# *Haemophilus influenzae* type b conjugate vaccines:

## A systematic review of data from randomized controlled trials of childhood schedules

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# Abstract

*Background:* Summaries of evidence are needed to inform decisions about optimal vaccine schedules. We systematically reviewed the effects of the different of *Haemophilus influenzae* type b (Hib) conjugate vaccine schedules.

*Methods:* We searched 21 databases up to May 2010 (20 databases) or June 2012 (MEDLINE).We selected randomized controlled trials (RCTs) or quasi-RCTs that made head-to-head comparisons between Hib schedules and reported clinical efficacy, nasopharyngeal carriage or immunological outcomes. We also selected trials that compared Hib vaccination to no Hib vaccination and reported clinical efficacy or carriage. We used meta-analysis to combine results where appropriate and assessed the risk of bias in individual trials.

*Results:* Forty trials conducted in 20 countries were eligible. Trials were often not clearly reported enough to assess their risk of bias. Immunological data showed few consistent or clinically relevant differences between Hib conjugate vaccine schedules with two or three primary doses or between schedules with different intervals between doses. Participants receiving booster doses were more likely to be seropositive than those of the same age who did not. No trials made head-to-head comparisons of schedules and reported clinical efficacy, but good protection against invasive Hib disease with 2p+0 schedules using PRP-OMP, (intention-to-treat vaccine efficacy, ITT VE, 95%, 95%CI 72, 99), and with 3p+0 schedules using PRP-T or PRP-HbOC (ITT VE 79%, 95%CI 63, 88).

*Conclusions:* No evidence is available from trials that compare Hib conjugate vaccine schedules and collect clinical outcome data to show that any 2p+1, 3p+0 or 3p+1 schedule provides better protection against Hib disease than other schedules. There is also no clear evidence from trials with immunological endpoints that any schedule produces an antibody response that will provide better protection against Hib disease. The optimal Hib vaccination schedule is likely to be determined by the epidemiological and programmatic conditions in individual settings.

# Contents

# 1 Abbreviations

| | |
|---|---|
| b | booster (denotes the use of a Hib conjugate vaccine booster when used in abbreviation of vaccine schedules) |
| CI | confidence interval |
| ELISA | enzyme-linked immunosorbent assay |
| FDA | United States Food and Drug Administration |
| GMC | geometric mean (antibody) concentration |
| Hib | *Haemophilus influenzae* type b |
| $I^2$ | $I^2$ statistic, a statistical measure of between-trial heterogeneity |
| ITT | intention-to-treat analysis |
| mITT | modified intention-to-treat analysis |
| OR | odds ratio |
| p | Denotes the number of primary doses, when used in the abbreviation of a vaccination schedule, e.g. 3p means 3 primary doses |
| PP | per protocol analysis |
| PRP | Hib capsular polysaccharide (polyribosylribitol phosphate) |
| PRP-HbOC | PRP conjugated to diphtheria CRM197 protein |
| PRP-OMP | PRP conjugated to meningococcal outer membrane protein |
| PRP-T | PRP conjugated to tetanus toxoid |
| RCT | randomized controlled trial |
| RD | risk (or prevalence) difference |
| SAE | serious adverse event |
| USA | United States of America |
| VE | vaccine efficacy |
| vs | versus |
| WHO | World Health Organization |

# 2 Definitions and clarifications

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| Adverse event (AE) | Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigation) product [1]. |
| Booster | For the purposes of this report, a booster is defined as a vaccine dose given after the last dose in a primary series, at 10 months of age or older and after an interval longer than that between doses in the primary series. |
| Catch-up dose(s) | Hib conjugate vaccine schedules started after 12 months of age, with no doses of Hib conjugate vaccine having been given in infancy. |
| Death from all causes | All deaths, regardless of cause. |
| Definitive Hib pneumonia | Pneumonia with a positive *Haemophilus influenzae* type b culture from a sample taken from the lung in conditions that minimize contamination of the sample (e.g. transthoracic lung biopsy). Different levels of diagnostic certainty are included in this definition (e.g. clinical diagnoses of pneumonia, radiographically confirmed pneumonia and radiographically confirmed pneumonia using WHO criteria). Levels of diagnostic certainty are analyzed separately where possible. In this review, pneumonia with a positive *Haemophilus influenzae* type b culture from blood or another normally sterile site is considered a sub-group of invasive Hib disease, not as definitive Hib pneumonia. |
| Intention-to-treat analysis | For the purposes of this report, intention-to-treat analyses are those where no randomized individuals are excluded from the analysis. |
| Invasive Hib disease | A positive *Haemophilus influenzae* type b culture from a normally sterile body fluid (cerebrospinal fluid, blood, synovial fluid). |
| Modified intention-to-treat analysis | For the purposes of this report, modified intention-to-treat analyses are those that are similar to intention-to-treat analyses but have modified inclusion criteria. For example, some analyses included only participants who had received the first dose of vaccine but did not exclude those with other protocol violations. For ease of description, these analyses are called intention-to-treat analyses throughout the report, except for in the risk of bias section. |
| Pneumonia from all causes | All cases of pneumonia, regardless or causative organism or pathogen. Different levels of diagnostic certainty are included in this definition (e.g. clinical diagnoses of pneumonia, radiographically confirmed pneumonia and radiographically confirmed pneumonia using WHO criteria). Levels of diagnostic certainty are analyzed separately where possible. |
| Primary series | Vaccination doses given in infancy and completed before 12 months of age. Intended intervals between doses should be the same. Vaccine doses started after 12 months are referred to as catch-up doses. |
| Per protocol analysis | For the purposes of this report, per-protocol analyses are those where individuals with protocol violations (such as not receiving the intended vaccination schedule) were excluded from the analysis. |

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| Seropositivity | An antibody concentration or titer above a defined threshold. Thresholds examined in this report are PRP antibody concentrations of ≥0.15µg/ml or ≥1.0µg/ml [2] |
| Vaccine efficacy | Efficacy has been defined as "the extent to which a specific intervention, procedure, regimen or service provides a beneficial result under ideal conditions" [3]. In this review, it is used to refer to any result, not only those that are beneficial. Vaccine efficacy is estimated as: $$Vaccine\ efficacy = \left(1 - \frac{rate\ (or\ risk)\ in\ vaccinated}{rate\ (or\ risk)\ in\ unvaccinated}\right) \text{x } 100$$ |

# 3 Introduction

Haemophilus influenzae type b (Hib) conjugate vaccines have led to large reductions in the incidence of invasive Hib disease, including meningitis and pneumonia, in countries that include them into their routine immunization schedule [4]. Nevertheless, there are still more than seven million cases of severe Hib disease worldwide annually in children under five years [5]. Conjugate vaccines that remain licensed in 2012 contain Hib capsular polysaccharide (polyribosylribitol phosphate, PRP) conjugated to diphtheria CRM197 protein (PRP-HbOC), meningococcal outer membrane protein (PRP-OMP) or, most commonly tetanus toxoid (PRP-T) [4].

Countries are faced with decisions about optimal schedules for vaccines recommended for infants. In 2012, most countries using Hib vaccine used a three-dose primary schedule with no booster dose (3p+0 schedule), in line with the World Health Organization position paper in 2006 [6]. Some countries, mainly in Europe and the Americas, have added a booster dose to this schedule (3p+1 schedule) and others, mainly in Europe, use schedules with two primary doses and a booster (2p+1 schedule) [7]. Variation in vaccination schedules reflects, in part, uncertainties about the optimal number of primary doses, the interval between doses in the primary schedule and the need for a booster dose [8]. Whilst the clinical efficacy of Hib conjugate vaccines has been summarized [9-12], there have been no systematic reviews about the relative effects of different Hib vaccine schedules that consider immunological and carriage outcomes as well as clinical outcomes. Here we systematically review the evidence from randomized controlled trials (RCTs) or quasi-randomized trials about the relative effects of 2p+0, 3p+0, 2p+1 and 3p+1 schedules and the effects of different timing of Hib conjugate vaccine doses. Evidence from observational studies is the subject of another review.

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.

# 4 Review methods

A search was conducted in 21 electronic databases from the earliest citation until May 2010. There were five databases of published articles (AIM, CENTRAL, LILACs, IndMED, MEDLINE), three trial registries, 11 vaccine manufacturer databases and two regulatory authority websites. The full search strategy is available in Appendix 1. In June 2012 the Medline search was updated, using a filter to identify RCTs, and eligible trial registrations found in the 2010 search were checked for new publications.

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. This is because adverse event data are typically collected for short periods of time after each vaccine dose and might not reflect the effect of vaccine over longer period.

***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 (GMC)

Comparisons between groups receiving different schedules of Hib conjugate vaccine ("head-to-head comparisons") were eligible for analyses of clinical, carriage and immunological data. 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.[13] For clinical outcomes we combined ratio measures derived from intention to treat (ITT) vaccine efficacy (VE) estimates reported in publications (ratio measure = 1 - (VE / 100)). When VE was not reported, we calculated ITT risk ratios using the numbers randomized and number of cases in each trial arm. We analyzed data from individually- and cluster-randomized trials separately. For nasopharyngeal carriage outcomes we calculated the odds ratio (with 95% confidence intervals, CI) of carriage in children receiving Hib vaccine compared with those not receiving Hib vaccine.[14] For immunological outcomes we calculated the difference between groups in proportions seropositive (with 95% confidence intervals) and reported the risk difference as a proportion. A risk difference of 0.08 would indicate that an additional 8% of individuals in the first comparison group were seropositive than in the second comparison group (e.g. 88% vs. 80%). Seropositivity was defined by IgG antibody levels measured by enzyme-linked immunoassay (ELISA) or Farr-type radio-assay at threshold values of 0.15µg/ml and 1.0µg/ml. Immunogenicity data were stratified according to the conjugated molecule (PRP-HbOC, -OMP or -T). We report GMC data where seropositivity data were not available.

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).

# 5 Results

A total of 4337 items were identified in searches (Figure 1). Of these, 100 items comprising 40 RCTs conducted in 20 countries were eligible for this review (Table 1 and Appendix 2). Eighteen different types of schedule comparison were examined among these RCTs, including 13 head-to-head comparisons of Hib conjugate vaccine schedules and five comparisons of a Hib-containing schedule to a schedule with no Hib vaccine (Table 2). Twenty-seven trials made head-to-head comparisons of Hib conjugate vaccine schedules and reported immunological data. Five of these trials also reported mortality data and none reported other eligible clinical outcomes. Six trials compared Hib vaccination to no Hib vaccination and reported invasive Hib disease, meningitis, or

pneumonia. Of these six trials, one also reported carriage, and four mortality. Immunological outcomes for comparisons of Hib vaccination to no Hib vaccination were not eligible for this review (see section 4). Seven additional trials reported mortality as the only eligible outcome (two with head-to-head comparisons, and five with comparisons to no Hib vaccine). Mortality data are not presented in this document because many trials that reported mortality data stated that there were no deaths. Mortality data were therefore scarce.

The median number of trial participants was 212 (range 54 - 1782) for trials reporting immunological outcomes and making head-to-head comparisons of Hib schedules. The median was 48,961 (range 5190 - 76533) in trials reporting invasive Hib disease, meningitis, pneumonia and comparing Hib vaccination to no Hib vaccination.

Outcome data from 26 trials are reported in this review. The remaining 14 trials reported mortality only (seven trials) or reported comparisons not prioritized in this review (seven trials, Table 2).

## 5.1 Design features of included trials and the risk of bias

Of the 26 trials for which data are reported, twenty-four trials individually assigned participants to intervention groups, two of which were judged to be quasi-randomized (USA2, USA8). Quasi-randomized trials are at higher risk of bias than randomized trials with adequate sequence generation and allocation concealment (see below) [15]. Two trials assigned participants by cluster. In one, (Indonesia2), each hamlet was randomly allocated to intervention or control groups (referred to as cluster-randomized). In the other trial (Chile3) two groups of health centers were manually assembled and randomly assigned to intervention and control groups (referred to as cluster-assigned). The latter trial is more at risk of bias than the former because the total number of randomized units is only two, compared to 818 in the former trial.

Other key design features which could influence the risk of bias in individual trials are presented in Table 3. These features include the adequacy of allocation concealment, the use of outcome assessor blinding and the type of analysis (intention to treat or per protocol). Features are summarized only for trials which contributed data to analyses presented in this report (26 trials).

Allocation concealment could only be assessed as adequate in four of the 26 trials (two with clinical and three with immunological outcomes). In 19 trials allocation concealment was not well enough described to be fully assessed (two with clinical outcomes). Outcome assessors were assessed to be blinded in four of six trials with clinical outcomes and 11 of 20 trials with immunological outcomes.

Modified intention-to-treat analyses are those that are similar to intention-to-treat analyses but have some modifications to inclusion criteria. For example, some analyses included only participants who had received the first dose of vaccine but did not exclude those with other protocol violations. Excluding individuals after randomization increases the potential for bias in the results of RCTs [16]. All trials which examined clinical outcomes reported intention to treat (ITT) or modified ITT (mITT) analyses and four also reported per protocol (PP) analyses. Four of 20 trials which examined immunological outcomes reported mITT analyses (three of which also conducted PP analyses but reported only that results were similar to mITT results). A further nine of the 20 trials reported PP analyses and for seven trials it was not clear which analysis was reported.

Additionally, some trials provided immunological data for schedule comparisons where the interval between the last vaccine dose and blood sampling was different for the intervention groups being compared. In graphs of immunological data, these trials are presented separately from other trials because they do not provide a fair comparison of schedules.

## 5.2 Hib conjugate vaccine head-to-head comparisons of schedules

There were no eligible data about invasive Hib disease, meningitis, pneumonia or carriage from trials for any of the head-to-head comparisons of schedules described below (sections 5.2.1 - 5.2.11). All available data from trials for these comparisons are immunological.

### 5.2.1 2p+0 vs 1p+0 schedules, immunological data

Three trials provided immunological data for this comparison (Niger1, USA4, USA5). Each trial examined a different Hib conjugate vaccine (PRP-T, PRP-OMP, PRP-HbOC). Two trials reported seropositivity data (Niger1, USA4) and all trials reported GMC. Seropositivity results for this comparison are presented in Figure 2, stratified by conjugate type and the antibody concentration used to define seropositivity (0.15µg/ml and 1.0µg/ml). The proportion seropositive 1m after vaccination was high for both 2p and 1p schedules at 0.15µg/ml (one trial). Lower proportions were seropositive at 1.0µg/ml (two trials). The study which reported only GMC (USA5) examined PRP- HbOC and compared a birth dose plus a dose at 2 months of age to a single dose at 2 months of age. GMC was measured 2 months after the last dose of vaccine. The 2p group (birth-dose group) had a GMC of 0.16µg/ml (95%CI 0.10-0.25) and the 1p group 0.05µg/ml (95%CI 0.02-0.08).

### 5.2.2 3p+0 vs 2p+0 schedules, immunological data

Seven trials provided immunological data for this comparison (Chile4, Chile5, Guatemala, Netherlands, Niger1, Sweden, USA5). Six examined PRP-T, and two examined PRP-HbOC (one trial examined both). Six trials reported seropositivity data (Chile4, Chile5, Guatemala, Netherlands, Niger1, Sweden) and all trials reported GMC.

Seropositivity results for this comparison where the same Hib conjugate vaccine was used in both arms are presented in Figures 3-6, stratified by conjugate type. In three trials examining PRP-T (Chile2, Niger1, Sweden), the proportion seropositive around 1m after vaccination was high for both 3p and 2p schedules at 0.15µg/ml. The proportions seropositive were lower at the 1.0µg/ml threshold and at 6m after last dose in the primary schedule. Neither the 2p nor the 3p schedule was consistently favored in analyses. By six months after the last primary dose, there was no statistical evidence of a difference between the schedules at the 1.0µg/ml threshold (pooled risk difference -0.02, 95%CI -0.10, 0.06, $I^2$ 0%) but it remained high at the 0.15µg/ml threshold (pooled risk difference 0,02 95%CI -0.10, 0.14 , $I^2$ 75%). One trial (Chile2) examined PRP-HbOC and presented seropositivity data. Point estimates favored the 3p group but the confidence interval crossed the null effect at both two and six months after the last dose and for both thresholds.

The trial which reported only GMC (USA5) examined PRP-HbOC and compared a birth dose plus doses at 2 and 4 months of age to doses at 2 and 4 months of age. Two months after the last dose, the GMC in the 3p group (birth-dose group) was 0.93µg/ml (95%CI 0.48, 1.69) and 0.20µg/ml (95%CI 0.10, 0.29) in the 2p group.

In addition, five trials (Lithuania, Thailand, USA4, USA6, USA7) presented data comparing three primary doses of a Hib conjugate vaccine (often PRP-T) to two primary doses of another Hib conjugate vaccine (often PRP-OMP). These data are not presented in this report.

### 5.2.3 2p+1 vs 2p+0 schedules, immunological data

No immunological data were available for this comparison.

### 5.2.4 3p+0 vs 2p+1 schedules, immunological data

One trial provided immunological data for this comparison (Sweden) using PRP-T. This trial reported seropositivity and GMC data. Seropositivity results for this trial are presented in Figures 7 and 8. At 13 months of age (seven months after the 3p group received their last primary dose and one month after the 2p+1 group received their booster), the 2p+1 schedule resulted in higher seropositivity than the 3p schedule at both the 0.15µg/ml and 1.0µg/ml thresholds. The risk difference was -0.79 (95%CI -0.87, -0.71) at the 1.0µg/ml threshold (favors the 2p+1 schedule) and -0.20 (95%CI -0.27, -0.13) at 0.15µg/ml. The proportion seropositive at the 0.15µg/ml threshold remained high at around 6 months after a 3p schedule. This proportion was lower at the 1.0µg/ml threshold.

Additionally, six trials included in this review reported data for an individual trial arm receiving a 3p schedule or a 2p+1 schedule (Chile4, Chile5, Guatemala, Netherlands, Niger1, Sweden). Non-comparative seropositivity data from these trial arms are presented in Figures 9 and 10. High

proportions of individuals remained seropositive at the 0.15µg/ml threshold 6 months after a 3p schedule. The proportion was lower at the 1.0µg/ml threshold but there was variability between trials.

### 5.2.5 3p+1 vs 2p+1 schedules, immunological data

Two trials provided immunological data for this comparison (Netherlands, Sweden). Both trials examined PRP-T and both reported seropositivity and GMC data. Seropositivity results for this comparison are presented in Figures 11-14. Proportions seropositive one month after the booster vaccinations were high and showed little difference between the schedules groups (pooled risk difference 0.01 95%CI -0.03, 0.05, $I^2$ 56% at the 1.0µg/ml threshold; 0.01 95%CI -0.01, 0.02, $I^2$ 24% at 0.15µg/ml).

### 5.2.6 3p+1 vs 3p+0 schedules, immunological data

Two trials provided immunological data for this comparison (Canada3, Europe). Both examined PRP-T, and one reported seropositivity data (Europe). Both trials reported GMC. Seropositivity results for this comparison are presented in Figures 15 and 16, stratified by conjugate type.

At 13 months of age (one month after the 3p+1 group received their booster dose), the 3p+1 schedule resulted in higher seropositivity than the 3p schedule at both the 1.0µg/ml (risk difference 0.59, 95%CI 0.52, 0.67) and 0.15µg/ml thresholds (risk difference 0.16, 95%CI 0.11, 0.22).

One trial reported only GMC (Canada3). Multiple trial groups were available for comparison and not all are presented here. At 16 months of age a group which received a 3p schedule with a booster dose at 15 months of age achieved a GMC of 29.2µg/ml (95%CI 24.58, 36.43) and a group which had received a 3p schedule with no booster dose by 16 months of age achieved a GMC of 0.32µg/ml (95%CI 0.25, 0.41).

