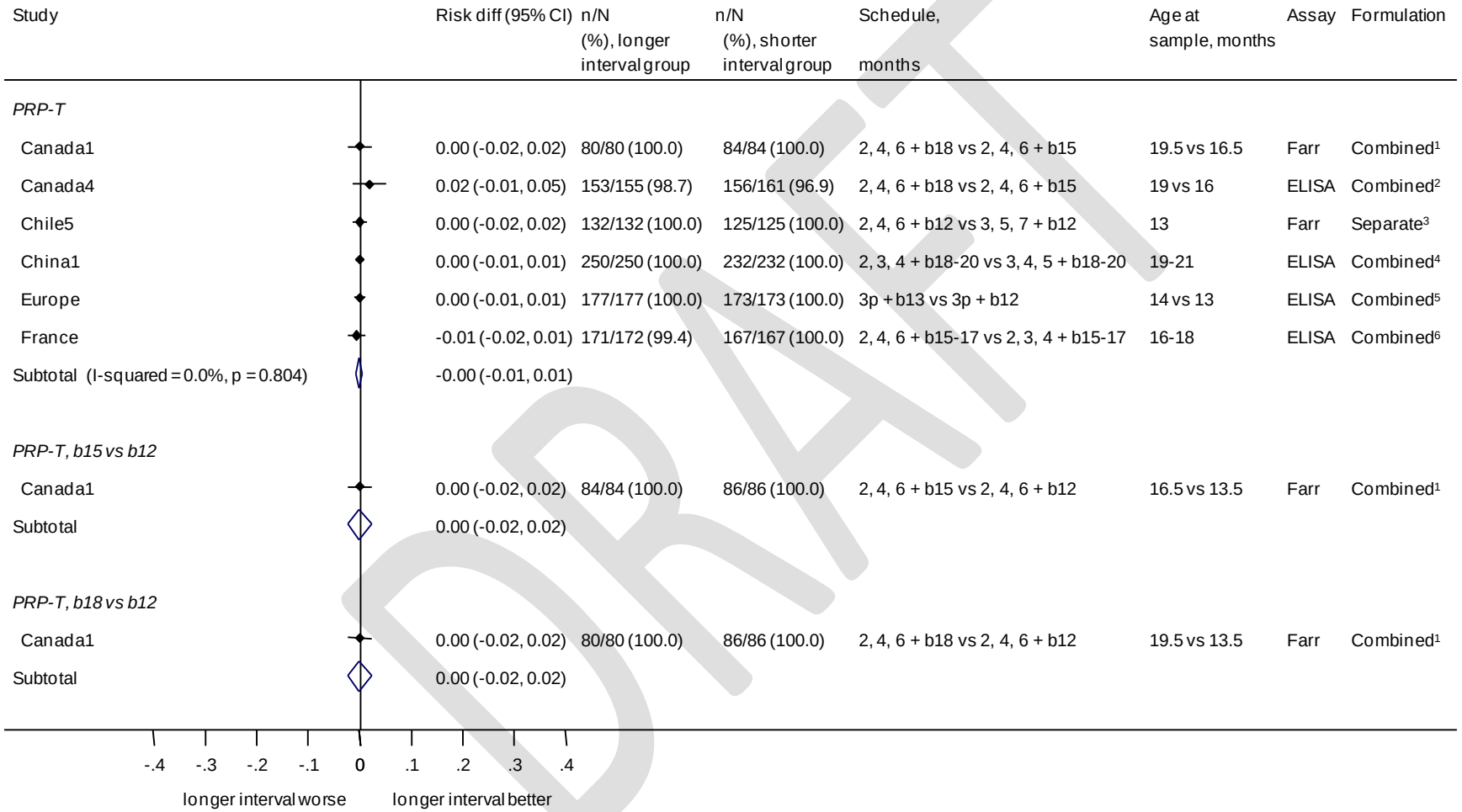
Figure 29: 4-month vs 2-month interval, pre-booster, 1.0µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.
1DTP, OPV, MMR given to both groups "according to published guidelines"

