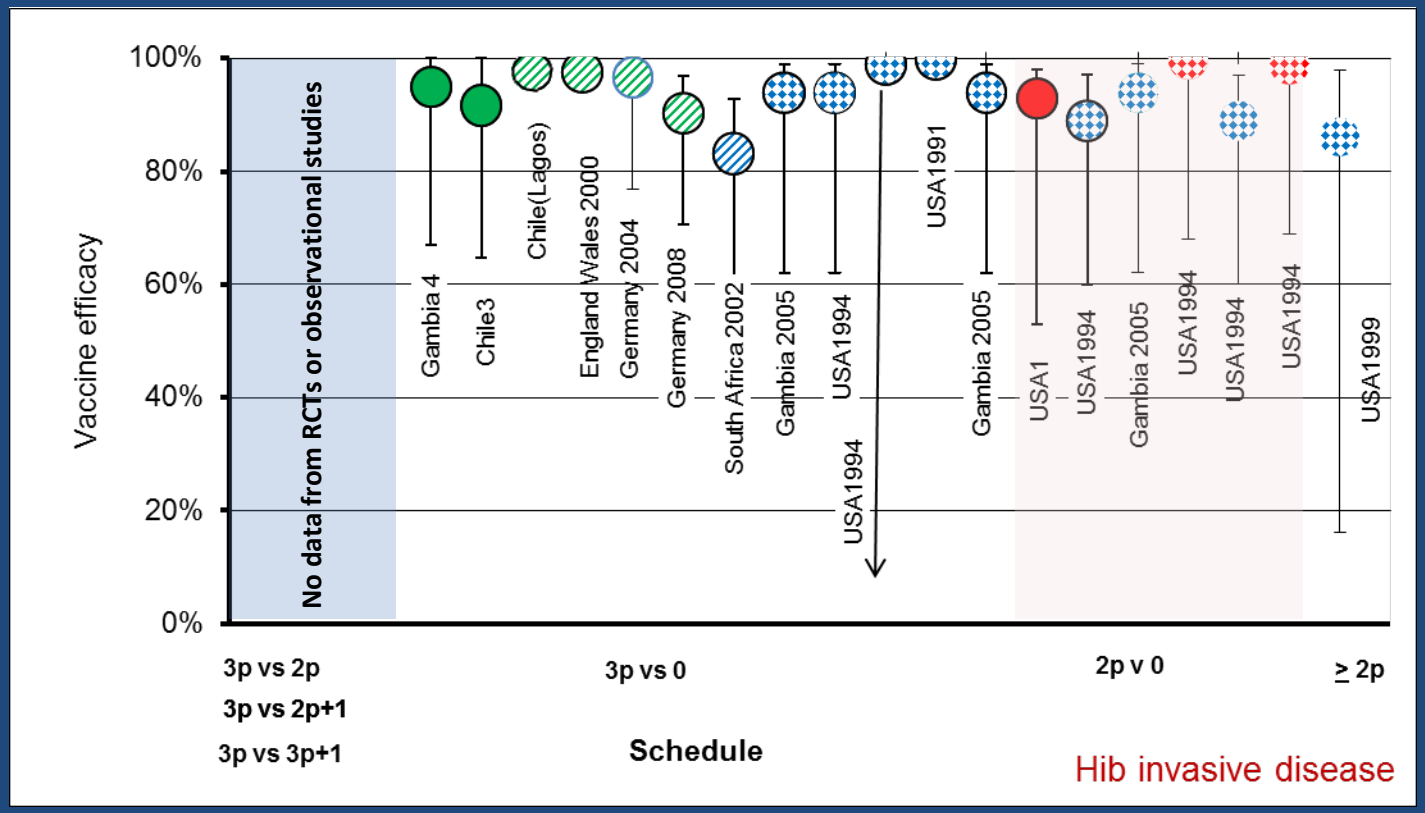
Hib Immunization Schedules

POLICY QUESTION

What are the optimal immunization schedules for *Haemophillus influenzae* type *b* vaccines (Hib) for children living in different epidemiological settings?

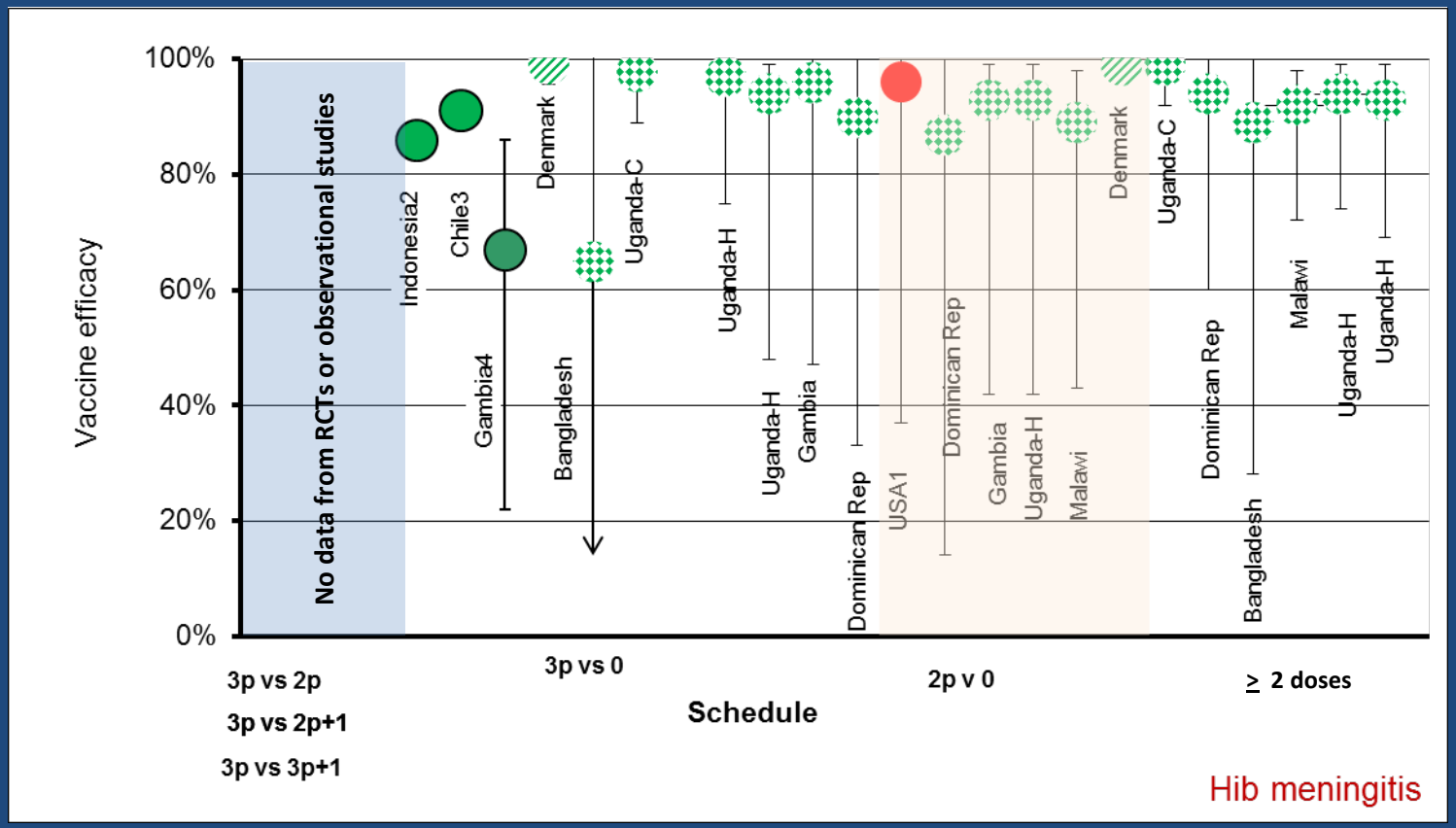
Number of doses
Age at administration of first dose
Interval between doses
Immunization of HIV infected children
Immunization of children in emergency settings

Effect of number of doses of Hib vaccine on invasive Hib disease



RCT	solid		PRP-T
Cohort	diagonal		HbOC
Case c	diamonds		OMP

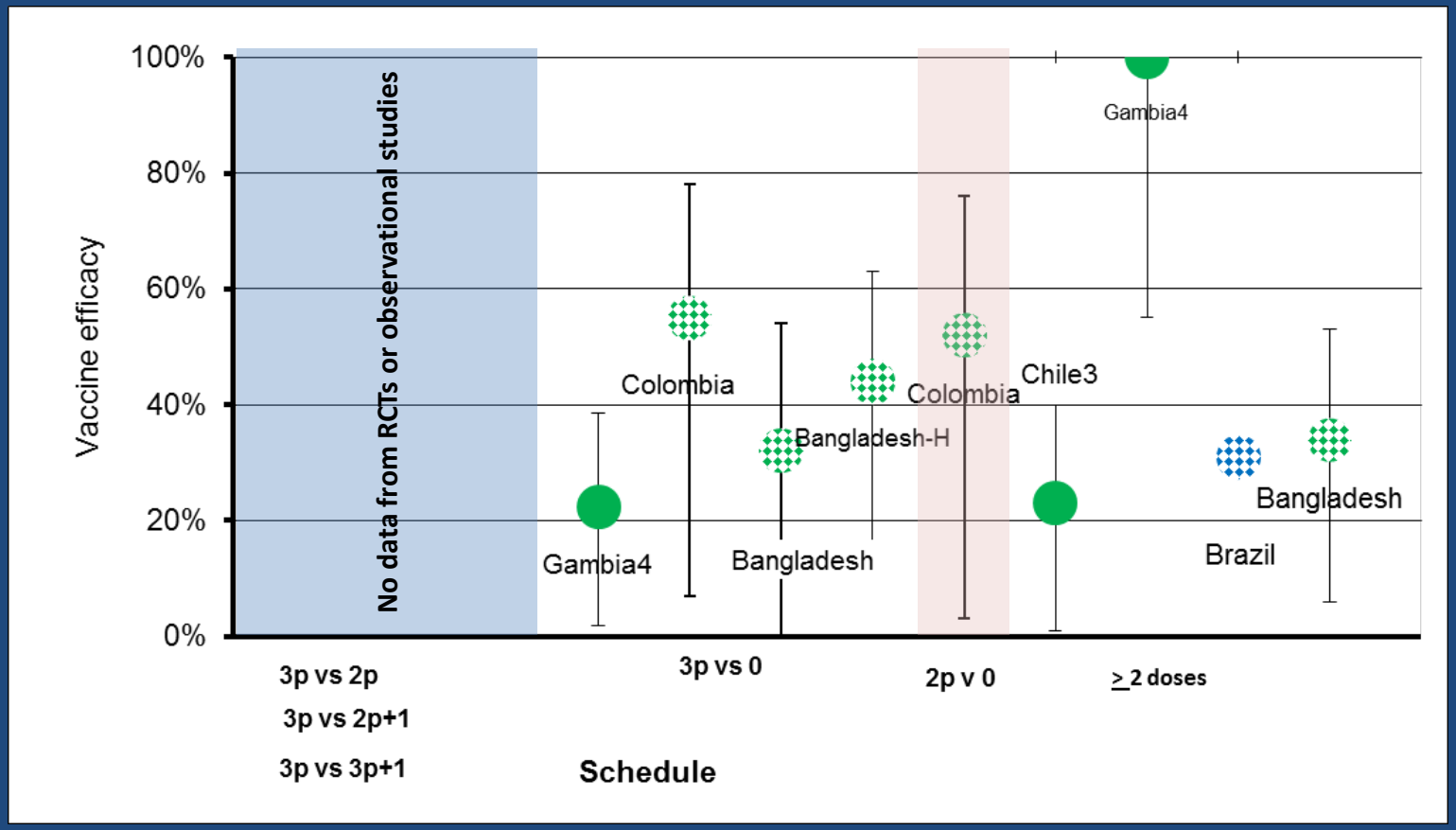
Effect of number of doses of Hib vaccine on Hib meningitis



RCT solid
Cohort diagonal
Case c diamonds

PRP-T
HbOC
OMP

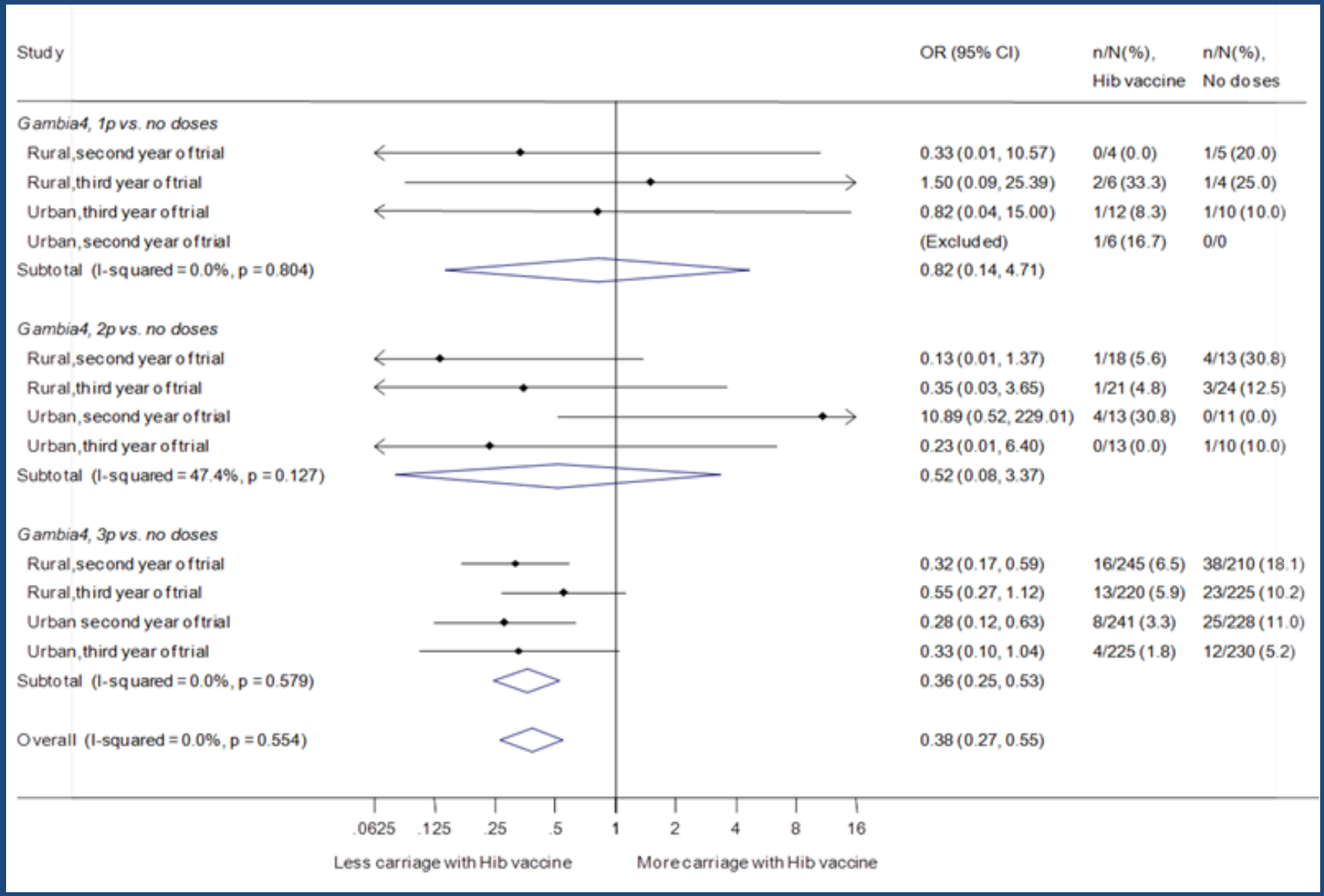
Effect of number of doses of Hib vaccine on radiologically confirmed pneumonia



RCT solid
Cohort diagonal
Case c diamonds

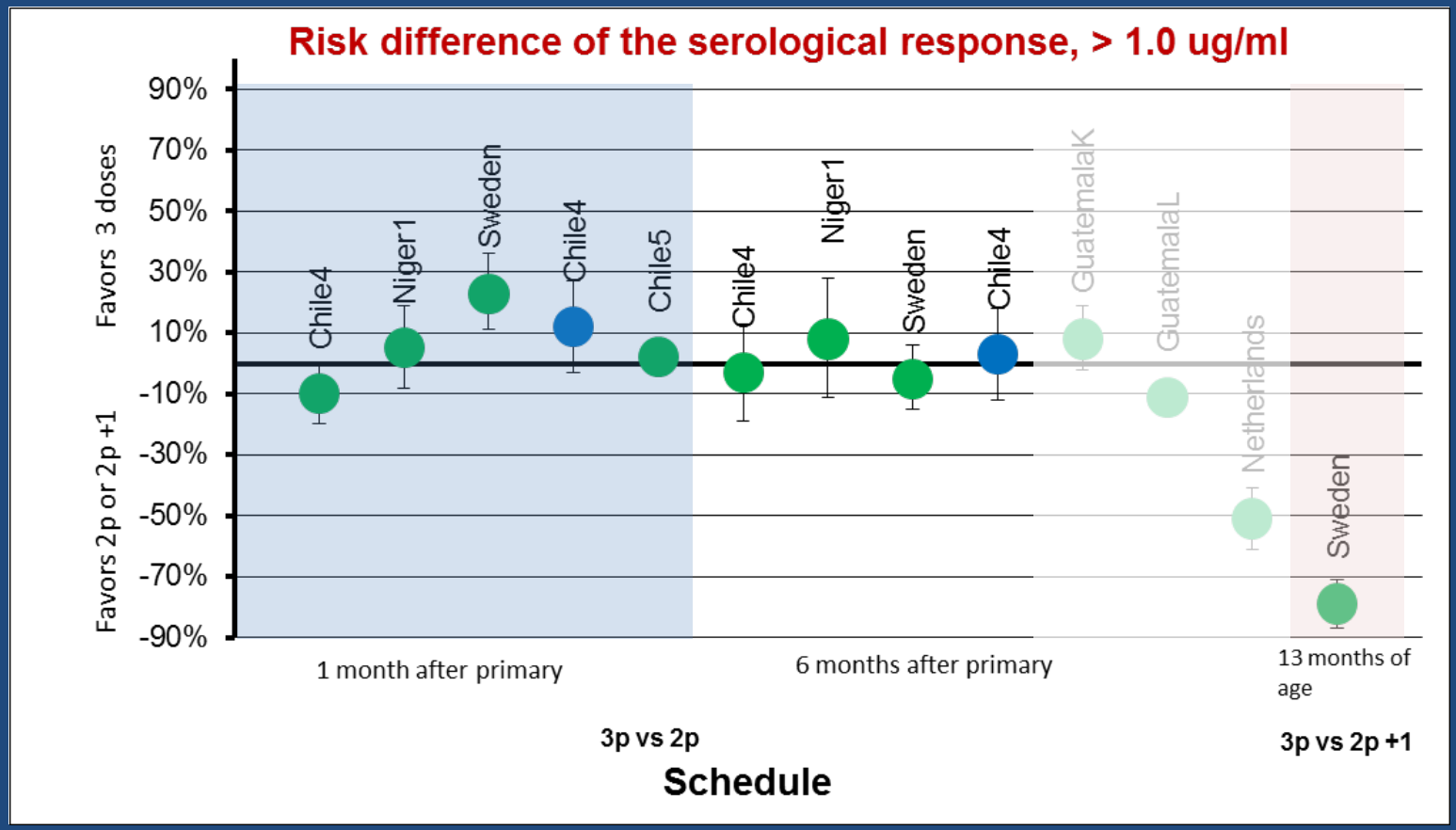
PRP-T
HbOC
OMP

Hib carriage, all available schedules (The Gambia)