### 5.2.7 Birth dose vs no birth dose schedules, immunological data

A single trial examined a birth dose of Hib conjugate vaccine (USA5). This study reported only GMC and examined PRP- HbOC. A birth dose plus doses at 2, 4 and 6 months of age was compared to doses at 2, 4 and 6 months of age. GMC was measured 1 month after the last dose of vaccine.

Authors of this trial concluded that a birth dose of PRP-HbOC does not lead to earlier or higher antibody levels. The group which received the birth-dose schedule (the 4p group) had a GMC of 4.55µg/ml (95%CI 2.72-7.61), and the no birth-dose group (3p group) 1.58µg/ml (95%CI 0.99-2.16). GMC after 3 doses of vaccine could not be compared as different intervals between last dose and blood sampling were used in the two groups. Two months after the second dose of vaccine the birth-dose group had a GMC of 0.16µg/ml (95%CI 0.10-0.25) and the no birth-dose group 0.20µg/ml (95%CI 0.10-0.29).

### 5.2.8 Late vs early start schedules, immunological data

Eight trials provided immunological data for this comparison (Belgium2, Chile5, China1, China2, Gambia1, Gambia2, Netherlands, Turkey) excluding the single trial which examined a birth dose (section 5.2.7). Seven examined PRP-T, and one examined PRP-OMP. Seven trials reported seropositivity data and eight reported GMC. Seropositivity results for this comparison are presented in Figures 17-22, stratified by conjugate type.

There were only small differences in seropositivity between the schedules available for comparison and heterogeneity was very low (pooled risk difference one month after the last primary dose 0.02 95%CI -0.01, 0.05, $I^2$ 1% at the 1.0µg/ml threshold; 0.01 95%CI 0.00, 0.02, $I^2$ 0% at 0.15µg/ml). However, it should be noted that some schedule comparisons differed in both the age at first dose and in the interval between doses in the primary schedule.

The study which reported only GMC (Gambia2) examined PRP- T and compared doses at 2 and 4 months of age to doses at 1 and 3 months of age. GMC was measured 1 month after the last dose of vaccine. The GMC was 0.41µg/ml (95%CI 0.28-0.61) in the 2 and 4 month group and 0.26µg/ml (95%CI 0.19-0.35) in the 1 and 3 month group.

### 5.2.9 Two- month vs one-month intervals in primary schedules, immunological data

Four trials compared two-month intervals to one-month intervals (Belgium2, France, Turkey, USA8); three used 3p schedules with PRP-T and reported both seropositivity and GMC data (Belgium2, France, Turkey) and one used a 2p schedule with PRP-OMP and reported GMC data only (USA8).

Seropositivity results for the comparison of 2 month and 1 month intervals are presented in Figures 23-28. One month after the last primary dose, neither schedule was consistently favored at the 1.0µg/ml threshold and results were heterogeneous (pooled risk difference 0.03 95%CI -0.07, 0.12, $I^2$ 70%). At the 0.15 µg/ml threshold, no difference was seen between the schedules and heterogeneity was low (pooled risk difference 0.00 95%CI -0.02, 0.02, $I^2$ 0%). After a booster dose, there was little difference between the schedules at either threshold.

The trial which compared two-month intervals to one-month intervals using PRP-OMP (USA8) used alternation for assignment of interventions and was therefore quasi-randomized. The mean age at first vaccination was unintentionally older in the two-month-interval group than in the one-month-interval group (4.1 months and 3.2 months respectively). Age adjusted GMCs one month after the second vaccinations were 3.95µg/ml (95%CI 2.63-5.92) in the two-month-interval group and 2.32µg/ml (95%CI 1.48-3.64) in the one-month-interval group.

### 5.2.10 Four- month vs two-month intervals in primary schedules, immunological data

One trial compared 4-month intervals to two-month intervals using PRP-OMP (USA4). Seropositivity results for the comparison of 4 month and 2 month intervals are presented in Figures 29-30. Results were difficult to interpret because the interval between vaccination and blood-sampling differed between the groups being compared.

### 5.2.11 Longer vs shorter intervals between primary and booster schedules, immunological data

Seven trials provided immunological data for this comparison (Canada1, Canada3, Canada4, Chile5, China1, Europe, France). All examined PRP-T and all reported seropositivity and GMC data. However, one study which had multiple groups and multiple long- vs short-interval to booster comparisons (Canada3) did not report seropositivity and GMC data for all comparisons. Seropositivity results for the seven trials are presented in Figures 31-32. Differences in seropositivity one month after the booster dose were very small (pooled risk difference 0.00 95%CI -0.01, 0.01, $I^2$ 14% at the 1.0µg/ml threshold, Figure 5; 0.00 95%CI -0.01, 0.01, $I^2$ 0% at 0.15µg/ml).

## 5.3 Comparisons of Hib-containing schedules to no Hib vaccine

Immunological data comparing Hib vaccination to no Hib vaccination were not eligible for this review. Of six trials that reported an eligible clinical outcome, one trial randomized to 2p+0 or no doses of Hib vaccine and five randomized to 3p+0 to no doses.

Clinical results for all comparisons are presented in Figures 33-36. 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 due to protocol violations. 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.

Carriage data were reported by one trial and are presented in Figure 37.

## 5.3.1 1p+0 vs no doses, clinical and carriage data

No trials reporting clinical data randomized participants to 1p or no Hib doses. All data presented for this comparison is from individuals who had not completed their intended vaccination schedule, or from individuals between the receipt of the first and second doses. These data are might not accurately reflect results that would be obtained from a trial randomizing participants to 1p or no Hib doses and are presented here for completeness only.

### 5.3.1.1 Invasive Hib disease (combined outcome)

Two trials presented data about invasive Hib disease for this comparison (USA1 and Gambia 4, Figures 33 and 34). Data from USA1 was collected from individuals with onset of invasive Hib disease before their second dose. This trial used PRP-OMP, and the reported ITT VE was 100% (95%CI 41, 100) and PP VE100% (95%CI 15,100). Gambia4 (PRP-T) only reported PP analyses. The reported PP VE after one dose was 44% (95%CI -85, 85), and within 56 days of the first dose 71% (95%CI 50, 97).

### 5.3.1.2 Pneumonia

No data were available for this outcome and comparison.

### 5.3.1.3 Carriage

One trial presented data about carriage for this comparison (Gambia4, Figure 37). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was low ($I^2$ 0%). The point estimate showed slightly less carriage with one dose of PRP-T compared to no doses but confidence intervals were very wide (pooled odds ratio 0.82, 95%CI 0.14, 4.71).

## 5.3.2 2p+0 vs no doses, clinical and carriage data

The only trial randomizing to a 2p+0 schedule (USA1) used PRP-OMP, was individually randomized and reported on invasive disease and meningitis. One additional trial compared carriage in those receiving 2 doses to those receiving no doses but was not randomized to this comparison (Gambia4, PRP-T).

### 5.3.2.1 Invasive Hib disease (combined outcome) and meningitis

The reported ITT VE from USA1 against invasive disease was 95% (95%CI 72, 99, Figure 33) and the PP VE was 93% (95%CI 53, 98, Figure 34). The ITT VE against meningitis was calculated by reviewers to be 96% (95%CI 37, 100%).

### 5.3.2.2 Pneumonia

No data were available for this outcome and comparison.

### 5.3.2.3 Carriage

One trial presented data about carriage for this comparison although it was randomized trial of a 3p schedule (Gambia4, Figure 37). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was moderate ($I^2$ 47%). The point estimate showed less carriage with two doses of PRP-T compared to no doses but confidence intervals were very wide (pooled odds ratio 0.52, 95%CI 0.08, 3.37).

## 5.3.3 3p+0 vs no doses, clinical and carriage data

Five trials randomized to a 3p+0 schedule or no Hib vaccine and reported on invasive disease, meningitis or pneumonia (Chile3, Gambia4, Indonesia2, USA2 and USA3). One of these trials also reported on carriage (Gambia4).

#### 5.3.3.1 Invasive Hib disease (combined outcome) and meningitis

Four trials reported on invasive Hib disease (Chile3, Gambia4, USA2 and USA3), three on meningitis (Indonesia2, Chile3, Gambia4). The combined ITT VE against invasive Hib disease for the two individually randomized trials was 76% (95%CI 55, 88, $I^2$ 0%) with PRP-T and 84% (95%CI 58, 94) for the quasi-randomized trial using PRP-HbOC (Figure 33). The pooled ITT VE estimate from these three trials was 79% (95%CI 63, 88). The ITT VE against invasive Hib disease in the cluster-assigned trial (Chile3) was 90% (95%CI 74, 100). Additionally, in an analysis where the four trials reporting invasive Hib disease for 3p schedules (Gambia4, USA2, USA3, Chile3) were analyzed together, the combined ITT VE estimate was 83% (95%CI 72, 89) with low between trial heterogeneity ($I^2$ 0%). PP VE estimates, when reported, were either similar or somewhat higher than ITT estimates (Figure 34).

Data about meningitis were incompletely reported. For the individually randomized trial the ITT VE against meningitis was calculated to be 67% (95%CI 22, 86, Gambia4), for the cluster-randomized trial the point estimate was 86% (Indonesia2) and the cluster-assigned trial 91% (Chile3).

#### 5.3.3.2 Pneumonia

Three trials reported on pneumonia (Indonesia2, Chile3, Gambia4). The reported ITT VE against clinical pneumonia was 7% (95%CI -2, 15) for the individually randomized trial (Gambia4) and 4% (95%CI1, 7) in the cluster-randomized trial (Indonesia2, Figure 35). In an analysis where these two trials were analyzed together, the combined ITT VE was 4% (95%CI 1, 7) with low between trial heterogeneity ($I^2$ 0.0%). For the individually randomized trial (Gambia4) ITT VE against radiologically confirmed pneumonia was 21% (95%CI 5, 35). PP VE estimates were similar to ITT estimates (Figure 36).

#### 5.3.3.3 Carriage

One trial, comparing three primary doses of PRP-T at 2, 3 and 4 months with no Hib doses, reported carriage data (Gambia4). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was low ($I^2$ 0%). The combined odds ratio comparing three doses of PRP-T to no doses was 0.36 (95%CI 0.25, 0.53, $I^2$ 0%, Figure 37).

### *5.3.4 2p+0 or 3p+0 schedules vs no doses, clinical and carriage data*

No trials reporting clinical data randomized participants to this comparison. However, this comparison is the only one for which data about definitively diagnosed Hib pneumonia were available and so this comparison is reported for completeness.

#### 5.3.4.1 Invasive Hib disease (combined outcome)

PP VE against invasive Hib disease was calculated by reviewers to be 93% (95%CI 71, 98) after 2 or 3 doses (Gambia4).

#### 5.3.4.2 Pneumonia

PP VE of two or three primary doses of vaccine against definitively diagnosed Hib pneumonia was 100% (95%CI 55, 100) after 2 or 3 doses (Gambia4).

#### 5.3.4.3 Carriage

There were no data available for this outcome and comparison.

### *5.3.5 2p+1 and 3p+1 schedules vs. no doses, clinical and carriage data*

There we no available clinical or carriage data from trials comparing 2p+1 or 3p+1 Hib conjugate vaccine schedules to no Hib vaccine.

# 6 Discussion

## 6.1 Main findings

Immunological data in this systematic review showed few consistent or clinically relevant differences between Hib conjugate vaccine schedules with two or three primary doses or between schedules with different intervals between doses. Participants who had received booster doses were more likely to be seropositive than those of the same age who had not. There is an absence of clinical outcome or nasopharyngeal carriage data in head-to-head comparisons of Hib schedules. Limited clinical and carriage data from trials comparing either two or three primary dose to no Hib vaccine do not provide strong evidence of a difference between 2p and 3p schedules.

## 6.2 Strengths and limitations

This study is, to our knowledge, the first systematic review to examine the evidence from head-to-head comparisons of different Hib conjugate vaccine schedules. The wide search means that relevant RCTs are unlikely to have been missed. We also attempted a detailed assessment of potential sources of heterogeneity and bias but many trials were not reported completely enough for the risk of bias to be assessed. We did not include data from observational studies because well-conducted RCTs are at lower risk of bias than observational study designs [17, 18] and because observational studies have been summarized elsewhere. The potential for bias does remain, however, in many of the included trials.

A limitation identified by this review was the paucity of data on several outcomes and comparisons of interest. There were insufficient studies to formally investigate sources of heterogeneity through methods such as meta-regression. For example, in the 2 vs. 1 month interval comparison, one trial (France) favors the 2 month interval more strongly than the other two trials and cannot be determined from the available trials why this is the case.

Most of the immunological data related to PRP-T and findings might not be generalizable to other Hib conjugate vaccines where they are not represented in a comparison. It is also challenging to draw conclusions about clinical efficacy based on immunological findings because the clinical relevance of Hib seropositivity levels and GMCs are not well established [2] .

## 6.3 Interpretation

The immunological data from available trials do not clearly favor either a two-dose or a three-dose primary schedule. There were also no important differences in seropositivity for PRP-T schedules starting at either 2 vs. 3 months or PRP-OMP schedules starting at 1 vs. 2 months of age. The available clinical data show good protection against invasive Hib disease with 2p+0 schedules using PRP-OMP and with 3p+0 schedules using PRP-T or PRP-HbOC, when compared to no Hib vaccine. However, estimates of VE from different trials cannot be compared directly as evidence of equivalence or superiority of one particular schedule and there were too few trials for a network meta-analysis, which would allow such a comparison [19, 20].

Two months intervals between doses in the primary schedule were not shown to be consistently more immunogenic than one month intervals. Meta-analyses either showed marked heterogeneity or showed little heterogeneity and no difference between two and one month intervals. It is challenging to draw conclusions about clinical efficacy based on these findings not only because the lack of certainty about the meaning of immunological data but because of differences in the schedules compared within each study in addition to the difference of interest.

A booster dose after a primary series of either two or three doses of Hib conjugate vaccine results in high levels of seropositivity. There was no evidence from trials that the age at which the booster dose is given, or the interval between the primary series and the booster dose affect the level of seropositivity. Seropositivity levels in children after a booster dose are much higher than in children who received the same primary schedule without a booster. The interval between the last vaccine dose and blood draw is, however, shorter in children receiving the booster than in those who received only the primary schedule, and it is not clear if differences in antibody levels can be interpreted as differences in protection from Hib disease [2]. The UK experienced an increase in

Hib cases several years after an initial decline in cases subsequent to the introduction of a 3p+0 schedule (2, 3, 4 months) alongside an early catch-up campaign. Cases again declined after two booster campaigns and the introduction of a routine booster dose to the vaccine schedule [21]. However, the situations in which a booster dose should be used remain unclear, and might relate to local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors [22, 23].

This review did not examine the effects of co-administrated vaccines on Hib conjugate vaccine efficacy by including trials that compared groups differing in co-administered vaccines. However, in the analyses in this review which included both trials in which wP was co-administered and trials in which aP was co-administered, the relative effects of different schedules of Hib vaccine did not change substantially between studies. Further carefully conducted systematic reviews of RCTs, as well as of observational data, could provide useful information about this and other questions about Hib vaccine scheduling.

## 6.4 Implications

Hib conjugate vaccine 2p+1, 3p+0 and 3p+1 schedules are likely to provide protection against Hib disease but the optimal schedule is likely to depend on setting. For example, in settings where the burden of severe Hib disease lies with children under one year of age it might be more appropriate to provide three doses of Hib vaccine early in life. However, in settings where the disease burden occurs later, or where a resurgence of Hib cases is seen after the introduction of Hib vaccine, it might be advantageous to use a schedule where the third dose is given as a booster. Programmatic considerations are also likely to influence the choice of Hib vaccine schedule. Costs of vaccine administration are likely to be lower and vaccine coverage higher if vaccine administration is combined with other routine scheduled health visits. Additionally, most Hib vaccines are administered as combined vaccines, which means that the scheduling of the other co-administered vaccines must also taken in to account when choosing a Hib vaccine schedule.

Future decisions relating to Hib vaccination could be informed by well-conducted randomized controlled trials with head-to-head comparisons of schedules that collect data on clinical outcomes. Trials comparing schedules would need to be extremely large to provide sufficient statistical power to show difference between schedules, but trials of this type have been conducted for other vaccines [24].

## 6.5 Conclusions

Variation in the burden of disease, health infrastructures and scheduling of other vaccines creates complexity in determining optimal vaccination schedules. Thus, information on the benefits of different vaccine schedules is essential if informed decisions are to be made. In this comprehensive systematic review, we highlight the absence of clinical and carriage data from trials comparing Hib vaccine schedules and scarce immunological data from such comparisons. We show there is no clear evidence from vaccine trials that any 2p+1, 3p+0 or 3p+1 schedule of Hib conjugate vaccine provides better protection against Hib disease than other schedules. Therefore the optimal Hib vaccination schedule is likely to be determined by the epidemiological and programmatic conditions in individual settings.

# 7 Index of tables and figures

## 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 [25] | PRP-T | 3, 4, 5 +b14 | 13.4 (0.6) | | 46 | Seropositivity |
| | | 14 | 13.5 (0.6) | Placebo[1] | 45 | GMC |
| | | | Primary: NR | | | |
| Belgium2 [26] | PRP-T | 3, 4, 5[2] | 3.0 (0.1)<br>4.0 (0.1)<br>5.0 (0.2) | | 49[3] | Seropositivity<br>GMC |
| | | 2, 4, 6[2] | 2.1 (0.2)<br>4.0 (0.2)<br>5.9 (0.2) | | 54[3] | |
| Canada1 [27] | PRP-T | 2, 4, 6 + b18 | NR[4] | | 82 | Seropositivity |
| | | 2, 4, 6 + b15 | | | 85 | GMC |
| | | 2, 4, 6 + b12 | | | 86 | |
| Canada2 [28] | PRP-T | 2, 4, 6 +b18 +b48-60 | NR | | 106[3] | Seropositivity<br>GMC |
| | | 2, 4, 6 +b18 | | DTwP-IPV or DTaP-IPV[1] | 106[3] | |
| Canada3 [29] | PRP-T | 3p+ b18 | 18.3 (0.3) | | 438 | Seropositivity |
| | | 3p+ b17 | 17.4 (0.3) | | 450 | GMC |
| | | 3p+ b16 | 16.4 (0.3) | | 449 | |
| | | 3p+ b15 | 15.4 (0.3) | | 445 | |
| | | | Primary: NR | | | |
| Canada4 [30] | PRP-T | 2, 4, 6 +b18 | 18.3 (0.3) | | 167 | Seropositivity |
| | | 2, 4, 6 +b15 | 15.3 (0.3) | | 168 | GMC |
| | | | Primary: NR | | | |
| Chile1 [31] | PRP-T | 2, 4, 6 | 2.1 (0.1) | | 187 | Mortality |
| | | | Other doses: NR | | | |
| | | No doses | | DTP or Placebo | 93 | |
| Chile2 [32] | PRP-T | 2, 4, 6 | NR | | 186 | Mortality |
| | | No doses | | DTP and Placebo or Placebo | 91 | |
| Chile3 [33] | PRP-T | 2, 4, 6 | NR | | 38829 | Invasive Hib disease |
| | | No doses | | DTP + OPV | 37704 | Hib meningitis<br>All-cause pneumonia |