Long vs short interval between primary and booster schedules

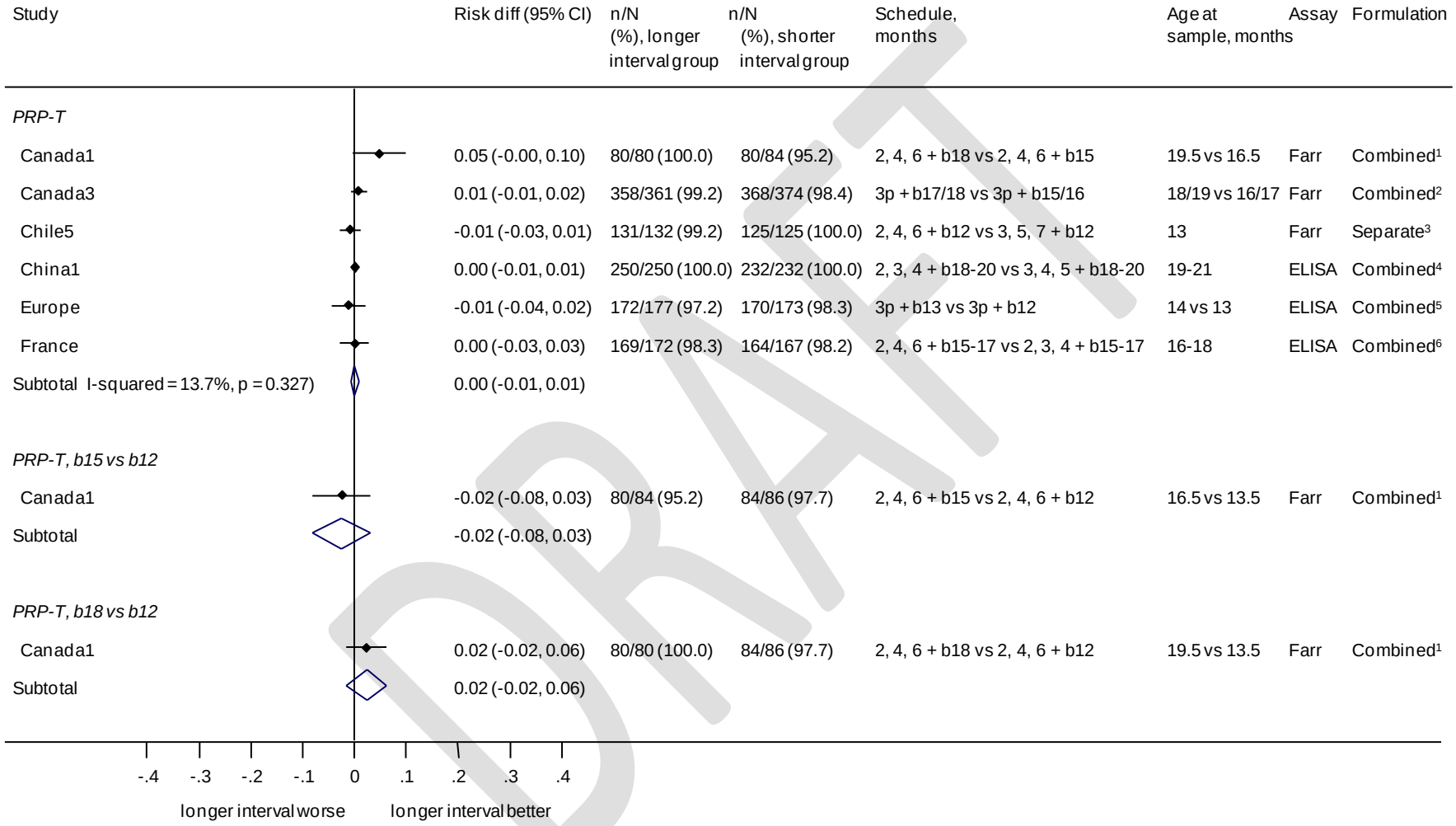
Figure 30: Long vs short interval between primary and booster, 1m post-booster, 0.15µg/ml



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTP-IPV/Hib. Not stated if aP or wP. MMR given separately at 12m; 2 DTaP-IPV/Hib. PCV7 given at the same time but separate to other vaccines; 3 DTaP 2, 4, 6 both groups; 4 DTaP-IPV/Hib; 5 DTaP-hepB-IPV/Hib. Men ACWY given at 12m in both groups; 6 DTaP-hepB-IPV/Hib

Figure 31: Long vs short interval between primary and booster, 1m post-booster, 1.0µg/ml