Immune Response

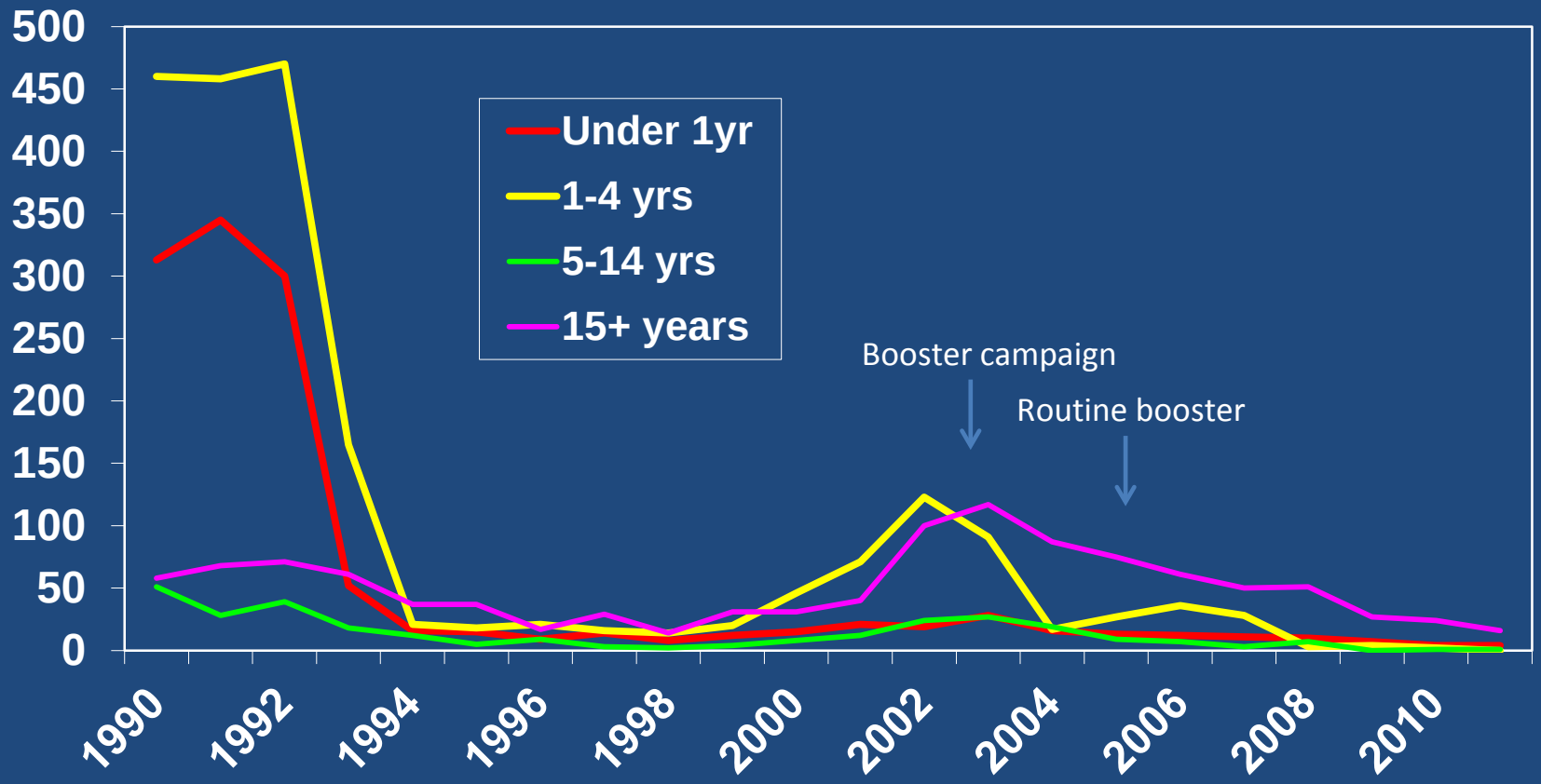
Effect of number of doses of Hib vaccine on serologic response (anti PRP antibodies > 1.0 ug/ml)



RCT	solid	
Cohort	diagonal	
Case c	diamonds	

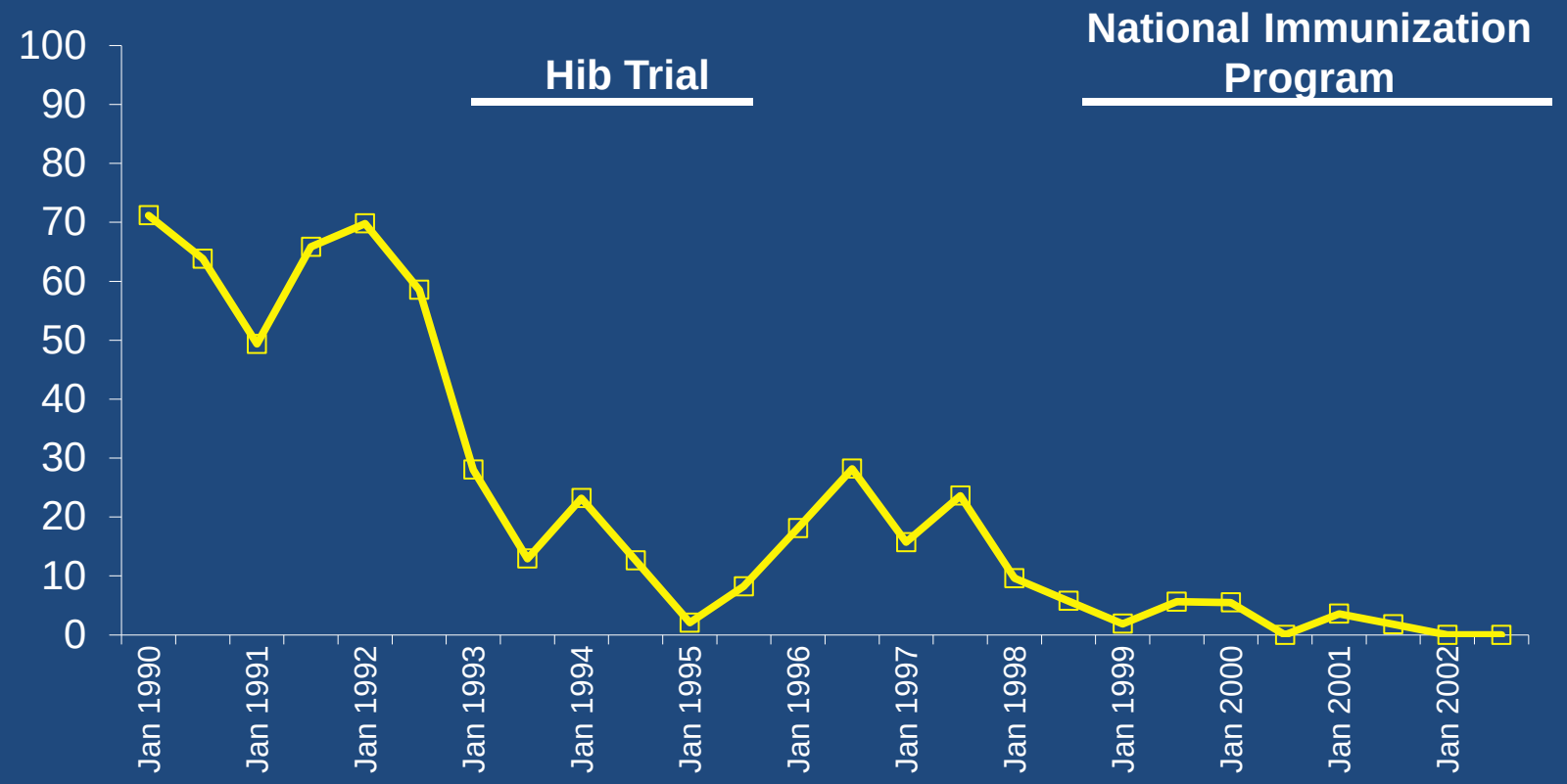
PRP-T	
HbOC	
OMP	

Invasive Hib disease by age group, 1990-2011
England and Wales, HPA Centre for Infections



Courtesy Dr Mary Ramsay, HPA

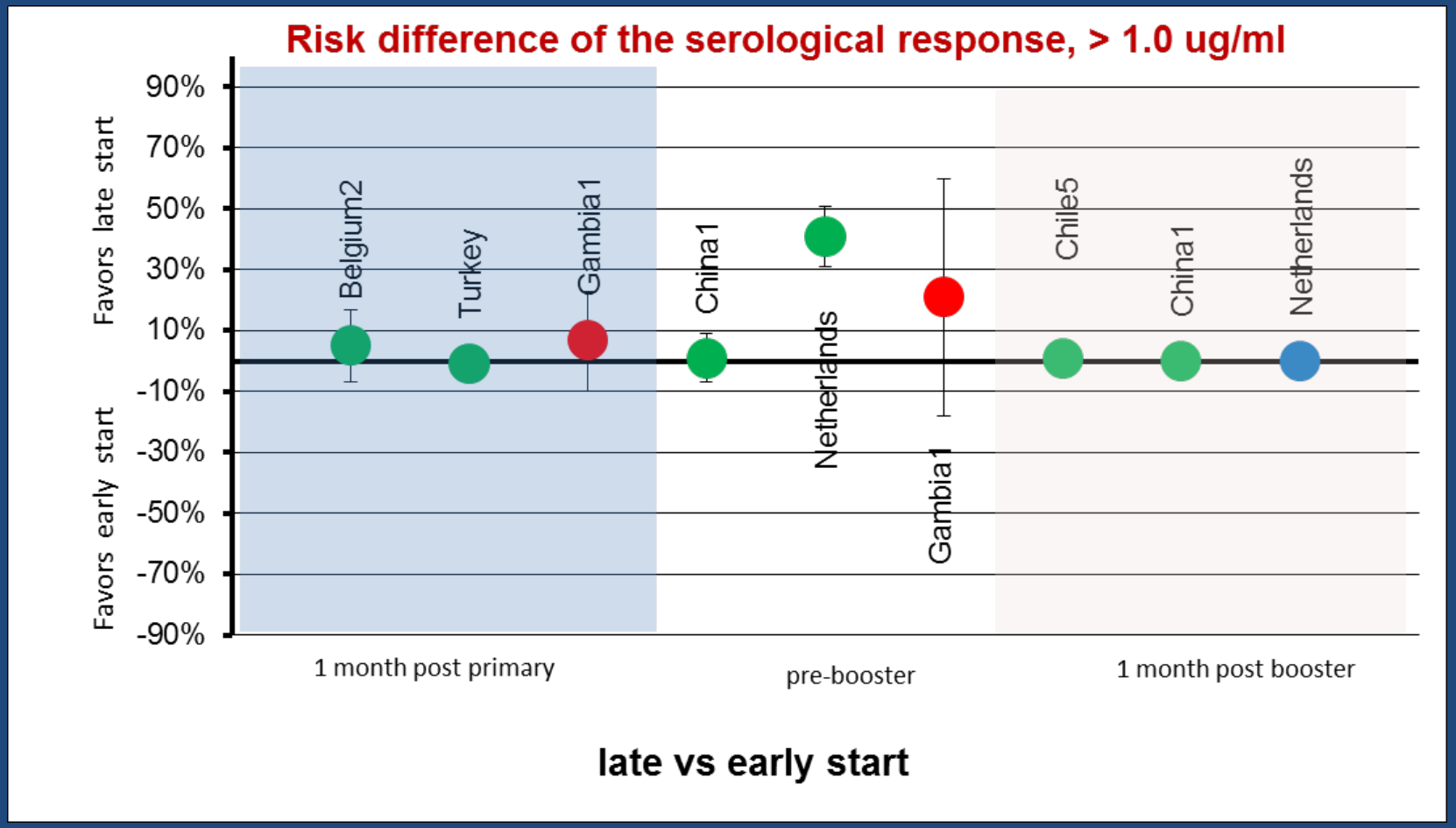
The Gambia: Incidence of Hib meningitis in children under 5 yrs of age (cases per 100,000 per year)



Source: Adegbola et al., *Lancet* 2005; 366:144-150

Age at First dose

Effect of age at administration of first dose of Hib vaccine on serologic response – no difference between 6 wks vs 8 wks

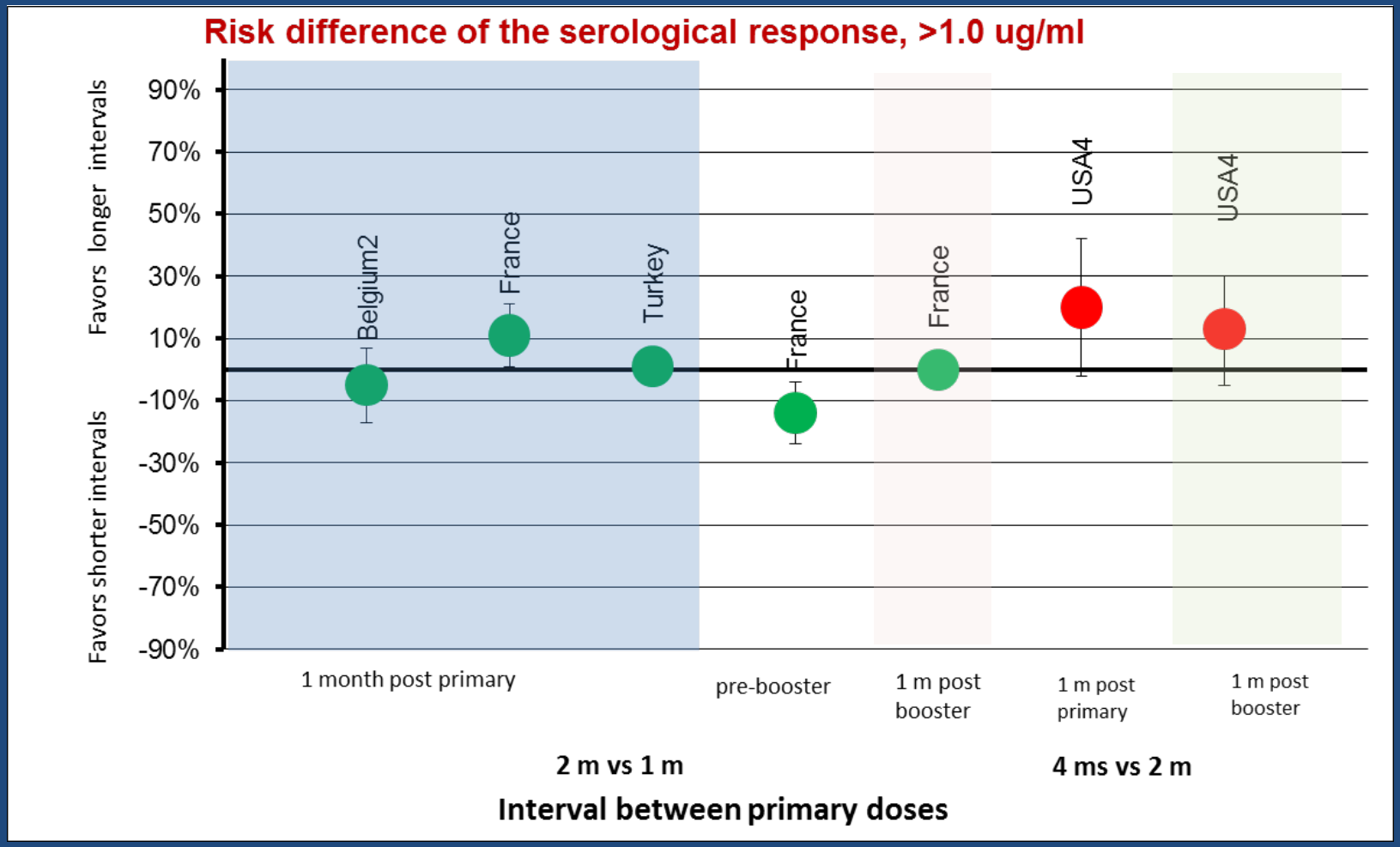


Effect of the interval between primary doses of Hib vaccine on selected outcomes - Observational studies

In most reported case-control studies, doses were separated by either one month (6, 10, 14 weeks and 2, 3, 4 months) or two months (2, 4, 6 months and 2, 4, 12 months):

No clear difference in effectiveness against Hib meningitis, invasive Hib disease or radiologically confirmed pneumonia between studies using different intended dosing intervals

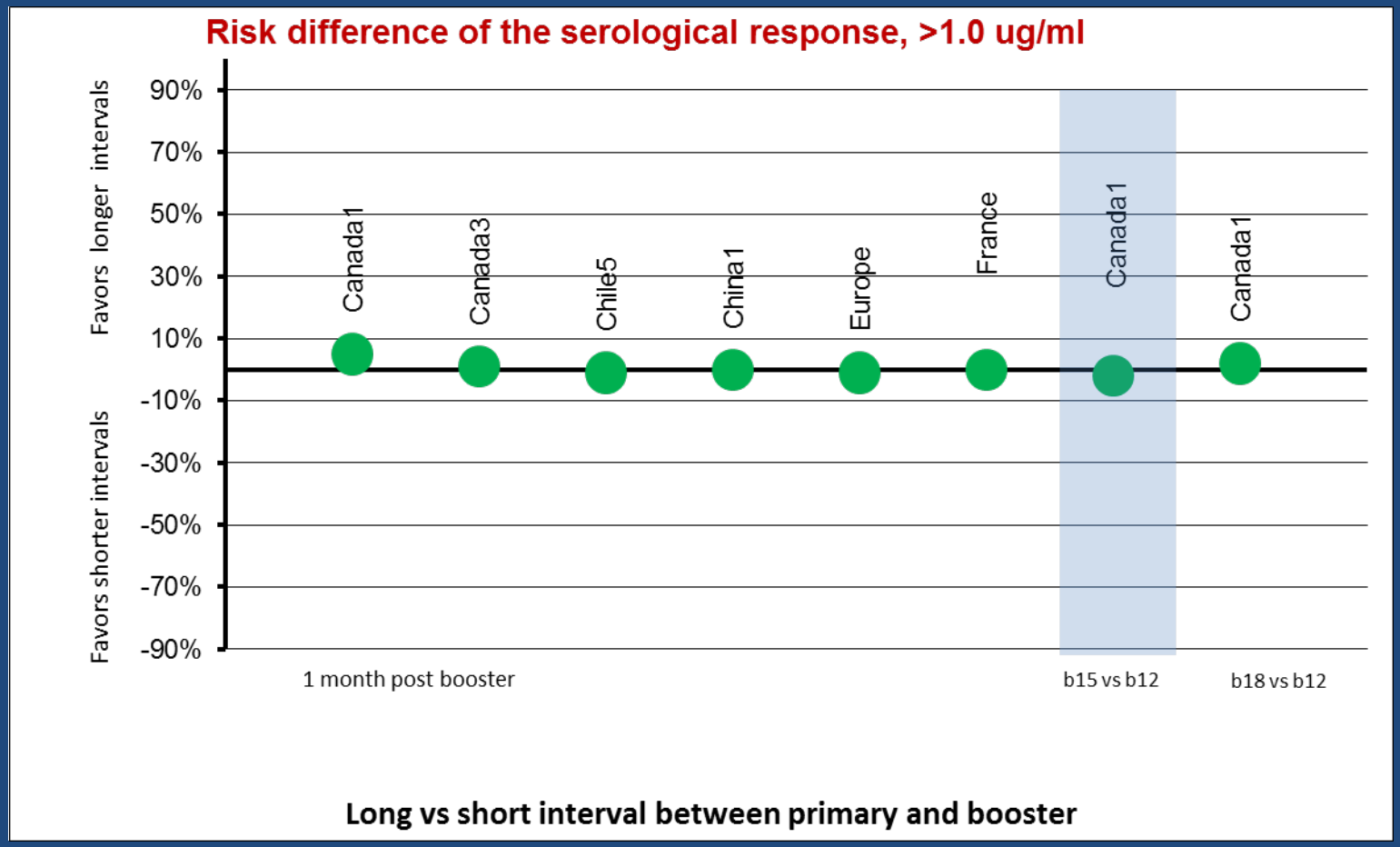
Effect of the interval between primary doses of Hib vaccine on serologic response, > 1.0 ug/ml



RCT solid
Cohort diagonal
Case c diamonds

PRP-T
HbOC
OMP

Effect of the interval between last primary dose and booster dose of Hib vaccine on serologic response – 1 mo after booster



Hib vaccine in HIV-infected children

HIV-infected children have an almost 6-fold increased risk of Hib invasive disease compared to HIV-uninfected children

Hib vaccines have lower effectiveness in this population

Limited evidence (mainly from South Africa) suggests that HIV-infected children would benefit from receiving a booster dose regardless of the number of primary doses received and regardless of ARV therapy

(Mangtani P et al. 2010)

Hib vaccine in emergency settings - Evidence from relevant observational studies

Data from other settings have shown that a single dose of Hib vaccine will induce adequate immune response in children >12 months old; Two doses are needed for optimal protection in children <12 months old

Therefore, in emergency settings, children would benefit from at least one dose of Hib vaccine (if <6mos old, Hib-OMP vaccine is preferred as a 1st dose when available)

Decline of reported Hib meningitis cases after Hib vaccine use in toddlers in the USA, 1980-1991