| 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) | | | |
| Chile4 | PRP-T | 2, 4, 6 | NR | | 78 | Seropositivity |
| [34] | | 4, 6 | | | 79 | GMC |
| | PRP-HBOC | 2, 4, 6 | | | 78 | |
| | | 4, 6 | | | 78 | |
| Chile5 | PRP-T | 3, 5, 7 + b12[5] | NR | | 710[6] | Mortality |
| [35] | | 2, 4, 6 + b12[5] | | | | Seropositivity |
| | | | | | | GMC |
| China1 | PRP-T | 3, 4, 5 +b18-20[7] | NR | | 264 | Mortality |
| [36] | | 2, 3, 4 +b18-20[7] | | | 264 | Seropositivity |
| | | | | | | GMC |
| China2 | PRP-T | 3, 4, 5[8] | 3.3 (0.3) | | 324 | Mortality |
| [37] | | 2, 3, 4[8] | 2.3 (0.3) | | 330 | Seropositivity |
| | | | dose 2-3:NR | | | GMC |
| Europe | PRP-T (booster)[9] | 3p +b13[10] | NR | | 220 | Mortality |
| [38] | | 3p +b12[10] | 14.9 (3.2) | | 224 | Seropositivity |
| (Austria, Germany, Greece) | | | primary NR | | | GMC |
| France | PRP-T | 2, 4, 6 + b15-17 | NR | | 258 | Seropositivity |
| [39] | | 2, 3, 4 + b15-17 | | | 258 | GMC |
| Gambia1 | PRP-OMP | 2, 4 | NR[11] | NR | 95 | Seropositivity |
| [40] | | 1, 3 | | | 99 | GMC |
| Gambia2 | PRP-T | 2, 4 | NR | NR | 43 | GMC |
| [41] | | 1, 3 | | | 45 | |
| Gambia3 | PRP-HbOC | 2, 3, 4 | NR | | 29 | Mortality |
| [42] | | No doses | | PCV5 + DTP | 60 | |
| Gambia4 | PRP-T | 2, 3, 4 | Median (IQR) | | 21490 | Mortality |
| [43] | | | 2.6 (2.2-3.1) | | | Invasive Hib disease |
| | | | 4.1 (3.5-5.0) | | | Hib meningitis |
| | | | 5.6 (4.8-6.9) | | | All-cause pneumonia |
| | | No doses | | DTP + Placebo | 21358 | Definitive Hib pneumonia |
| | | | | | | Carriage |
| Guatemala | PRP-T | 2, 4, 6 | NR | | 325 | Seropositivity |
| [44] | | 7, 9 | | DTwP[1] | 106 | 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)** | | | |
| Indonesia1 [45] | PRP-T | 2, 4, 6 + b15-18 | Over all groups:<br>3.3<br>4.9<br>6.7 | | 357[3] | Seropositivity<br>GMC |
| | | 15-18 | | DTaP[1] | 172[3] | |
| Indonesia2 [46] | PRP-T | 1.5, 2.5, 3.5 | 2.6<br>3.5<br>4.7 | | 28147[3] | Mortality<br>Hib meningitis<br>All-cause pneumonia |
| | | No doses | | DTP | 26926[3] | |
| Lithuania [47] | PRP-OMP/HbOC/T | 3, 4.5, 6 (PRP-T)<br>3, 4.5, 6 (PRP-HbOC)<br>3, 6 (PRP-OMP) | NR | | 329<br>110<br>110 | Seropositivity<br>GMC |
| Mali [48] | PRP-T | 24-36, 25-37<br>No doses | NR | <br>Malaria vaccine | 120<br>120 | Mortality |
| Netherlands [49] | PRP-T | 3, 4, 5 + b11[12]<br>6, 7 + b13[12] | NR | | 181<br>182 | Seropositivity<br>GMC |
| Niger1 [50] | PRP-T | 1.5, 2.5, 3.5<br>2.5, 3.5 | Over all groups, mean (range):<br>1.9 (0.9-2.8)<br>3.0 (2.1-5.1)<br>4.2 (3.0-6.8) | <br>Men A and C polysaccharide vaccine | 59<br>62 | Seropositivity<br>GMC |
| Niger2 [51] | PRP-T | 1.5, 2.5, 3.5<br>No doses | Over all groups:<br>1.5 (0.2)[13]<br>dose 2-3:NR | <br>Combinations of placebo, Men A and C vaccines | 37<br>143 | Mortality |
| Spain [52] | PRP-MenC-T | 2, 4, 6 +b13-14<br>2, 4, 6 | 13.4 (0.5)<br>Primary: NR | <br>MMR[1] | 206<br>91 | Mortality[14] |
| Sweden [53] | PRP-T | 2, 4, 6 +b13<br>3, 5 +b12 | NR[15] | | 118<br>118 | Mortality<br>Seropositivity<br>GMC |
| Thailand [54] | PRP-T<br>PRP-OMP | 2, 4, 6<br>2, 4 | NR | | 140[16]<br>66[16] | Seropositivity<br>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)** | | | |
| Turkey [26] | PRP-T | 3, 4, 5* | 3.0 (0.1)<br>4.0 (0.2)<br>5.1 (0.3) | | 78[3] | Seropositivity<br>GMC |
| | | 2, 4, 6* | 2.1 (0.2)<br>4.0 (0.3)<br>5.9 (0.3) | | 81[3] | |
| USA1 [55] | PRP-OMP | 1.5-3, 2.5-5 | mean (range) | | 2588 | Mortality |
| | | No doses | 1.8 (1.2-3.5)<br>dose 2: NR | Placebo | 2602 | Invasive Hib disease<br>Hib meningitis |
| USA2 [56] | PRP-HbOC | 2, 4, 6 | Mean (range)<br>7.2 (4.8-11.7)<br>dose 1-2: NR | | 30400[3] | Invasive Hib disease[17] |
| | | No doses | | DTP + OPV | 30680[3] | |
| USA3 [57] | PRP-T | 2, 4, 6 | 2.2<br>4.6<br>6.9 | | 5208 | Mortality<br>Invasive Hib disease |
| | | No doses | | HepB + DTP | 5109 | |
| USA4 [58] | PRP-OMP<br>PRP-HbOC | 2, 4, 6 (dose 1 PRP-OMP, 2-3 PRP-HbOC)[18] | NR | | 36[16] | Seropositivity<br>GMC |
| | | 2, 4, 6 (dose 1 PRP-HbOC, 2-3 PRP-OMP)[18] | | | 35[16] | |
| | | 2, 4, 6 (HbOC)[18] | | | 96[16] | |
| | | 2, 6 (PRP-OMP)[18] | | | 36[16] | |
| | | 2, 4 (PRP-OMP)[18] | | | 39[16] | |
| USA5 [59] | PRP-T<br>PRP-HbOC | 2, 4, 6 (PRP-T) | NR[19] | | 150[20] | Seropositivity<br>GMC |
| | | 2, 4, 6 (PRP-HbOC) | | | | |
| | | 0, 2, 4, 6 (PRP-HbOC) | | | | |
| USA6 [60] | PRP-T<br>PRP-OMP | 2, 4, 6 (dose 1 PRP-OMP, 2-3 PRP-T) | Over all groups:<br>2.1 (0.3)<br>4.2 (0.3) | | 34 | Seropositivity<br>GMC |
| | | 2, 4, 6 (PRP-T) | 6.4 (0.4) | | 35 | |
| | | 2, 4 (PRP-OMP) | | | 35 | |
| USA7 [60] | PRP-T<br>PRP-OMP | 2, 4, 6 (PRP-T) | Over all groups:<br>2.2 (0.3)<br>4.4 (0.4)<br>6.5 (0.5) | | 58 | Seropositivity<br>GMC |
| | | 2, 4 (PRP-OMP, PRP-T) | | | 62 | |
| | | 2, 4 (PRP-OMP) | | | 61 | |
| USA8[61] | PRP-OMP | 2-6, 4-8 | 4.1 (1.6)<br>6.1 (1.6) | | 27 | GMC (adjusted) |
| | | 2-6, 3-7 | 3.2 (1.3)<br>4.2 (1.3) | | 27 | |

| 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 [62] (The Gambia, Mali) | PRP-T | | Median (range): | | | Mortality |
| | | 3p + b12-23 + b22-34 | 18 (12-23), 28 (20-32) | | 66[3] | |
| | | 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. Intended schedules shown do not give details of co-administered vaccines. Multiple groups within each trial with the same Hib schedule are not shown in this table. Only groups used in comparative analyses are displayed here. Further details about co-administered vaccines, groups which are compared in analyses, and groups which are not shown in this table are given in footnotes of this table and Appendix 2.

3p – 3-dose primary schedule where intended ages at vaccination not specified; +b – booster dose given at number of months indicated; combined – Hib vaccine mixed in same syringe as other vaccines; 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; 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 – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).

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 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.

3 N children who received vaccine; number of randomized children not reported

4 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)”

5 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 in the same syringe as DTaP and eIPV

6 Number randomized not reported. 710 infants randomized to five groups (not all included here)

7 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).

8 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.

9 Type of conjugate vaccines for the primary series was not specified in this trial.

10 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 at 12 months.

11 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).”

12 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

13 if assume first dose is at recruitment

14 Immunological data reported but not available for schedule comparison

15 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”

16 Number followed up. Number randomized not reported

17 Other outcomes reported, but analysis method meant that many individuals were analyzed in a group to which they were not assigned and therefore the analysis was not randomized or quasi-randomized

18 All groups received unconjugated-PRP booster at 15m. Comparisons after unconjugated-PRP booster not shown.
19 Group receiving 2, 4, 6 HbOC received 3rd dose at 6.7m. Other groups and doses not reported.
20 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**<br>2p vs 1p | Niger1 | 1.5, 2.5<br>2.5 | PRP-T | NR | 3.5 | 3.5 | 3.5 |
| | USA4 | 2, 4<br>2 | PRP-OMP | NR | NR | 6 | 6 |
| | USA5 | 0, 2<br>2 | PRP-HbOC | NR | NR | NR | 4[3] |
| **Comparison B**<br>3p vs 1p | No RCTs | | | | | | |
| **Comparison C**<br>3p vs 2p | Chile4 | 2, 4, 6<br>4, 6 | PRP-T | NR | 8, 12 | 8, 12 | 8, 12 |
| | Chile4 | 2, 4, 6<br>4, 6 | PRP-HbOC | NR | 8, 12 | 8, 12 | 8, 12 |
| | Chile5 | 2, 4, 6[4]<br>3, 5[4] | PRP-T | NR | 7 | 7 | 7 |
| | Guatemala | 2, 4, 6<br>7, 9 | PRP-T | NR | 12 | 12 | 12 |
| | Netherlands | 3, 4, 5[5]<br>6, 7[5] | PRP-T | NR | 11 | 11 | 11[3] |
| | Niger1 | 1.5, 2.5, 3.5<br>2.5, 3.5 | PRP-T | NR | 4.5, 9 | 4.5, 9 | 4.5, 9 |
| | Sweden | 2, 4, 6<br>3, 5 | PRP-T | NR | 7, 13<br>6, 12 | 7, 13<br>6, 12 | 7[3], 13[3]<br>6[3], 12[3] |
| | USA5 | 0, 2, 4<br>2, 4 | PRP-HbOC | NR | NR | NR | 6[3] |
| **Comparison D**<br>2p+1 vs 2p | No RCTs | | | | | | |
| **Comparison E**<br>3p vs 2p+1 | Sweden | 2, 4, 6<br>3, 5 + b12 | PRP-T | NR | 7, 13<br>13 | 7, 13<br>13 | 7[3], 13[3]<br>13[3] |
| **Comparison F**<br>3p+1 vs 2p+1 | Netherlands | 3, 4, 5 +b11[5]<br>6, 7 + b13[5] | PRP-T | NR | 12<br>14 | 12<br>14 | 12[3]<br>14[3] |
| | Sweden | 2, 4, 6 + b13<br>3, 5 + b12 | PRP-T | 14[6] | 14, 5.5y<br>13, 5.5y | 14, 5.5y<br>13, 5.5y | 14[3], 5.5y[3]<br>13[3], 5.5y[3] |

| 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 G** 3p+1 vs 3p | Canada3 | 3p + b15[7]<br>3p[7] | PRP-T | NR | NR | NR | 16 |
| | Europe | 3p + b12[8]<br>3p[8] | PRP-T | NR | 13 | 13 | 13 |
| | Spain | 2, 4, 6 + b13-14<br>2, 4, 6 | PRP-MenC-T | 42 days after 13-14m | NR | NR | NR |
| | West Africa | 3p + b12-23[9]<br>3p[9] | PRP-T[9] | 9 months after 12-23m | NR | NR | NR |
| | West Africa | 3p + b22-34[9]<br>3p[9] | PRP-T[9] | 15 months after 22-34m | NR | NR | NR |
| **Comparison H** 3p+2 vs 3p | West Africa | 3p + b12-23 + b22-34[9]<br>3p[9] | PRP-T[9] | 15 months after 22-34m | NR | NR | NR |
| **Comparison I** 3p+2 vs 3p+1 | Canada2 | 2, 4, 6, + b18 + b48-60<br>2, 4, 6 + b18 | PRP-T | NR | 49-61 | 49-61 | 49-61 |
| **Comparison J** Birth dose vs no birth dose | USA5 | 0, 2<br>2 | PRP-HbOC | NR | NR | NR | 4[3] |
| | USA5 | 0<br>2 | PRP-HbOC | NR | NR | NR | 2[3]<br>4[3] |
| | USA5 | 0, 2, 4<br>2, 4 | PRP-HbOC | NR | NR | NR | 6[3] |
| | USA5 | 0, 2<br>2, 4 | PRP-HbOC | NR | NR | NR | 4[3]<br>6[3] |
| | USA5 | 0, 2, 4, 6<br>2, 4, 6 | PRP-HbOC | NR | NR | NR | 7[3] |
| **Comparison K** Late start vs early start | Belgium2 | 3, 4, 5[10]<br>2, 4, 6[10] | PRP-T | NR | 6<br>7 | 6<br>7 | 6<br>7 |
| | Chile5 | 3, 5, 7[4]<br>2, 4, 6[4] | PRP-T | NR | NR | NR | 12 |
| | Chile5 | 3, 5, 7 + b12[4]<br>2, 4, 6 + b12[4] | PRP-T | Until 14m | 13 | 13 | 13 |
| | China1 | 3, 4, 5[11]<br>2, 3, 4[11] | PRP-T | Until 18-20m[5] | 6, 18-20<br>5, 18-20 | 6, 18-20<br>5, 18-20 | 6, 18-20<br>5, 18-20 |

| 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 |
| | China1 | 3, 4, 5 + b18-20[11] | PRP-T | Until 19-21m[5] | 19-21 | 19-21 | 19-21 |
| | | 2, 3, 4 + b18-20[11] | | | | | |
| | China2 | 3, 4, 5[12] | PRP-T | Until 6m | 6 | NR | 6 |
| | | 2, 3, 4[12] | | 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-T | NR | NR | NR | 3 |
| | | 1 | | | | | 2 |
| | Gambia2 | 2, 4 | PRP-T | NR | NR | NR | 5 |
| | | 1, 3 | | | | | 4 |
| | Netherlands | 6, 7 [5] | PRP-T | NR | 11 | 11 | 11[3] |
| | | 3, 4, 5[5] | | | 11 | 11 | 11[3] |
| | Netherlands | 6, 7 + b13[5] | PRP-T | NR | 14 | 14 | 14[3] |
| | | 3, 4, 5 +b11[5] | | | 12 | 12 | 12[3] |
| | Turkey | 3, 4, 5[10] | PRP-T | NR | 6 | 6 | 6 |
| | | 2, 4, 6[10] | | | 7 | 7 | 7 |
| **Comparison L** | Belgium2 | 2, 4, 6[10] | PRP-T | NR | 7 | 7 | 7 |
| 2 month vs 1 month interval | | 3, 4, 5[10] | | | 6 | 6 | 6 |
| | France | 2, 4, 6 | PRP-T | NR | 7, 15-17 | 7, 15-17 | 7[3], 15-17 |
| | | 2, 3, 4 | | | 5, 15-17 | 5, 15-17 | 5[3], 15-17 |
| | France | 2, 4, 6 + b15-17 | PRP-T | NR | 16-18 | 16-18 | 16-18[3] |
| | | 2, 3, 4 + b15-17 | | | | | |
| | Turkey | 2, 4, 6[10] | PRP-T | NR | 7 | 7 | 7 |
| | | 3, 4, 5[10] | | | 6 | 6 | 6 |
| | USA8 | 2-6, 4-8 | PRP-OMP | NR | NR | NR | 5-9 |
| | | 2-6, 3-7 | | | | | 4-8 |
| **Comparison M** | USA4 | 2, 6 | PRP-OMP | NR | NR | 7, 15 | 7, 15 |
| 4 month vs 2 month interval | | 2, 4 | | | | | |

| 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 N** longer vs shorter interval between primary and booster | Canada1 | 2, 4, 6 + b15 | PRP-T | NR | 16.5 | 16.5 | 16.5 |
| | | 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 + 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 |
| | Canada3 | 3p + b17/18[7] | PRP-T | NR | NR | 18/19 | 18/19[3] |
| | | 3p + b15/16[7] | | | | 16/17 | 16/17[3] |
| | Canada3 | 3p + b18[7] | PRP-T | NR | NR | NR | 19 |
| | | 3p + b17[7] | | | | | 18 |
| | Canada3 | 3p + b18[7] | PRP-T | NR | NR | NR | 19 |
| | | 3p + b16[7] | | | | | 17 |
| | Canada3 | 3p + b18[7] | PRP-T | NR | NR | NR | 19 |
| | | 3p + b15[7] | | | | | 16 |
| | Canada3 | 3p + b17[7] | PRP-T | NR | NR | NR | 18 |
| | | 3p + b16[7] | | | | | 17 |
| | Canada3 | 3p + b17[7] | PRP-T | NR | NR | NR | 18 |
| | | 3p + b15[7] | | | | | 16 |
| | Canada3 | 3p + b16[7] | PRP-T | NR | NR | NR | 17 |
| | | 3p + b15[7] | | | | | 16 |
| | Canada4 | 2, 4, 6 + b18 | PRP-T | NR | 19 | NR | 19 |
| | | 2, 4, 6 + b15 | | | 16 | | 16 |
| | Chile5 | 2, 4, 6 + b12[4] | PRP-T | Until 14m | 13 | 13 | 13 |
| | | 3, 5, 7 + b12[4] | | | | | |
| | China1 | 2, 3, 4 + b18-20[11] | PRP-T | Until 19-21m[5] | 19-21 | 19-21 | 19-21 |
| | | 3, 4, 5 + b18-20[11] | | | | | |
| | Europe | 3p + b13[8] | PRP-T | NR | 14 | 14 | 14 |
| | | 3p + b12[8] | | | 13, 14 | 13, 14 | 13, 14 |
| | France | 2, 3, 4 + b15-17m | PRP-T | NR | 16-18 | 16-18 | 16-18 |
| | | 2, 4, 6 + b15-17m | | | | | |

| 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 |
| | West Africa | 3p + b22-34[9]<br>3p + b12-23[9] | PRP-T[9] | 15 months after 22-34m | NR | NR | NR |
| **Comparison O**<br>Primary (+/- booster) vs catch-up | Belgium1 | 3, 4, 5 + b14<br>14 | PRP-T | NR | 15, 48-72 | 15, 48-72 | 15, 48-72 |
| | Indonesia1 | 2, 4, 6 + b15-18[13]<br>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 P**<br>1p vs 0 | Gambia4 | 2<br>No doses | PRP-T | Unclear | NA | NA | NA |
| | USA1 | 1.5-3<br>No dose | PRP-OMP | Until 2 months after dose 1 | NA | NA | NA |
| **Comparison Q**<br>2p vs 0 | USA1 | 1.5-3, 2.5-5<br>No dose | PRP-OMP | Until 15m<br>Until 18m | NA | NA | NA |
| **Comparison R**<br>3p vs 0 | Chile1 | 2, 4, 6[14]<br>No doses | PRP-T | Until 60 days after the third dose[5] | NA | NA | NA |
| | Chile2 | 2, 4, 6[14]<br>No doses | PRP-T | Until 60 days after the third dose[5] | NA | NA | NA |
| | Chile3 (cluster) | 2, 4, 6<br>No doses | PRP-T | Until April 1995 (18-30 months of follow up) | NR | NR | NR |
| | Indonesia2 | 1.5, 2.5, 3.5<br>No doses | PRP-T | Until 24m | NA | NA | NA |
| | Gambia3 | 2, 3, 4[15]<br>No doses | PRP-HbOC | Until 8m<br>Until 12m | NR | NR | NR |
| | Gambia4 | 2, 3, 4<br>No doses | PRP-T | Until March 1996 (5 months to 3 years of follow up)<br>Carriage at approx. 16m | 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 |
| | Niger2 | 1.5, 2.5, 3.5[16]<br>No doses | PRP-T | During study, approx. until 12m | NR | NR | NR |
| | USA2[17] | 2, 4, 6<br>No doses | PRP-HbOC | Until June 1990 or second birthday (0-22m follow up)% | NA | NA | NA |
| | USA3 | 2, 4, 6<br>No doses | PRP-T | Until Oct 1990 (1-16 months of follow up) | NA | NA | NA |
| **Comparison S**<br>2p or 3p vs 0 | Gambia4 | 2, 3, 4<br>No doses | PRP-T | Until March 1996 (5 months to 3 years of follow up) | NA | NA | NA |
| **Comparison T**<br>2p+1 vs 0 | No RCTs | | | | | | |
| **Comparison U**<br>3p+1 vs 0 | No RCTs | | | | | | |
| **Comparison V**<br>1 catch-up dose vs 0 | No RCTs | | | | | | |
| **Comparison W**<br>2 catch-up doses vs 0 | Mali | 24-36, 25-37<br>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 prioritized in this review and reported in main text. Four additional trials (Lithuania, Thailand, USA6 and USA7) reported on comparisons where schedules differed not only in the number of doses or timing, but also in the conjugated molecule. These comparisons are not reported here.