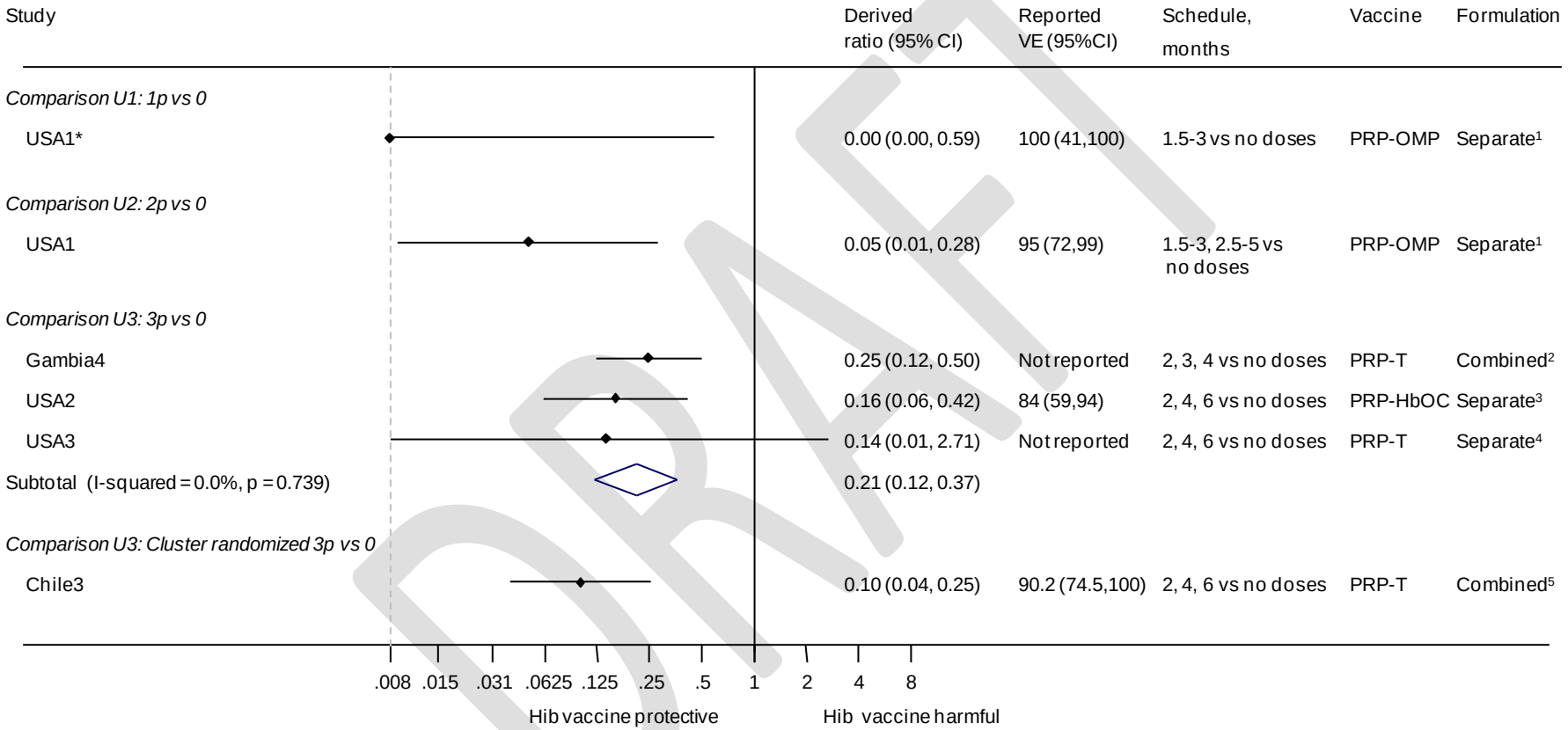


Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTP-IPV/Hib. Not stated if aP or wP. MMR given separately at 12m; 2 DTaP-IPV/Hib; 3 DTaP 2, 4, 6 both groups; 4 DTaP-IPV/Hib; 5 DTaP-hepB-IPV/Hib. Men ACWY given at 12m in both groups; 6 DTaP-hepB-IPV/Hib

Clinical data

Figure 32: Invasive Hib disease, intention to treat analyses, all available schedules