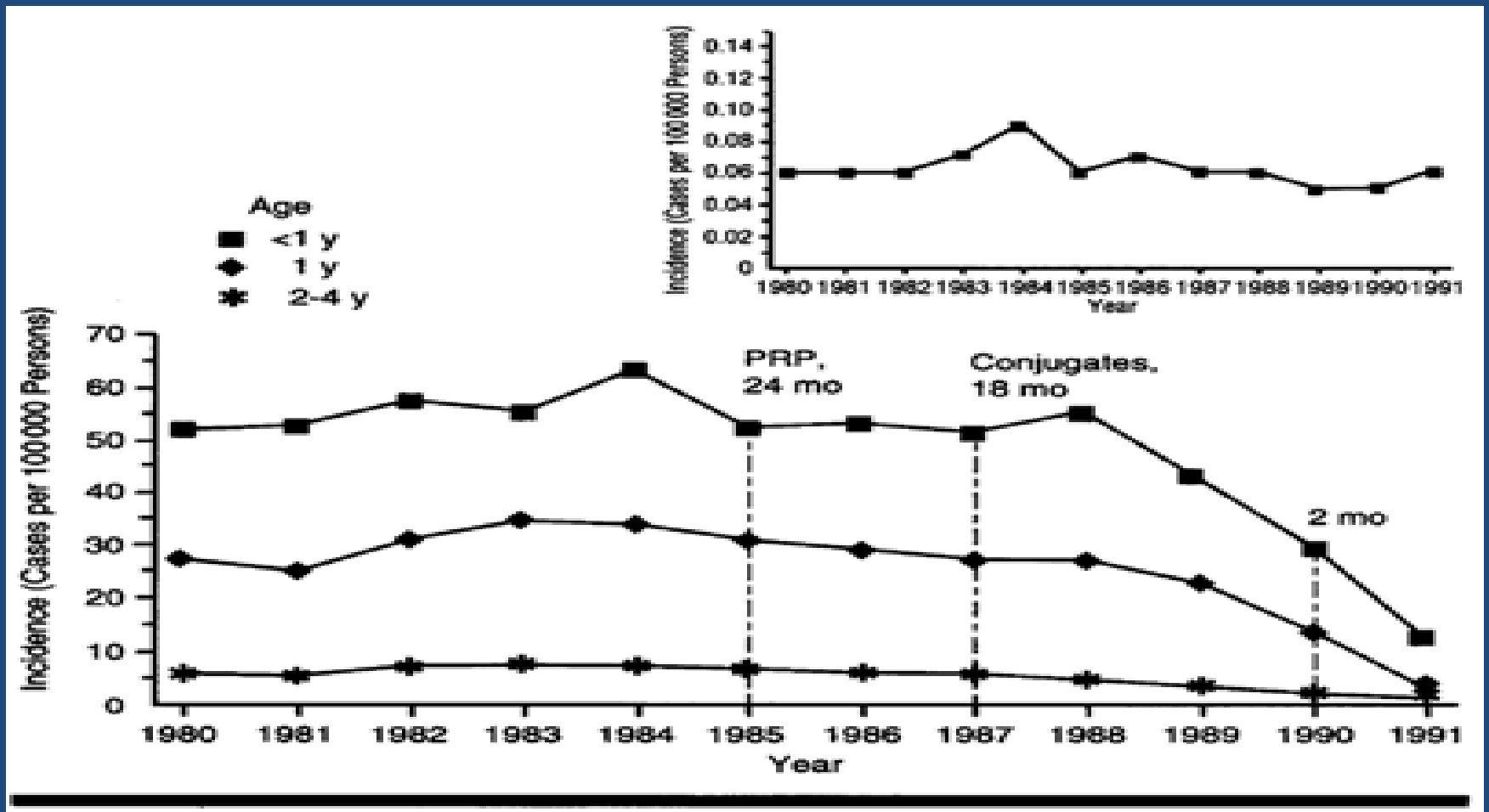


Fig 2.—*Haemophilus influenzae* meningitis cases by age in children less than 5 years old and at least 12 years old (inset) according to the National Bacterial Meningitis Reporting System, 1980 through 1991 (20 continuously reporting states). Licensure dates of polyribosyl-ribitol phosphate (PRP) and conjugate vaccines are indicated.

Adams et al. JAMA 1993

Research needs

Assess effectiveness of various Hib immunization schedules and need for booster dose in low income countries

Assess effectiveness of Hib vaccine in HIV-infected children (including need and timing of booster dose)

Assess the effect of co-administration of Hib vaccine with acellular pertussis vaccines on Hib vaccine effectiveness

Support strong disease surveillance systems in various epidemiological settings to monitor impact of vaccine and disease epidemiology

Evaluate feasibility and effectiveness of Hib vaccine administration to children in emergency settings

Additional slides

Limitations of the evidence

Number of doses of *Hib* vaccine

(T) Clinical and carriage data: no direct RCTs with comparisons within individual trials between these 2 schedules. Studies randomizing to 2p schedules are PRP-OMP, and those to 3p are PRP-T and PRP-HbOC.
(O) Limited control for confounding (particularly in cohort studies).
(L) There is no direct comparison of the two schedules. Few countries use a 2p+1 schedule. Comparisons must be made between countries which may result in confounding. Comparisons are difficult because there are no long term data from developing countries using a 2p+1 schedule and few developing countries are using a booster dose at all. Also, no industrialized countries reviewed are currently using a 3p schedule. Likely long term effectiveness must be inferred from immunogenicity and efficacy data. Reasons for increases in incidence in countries using 3p are not known. There are no impact data on use of a booster dose prior to 11 months of age.

Age at first dose

(T) Clinical and carriage data: no data. Immunological data: Only PRP-T and PRP-OMP in comparisons of seropositivity. Few data about birth dose and conclusions about birth dose differ depending on control group used (e.g. Lieberman 1995, HbOC)
(O) Studies mainly reported intended schedules rather than actual age at vaccination. Limited range in intended age at first dose (6 weeks, 2 months or 2-5 months).
The one study with intended age at initiation of 6 weeks and relatively low three-dose VE (83%) was carried out in a population with a high prevalence of HIV infection.
(L) There is limited variability in first dose timing in currently used schedules. Developing countries recommend the first dose at 6 or 8 weeks. Industrialized countries recommend the first dose mainly at 8 weeks with a few at 12 weeks. *Hib* continues to cause disease in all countries reviewed, with incidence highest in the first year of life. This suggests ongoing risk in young infants. No clear evidence of the superiority of either schedule.

POLICY QUESTION

What are optimal immunization schedules for *Haemophillus Influenzae type* b vaccines (*Hib*) for children living in different epidemiological settings?

Number of doses: at least 3 doses

Age at administration of first dose: at 6 weeks or soon thereafter

Interval between doses: 4-8 weeks between primary doses

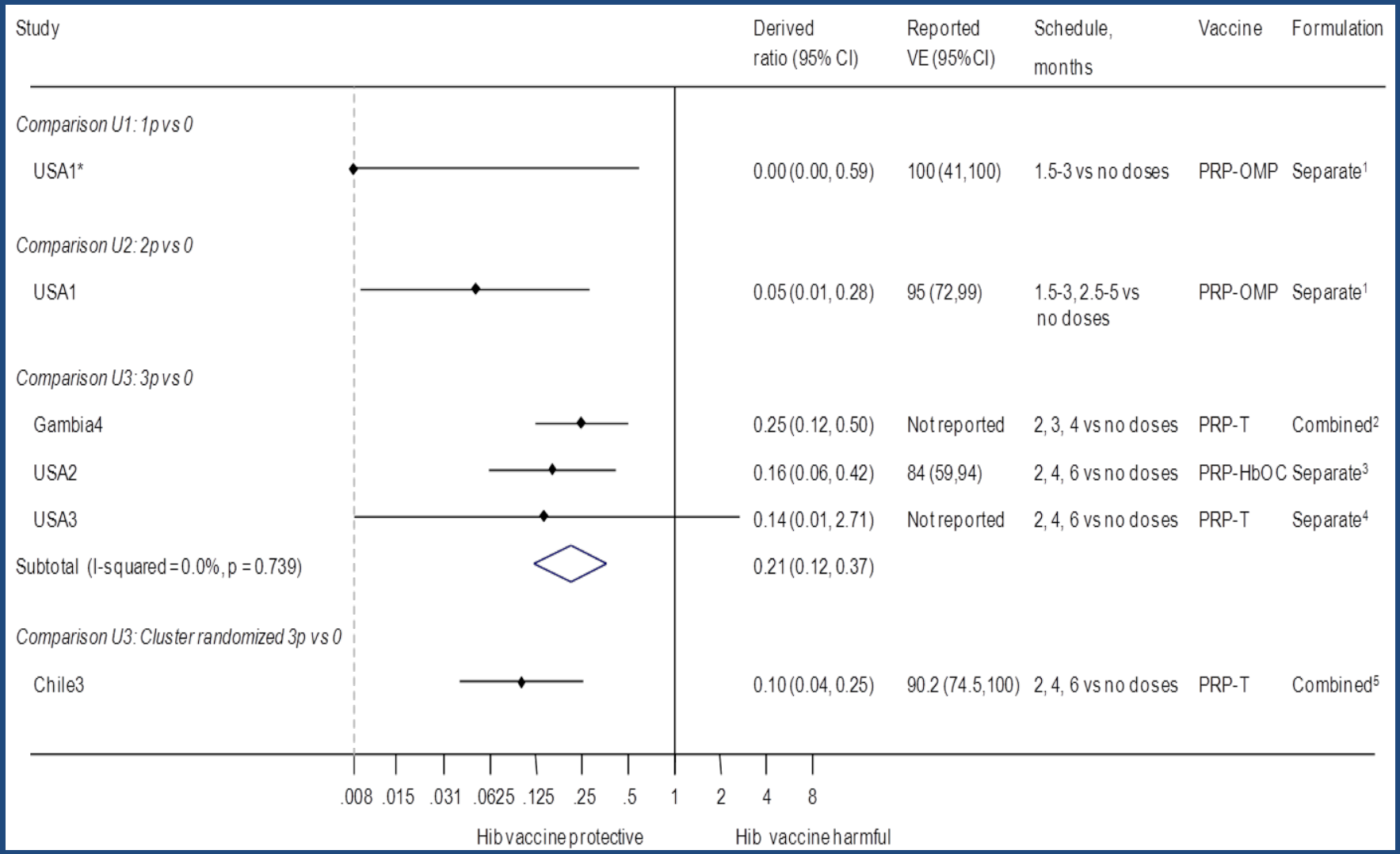
Immunization of children in emergency settings: for children < 12 months of age at least one dose should be given and, if conditions permit an additional dose should be provided. For young infants (< 6 months of age) OMP has reported higher immunogenicity and therefore is preferable

Immunization of HIV infected children: they would benefit from receiving a booster dose regardless of the number of primary doses received and irrespective of whether or not the child is receiving anti-retroviral therapy

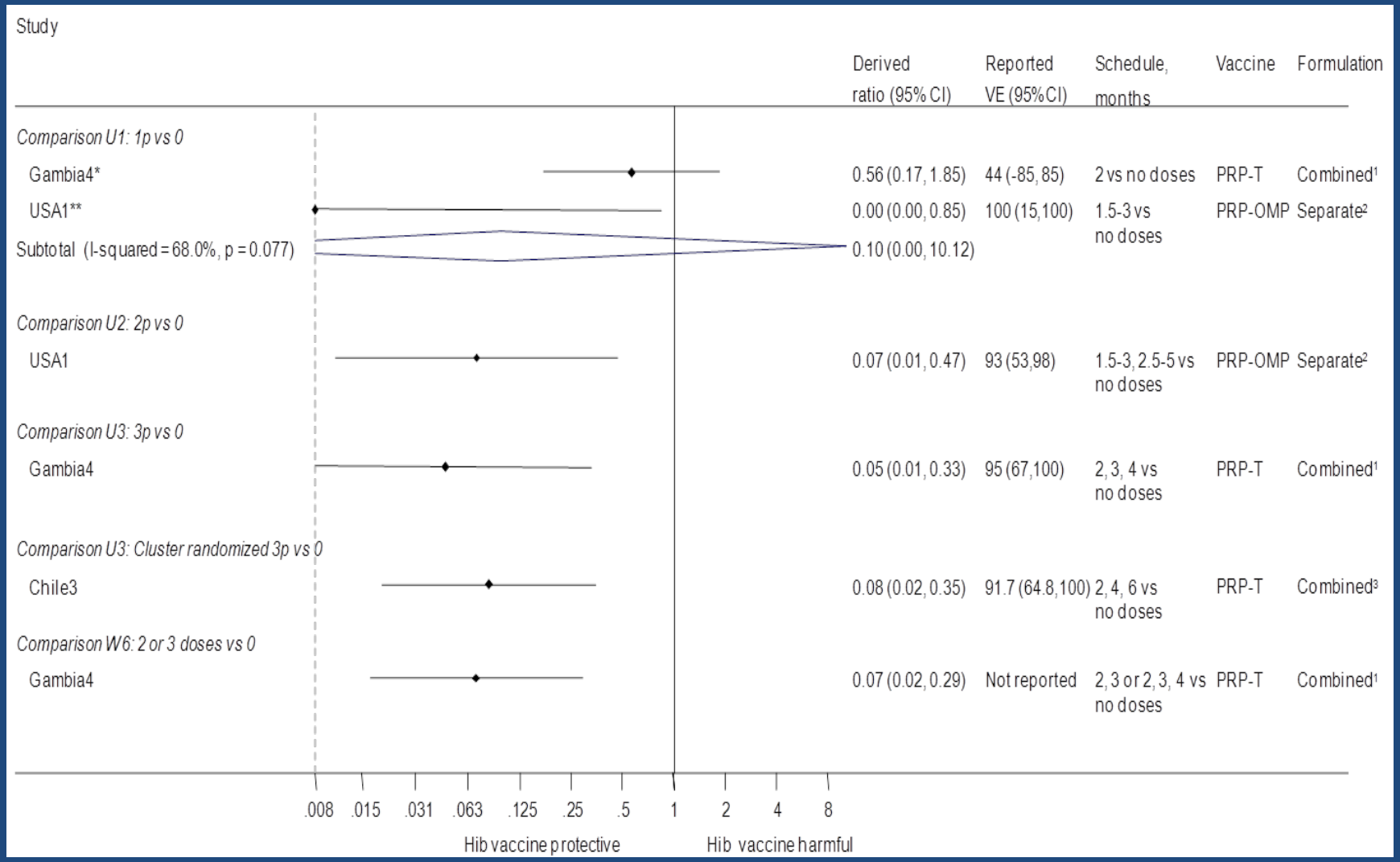
Effect of number of doses of *Hib* vaccine on invasive *Hib* disease

Type of studies	3p vs 2p	3p vs 2p+1	3p vs 0
RCTs	No data. X RCTs compared 2p vs. 0 and 3p vs 0	No data	4 RCTs X RCTs compared 2p vs. 0 and 3p vs 0
Observational	No data. 6 case control and cohort studies compared *Hib* vaccine to no vaccine	No data 4 cohort studies compared *Hib* vaccine to no vaccine	4 case control studies X cohort studies compared *Hib* vaccine to no vaccine
Long term impact	No data	Used in few countries but no specific impact data	No data

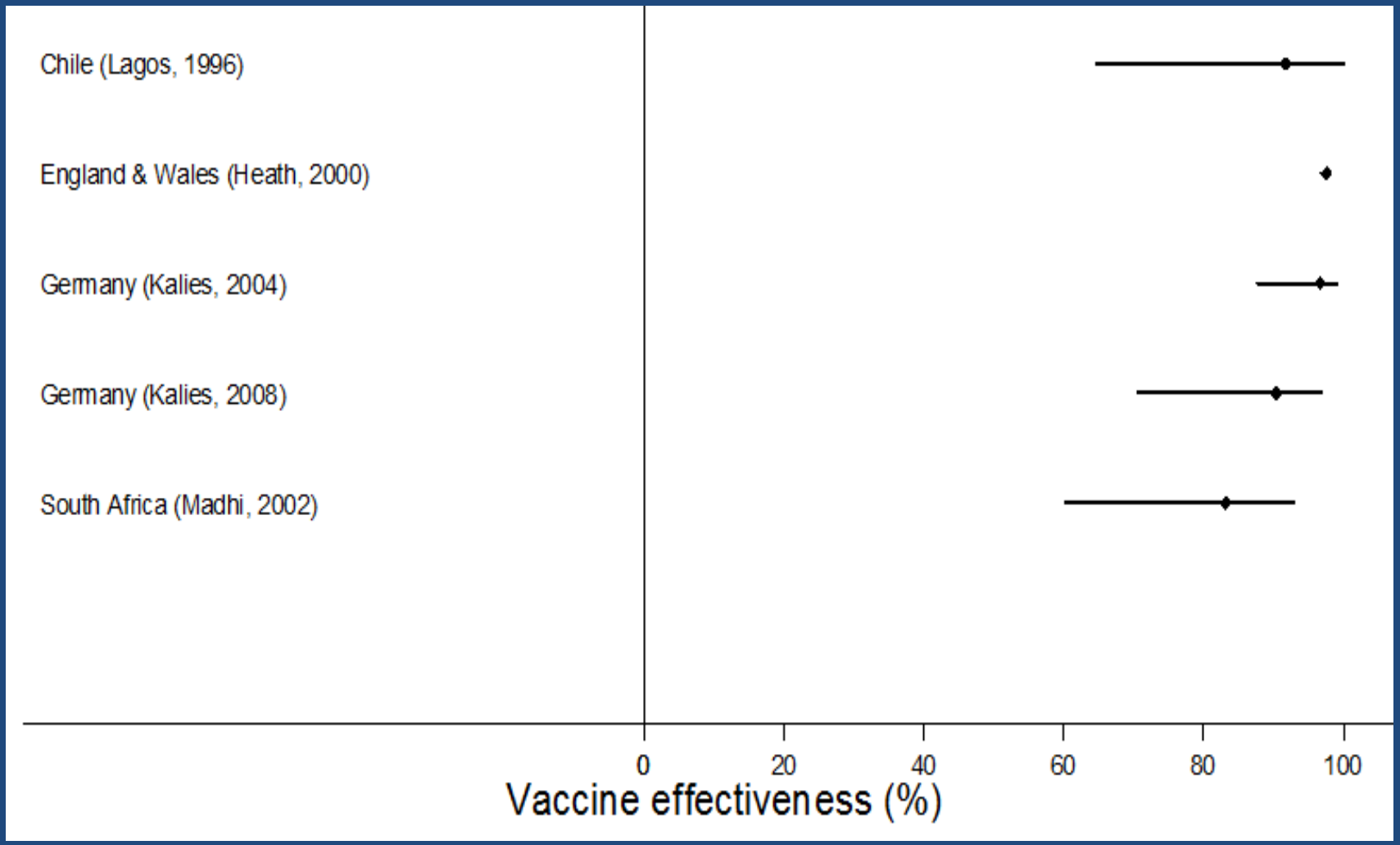
Invasive *Hib* disease, intention to treat analyses, all available schedules, from RCTs



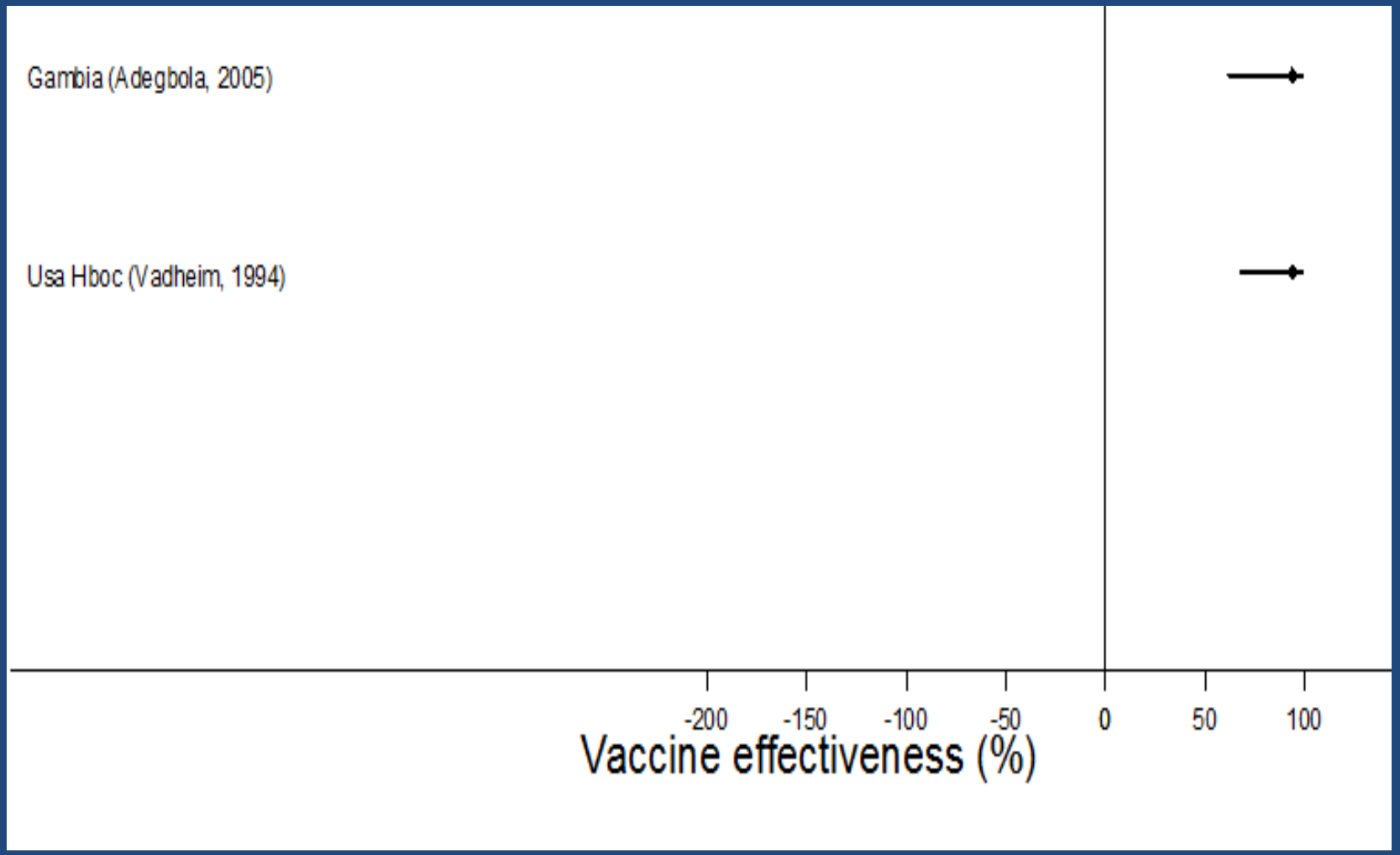
Invasive *Hib* disease, per protocol analyses, all available schedules, from RCTs