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 and Appendix 2.

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

3 Data incomplete (confidence intervals or number included in analysis not reported).

4 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

5 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

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

7 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.

8 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 at 12 months.

9 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.

10 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.

11 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).

12 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.

13 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

14 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.

15 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.

16 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.

17 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.

## Table 3: Methodological features of trials

| Study, vaccine (manufacturer) | Adequate randomization sequence generation | Adequate randomization allocation concealment | Blinding of patient or parent to exposure status | Blinding of outcome assessors (clinical outcomes) | Blinding of outcome assessors (immunological outcomes) | Blinding of other persons | Intention to treat or per protocol analyses, clinical outcomes | Modified Intention to treat or per protocol analyses, immunological outcomes |
|---|---|---|---|---|---|---|---|---|
| Belgium2 [26] | Unclear, randomization list but generation not reported | Unclear, not reported. Allocated "according to a randomization list and following chronological order of enrolment in the trial" | No, not possible due to schedule differences | NA | Yes | Unclear, not reported | NA | mITT (PP performed and "similar") |
| Canada1[27] | Yes, computer-generated list of random numbers | Unclear, sealed, serially-numbered envelopes that were opened in sequence, but not stated if opaque | No, not possible due to schedule differences | NA | Unclear, authors refer to "code-numbered samples", but no explicit description of blinding | Not reported | NA | mITT |
| Canada3[29] | Unclear, not reported | Unclear, not reported | No, not possible due to schedule differences | NA | Unclear, trial described as open-label | Unclear, trial described as open-label | NA | PP (ITT performed and "similar") |
| Canada4[30] | Unclear, not reported | Unclear, not reported | Parents blinded not blinded to age at vaccination | NA | Unclear, not reported | Unclear, not reported | NA | Unclear |
| Chile3[33] | No, two groups of health centers assembled non-randomly. Group receiving vaccine randomly selected | No | No, information about vaccine given only to vaccine group | Unclear if doctors aware of vaccination status. Laboratory staff & radiologist blinded | NA | Unclear, not reported | ITT and PP but not all outcomes have both | NA |
| Chile4[34] | Unclear not reported how "list of correlative numbers" generated | Unclear, not well reported | No, not possible due to schedule differences | NA | Yes | Vaccinators not blinded | NA | Unclear |

| Study, vaccine (manufacturer) | Adequate randomization sequence generation | Adequate randomization allocation concealment | Blinding of patient or parent to exposure status | Blinding of outcome assessors (clinical outcomes) | Blinding of outcome assessors (immunological outcomes) | Blinding of other persons | Intention to treat or per protocol analyses, clinical outcomes | Modified Intention to treat or per protocol analyses, immunological outcomes |
|---|---|---|---|---|---|---|---|---|
| Chile5[35] | Unclear, does not report how "list of ... study numbers, in blocks of 10" generated | Unclear, not reported | No, not possible due to schedule differences | NA | Yes | Unclear, trial reported to be "open" | NA | mITT (PP analysis conducted with "identical results") |
| China1[36] | Unclear, not reported | Unclear, not reported | No, not possible due to schedule differences | NA | Yes | Unclear, trial reported to be "open" | NA | Unclear |
| China2[37] | Unclear, not reported | Unclear, not reported | No, not possible due to schedule differences | NA | Unclear, trial reported to be "open" | Unclear, trial reported to be "open" | NA | PP |
| Europe[38] (Austria, Germany, Greece) | Unclear, not reported | Unclear, not reported | No, not possible due to schedule differences | NA | Unclear, trial reported to be "open" | Unclear, trial reported to be "open" | NA | PP |
| France[39] | Unclear, not reported | Unclear, not reported | Unclear, but unlikely due to schedule differences | NA | Unclear, trial reported to be "open" | Unclear, trial reported to be "open" | NA | PP (ITT performed and reported to be 'consistent with PP) |
| Gambia1[40] | Unclear, "using a system of random numbers" | Yes, on site computer system, with automated and consecutive allocation of vaccination codes corresponding to coded vials. | No, not possible due to schedule differences | NA | Yes | Field workers not blinded | NA | PP |

| Study, vaccine (manufacturer) | Adequate randomization sequence generation | Adequate randomization allocation concealment | Blinding of patient or parent to exposure status | Blinding of outcome assessors (clinical outcomes) | Blinding of outcome assessors (immunological outcomes) | Blinding of other persons | Intention to treat or per protocol analyses, clinical outcomes | Modified Intention to treat or per protocol analyses, immunological outcomes |
|---|---|---|---|---|---|---|---|---|
| Gambia2[41] | Unclear, "system of random numbers incorporated into a computerized call program" | Yes, on site computer system, with automated and consecutive allocation of vaccination codes corresponding to coded vials. | No, not possible due to schedule differences | NA | Yes, laboratory staff blinded | Unclear, not reported | NA | Unclear |
| Gambia4[43] | Unclear. Allocation was by last digit of health card number, but not stated if digit allocation to intervention was randomized | Unclear, allocation was by last digit of health card number, but if digit allocation to intervention was randomized and all vials appeared identical then possibly adequate. | Unclear. Described as double blind, attempt of parent blinding is very likely. | Yes, radiographs assessed blindly and doctors ordering radiographs and other tests are likely to be blinded. | NA | Those performing the statistical analyses were blinded<br>An attempt was made to blind study physicians, but due to allocation method, study physicians may have been unblinded. | ITT, and PP | NA |
| Guatemala[44] | yes, computer generated random numbers | Unclear, sequentially numbered sealed envelopes. Not stated if opaque or if linked to individuals before opening | Unclear, trial reported to be "open" | NA | Unclear, trial reported to be "open" | Described as "open study" | NA | Unclear |
| Indonesia2[46] | yes, computer random-number generation (district level stratification) | Likely yes, vaccine vials were coded by four colors (two for DTP and two for DTP-PRP-T) and one investigator assigned districts to one of the four color groups using a computerized random-number generator. This investigator was reported to be unaware of the vaccination given in each color group. | Yes, attempt of blinding was made, but unblinding could have occurred during trial if vaccinated clustered had noticeably less Hib disease. Code unknown until after primary analyses were completed | Yes, attempt was made. We assume allocation of hamlets did not become known during trial. Code unknown until after primary analyses were completed | NA | Entire study team reported to be blinded. Manufacturer kept the vaccine code and was not involved in statistical analyses. We assume that the allocation of hamlets did not become known during trial. Code unknown until after primary analyses were completed | mITT and PP | NA |

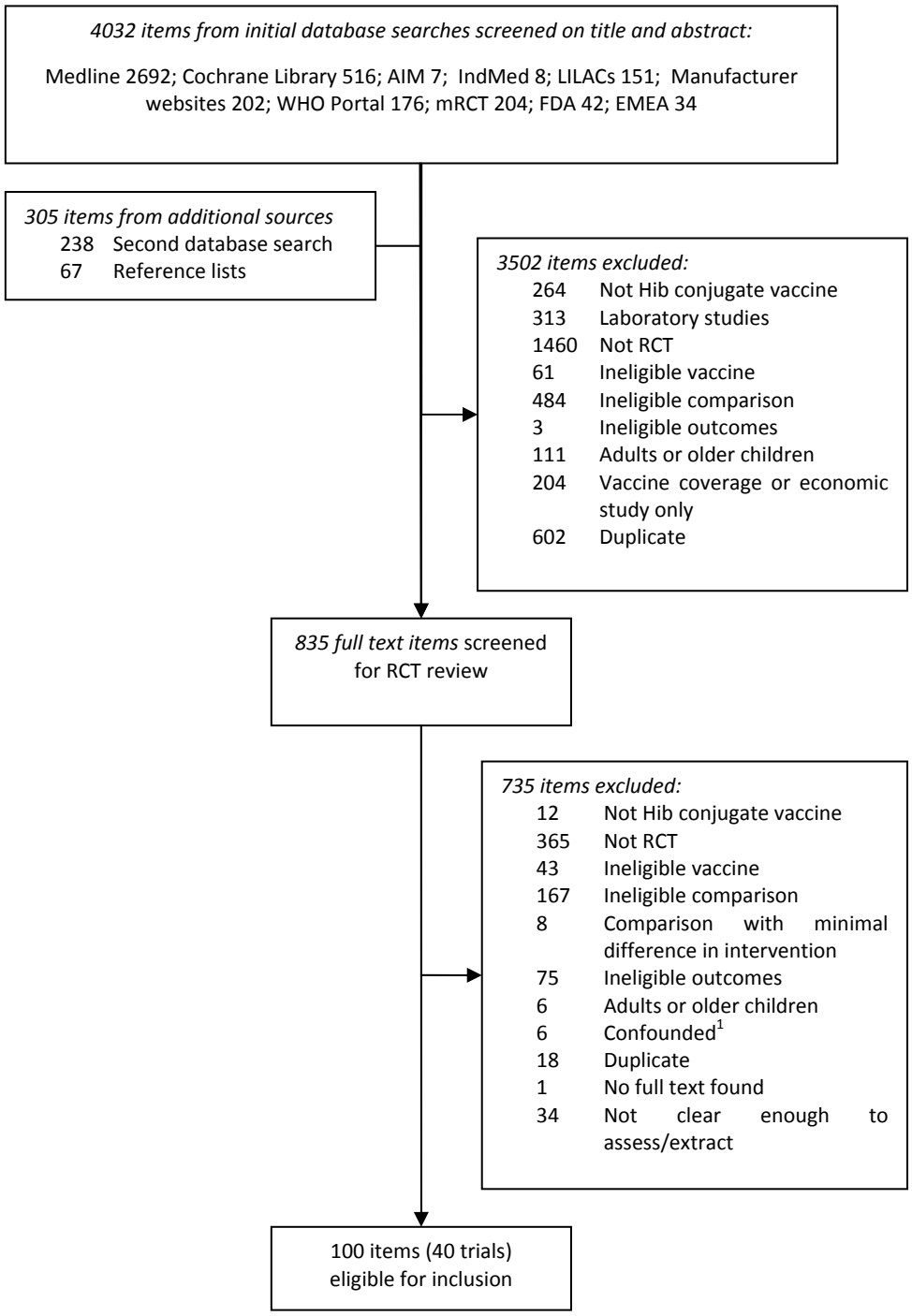
| Study, vaccine (manufacturer) | Adequate randomization sequence generation | Adequate randomization allocation concealment | Blinding of patient or parent to exposure status | Blinding of outcome assessors (clinical outcomes) | Blinding of outcome assessors (immunological outcomes) | Blinding of other persons | Intention to treat or per protocol analyses, clinical outcomes | Modified Intention to treat or per protocol analyses, immunological outcomes |
|---|---|---|---|---|---|---|---|---|
| Netherlands[49] | Yes, computer generated list | Unclear, not reported | Unclear, not reported | NA | Yes | Unclear, not reported | NA | PP |
| Niger1[50] | Unclear, not reported | Unclear, not reported | Unclear, not reported | NA | Unclear, "assays were performed on coded specimens" but no additional description given. | Those who assess adverse events were blinded | NA | Unclear |
| Sweden[53] | Unclear, "randomly assigned, in blocks of 10", but sequence generation not reported | Unclear, not reported | No, not possible due to schedule differences | NA | Yes | Unclear, trial reported as "open" | NA | PP |
| Turkey[26] | Unclear, randomization list but generation not reported | Unclear, not reported. Allocated "according to a randomization list and following chronological order of enrolment in the trial" | No, not possible due to schedule differences | NA | Yes | Unclear, not reported | NA | mITT (PP performed and "similar") |
| USA1[55] | Unclear, "randomly assigned in blocks of 20" but generation not reported | Yes, randomization code not revealed until study end and vaccine and placebo appeared identical | Yes, explicitly reported to be blind, randomization code not revealed until study end | Yes, randomization code not revealed until study end | NA | Yes, investigators reported to be blind, randomization code not revealed until study end | ITT and PP | NA |

| Study, vaccine (manufacturer) | Adequate randomization sequence generation | Adequate randomization allocation concealment | Blinding of patient or parent to exposure status | Blinding of outcome assessors (clinical outcomes) | Blinding of outcome assessors (immunological outcomes) | Blinding of other persons | Intention to treat or per protocol analyses, clinical outcomes | Modified Intention to treat or per protocol analyses, immunological outcomes |
|---|---|---|---|---|---|---|---|---|
| USA2[56] | No, children born on 1st 5, 6 or 7 days of month not offered Hib vaccine, others offered | No | No, parents could choose not to vaccinate | Unclear, those reviewing possible Hib cases were blinded, but unclear if primary physicians blinded | NA | Unclear, not reported if doctors or others were blinded | ITT analysis is the only analysis eligible for this review | NA |
| USA3[57] | Yes, computer-generated randomization list. | Unclear, "blindly and sequentially assigned a study identification number ...The identification numbers were randomly preassigned..." | Yes | Yes | NA | Vaccinators not blinded | ITT | NA |
| USA4[58] | Unclear, site-specific randomization lists but generation not reported | Unclear. Vials supplied only with a code number but not reported if vials were identical in appearance. Unclear who randomized the infants. | Yes, placebo used | NA | Yes | "Investigators who enrolled, interviewed, or evaluated subjects or parents were blinded to study group assignment" | NA | PP |
| USA5[59] | Unclear, not reported* | Unclear, not reported | Yes | NA | Yes | Vaccinators not blinded. Those assessing safety were blinded. | NA | Unclear |
| USA8[61] | No, alternation | No, alternation | No, not possible due to schedule differences | NA | Unclear, not reported | Unclear, not reported | NA | PP |

**Legend:**
ITT - intention-to-treat analysis - analysis where no randomized individuals are excluded; mITT- modified intention-to- treat analysis - similar to an intention-to-treat analysis but with some modifications to inclusion criteria such as excluding those who did not receive a first dose of vaccine; NA - not applicable because eligible outcomes not reported in this trial; PP - per protocol analysis, analysis where individuals with protocol violations (such as not receiving the intended vaccination schedule) are excluded

# Figures

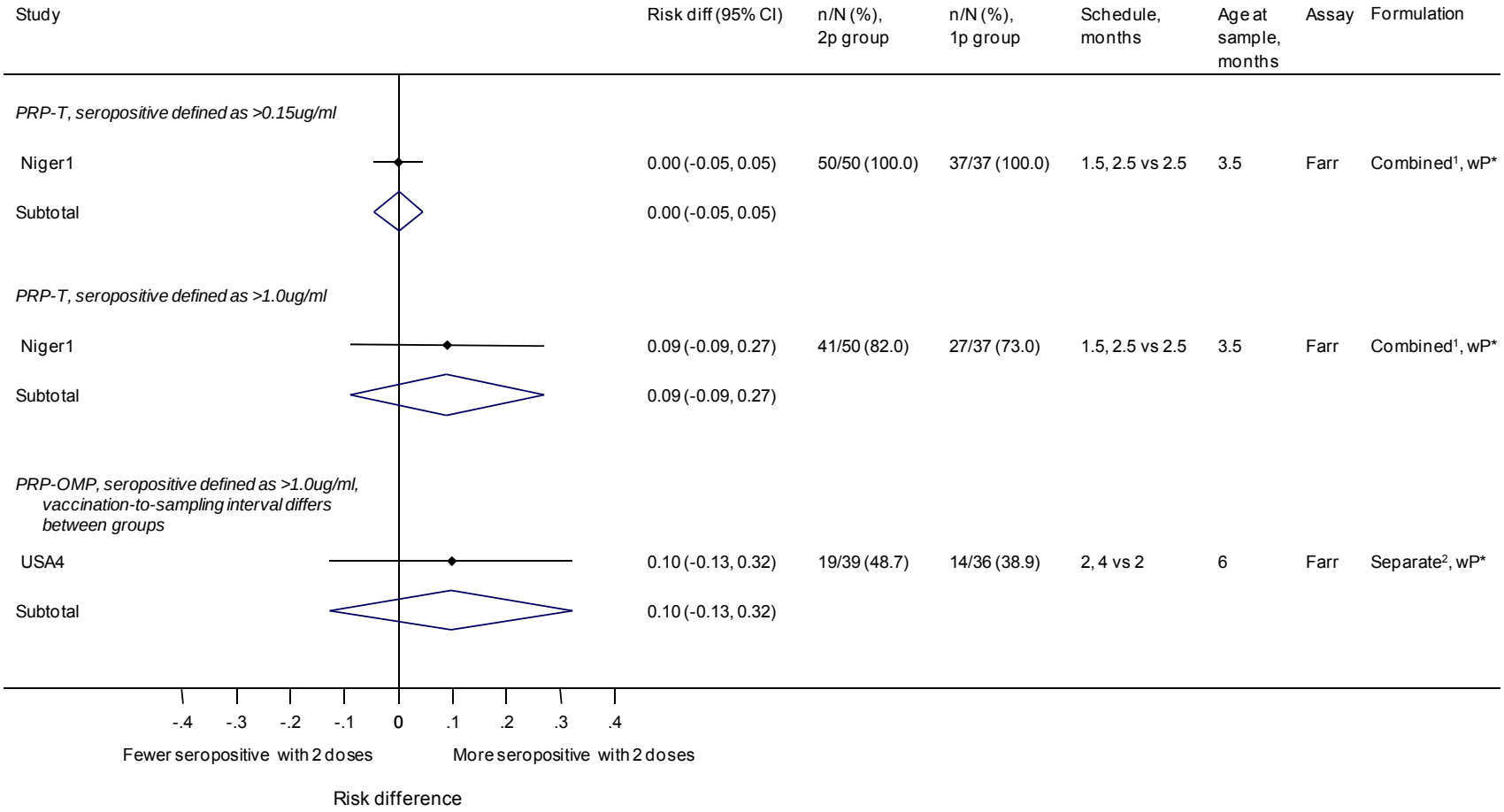
## Figure 1: Flow chart of studies




1 All 6 items relate to one trial where only eligible outcomes are pneumonia and death and children and randomized to either Hib and pneumococcal conjugate vaccine or to a malaria vaccine. Difference between groups could be due to Hib or pneumococcal vaccines.