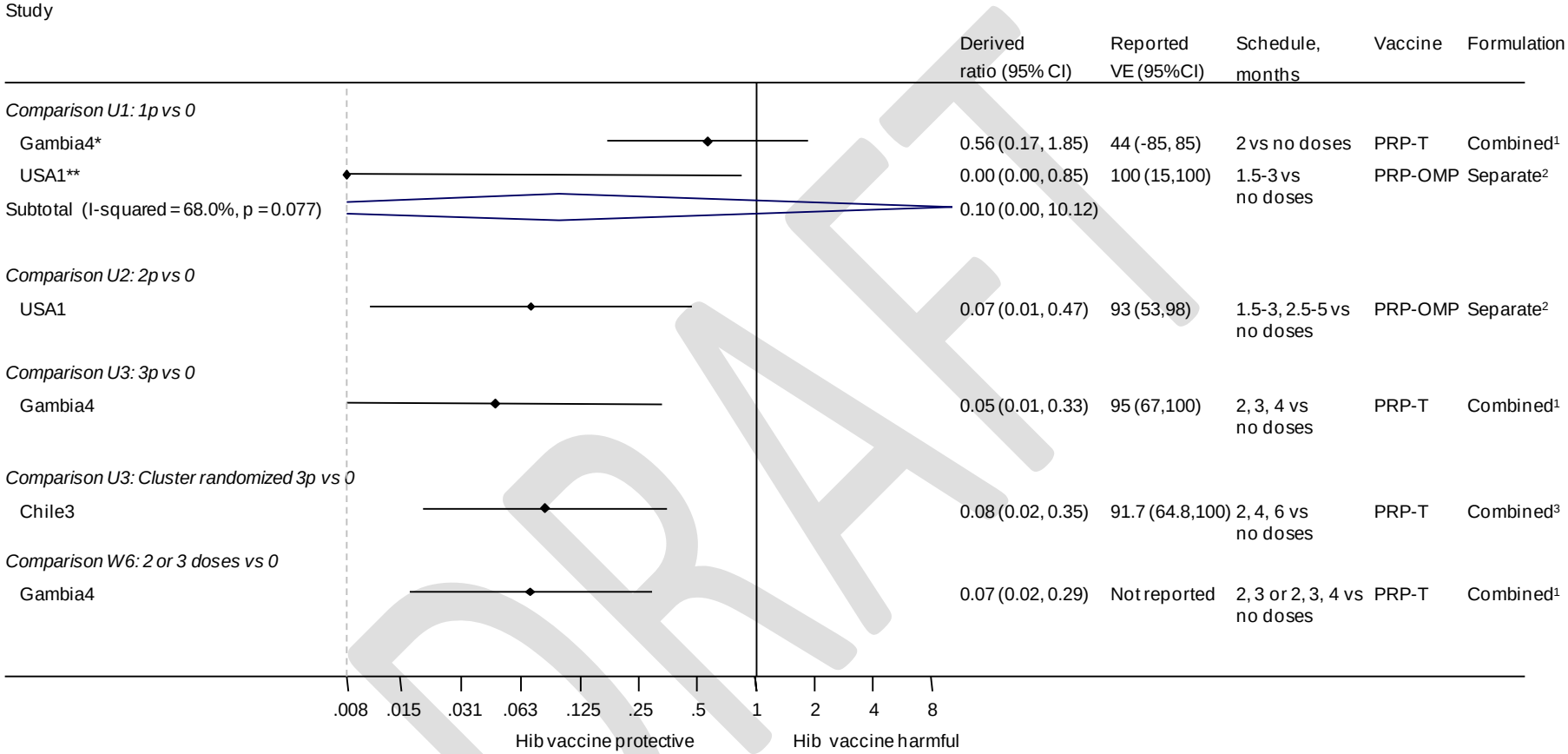


For the purposes of this graph, "intention to treat" is used to mean analyses where no individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.3p – 3-dose primary schedule, etc.; Hib – *Haemophilus influenzae* type b vaccine; VE - vaccine efficacy

* USA1 - onset before second dose

1 DTP and oral polio given at the same time but separately from Hib vaccine; 2 DTP/Hib. Not stated if aP or wP; 3 Other vaccines not described; 4 DTP/Hib. Not stated if aP or wP; 5 DTP/Hib. Not stated if aP or wP