Estimates of effectiveness of 3 doses of *Hib* vaccine against invasive *Hib* disease, from cohort studies



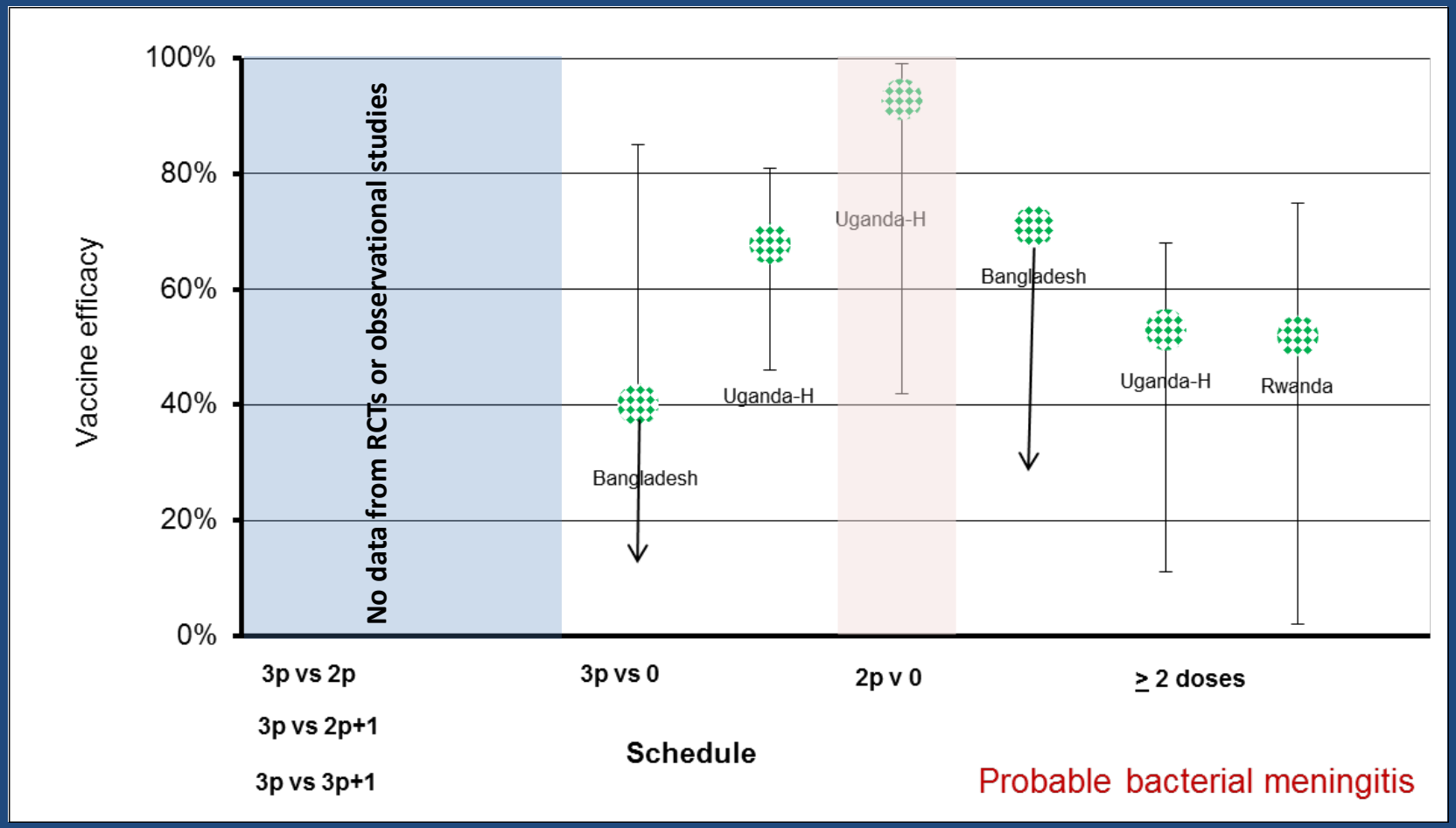
Estimates of effectiveness of 3 doses of *Hib* vaccine against invasive *Hib* disease, from case-control studies



Effect of number of doses of *Hib* vaccine on *Hib* meningitis

Type of studies	3p vs 2p	3p vs 2p+1	3p vs 0
RCTs	No data	No data	3 RCTs compared 3p vs 0
Observational	No data 5 control case studies and one cohort study compared *Hib* vaccine to no vaccine	No data	Case control studies: 5 studies compared 2p vs 0 5 studies compared 3p vs 0 1 cohort study compared 3p vs 0 and 2p vs 0
Long term impact	No data	Used in few countries but no specific impact data	Used in several countries in Africa and Latin America but no specific impact data

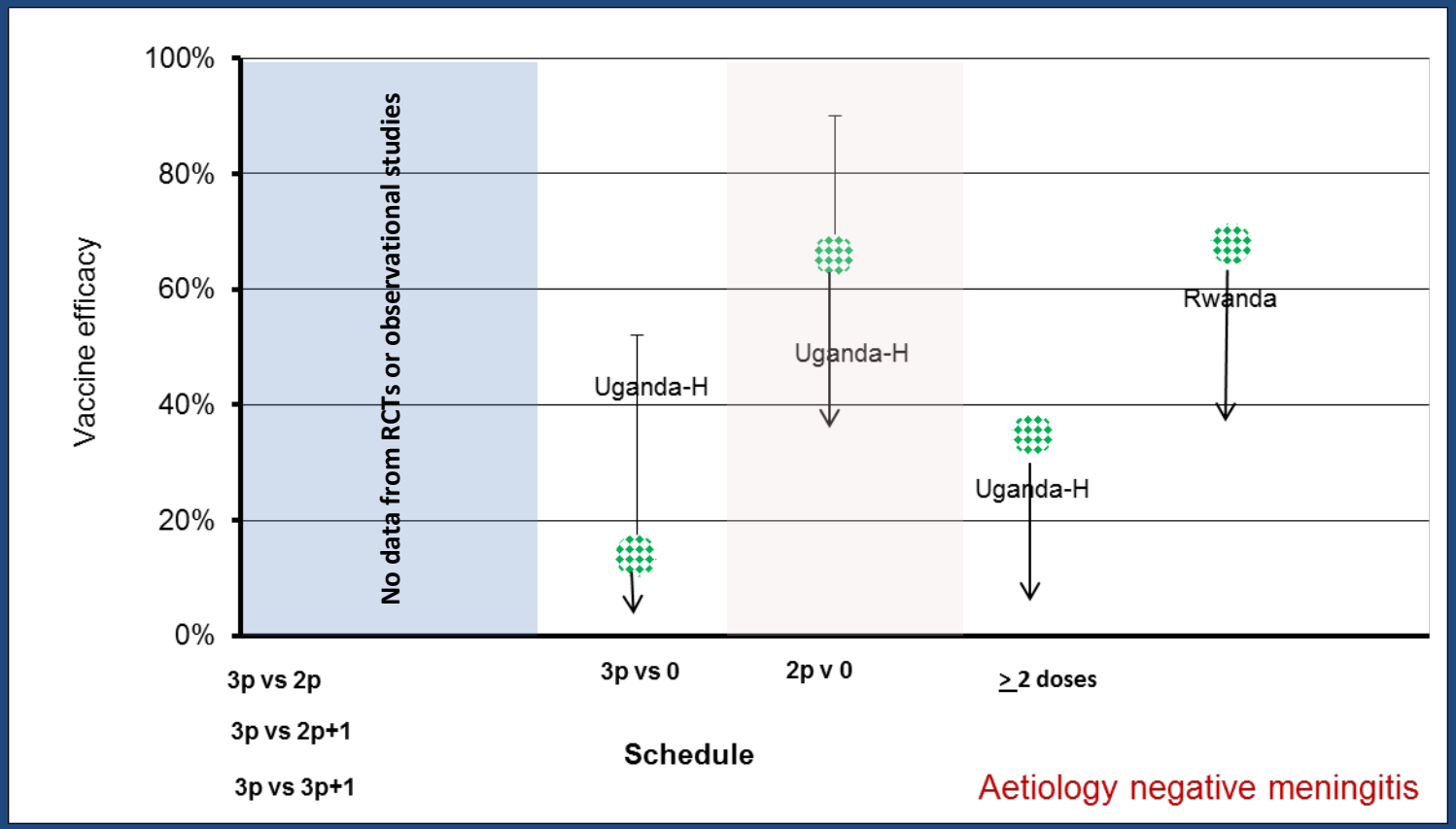
Effect of number of doses of *Hib* vaccine on probable bacterial meningitis



RCT solid
Cohort diagonal
Case c diamonds

PRP-T
HbOC
OMP

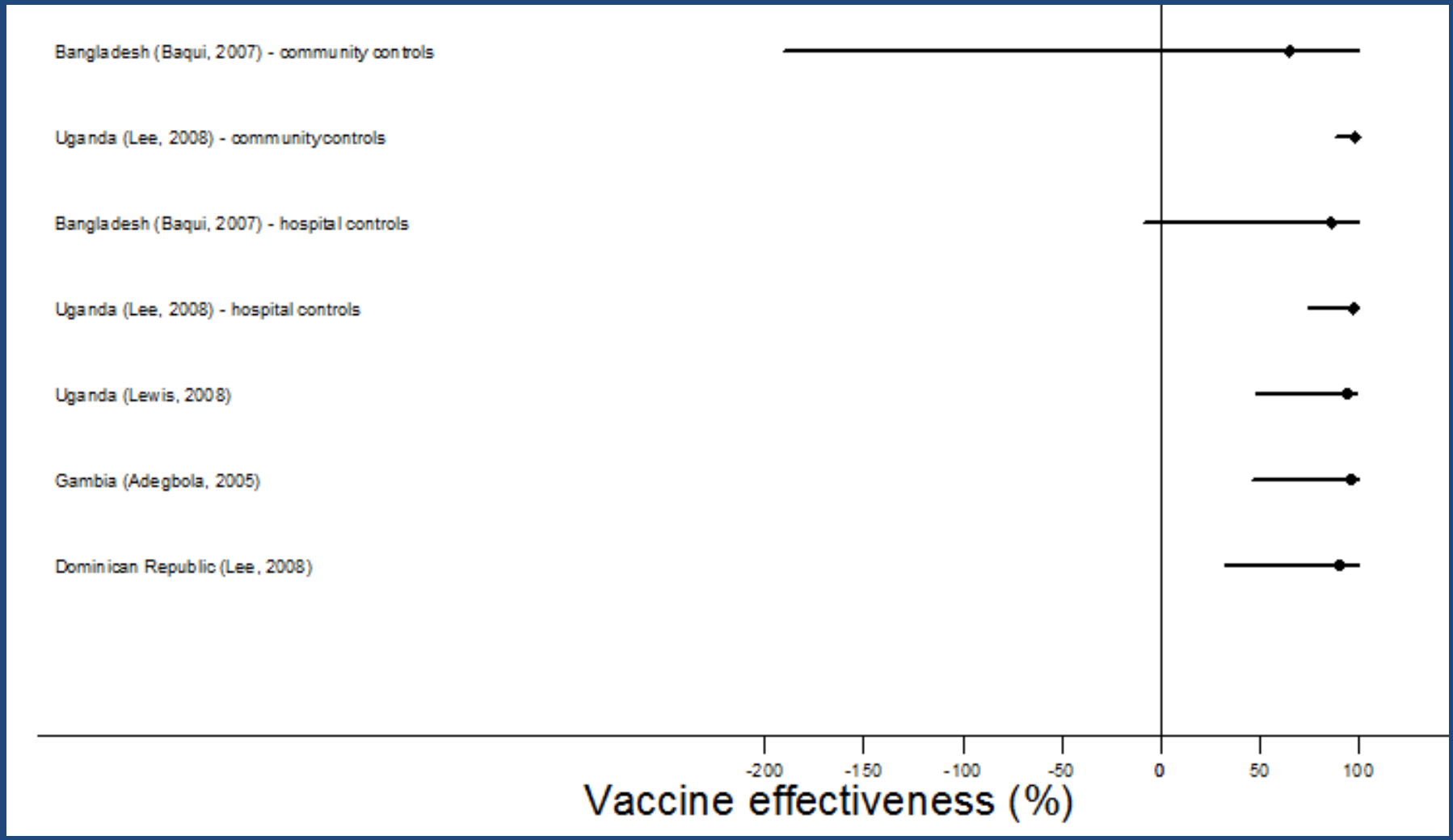
Effect of number of doses of *Hib* vaccine on aetiology negative meningitis



RCT solid
Cohort diagonal
Case c diamonds

PRP-T
HbOC
OMP

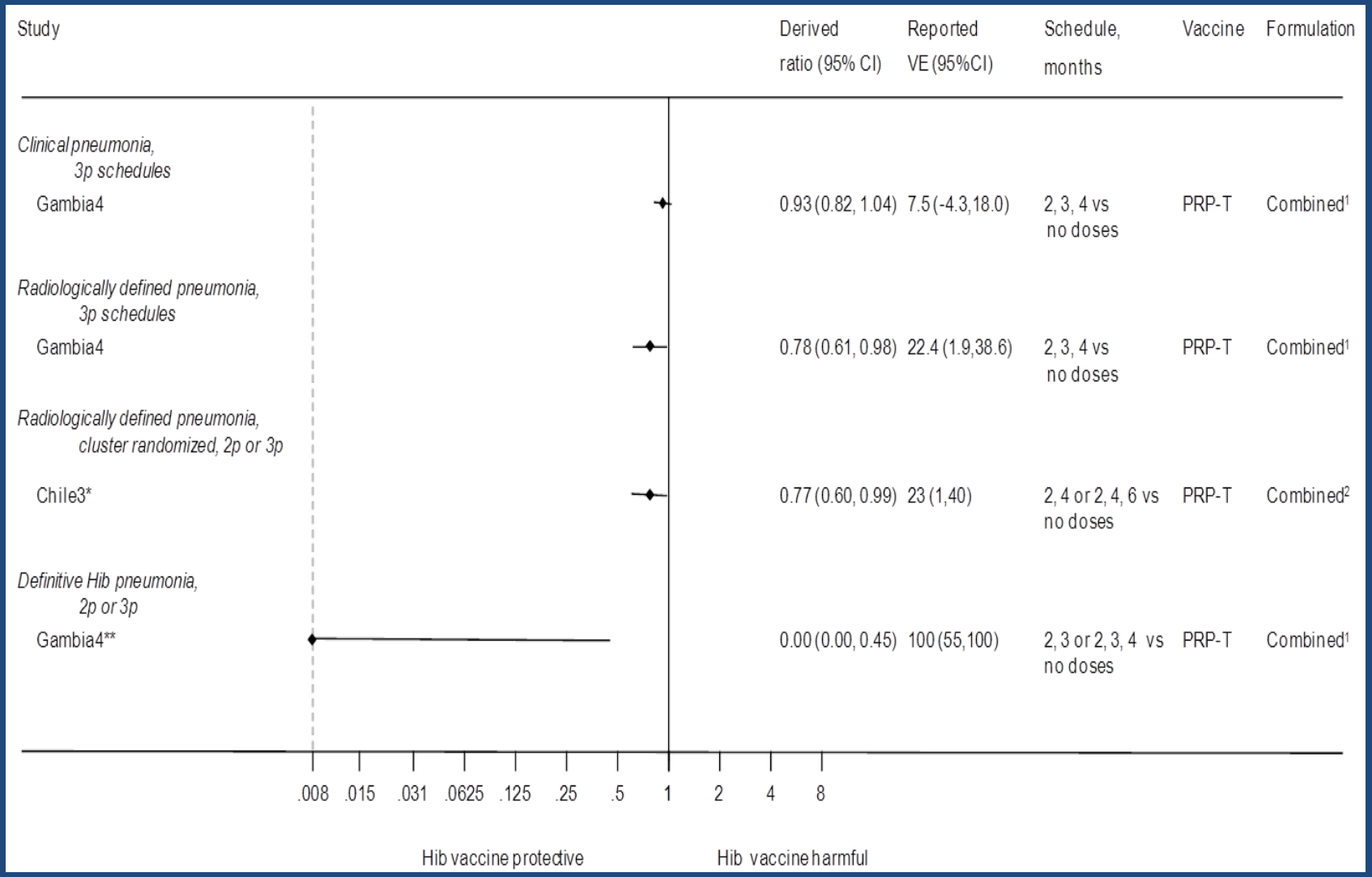
Estimates of effectiveness of 3 doses of *Hib* vaccine against confirmed *Hib* meningitis, from case-control studies



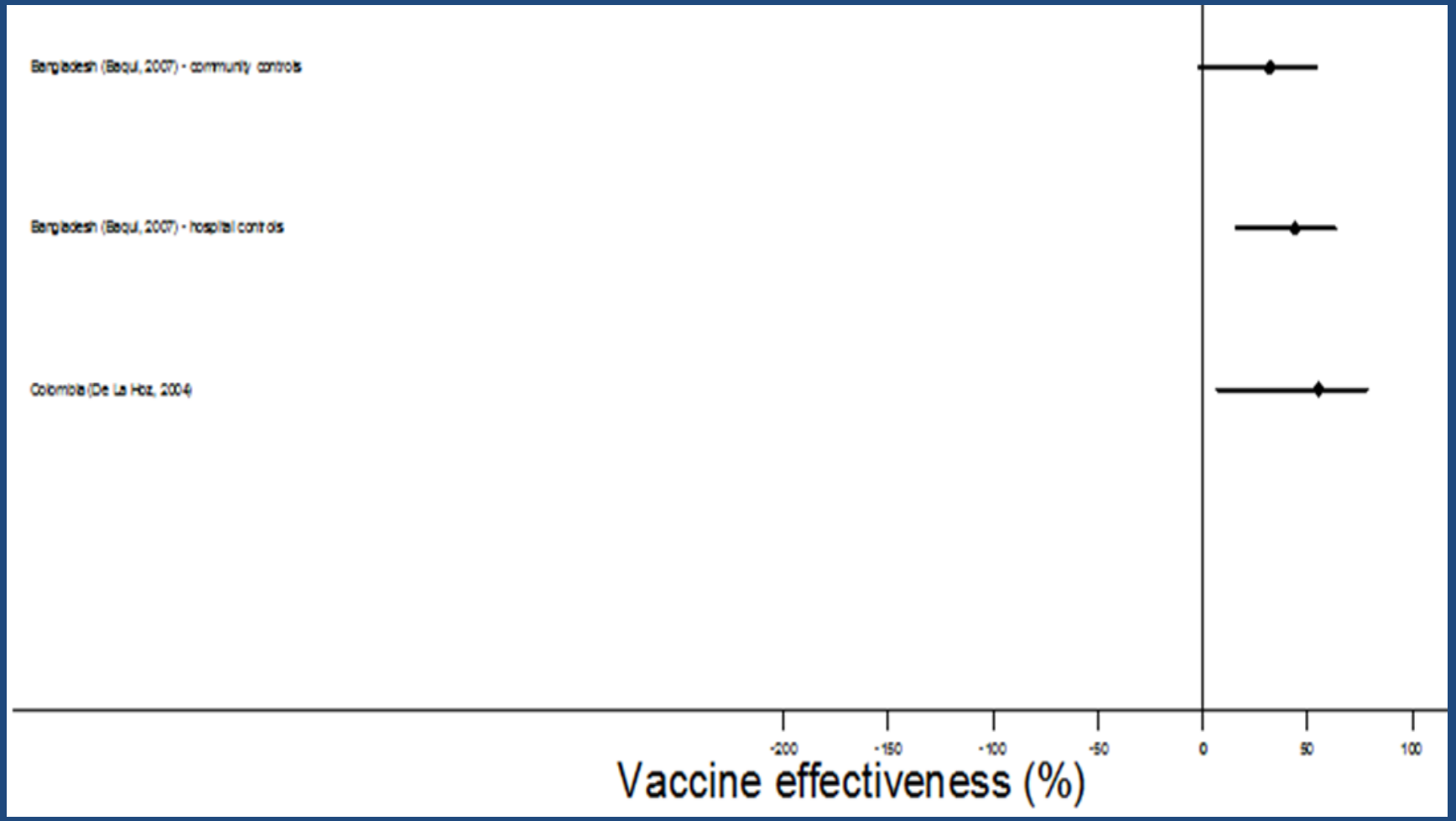
Effect of number of doses of *Hib* vaccine on *Hib* pneumonia