# Immunological data

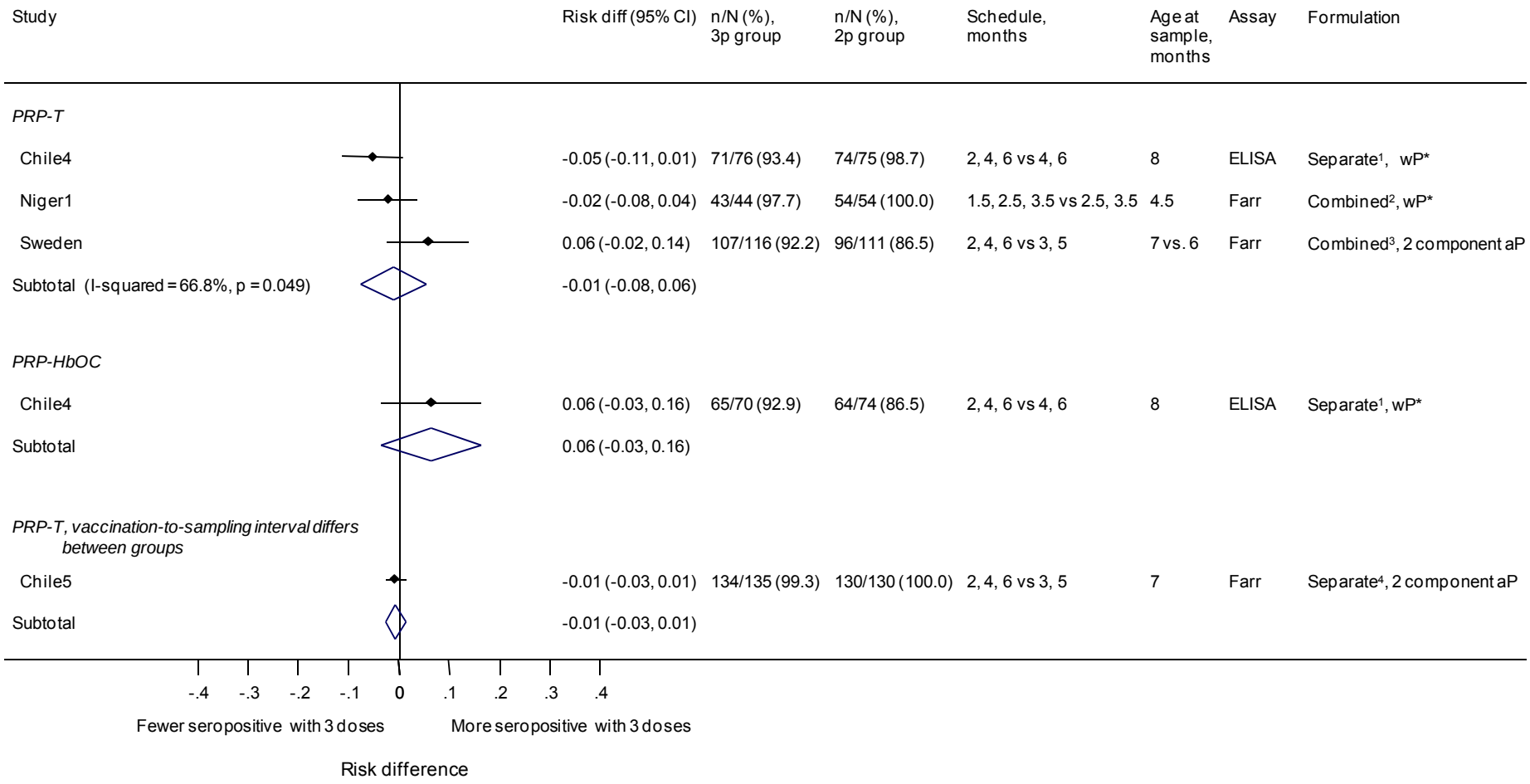
## Figure 2: 2p vs 1p, 1m post primary, 0.15µg/ml and 1.0µg/ml




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).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
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"

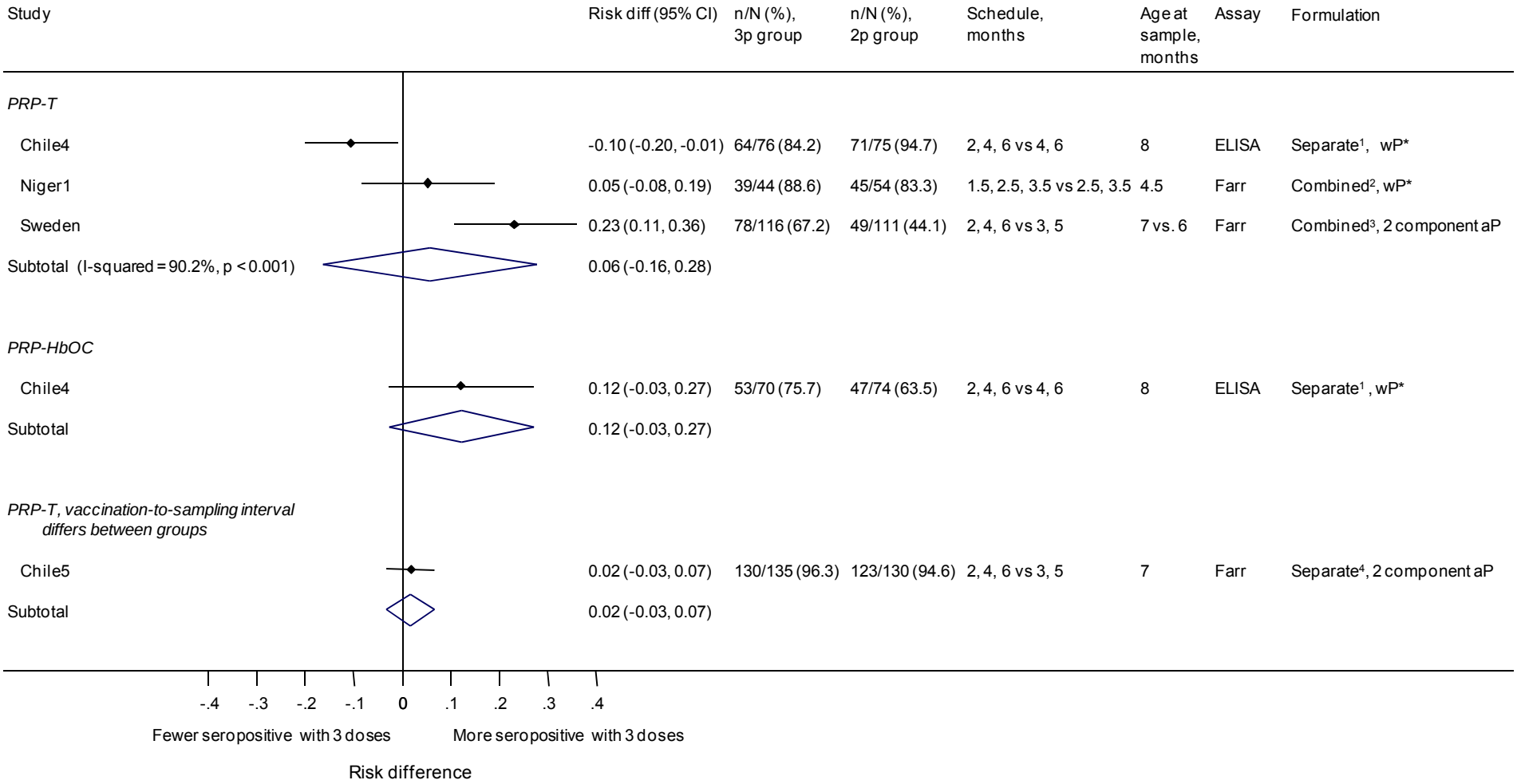
# 3p vs 2p schedules

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



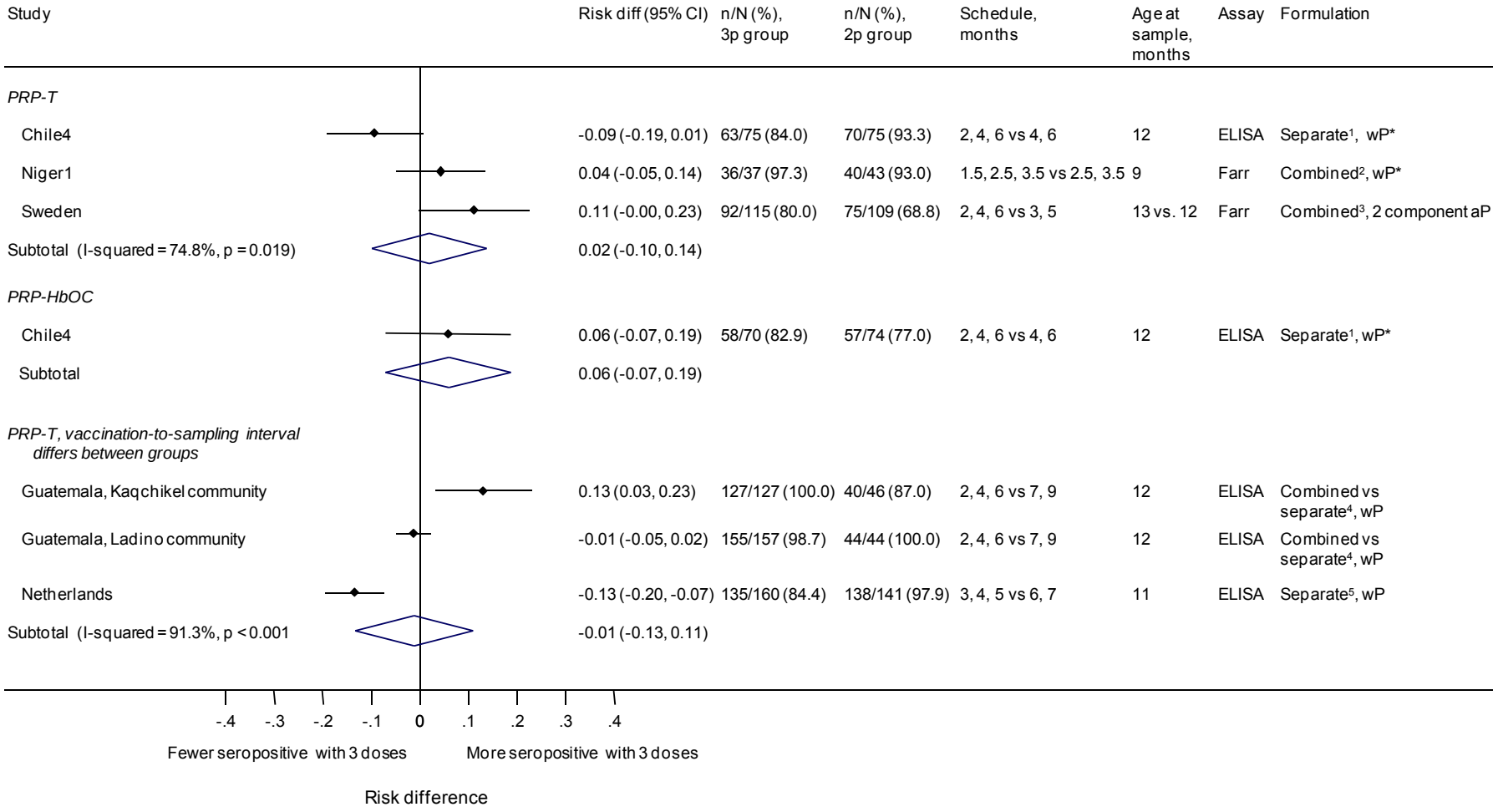

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
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 (2 component aP)
4 DTaP 2, 4, 6 both groups (2 component aP)

## Figure 4:3p vs 2p, approx. 1m post primary, 1.0µg/ml



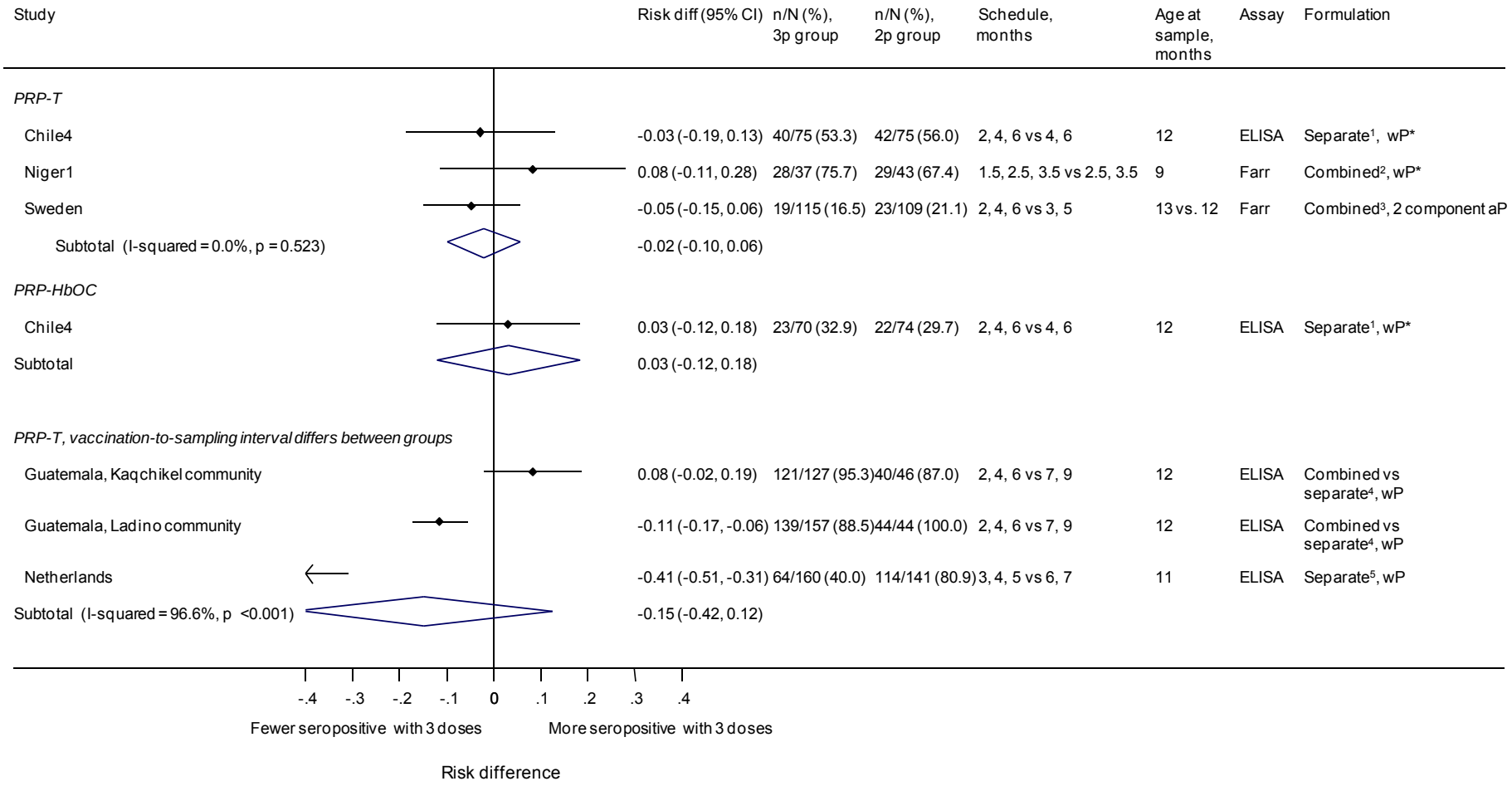

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
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 (2 component aP)
4 DTaP 2, 4, 6 both groups (2 component aP)

## Figure 5: 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).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
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 (2 component aP)
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

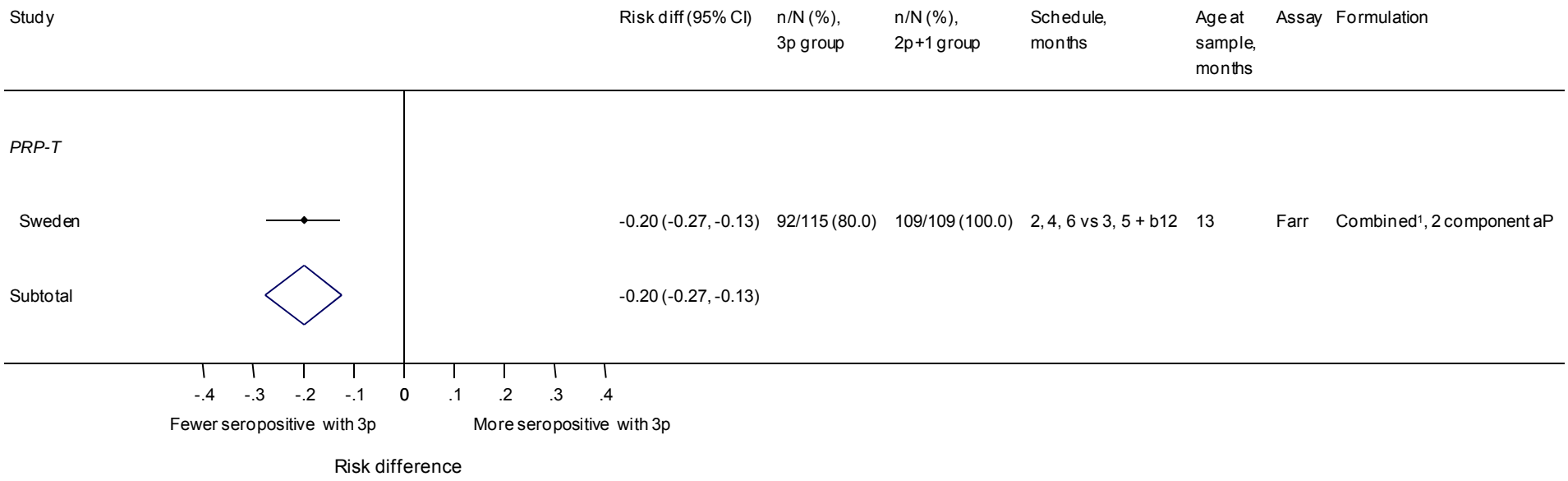
## Figure 6: 3p vs 2p, approx. 6m post primary, 1.0µg/ml




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).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
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 (2 component aP);
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