Figure 33: Invasive Hib disease, per protocol analyses, all available schedules



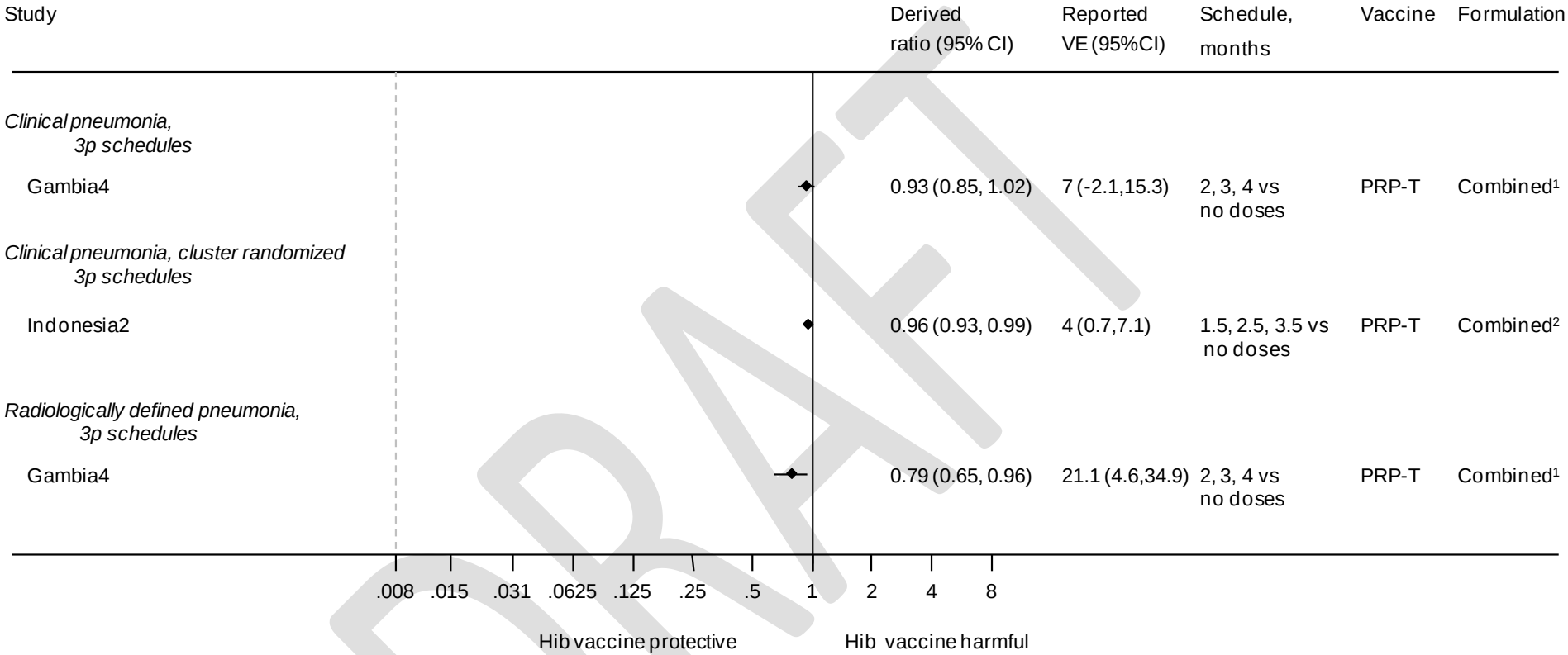
For the purposes of this graph, "intention to treat" is used to mean analyses where no individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.3p – 3-dose primary schedule, etc.; Hib – *Haemophilus influenzae* type b vaccine; VE - vaccine efficacy

*Gambia 4 - onset after one dose. Onset before second dose also available: "Efficacy against all invasive disease after a single dose of vaccine was 44% (PRP-T vaccinees five, controls nine [95% CI 85, 85]). Amongst children who had received one dose only less than 56 days before their admission there were two cases of invasive disease in the vaccine group and seven in the control group. Thus, the short-term vaccine efficacy after one dose was 71% (CI 50,97)."

** USA1 - onset before second dose.

1 DTP/Hib. Not stated if aP or wP; 2 DTP and oral polio given at the same time but separately from Hib vaccine; 3 DTP/Hib. Not stated if aP or wP. OPV at same time.