Type of studies	3p vs 2p	3p vs 2p+1	3p vs 0
RCTs	No data	No data	3 RCTs All use PRP-T
Observational	No data One case control study compared *Hib* vaccine to no vaccine	No data	One case control study reported 3p vs 0 and 2p vs 0
Long term impact	No data	No data	No data

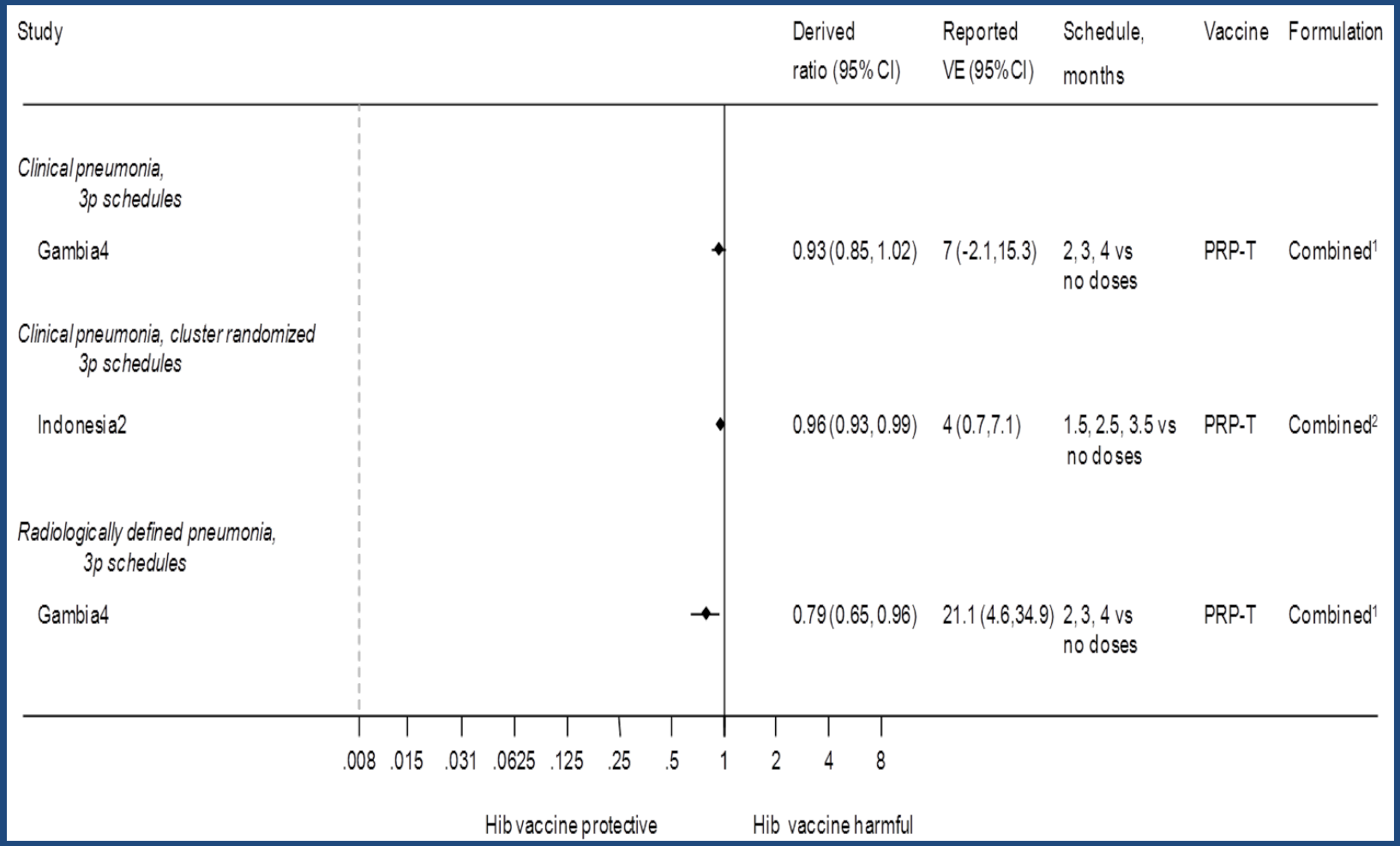
Pneumonia, per protocol analyses, all available schedules, from RCTs



Estimates of effectiveness of 3 doses of *Hib* vaccine against radiologically confirmed pneumonia, from case-control studies



Pneumonia, intention to treat analyses, all available schedules, from RCTs



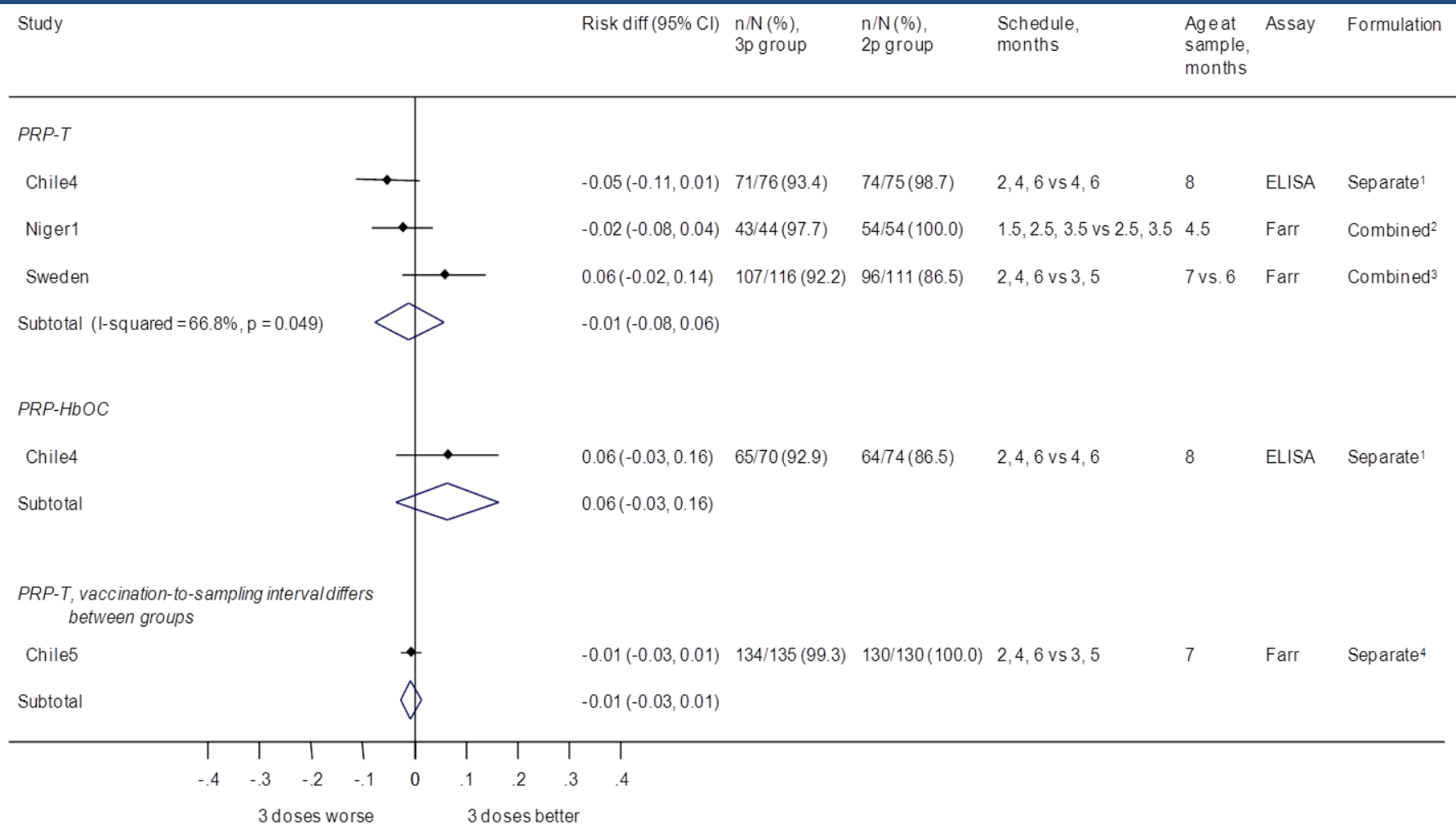
Effect of number of doses of *Hib* vaccine on *Hib* carriage

Type of studies	3p vs 2p	3p vs 2p+1	3p vs 0
RCTs	No data 3 RCTs compared *Hib* vaccine against no vaccine	No data	One trial compared 3p vs 0 and 2p vs 0
Observational	Limited data (reviewed non-systematically) showed no clear relationship between carriage and number of doses	No data	3 Studies reported VE
Long term impact	No data	No data	No data

Effect of number of doses of *Hib* vaccine on proportion seropositive after *Hib* vaccine

Type of studies	3p vs 2p	3p vs 2p+1	3p vs 0
RCTs	6 RCTs 1 and 6 months post primary PRP-T and PRP-HbOC	6 RCTs 1 and 6 months post primary 13 months of age PRP-T and PRP-HbOC	6 RCTs 1 and 6 months post primary
Observational	1 study Non systematic review PRP-T and PRP-HbOC	No data	No data from systematic review
Long term impact	No data	No data	No data

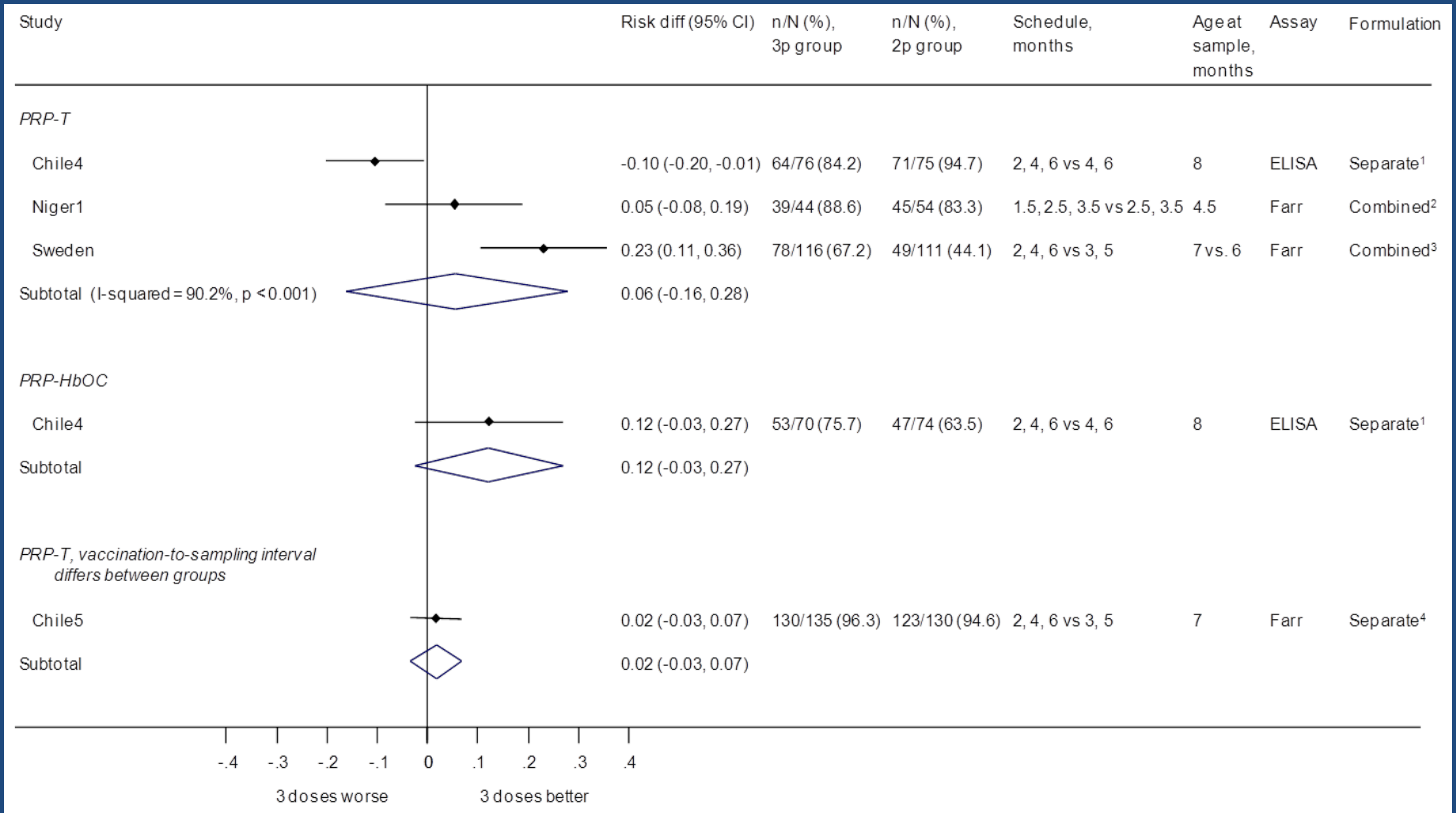
3p vs 2p, approx. 1m post primary, 0.15µg/ml, from RCTs



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

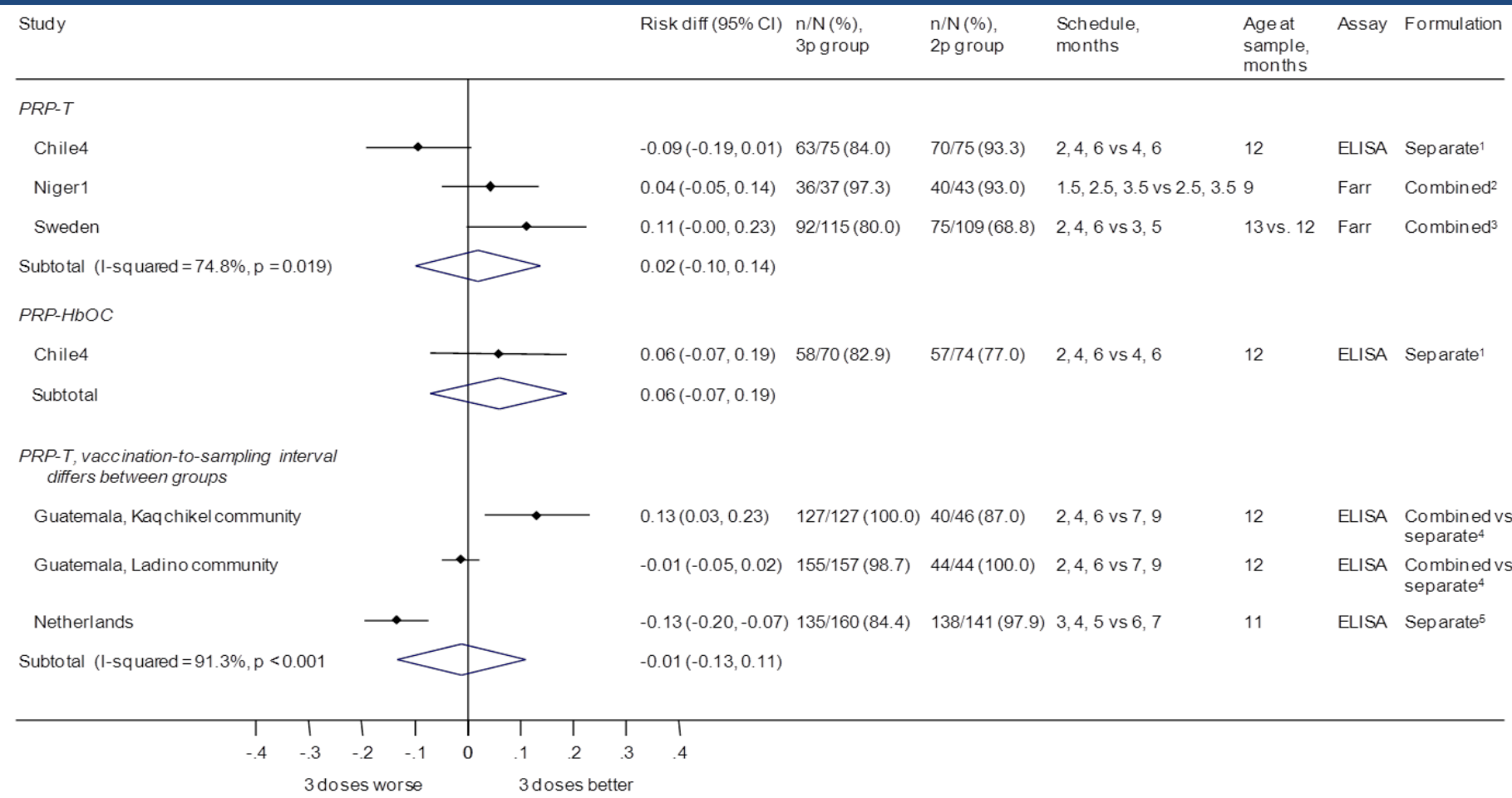
3p vs 2p, approx. 1m post primary, 1.0µg/ml, from RCTs



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

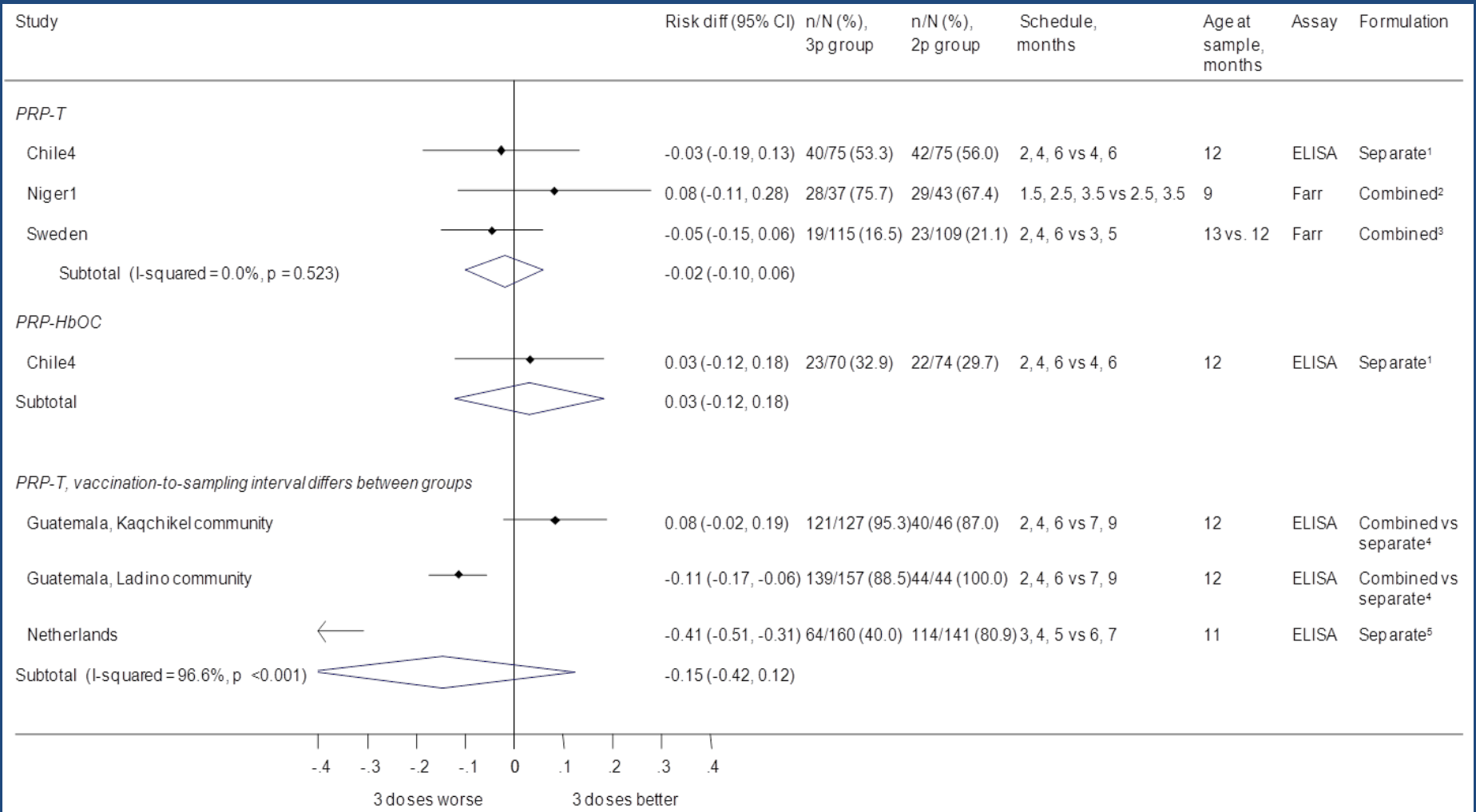
3p vs 2p, approx. 6m post primary, 0.15µg/ml, from RCTs



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.