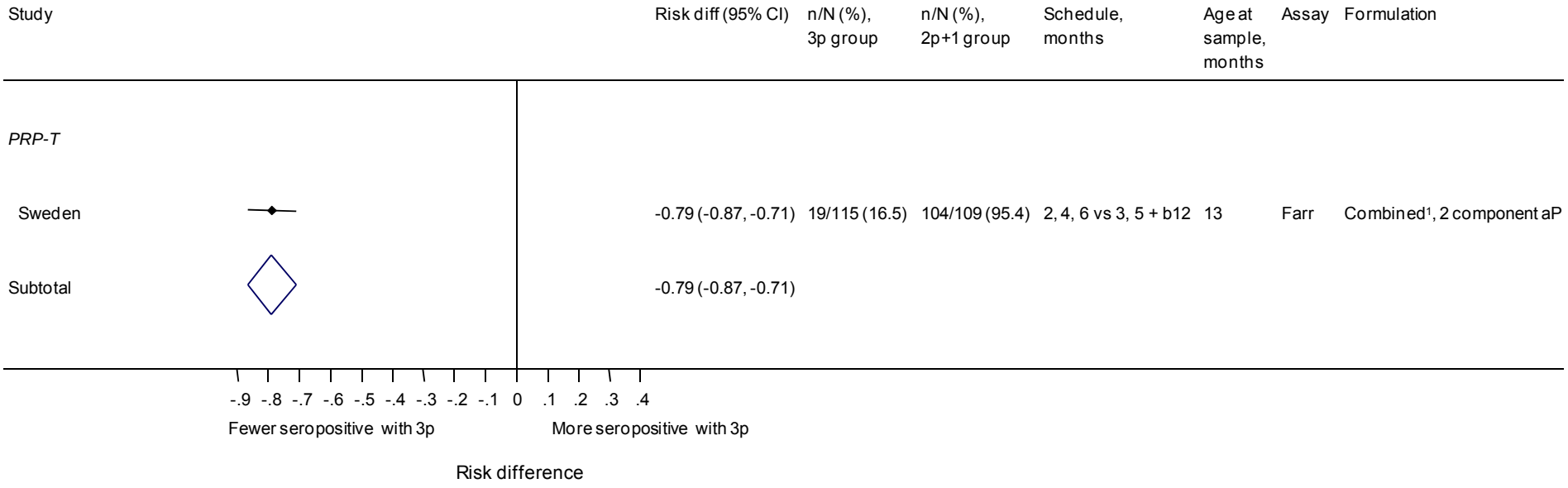
# 3p vs 2p+1 schedules

## Figure 7: 3p vs 2p+1, 13 months of age, 0.15µg/ml



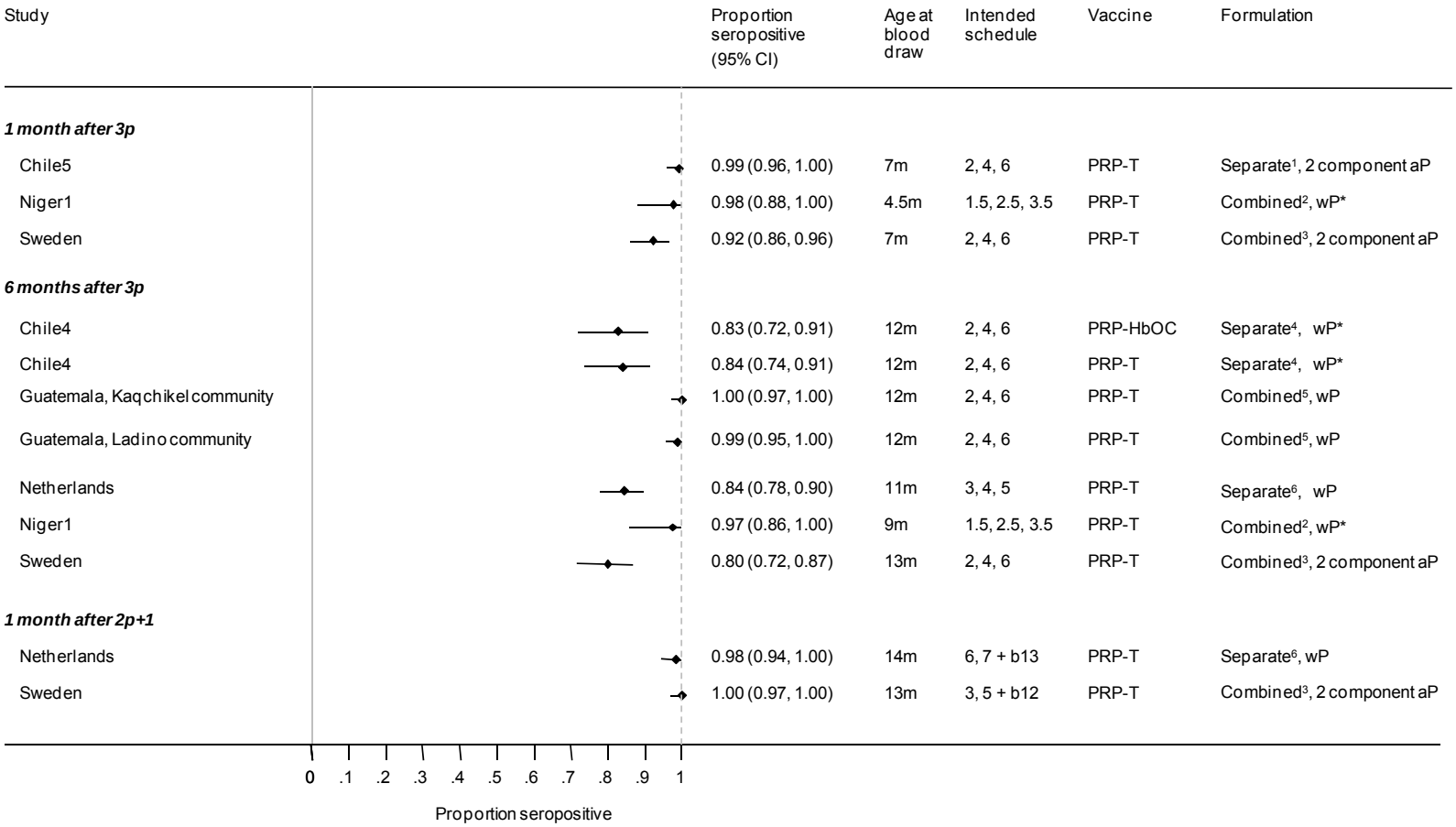

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
1 DTaP-IPV/Hib both groups (2 component aP)

## Figure 8: 3p vs 2p+1, 13 months of age, 1.0µg/ml



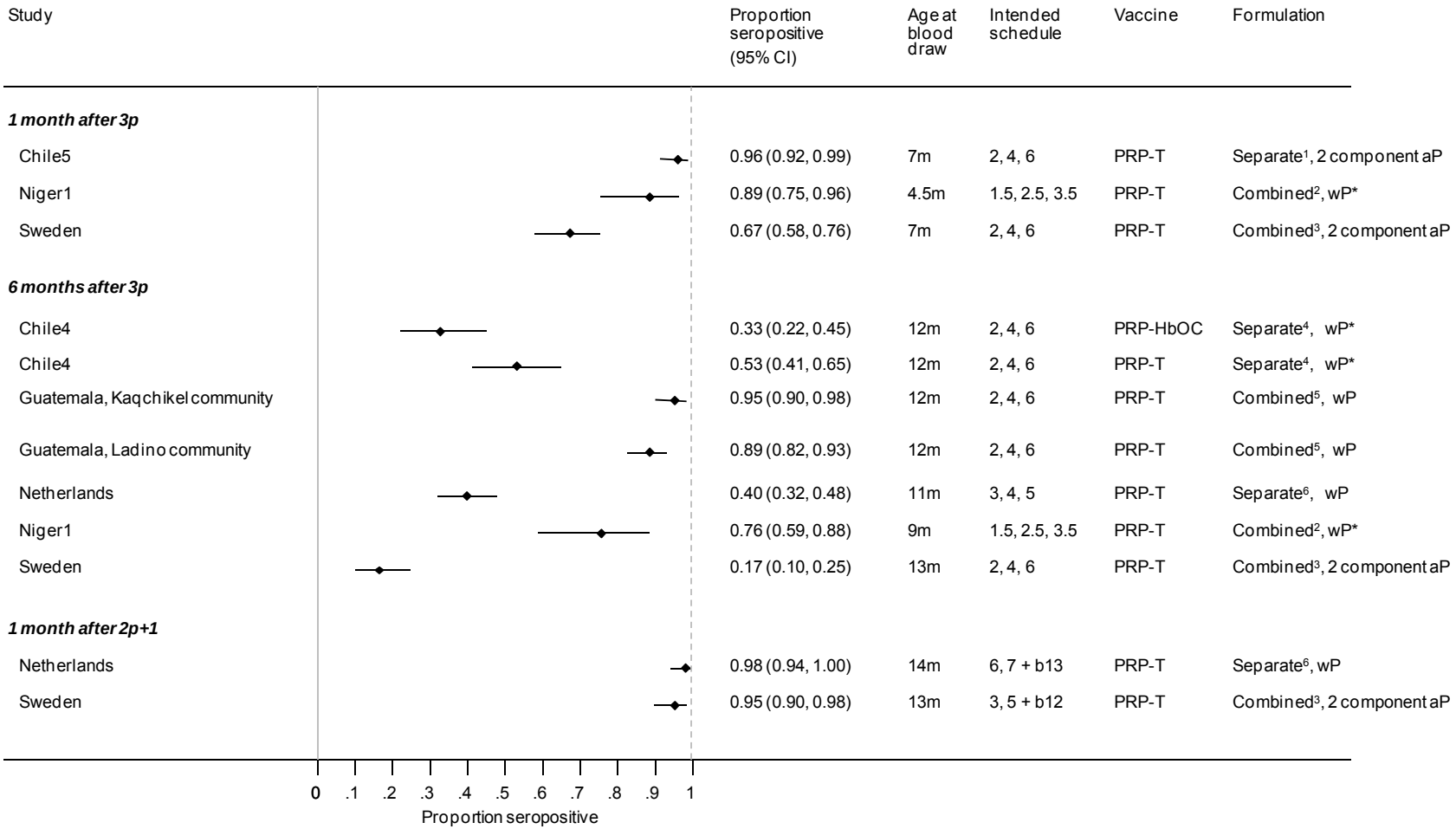

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
1 DTaP-IPV/Hib both groups (2 component aP)

## Figure 9: 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).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
1 DTaP 2, 4, 6 (2 component aP) 2 DTP at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine.
3 DTaP-IPV/Hib (2 component aP) 4 DTP at 2, 4, 6. Unclear if aP or wP
5 DTwP-hepB/Hib at 2, 4, 6 6 DTwP-IPV at 3, 4, 5

## Figure 10: Seropositivity after 3p and 2p+1, 1 and 6 months after 3p and 1 month after 2p+1, 1.0µg/ml



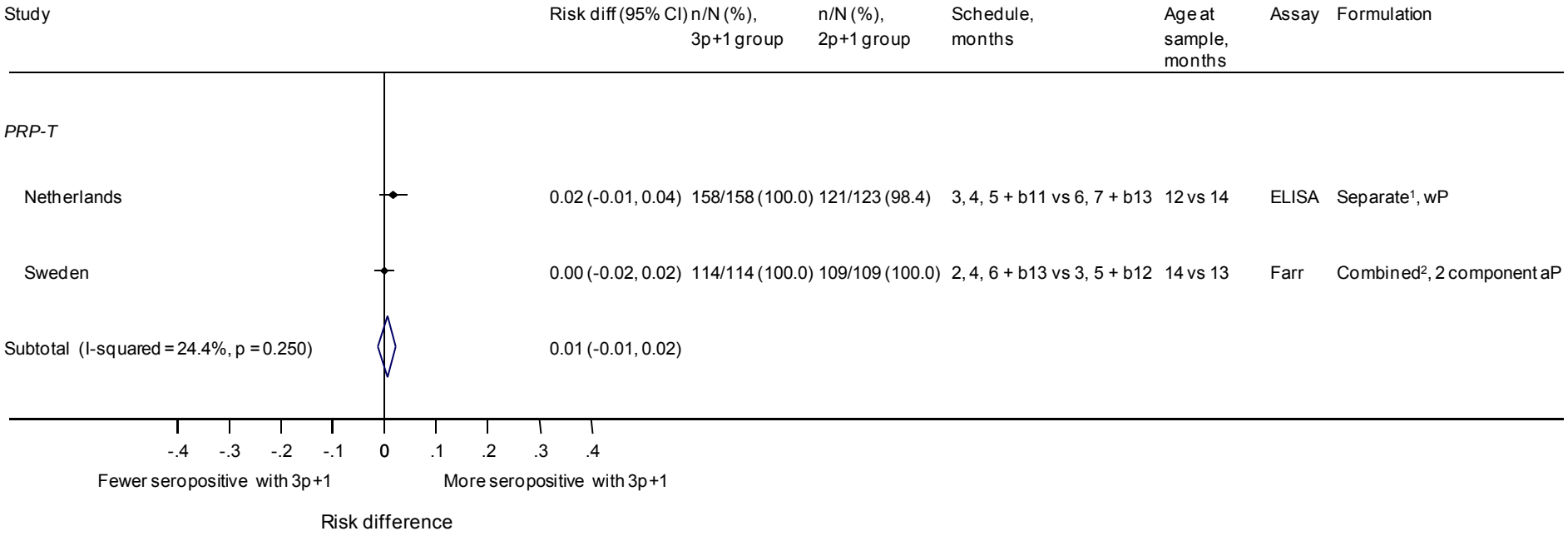

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).

* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted

1 DTaP 2, 4, 6 (2 component aP) 2 DTP at 1.5, 2.5, 3.5. Unclear if aP or wP. In one syringe with Hib vaccine.
3 DTaP-IPV/Hib (2 component aP) 4 DTP at 2, 4, 6. Unclear if aP or wP
5 DTwP-hepB/Hib 6 DTwP-IPV at 3, 4, 5

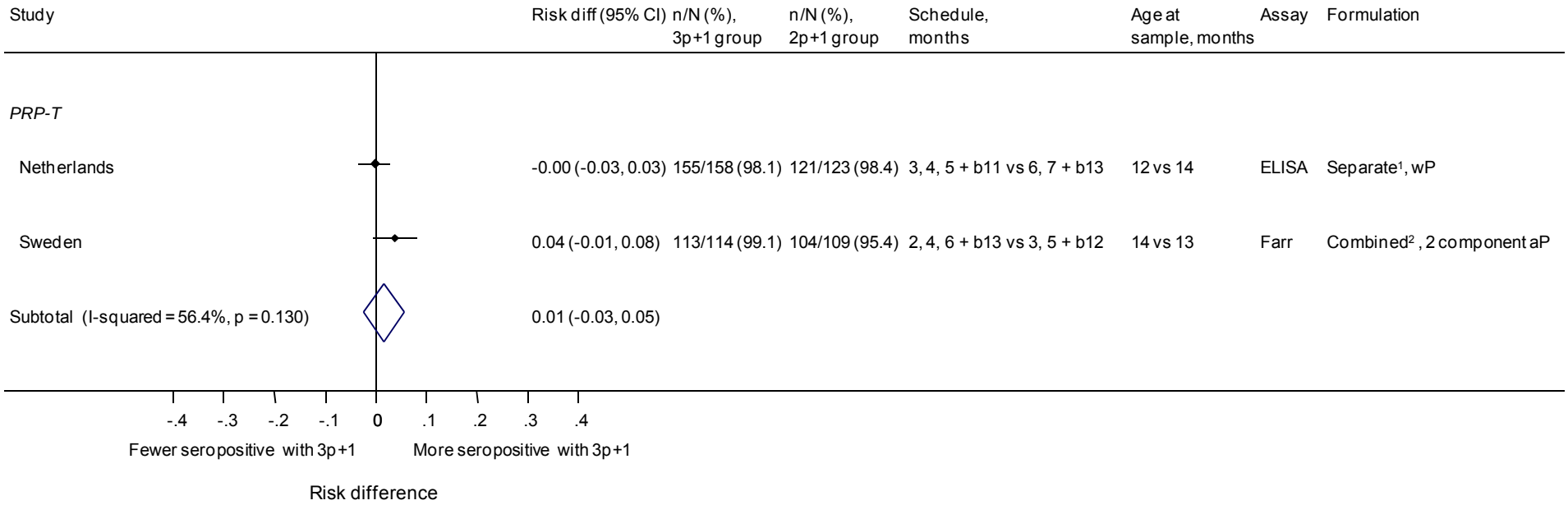
# 3p+1 vs 2p+1 schedules

## Figure 11: 3p+1 vs 2p+1, 1m post booster, 0.15µg/ml



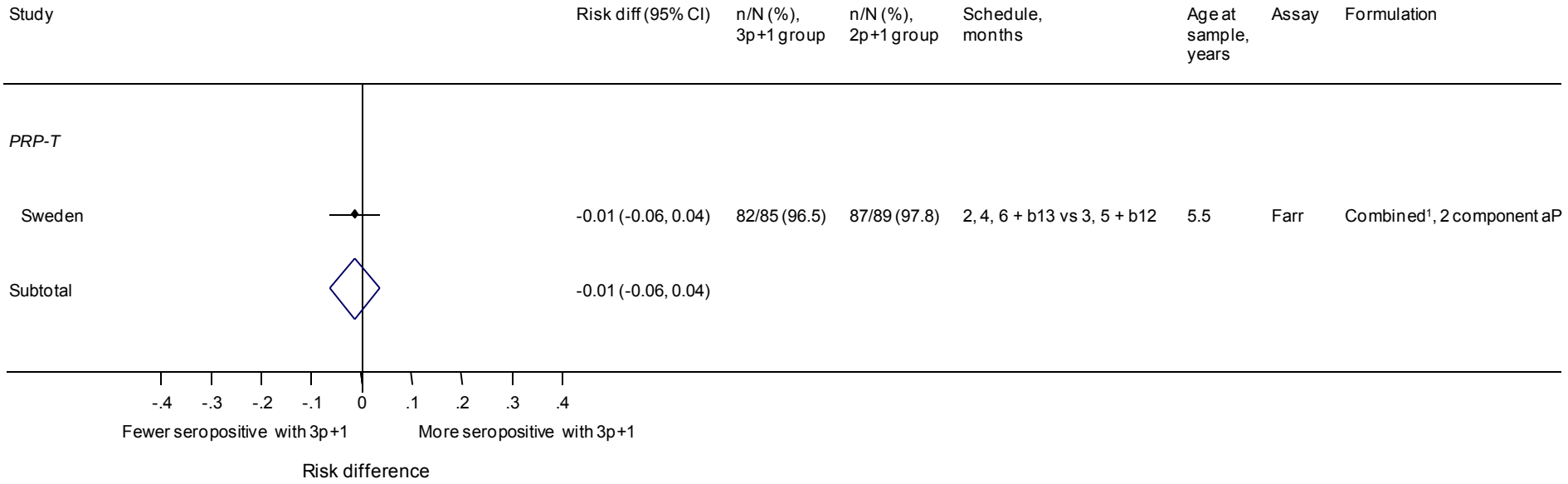

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
1 DTwP-IPV both groups at 3, 4, 5 2 DTaP-IPV/Hib both groups (2 component aP)

## Figure 12: 3p+1 vs 2p+1, 1m post booster, 1.0µg/ml



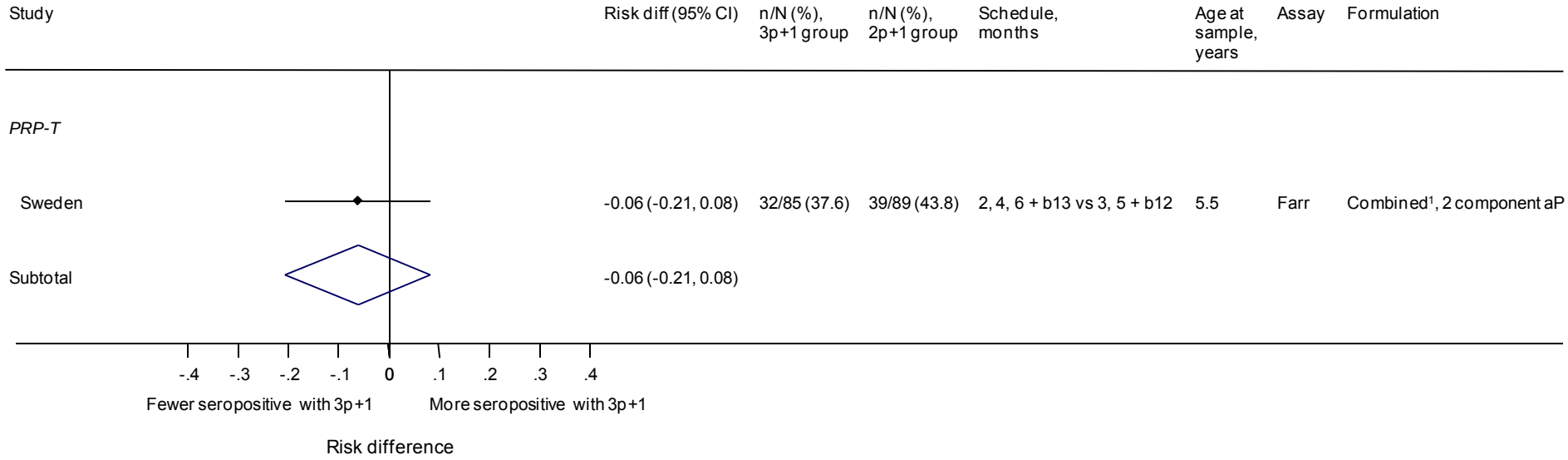

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
1 DTwP-IPV both groups at 3, 4, 5 2 DTaP-IPV/Hib both groups (2 component aP)