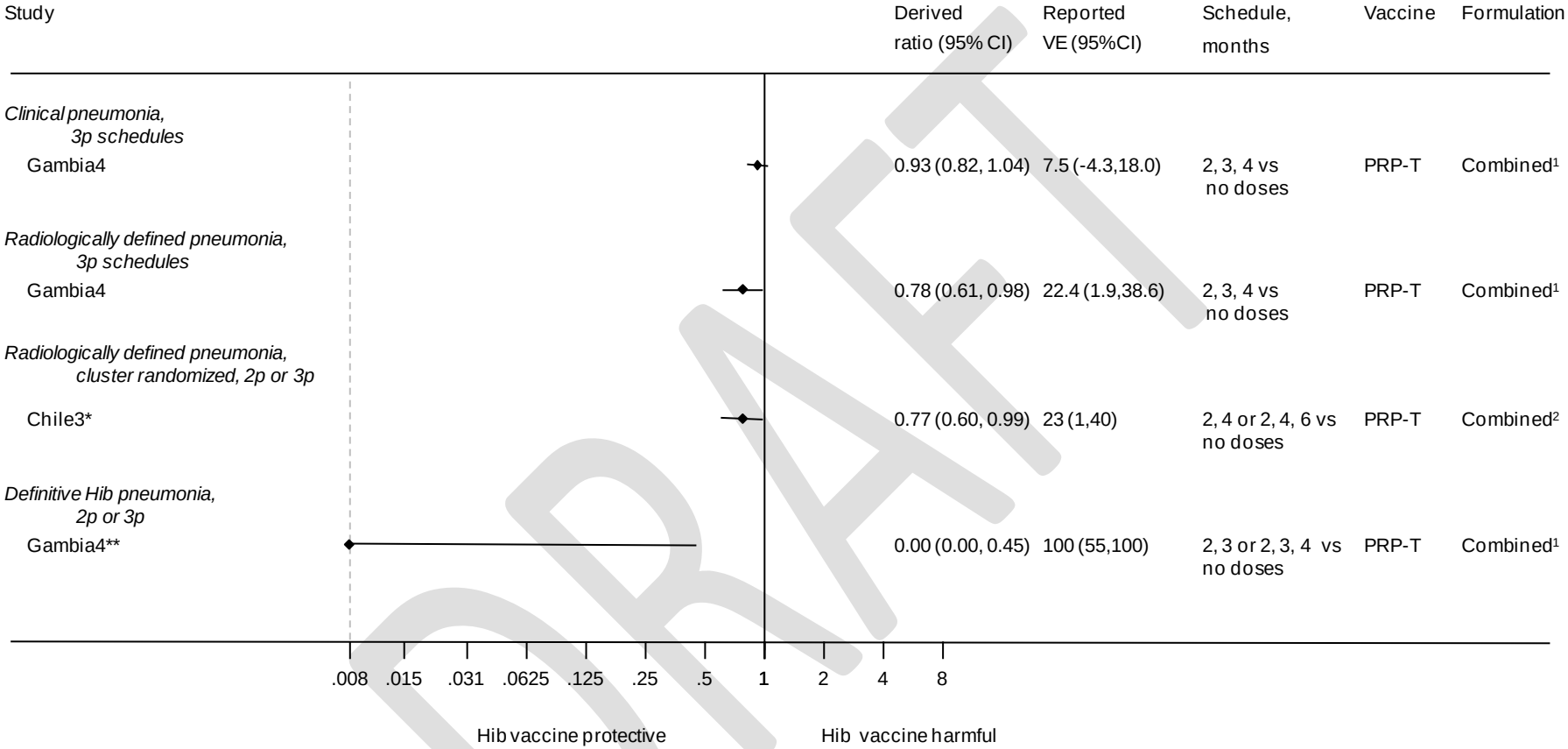
Figure 34: Pneumonia, intention to treat analyses, all available schedules



For the purposes of this graph, "per protocol" is used to mean analyses where some individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.3p – 3-dose primary schedule, etc.; Hib – *Haemophilus influenzae* type b vaccine; VE - vaccine efficacy