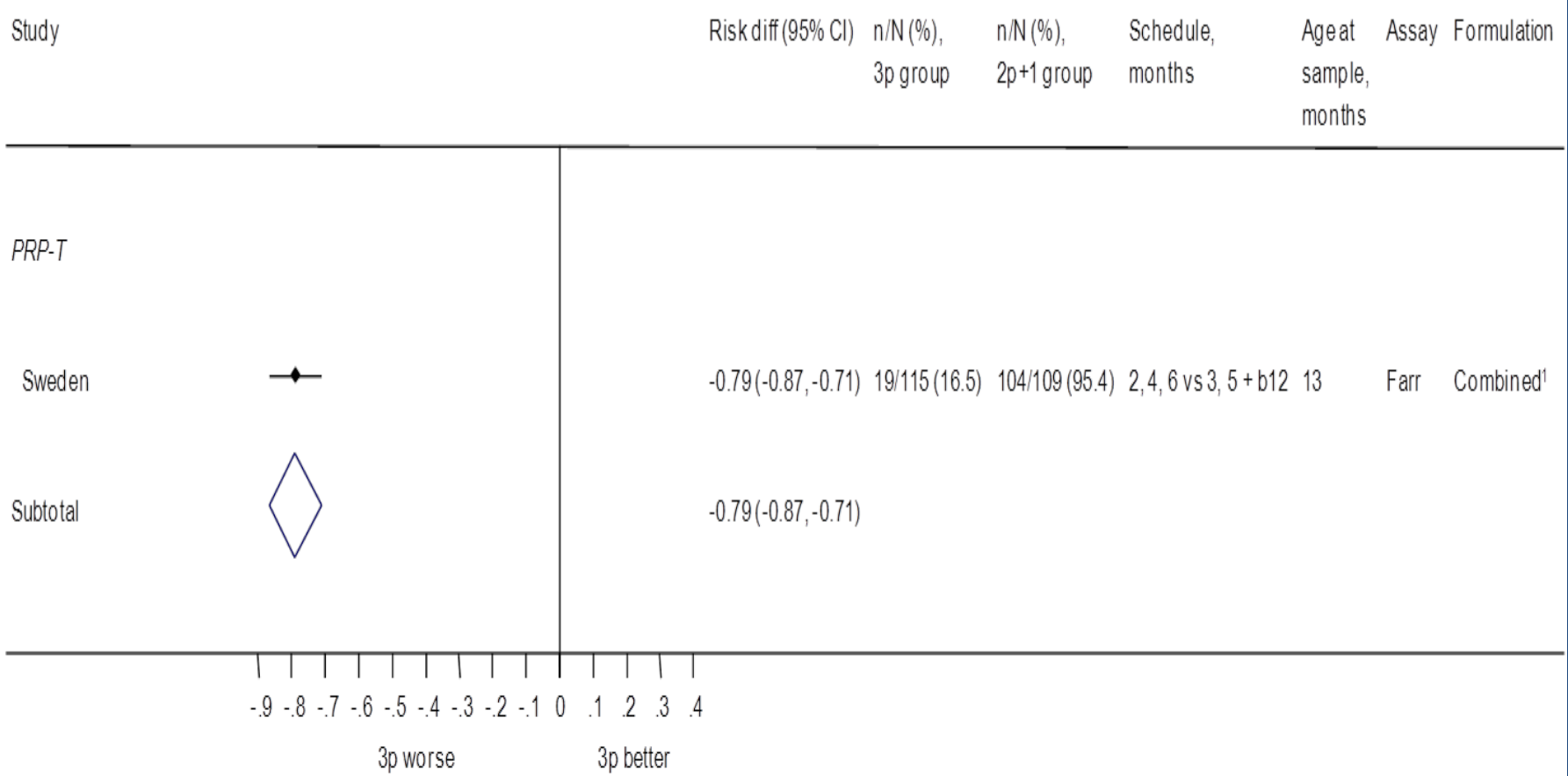
1 DTP both groups at 2, 4, 6. Unclear if aP or wP; 2 DTP both groups at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine when Hib given; 3 DTaP-IPV/Hib both groups; 4 DTwP-hepB/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hepB separately at 7, 9; 5 DTwP-IPV both groups at 3, 4, 5

3p vs 2p, approx. 6m post primary, 1.0µg/ml, from RCTs



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-hep B/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hep B separately at 7, 9; 5 DTwP-IPV both groups at 3, 4, 5

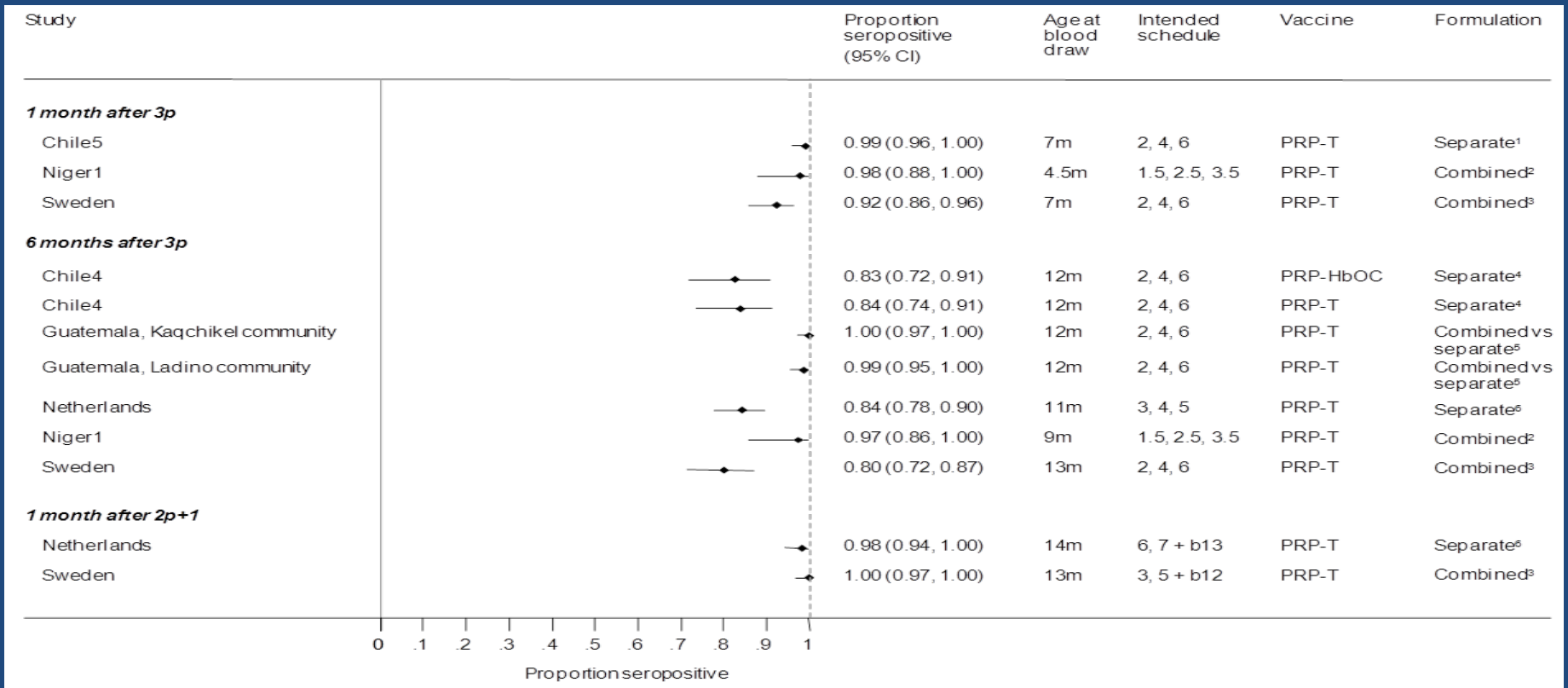
3p vs 2p+1, 13 months of age, 1.0µg/ml, from RCTs



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.

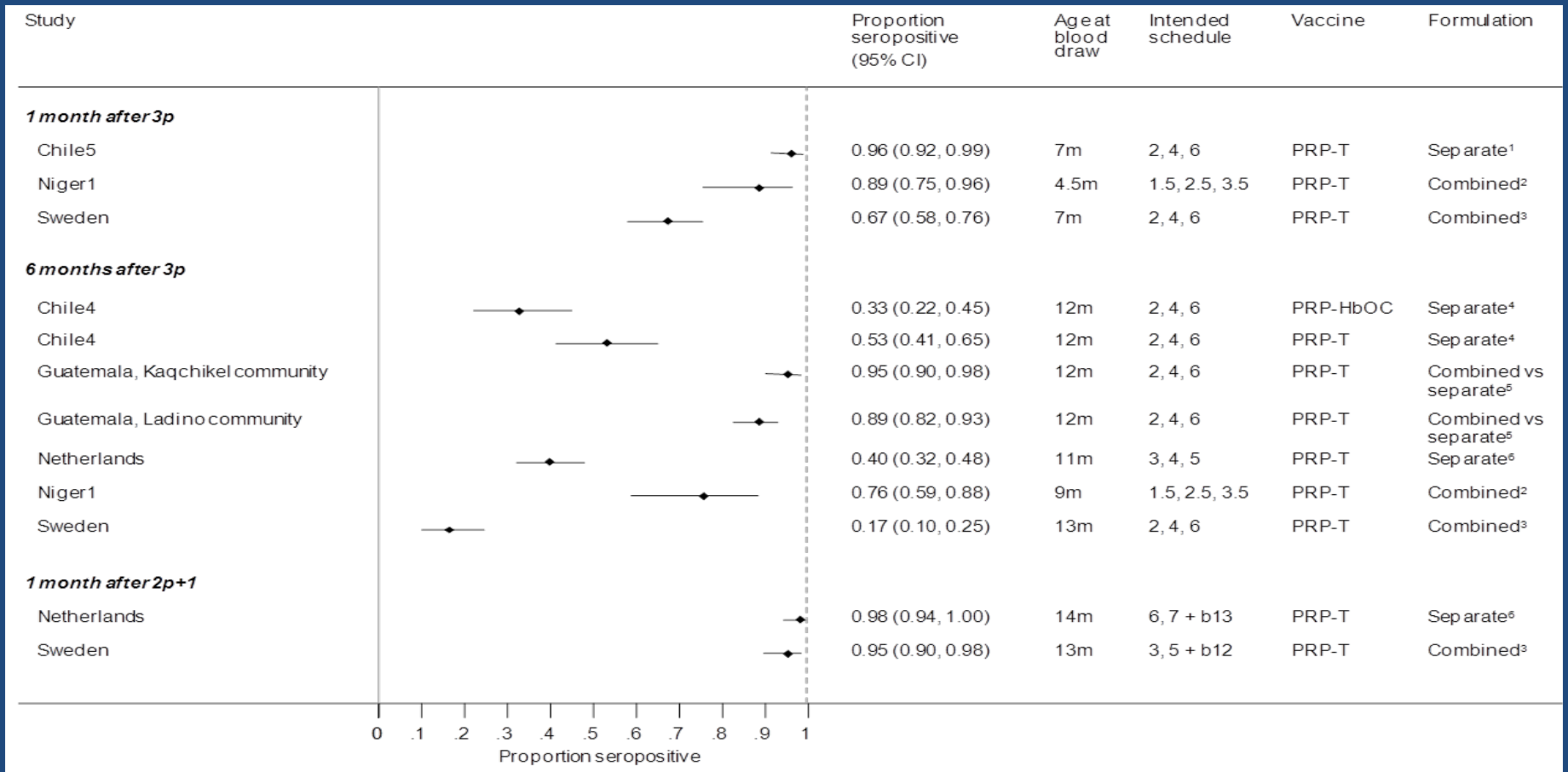
1 DTaP-IPV/Hib both groups

Figure 16: 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-hep B/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hep B separately at 7, 9; 6 DTwP-IPV both groups at 3, 4, 5

Seropositivity after 3p and 2p+1, 1 and 6 months after 3p and 1 month after 2p+1, 1.0µg/ml, from RCTs



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-hep B/Hib at 2, 4, 6 or DTwP at 2, 4, 6 and Hib and hep B separately at 7, 9; 6 DTwP-IPV both groups at 3, 4, 5

Effect of the age at administration of the first dose of *Hib* vaccines on selected outcomes

Type of studies	Evidence
RCTs	
Observational	
Long term impact	

Birth doses

- Kurikka – PRP-T
- Ward – PRP-OMP
  - 0,2,6 vs 2,4,6 mths
  - Lower levels in 0,2,6 persisted to 12 months of age

Filipino infants vaccinated at 6,10,14 weeks

	Post dose 1	Post dose 2	Post dose 3
PRP-OMP	0.70	0.90	1.15
HbOC	0.28	0.38	1.67
PRP-T	0.38	1.47	4.08

Vaccine 1998;16:1004-8

Gambian infants vaccinated at 2,3,4 months

	Post dose 1	Post dose 2	Post dose 3
PRP-OMP	0.30	1.04	1.12
PRP-T	0.12	2.05	5.70

PIDJ 1993;12:484-92 Vaccine 1996;14:905-9

PNG infants vaccinated at 1,2,3 months with PRP-T

	Post dose 2	Post dose 3
GMT (µg/ml)	1.5	5.0
% > 1.0 µg/ml	58	89

PNG Med J 2001;44:6-16

Age at initiation: neonatal dose

TABLE 3. Anti-Hib PS Antibody Concentrations at 2 Days and 4 Months of Age According to PRP-T Immunization Status: no PRP-T or PRP-T at 2 Days or at 2 Months of Age

	At 2 d	At 4 mo			Significance of the Difference Between the Groups at 4 mo	
		No PRP-T*	PRP-T at 2 d†	PRP-T at 2 mo‡	PRP-T at 2 d vs no PRP-T	PRP-T at 2 d vs 2 mo
n	115	201	115	119		
GMC of anti-Hib PS	0.34	0.08	0.12	0.11	$P < .001$§	$P > .1$‖
Range	0.06–22.20	0.06–1.24	0.06–1.90	0.06–1.02		
% >0.06 μg/mL	77	20	65	44	$P < .001$¶	$P = .001$¶
% >0.15 μg/mL	66	10	30	28	$P < .001$¶	$P > .01$¶
% >1.0 μg/mL	20	1	6	2	$P = .01$††	$P = .1$††

* Reference 37 and our unpublished data.
† Groups A and B.
‡ Our unpublished data.
§ Kruskall-Wallis test.
‖ Student's *t* test.
¶ Chi-square test.
†† Fisher's exact test.

Kurikka et al, Pediatrics, 1995, Finland

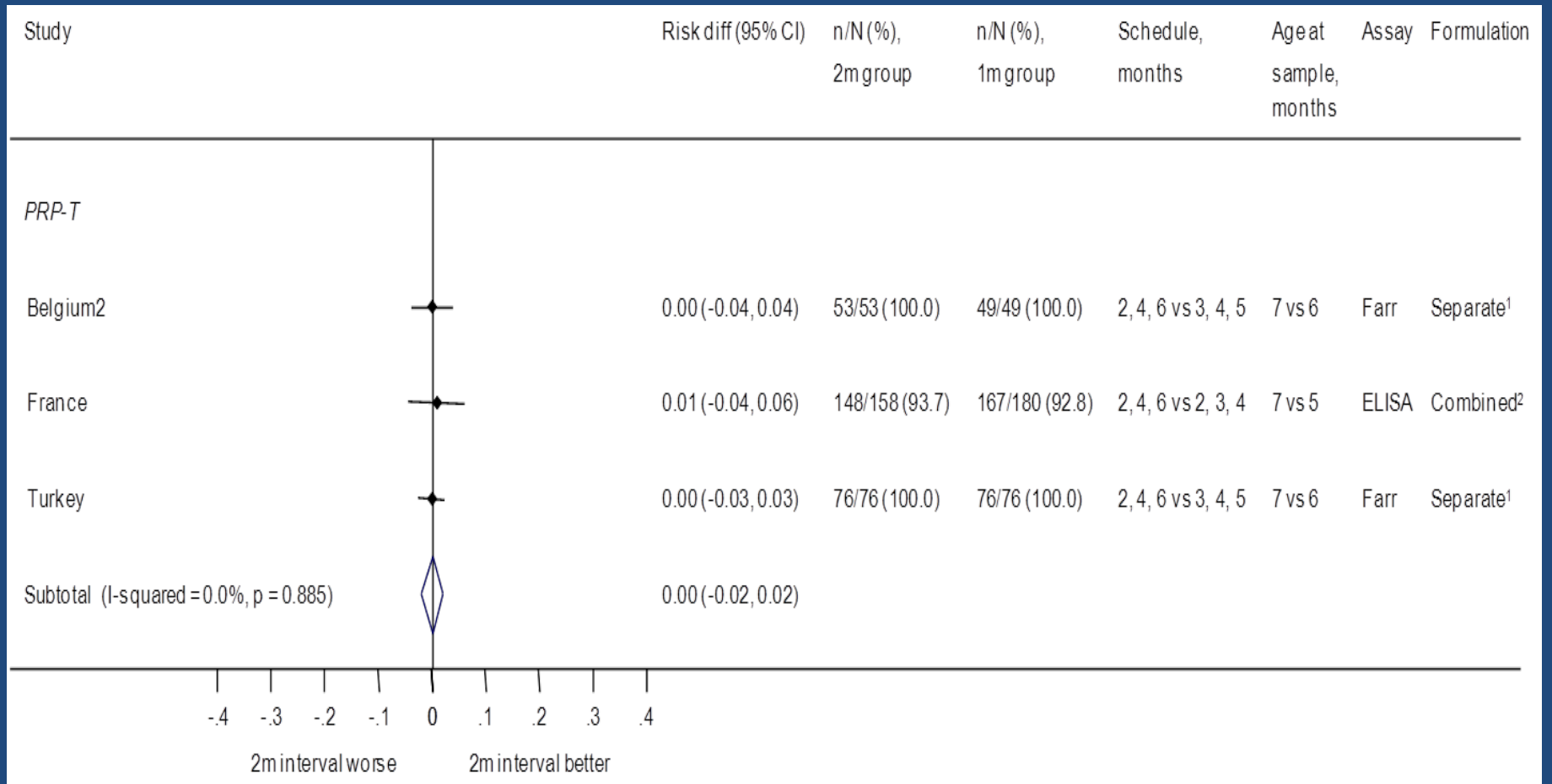
PRP-T at 2 days of age and at 2 months of age