## Figure 13: 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 (2 component aP)

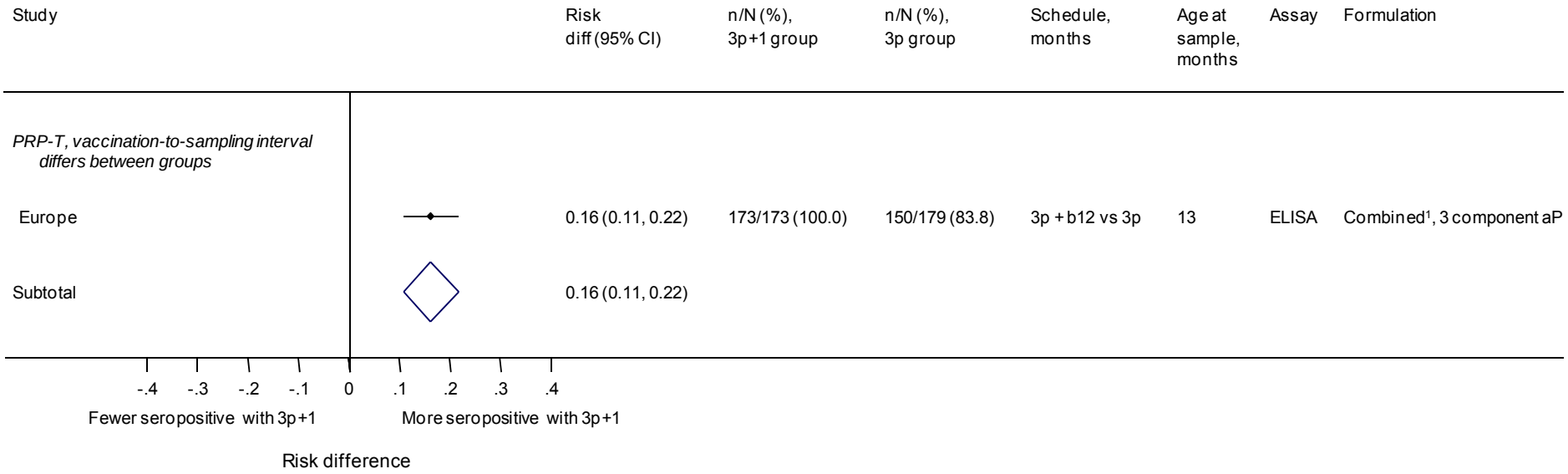
## Figure 14: 3p+1 vs 2p+1, approx. 4.5y post booster, 1.0µg/ml




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 (2 component aP)

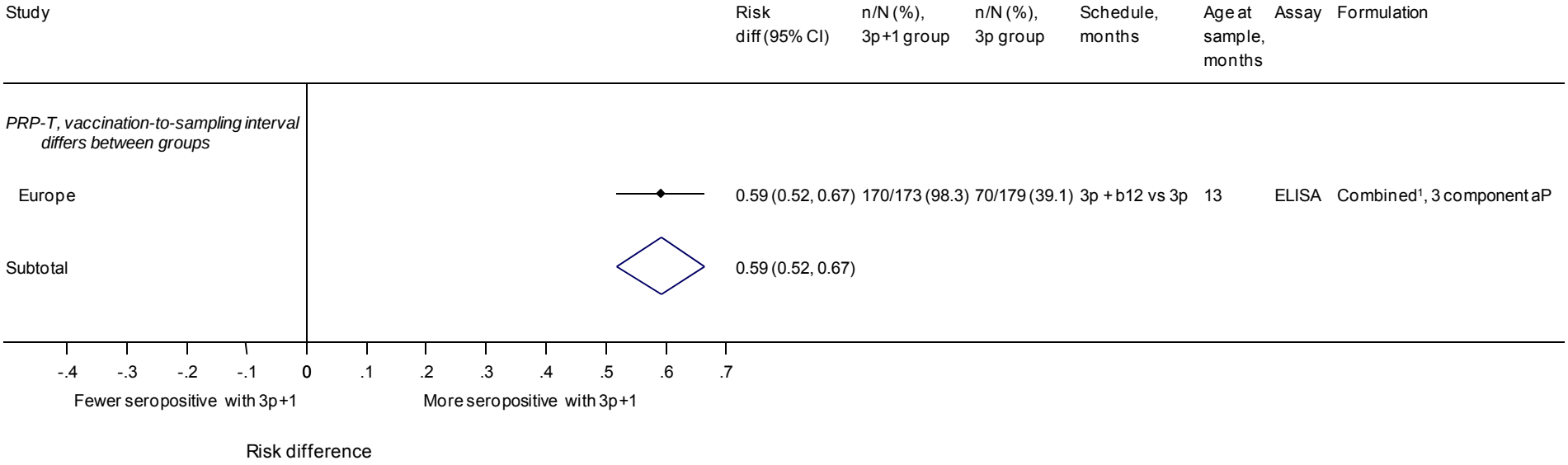
# 3p+1 vs 3p schedules

## Figure 15: 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 (3 component aP). Men ACWY given at 12m in both groups

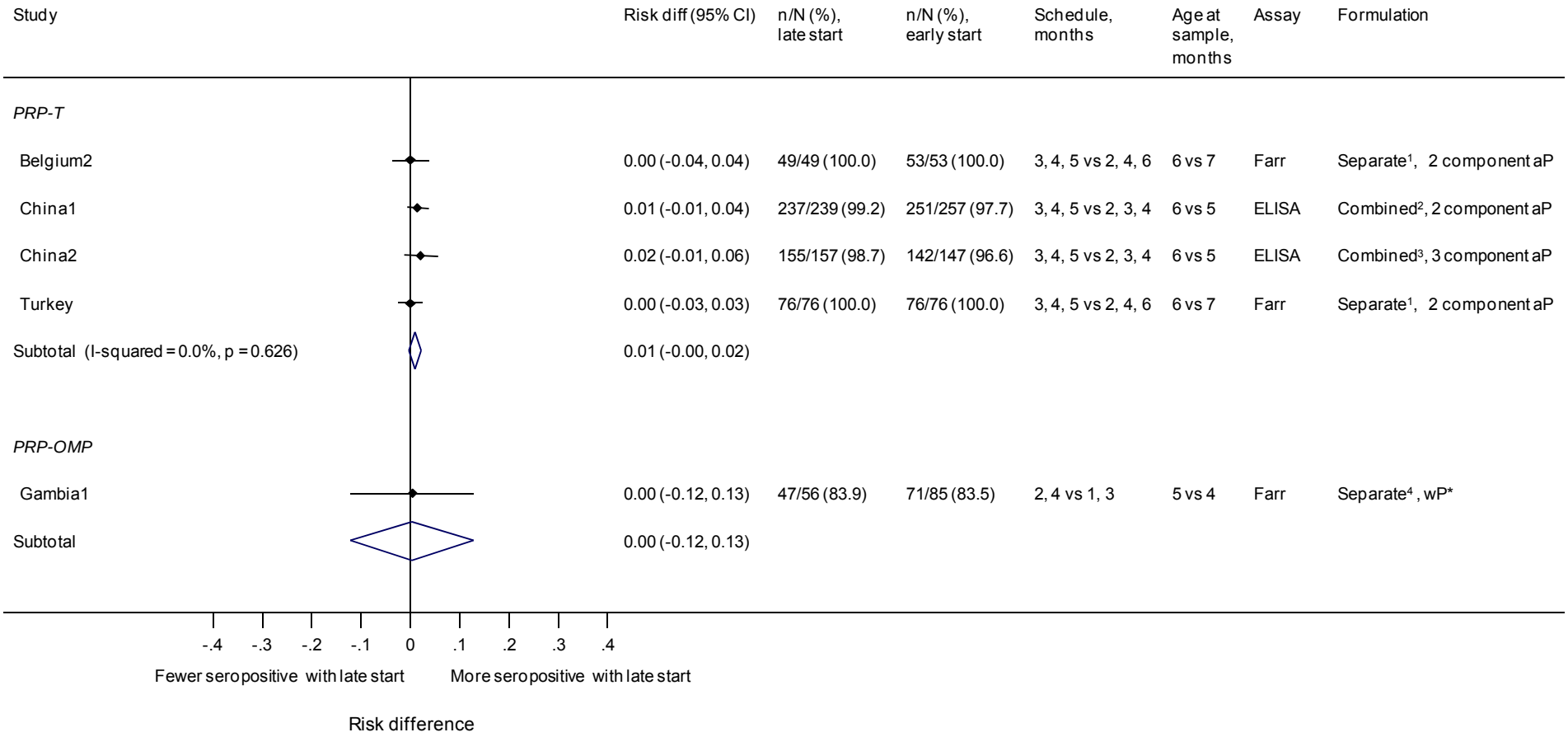
## Figure 16: 3p+1 vs 3p, 1m post booster, 1.0µg/ml




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 (3 component aP). Men ACWY given at 12m in both groups

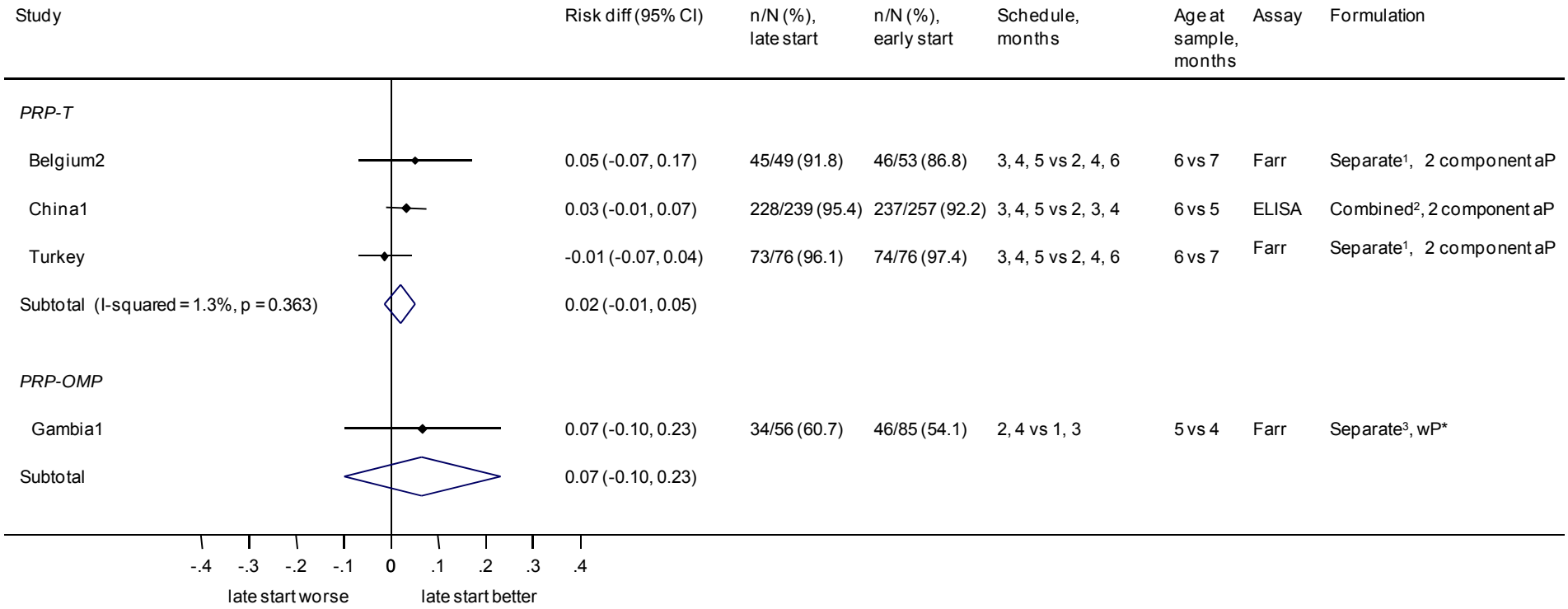
# Late vs early start schedules

## Figure 17: late vs early start, 1m post primary, 0.15µg/ml



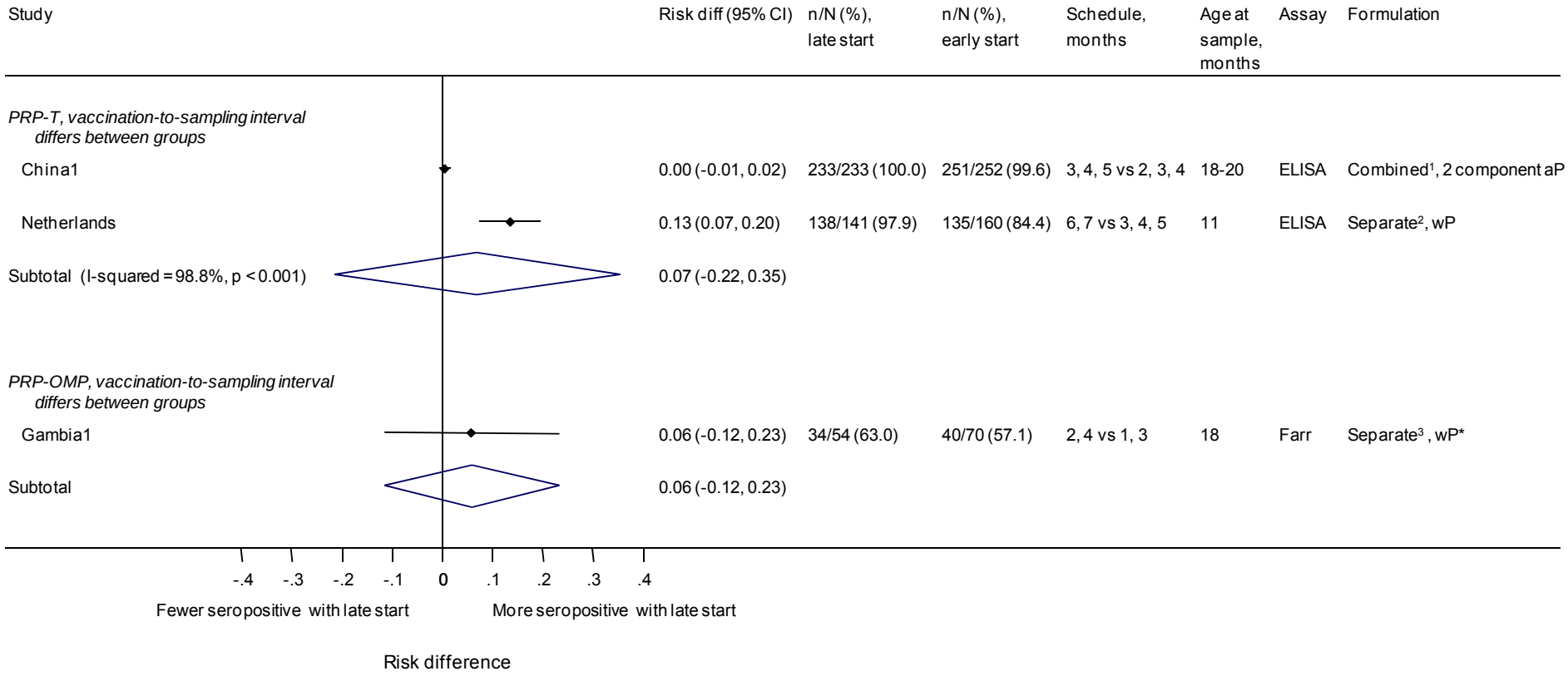

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
1 DTaP at same time as Hib in separate syringe (2 component aP) 2 DTaP-IPV/Hib (2 component aP) 3 DTaP-IPV/Hib (3 component aP)
4 DTP at 2, 3, 4m. Unclear if wP or aP. OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

## Figure 18: late vs early start, 1m post primary, 1.0µg/ml



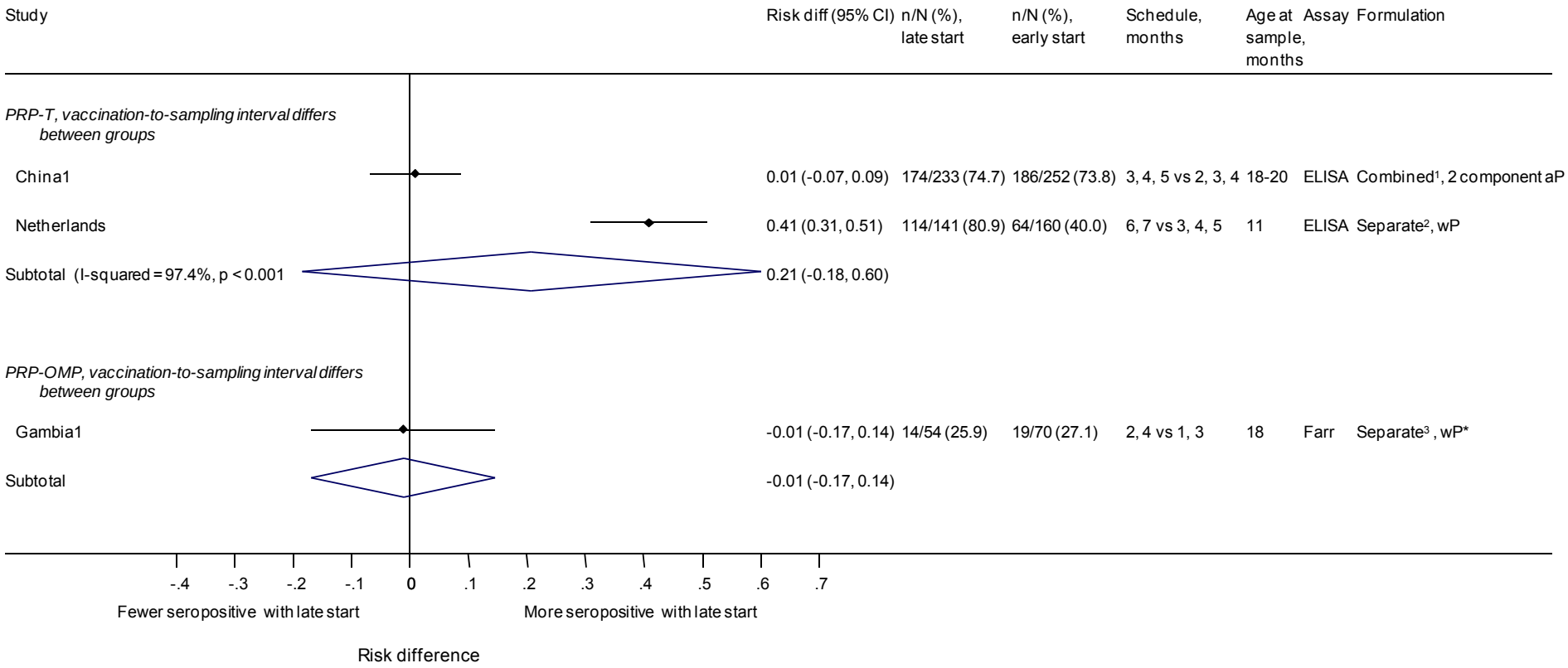

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
1 DTaP at same time as Hib in separate syringe (2 component aP) 2 DTaP-IPV/Hib (2 component aP)
3 DTP at 2, 3, 4m. Unclear if wP or aP. OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