1 DTP/Hib. Not stated if aP or wP; 2 DTP-Hib. Not stated if aP or wP

Figure 35: Pneumonia, per protocol analyses, all available schedules



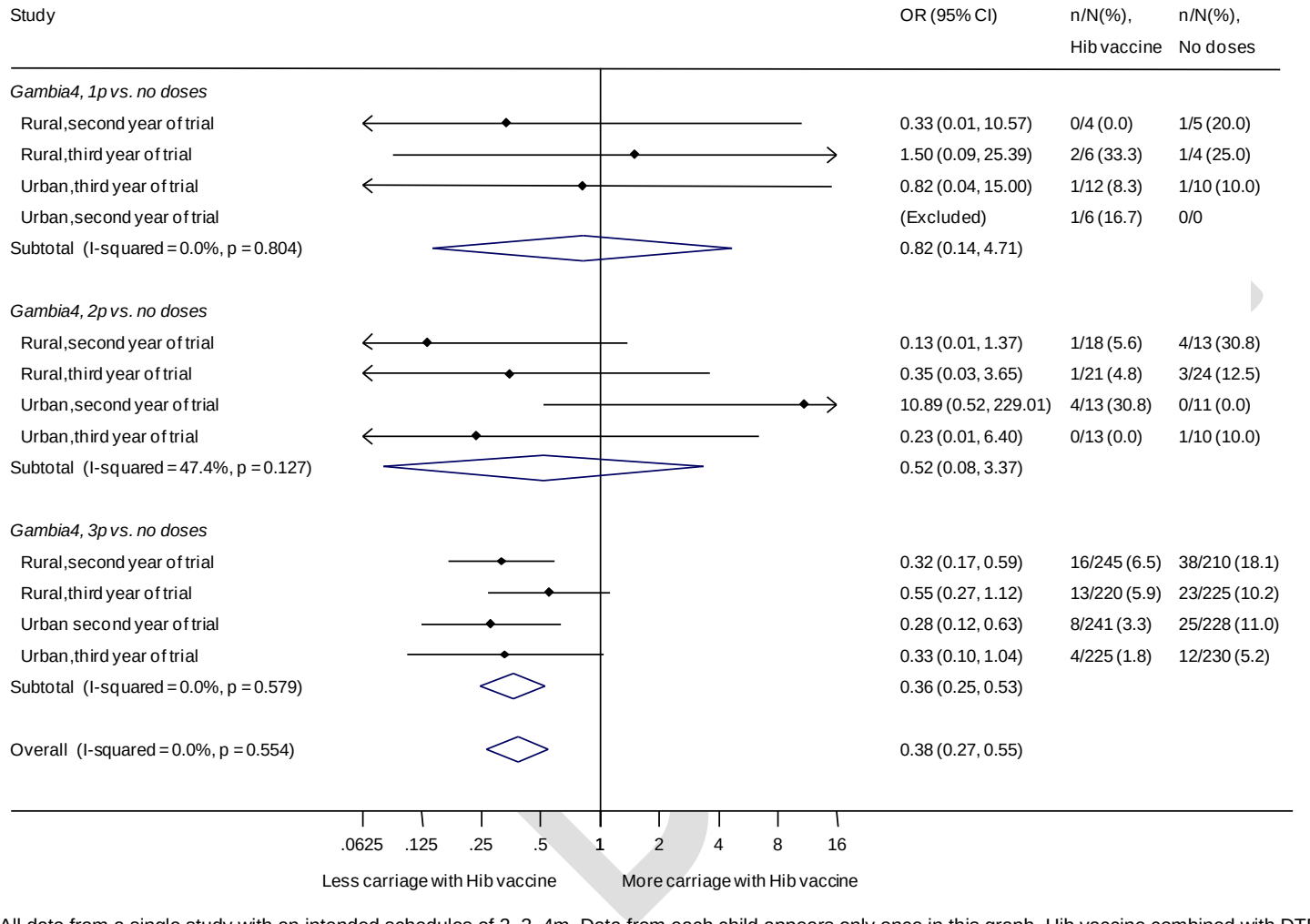
For the purposes of this graph, "per protocol" is used to mean analyses where some individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.3p – 3-dose primary schedule, etc.; Hib – *Haemophilus influenzae* type b vaccine; VE - vaccine efficacy

* Chile3 - data presented is for pneumonia with consolidation, effusion or and erythrocyte sedimentation rate ≥40mm/hour. 98% of include individuals had chest radiography performed.

**Gambia4 - analysis performed on a sub-group of individuals receiving either 2 or 3 doses of vaccine.

1 DTP/Hib. Not stated if aP or wP; 2 DTP/Hib. Not stated if aP or wP. OPV at same time.

Figure 36: Hib carriage, all available schedules



All data from a single study with an intended schedules of 2, 3, 4m. Data from each child appears only once in this graph. Hib vaccine combined with DTP. Not stated if aP or wP

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