Infants vaccinated in the neonatal period responded better to subsequent doses

Effect of the interval between primary doses on selected outcomes

Type of studies	Evidence
RCTs	
Observational	
Long term impact	

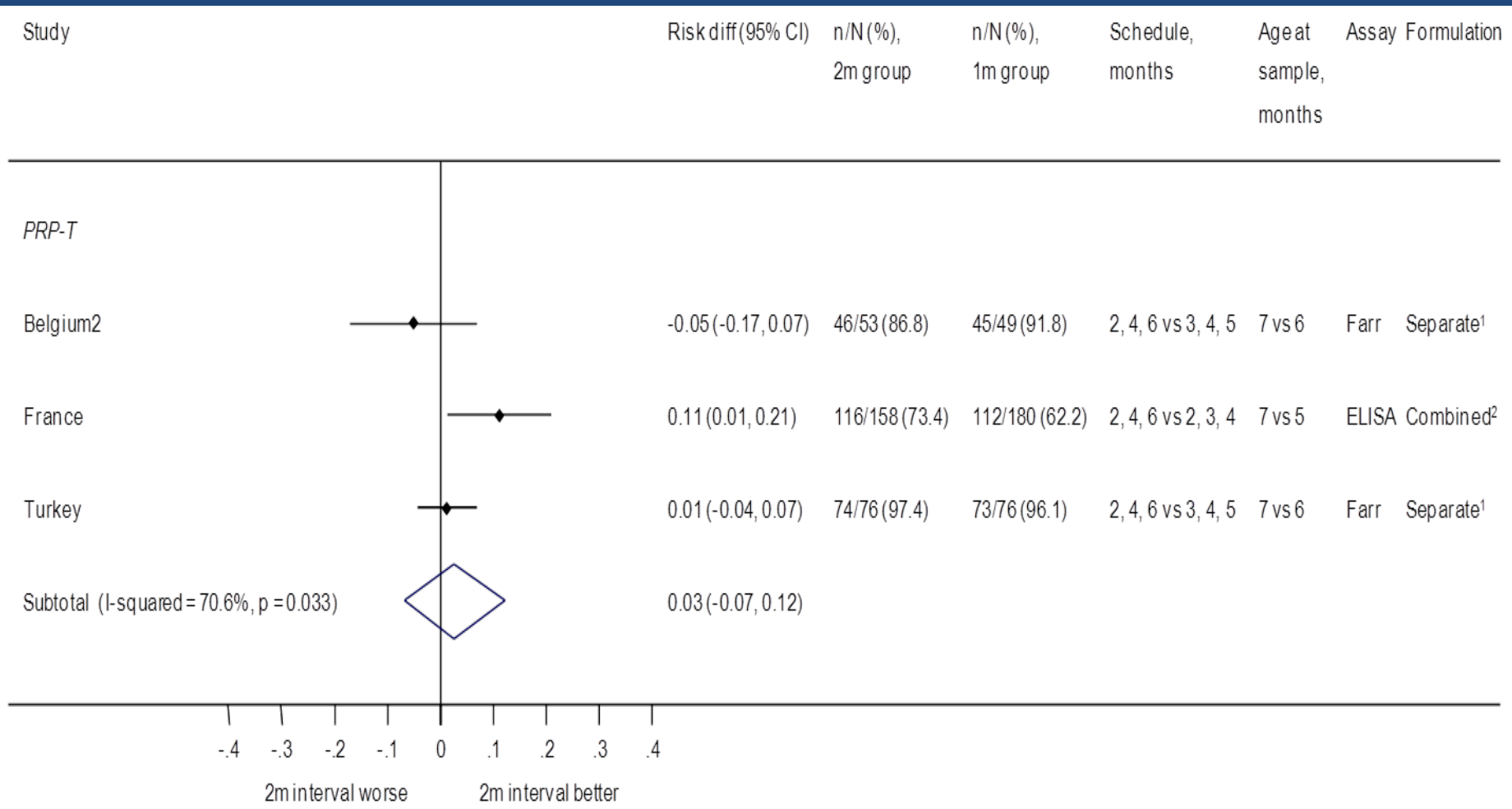
Immunization schedules with 2m vs 1m interval in primary course, 1m post primary, 0.15µg/ml, from RCTs



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

Immunization schedules with 2m vs 1m interval in primary course, 1m post primary, 1.0µg/ml, from RCTs



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1 DTaP at same time as Hib in separate syringe; 2 DTaP-hepB-IPV/Hib

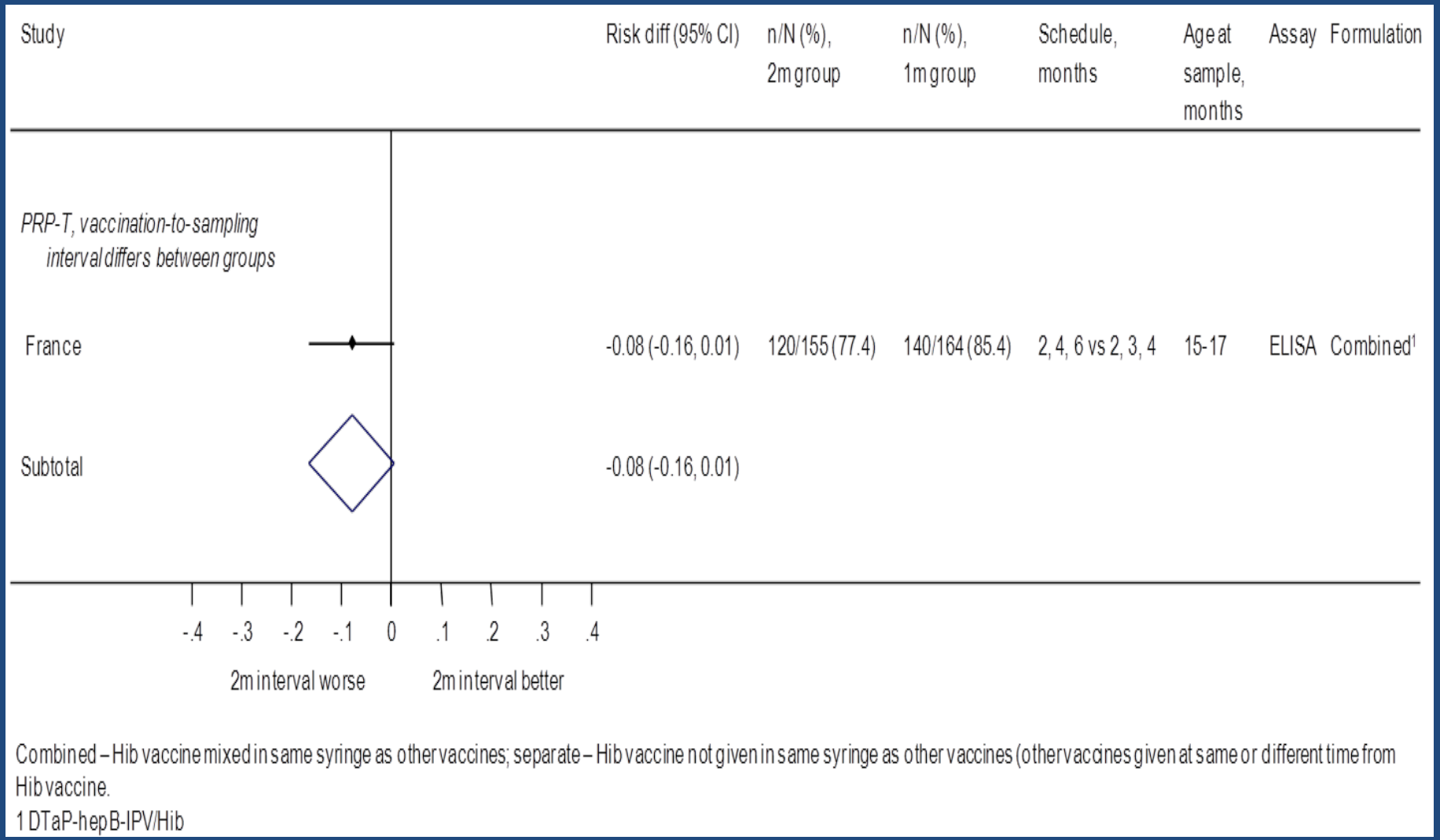
Immunization schedules with 2m vs 1m interval in primary course, 1m post booster, 0.15µg/ml, from RCTs

Study	Risk diff (95% CI)	n/N (%), 2m group	n/N (%), 1m group	Schedule, months	Age at sample, months	Assay	Formulation
PRP-T							
France	0.01 (-0.01, 0.02)	167/167 (100.0)	171/172 (99.4)	2, 4, 6 + b15-17 vs 2, 3, 4 + b15-17	16-18	ELISA	Combined[1]
Subtotal	0.01 (-0.01, 0.02)						

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

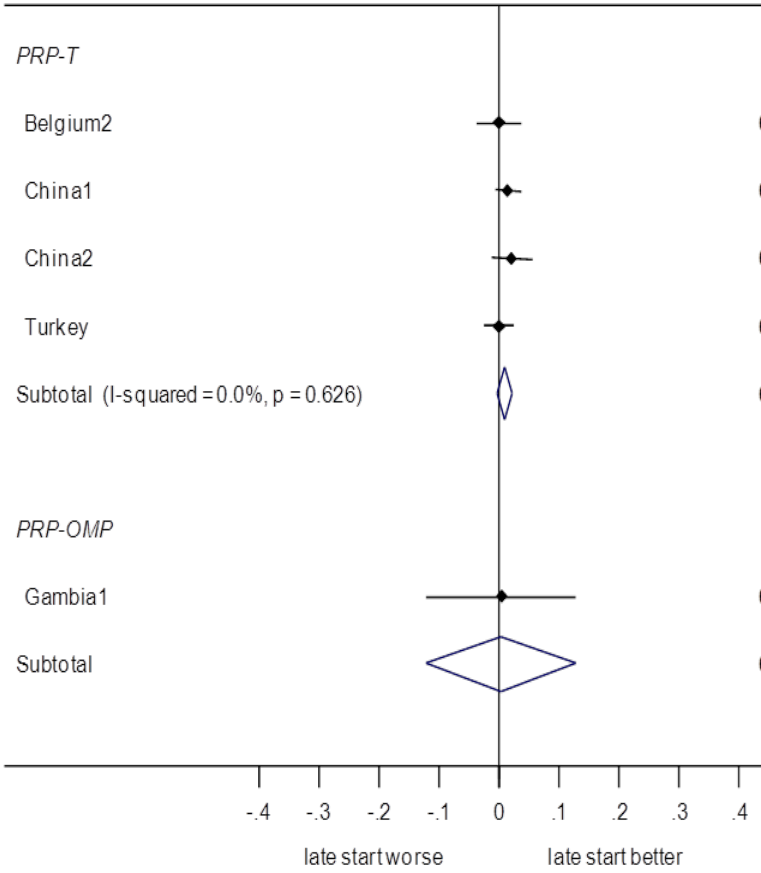
Immunization schedules with 2m vs 1m interval in primary course, pre-booster, 1.0µg/ml, from RCTs



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

Immunization schedules starting later vs earlier start, 1m post primary, 0.15µg/ml, from RCTs



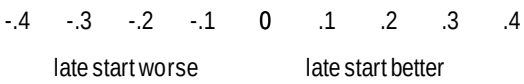
Study	Risk diff (95% CI)	n/N (%), late start	n/N (%), early start	Schedule, months	Age at sample, months	Assay	Formulation
PRP-T							
Belgium2	0.00 (-0.04, 0.04)	49/49 (100.0)	53/53 (100.0)	3, 4, 5 vs 2, 4, 6	6 vs 7	Farr	Separate[1]
China1	0.01 (-0.01, 0.04)	237/239 (99.2)	251/257 (97.7)	3, 4, 5 vs 2, 3, 4	6 vs 5	ELISA	Combined[2]
China2	0.02 (-0.01, 0.06)	155/157 (98.7)	142/147 (96.6)	3, 4, 5 vs 2, 3, 4	6 vs 5	ELISA	Combined[2]
Turkey	0.00 (-0.03, 0.03)	76/76 (100.0)	76/76 (100.0)	3, 4, 5 vs 2, 4, 6	6 vs 7	Farr	Separate[1]
Subtotal (I-squared = 0.0%, p = 0.626)	0.01 (-0.00, 0.02)						
PRP-OMP							
Gambia1	0.00 (-0.12, 0.13)	47/56 (83.9)	71/85 (83.5)	2, 4 vs 1, 3	5 vs 4	Farr	Separate[3]
Subtotal	0.00 (-0.12, 0.13)						

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

Immunization schedules starting later vs earlier start, 1m post primary, 1.0µg/ml, from RCTs

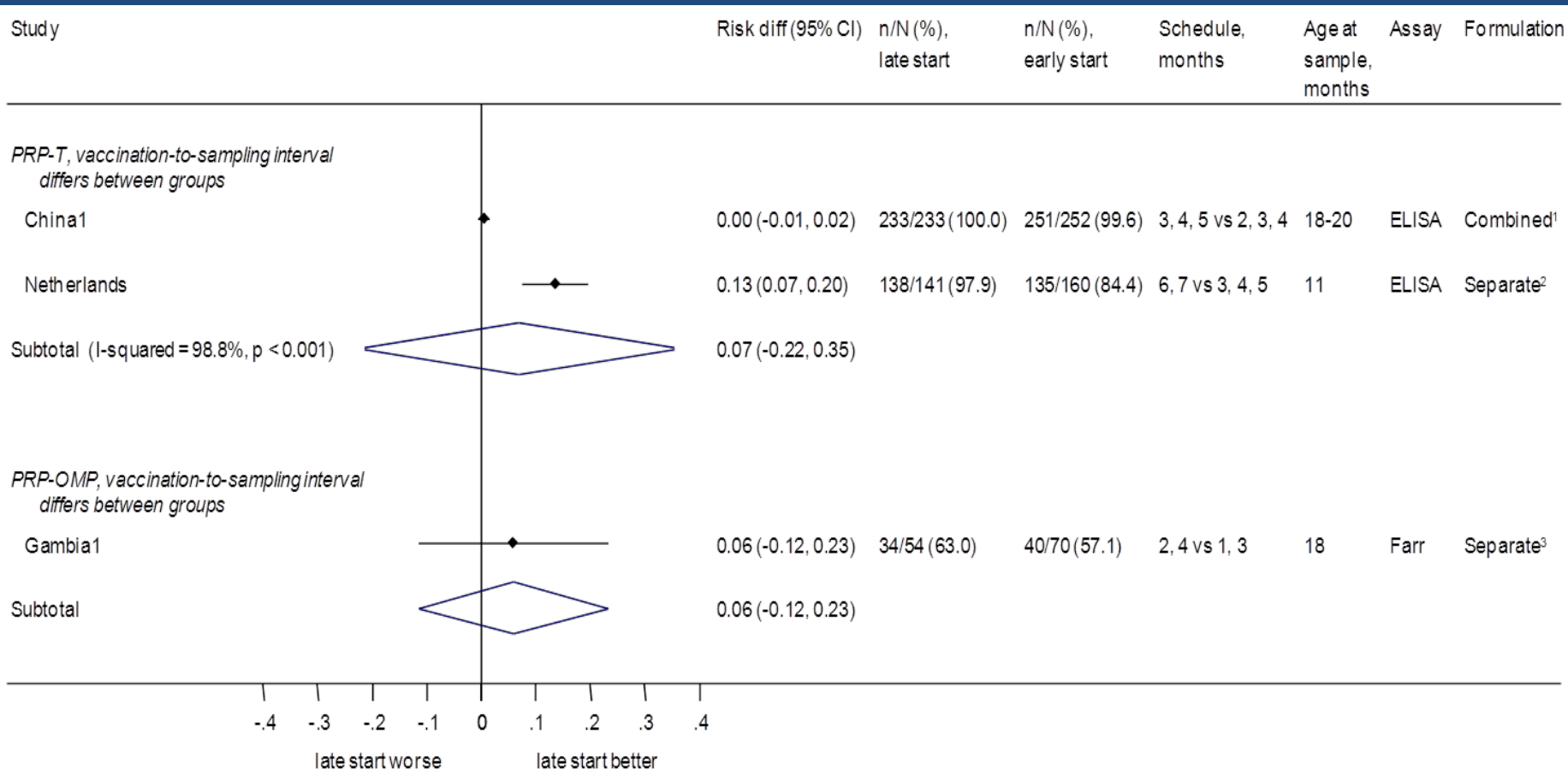
Study	Risk diff (95% CI)	n/N (%), late start	n/N (%), early start	Schedule, months	Age at sample, months	Assay	Formulation
PRP-T							
Belgium2	0.05 (-0.07, 0.17)	45/49 (91.8)	46/53 (86.8)	3, 4, 5 vs 2, 4, 6	6 vs 7	Farr	Separate[1]
Turkey	-0.01 (-0.07, 0.04)	73/76 (96.1)	74/76 (97.4)	3, 4, 5 vs 2, 4, 6	6 vs 7	Farr	Separate[1]
Subtotal (I-squared = 14.6%, p = 0.279)	0.00 (-0.06, 0.06)						
PRP-OMP							
Gambia1	0.07 (-0.10, 0.23)	34/56 (60.7)	46/85 (54.1)	2, 4 vs 1, 3	5 vs 4	Farr	Separate[2]
Subtotal	0.07 (-0.10, 0.23)						



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

Immunization schedules starting later vs earlier start, pre-booster, 0.15µg/ml, from RCTs

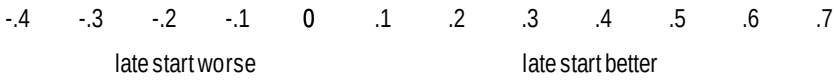


Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

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

Immunization schedules starting later vs earlier start, pre-booster, 1.0µg/ml, from RCTs

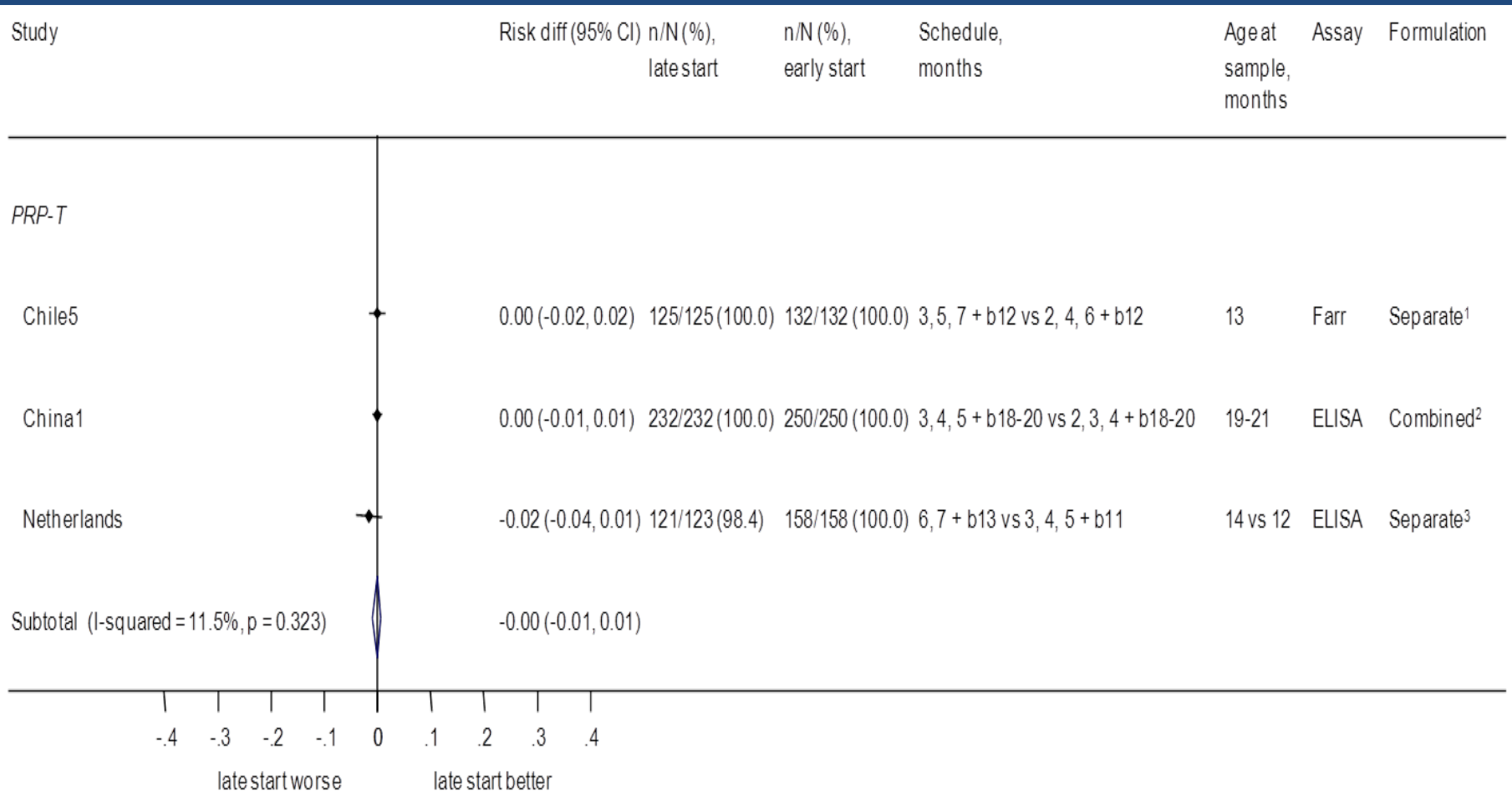
Study	Risk diff (95% CI)	n/N (%), late start	n/N (%), early start	Schedule, months	Age at sample, months	Assay	Formulation
PRP-T, vaccination-to-sampling interval differs between groups							
China1	0.01 (-0.07, 0.09)	174/233 (74.7)	186/252 (73.8)	3, 4, 5 vs 2, 3, 4	18-20	ELISA	Combined[1]
Netherlands	0.41 (0.31, 0.51)	114/141 (80.9)	64/160 (40.0)	6, 7 vs 3, 4, 5	11	ELISA	Separate[2]
Subtotal (I-squared = 97.4%, p < 0.001	0.21 (-0.18, 0.60)						
PRP-OMP, vaccination-to-sampling interval differs between groups							
Gambia1	-0.01 (-0.17, 0.14)	14/54 (25.9)	19/70 (27.1)	2, 4 vs 1, 3	18	Farr	Separate[3]
Subtotal	-0.01 (-0.17, 0.14)						



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

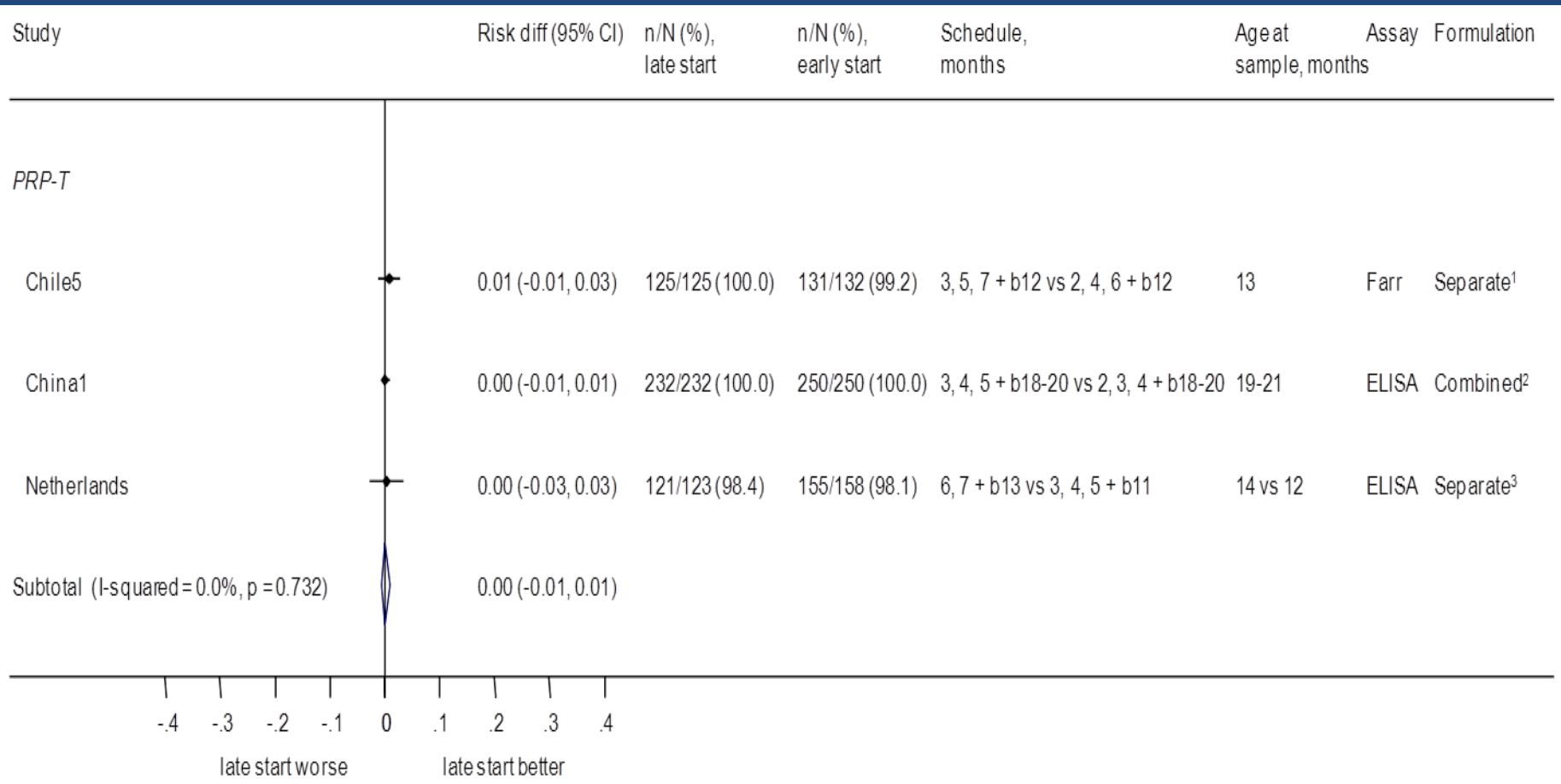
Immunization schedules starting later vs earlier start, 1m post booster, 0.15µg/ml



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

Immunization schedules starting later vs earlier start, 1m post booster, 1.0µg/ml



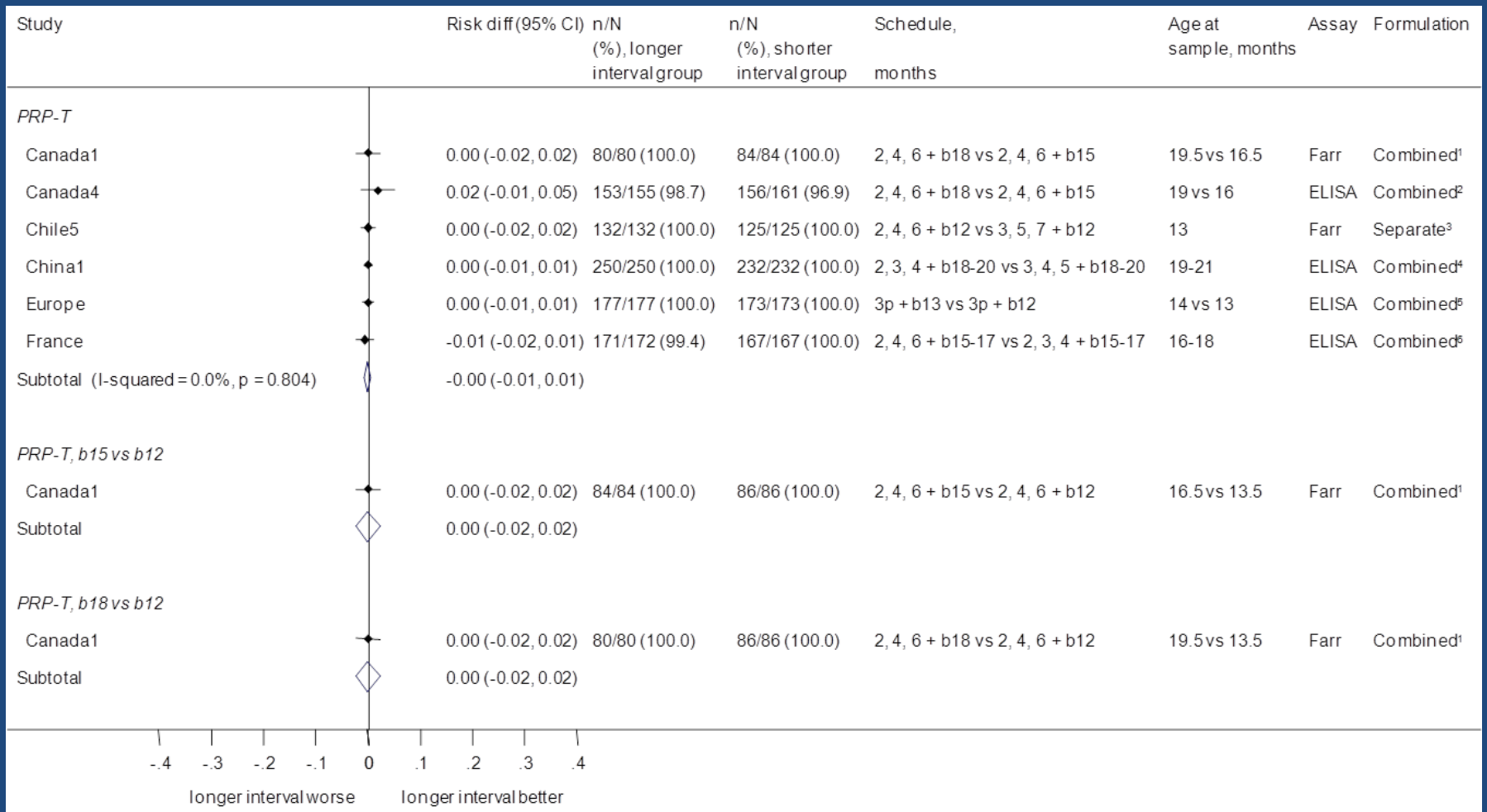
Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine.

1 DTaP 2, 4, 6 both groups; 2 DTaP-IPV/Hib; 3 DTwP-IPV both groups at 3, 4, 5

Effect of the interval between last primary dose and the booster dose of *Hib* vaccines on selected outcomes

Type of studies	Evidence
RCTs	
Observational	
Long term impact	

Long vs short interval between primary and booster, 1m post-booster, 0.15µg/ml, from RCTs

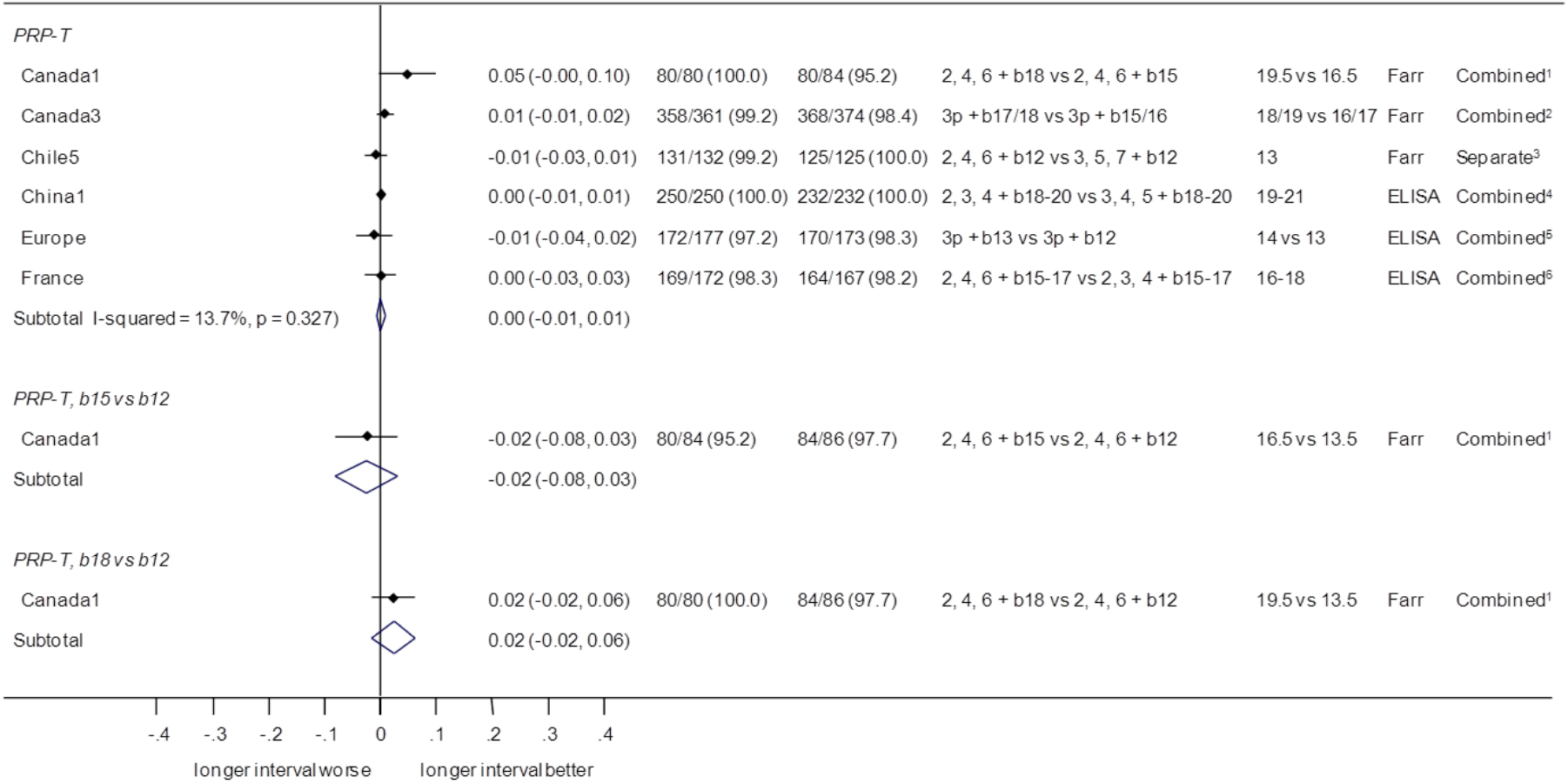


Study	Risk diff (95% CI)	n/N (%), longer interval group	n/N (%), shorter interval group	Schedule, months	Age at sample, months	Assay	Formulation
PRP-T							
Canada1	0.00 (-0.02, 0.02)	80/80 (100.0)	84/84 (100.0)	2, 4, 6 + b18 vs 2, 4, 6 + b15	19.5 vs 16.5	Farr	Combined[1]
Canada4	0.02 (-0.01, 0.05)	153/155 (98.7)	156/161 (96.9)	2, 4, 6 + b18 vs 2, 4, 6 + b15	19 vs 16	ELISA	Combined[2]
Chile5	0.00 (-0.02, 0.02)	132/132 (100.0)	125/125 (100.0)	2, 4, 6 + b12 vs 3, 5, 7 + b12	13	Farr	Separate[3]
China1	0.00 (-0.01, 0.01)	250/250 (100.0)	232/232 (100.0)	2, 3, 4 + b18-20 vs 3, 4, 5 + b18-20	19-21	ELISA	Combined[4]
Europe	0.00 (-0.01, 0.01)	177/177 (100.0)	173/173 (100.0)	3p + b13 vs 3p + b12	14 vs 13	ELISA	Combined[5]
France	-0.01 (-0.02, 0.01)	171/172 (99.4)	167/167 (100.0)	2, 4, 6 + b15-17 vs 2, 3, 4 + b15-17	16-18	ELISA	Combined[6]
Subtotal (I-squared = 0.0%, p = 0.804)	-0.00 (-0.01, 0.01)						
PRP-T, b15 vs b12							
Canada1	0.00 (-0.02, 0.02)	84/84 (100.0)	86/86 (100.0)	2, 4, 6 + b15 vs 2, 4, 6 + b12	16.5 vs 13.5	Farr	Combined[1]
Subtotal	0.00 (-0.02, 0.02)						
PRP-T, b18 vs b12							
Canada1	0.00 (-0.02, 0.02)	80/80 (100.0)	86/86 (100.0)	2, 4, 6 + b18 vs 2, 4, 6 + b12	19.5 vs 13.5	Farr	Combined[1]
Subtotal	0.00 (-0.02, 0.02)						

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

Long vs short interval between primary and booster, 1m post-booster, 1.0µg/ml, from RCTS



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Vaccination of children living in emergency settings

Type of studies	Evidence
RCTs	
Observational	
Long term impact	

Table 1. Hib vaccine effectiveness of (2 or more doses) HibCV in HIV-infected children.

Hib invasive disease type	Setting and year	Study type/source of data	Age group	VE HIV uninfected	VE HIV infected	VE overall
All invasive disease	Soweto, SA[a]	Before/after study 1997–2000, research cohorts [26]	<1 year	96.5 (74.4–99.5)	37.9 (−78.3 to 78.4)	81.7 (59.4–91.8)
All invasive disease	Soweto, SA	Extension of above before/after study 1997–2004 [31]	<2 years	90.8 (79.4–95.8)	54.7 (−4.6 to 80.3)	79.3 (65.7–95.8)
Meningitis	Blantyre Malawi[b]	Case–control 2003–2005. Controls hosp with Spn meningitis [32]	<5 years		100 (−39 to 100)	88% (63–96)

a HIV prevalence in children estimated to be 6.5%.

b HIV prevalence prenatally given as 15% nationwide. Assuming 26% vertical transmission rate prevalence in children would be 3.9%.

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Studies of immunogenicity of primary HibCV schedule (+/−booster) in HIV-infected or exposed children.

Vaccine type	Setting, year	Schedule	Study population[a]	Time since dose, % anti-PRP antibodies >1 μg/ml		Relationship to HIV progression
				Short term	Long term	
HibOC [36]	Baltimore, USA, 1990–1993	2, 4 and 6 months of age	23 HIV infected	3 months		Lower response if symptomatic at 1 year of age
			11 asymptomatic	82%		
			12 symptomatic	33%		
			24 uninfected	71%		
HbOC [37]	Philadelphia, USA, 1990–1994	2, 4 and 6 months +booster at 15 months		Before booster	4 months after booster	Numbers too small to examine relationship with HIV disease severity
			39 HIV infected	46%	63%>1 μg/ml	
			29 HIV uninfected	79%	78% 1 μg/ml	
HbOC al [40]	New York, USA, 1990–1995	2, 4 and 6 months +booster at 24 months (n = 16)	18 HIV infected	Before booster dose	4 months after booster	Mild or asymptomatic HIV more likely to have good antibody responses
		2 doses 2 months apart if 12–14 months of age (n = 2)		28%	45%	
HbOC [39]	Various US cities +Puerto Rico, 1990–1996	2,4 and 6 months +booster at 12–18 months		Before booster	At 24 months age after booster	No relationship with HIV disease severity but numbers small
			35 HIV infected	74%	76%	
			192 uninfected	73%	82%	
PRP-CRM I [31][b]	Soweto, SA, 1998–2000	6, 10 and 14 weeks		At 1 month		Those with mild disease more likely to have good response
			66 HIV infected-no ARTs	55%		
			127 uninfected	95.3%		
PRP-T [38]	Greece, 2001–2002	Primary immunisation at usual age not clear if in both groups or only controls			At median age 97 months	All clinical stage B (7) or C (2). No details given
			9 HIV infected		22%	
			7 on ARVs			
			9 Beta-Thalassaemia pts		100%	

[a] If ARVs used this is noted, otherwise children were not on ARVs.

[b] Also noted GMC titre needed to be higher in HIV infected cf. uninfected for 50% reduction in viability of Hib colony count. Also noted anti-Hib serum bactericidal antibodies titres >1:8 in 76.1% of 57 HIV-infected children not on ARTS cf. 97.2% with antibodies >1:8 in 102 uninfected children.

P. Mangtani et al. / Vaccine 28 (2010) 1677–1683

I will re draw this one to make it clear…!

The epidemiology of *Hib* disease in HIV-infected children

Immune suppression associated with HIV infection increases the risk of serious bacterial infections,

In a South African hospital setting, HIV infection increased the risk of *Hib*-related bacteraemic pneumonia by more than 20 times, and the risk of S. pneumoniae by more than 40 times also seen as the major causes of invasive disease in HIV-infected children in Zimbabwe and Rwanda. Bacterial disease is the most common presentation of acquired immunodeficiency syndrome (AIDS) in HIV-infected children not on ART

Clinically, HIV-infected children are more likely to present with bacteraemic *Hib* pneumonia than *Hib* meningitis

Compared to HIV-uninfected children, the risk of developing *Hib* meningitis is only slightly higher in HIV-infected children. However, its severity is increased: severe neurological sequelae in survivors were seen in 5/7 (71%) HIV-infected children compared to 7/30 (33%) HIV-uninfected children. HIV-infected children with *Hib* meningitis are also more likely to have concurrent pneumonia and local infections such as otitis media, mastoiditis or sinusitis together with malnutrition. In a Malawian hospital setting, presentation of any bacterial meningitis was also more likely to include shock if the child was HIV-infected

The only well-defined data on the incidence of *Hib* disease in HIV-infected children in the absence of vaccination comes from a South African pneumococcal vaccine efficacy trial . The risk of bacteraemic *Hib* pneumonia was higher in HIV-infected children as compared to uninfected children, with a relative risk of 18 (95% CI 6.9–47.1) in HIV-infected children less than 1 year [26] and [19] and an overall 5.9-fold (95% CI 2.7–12.6) increased risk of invasive *Hib* disease [26]. The additional burden of *Hib* pneumonia attributable to HIV was 822 per 100,000 among HIV-infected under 1 year olds (870 vs. 48 cases per 100,000 were seen in HIV-infected compared to uninfected children) [19]. The risk of *Hib* meningitis with HIV infection was 1.74 (0.23–13.2) fold higher in under 1 year olds but with confidence intervals that included one.

In unvaccinated developing country populations, over 80% of childhood *Hib* cases occur before the age of 2 years. In contrast, *Hib* disease tends to infect HIV-infected children at older ages. In a South African study, 5/19 HIV-infected children with bacteraemic *Hib* pneumonia were over 2 years of age, compared to none of the HIV-uninfected children. Similar age patterns were observed for *Hib* meningitis (2/8 children vs. 1/36 children; respectively); possibly because of continuing susceptibility resulting from progressive immunosuppression with age