## Figure 19: late vs early start, pre-booster, 0.15µg/ml



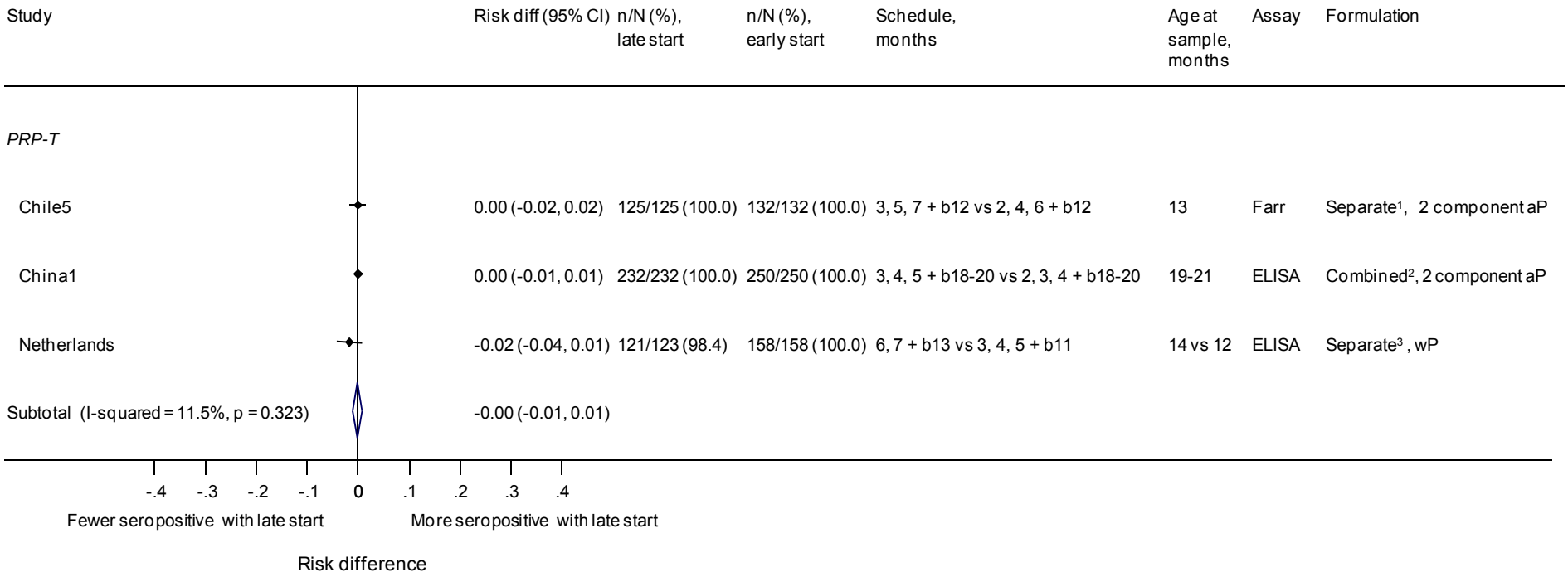

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
1 DTaP-IPV/Hib (2 component aP) 2 DTwP-IPV both groups at 3, 4, 5 3 DTP at 2, 3, 4m. Unclear if wP or aP. OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

## Figure 20: late vs early start, pre-booster, 1.0µg/ml



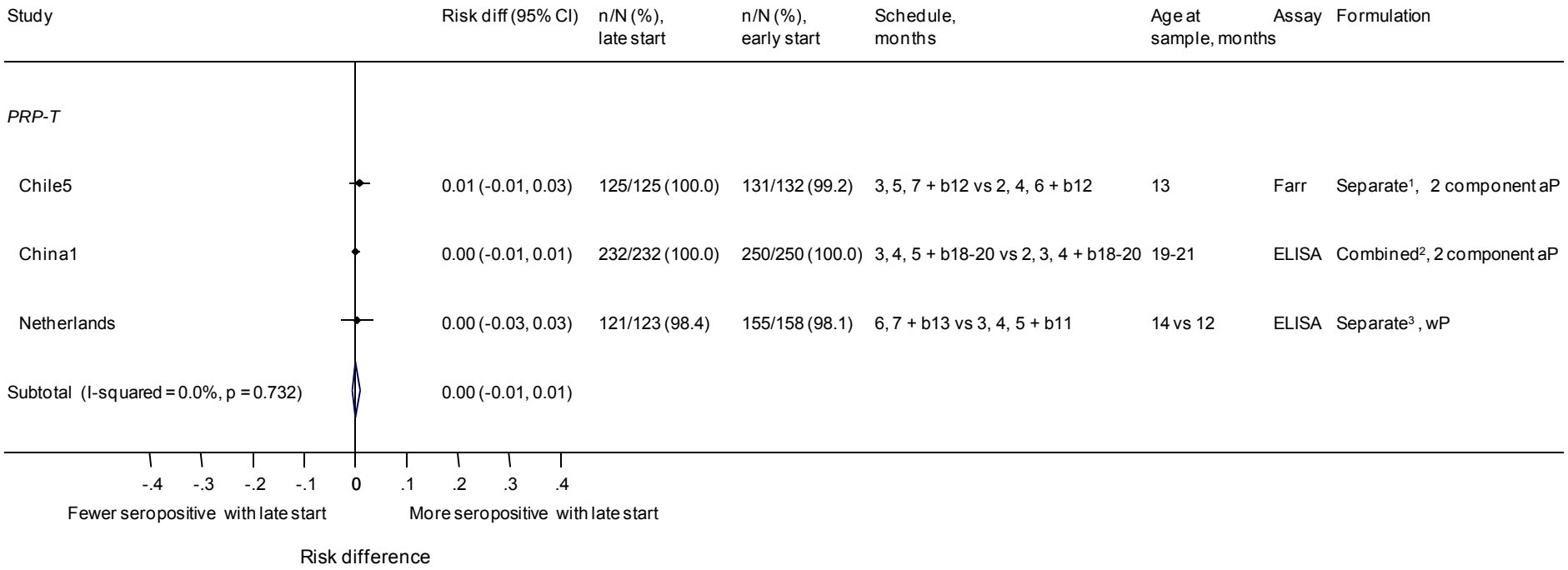

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
1 DTaP-IPV/Hib (2 component aP) 2 DTwP-IPV both groups at 3, 4, 5 3 DTP at 2, 3, 4m. Unclear if wP or aP. OPV given at 1, 2, 3, 4m and BCG at 1m in both groups

## Figure 21: 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 component aP) 2 DTaP-IPV/Hib (2 component aP) 3 DTwP-IPV both groups at 3, 4, 5

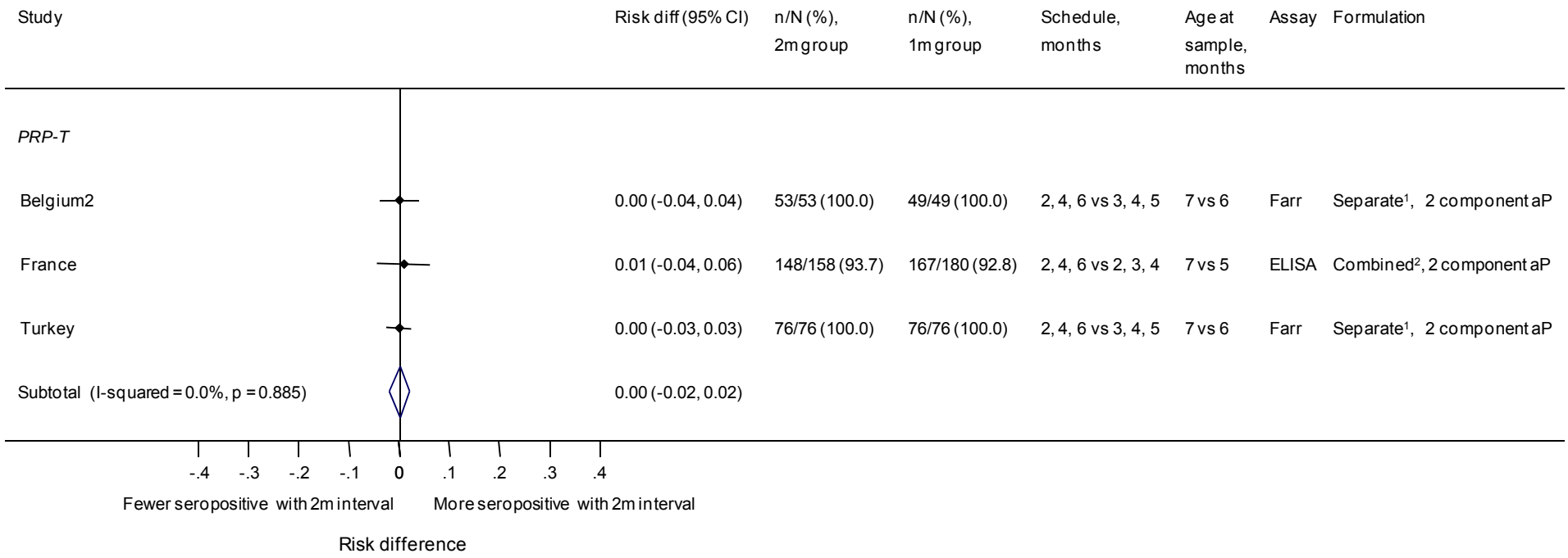
## Figure 22: late vs early start, 1m post booster, 1.0µg/ml




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 component aP) 2 DTaP-IPV/Hib (2 component aP) 3 DTwP-IPV both groups at 3, 4, 5

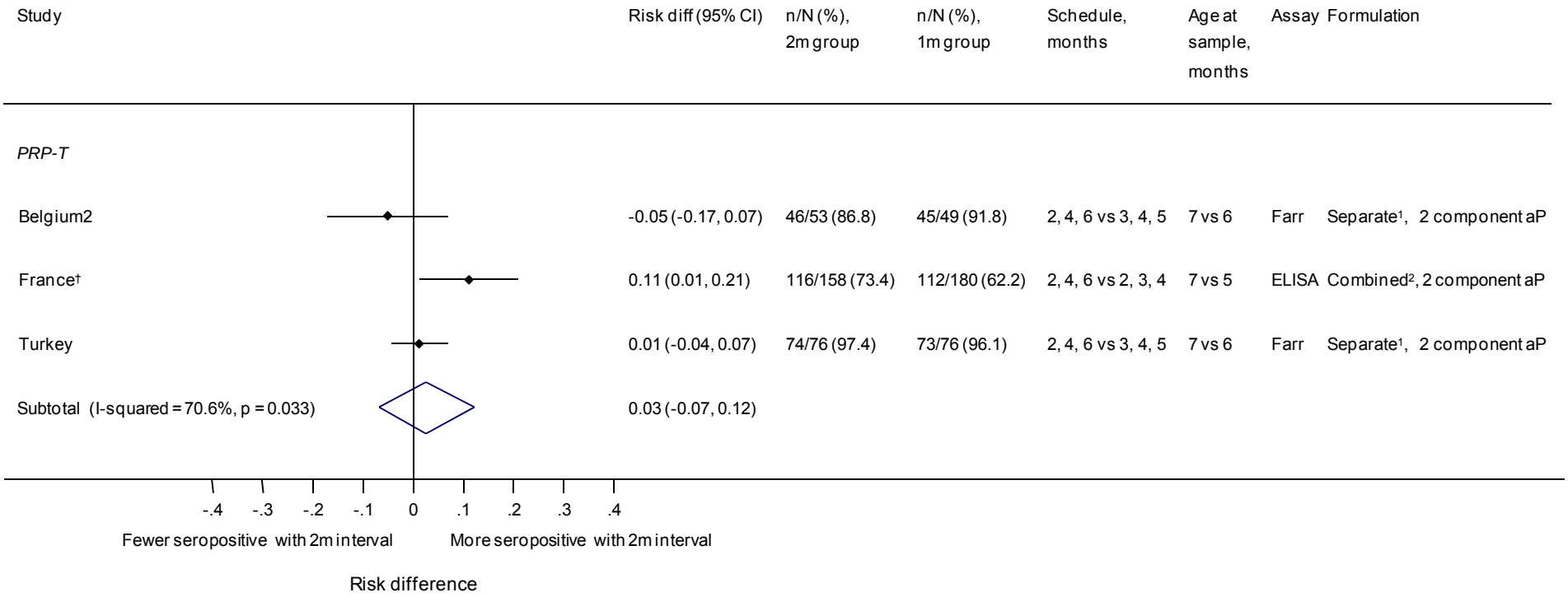
# 2-month vs 1-month interval schedules

## Figure 23: 2m vs 1m interval in primary course, 1m post primary, 0.15µg/ml



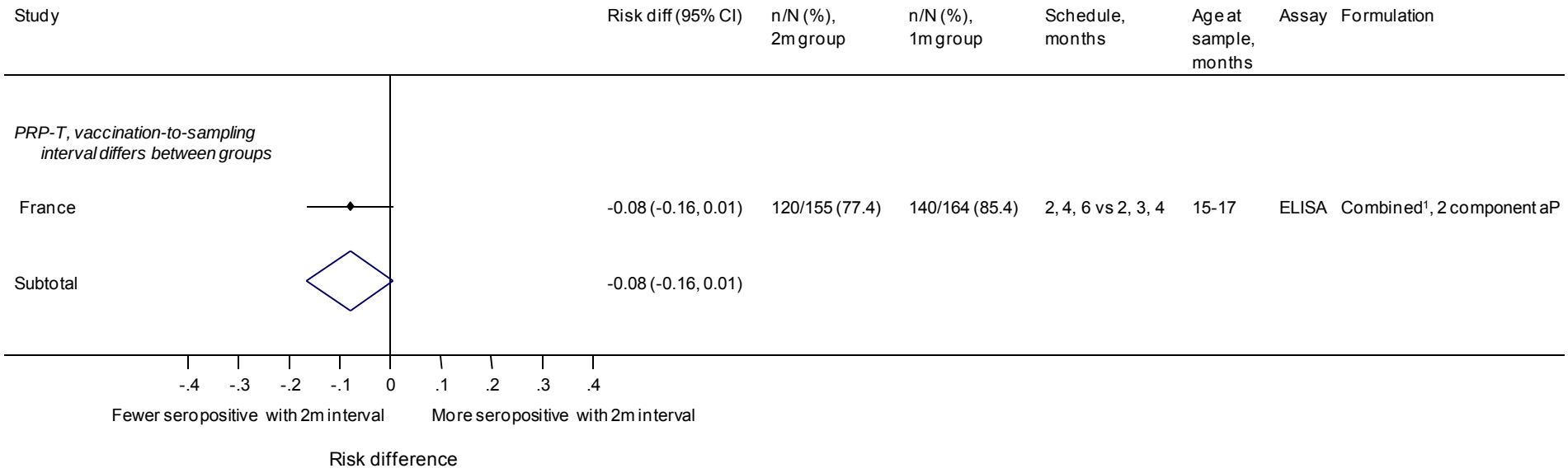

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
1 DTaP at same time as Hib in separate syringe (2 component aP) 2 DTaP-hepB-IPV/Hib (2 component aP)

## Figure 24: 2m vs 1m interval in primary course, 1m post primary, 1.0µg/ml



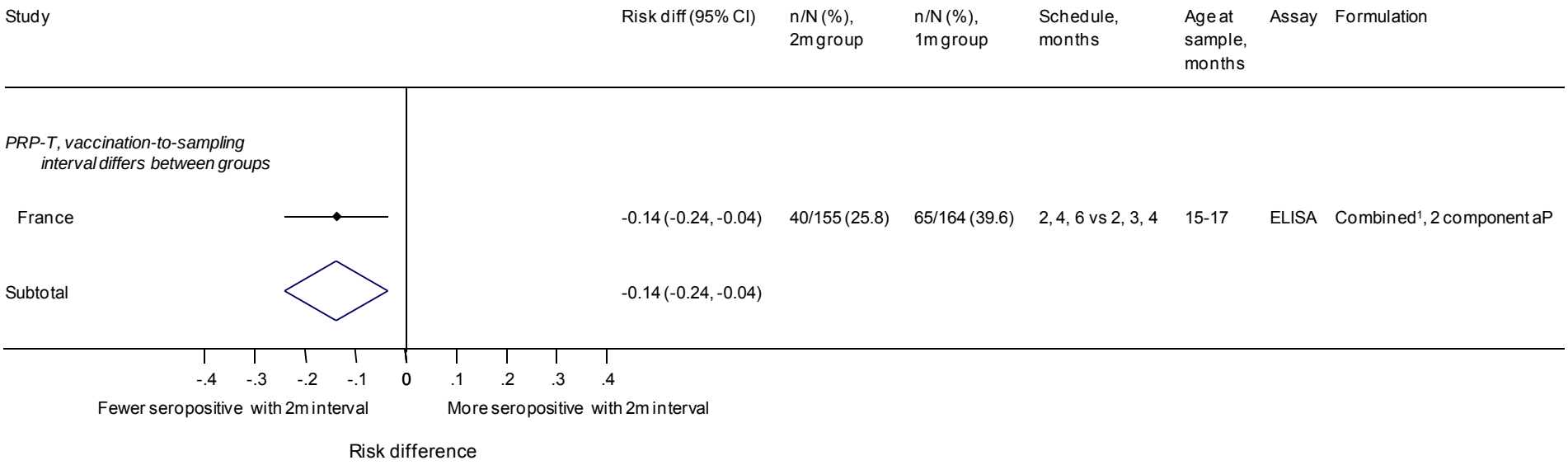

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
† Data for this trial unclearly reported at this time point and for this definition of seropositivity
1 DTaP at same time as Hib in separate syringe (2 component aP) 2 DTaP-hepB-IPV/Hib (2 component aP)

## Figure 25: 2m vs 1m interval in primary course, pre-booster, 0.15µg/ml



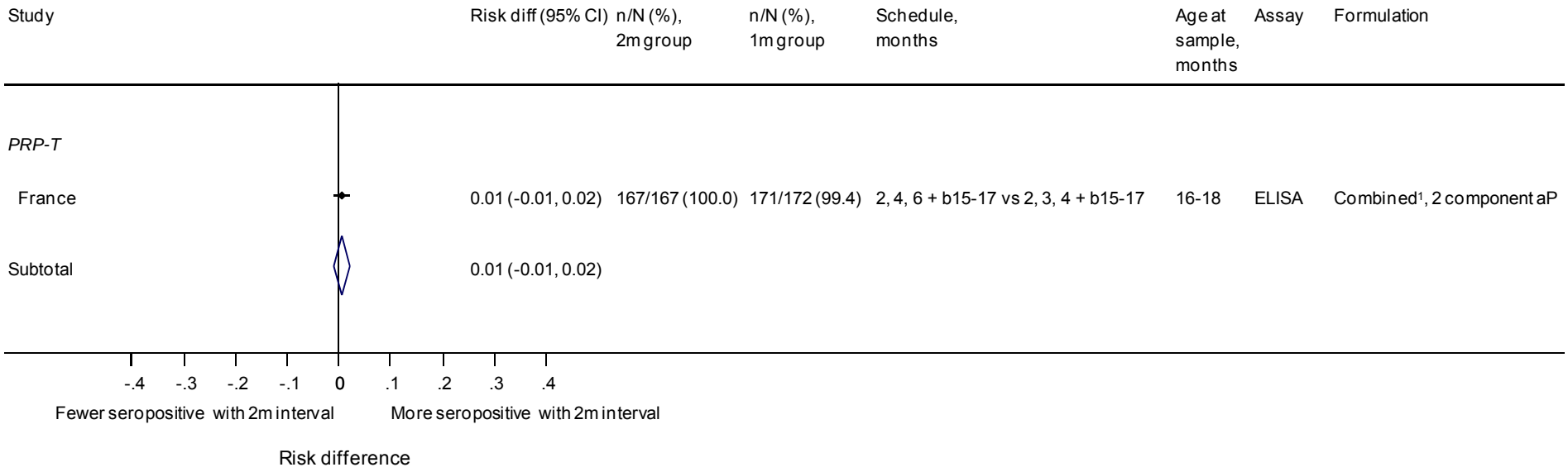

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
1 DTaP-hepB-IPV/Hib (2 component aP)

## Figure 26: 2m vs 1m interval in primary course, pre-booster, 1.0µg/ml



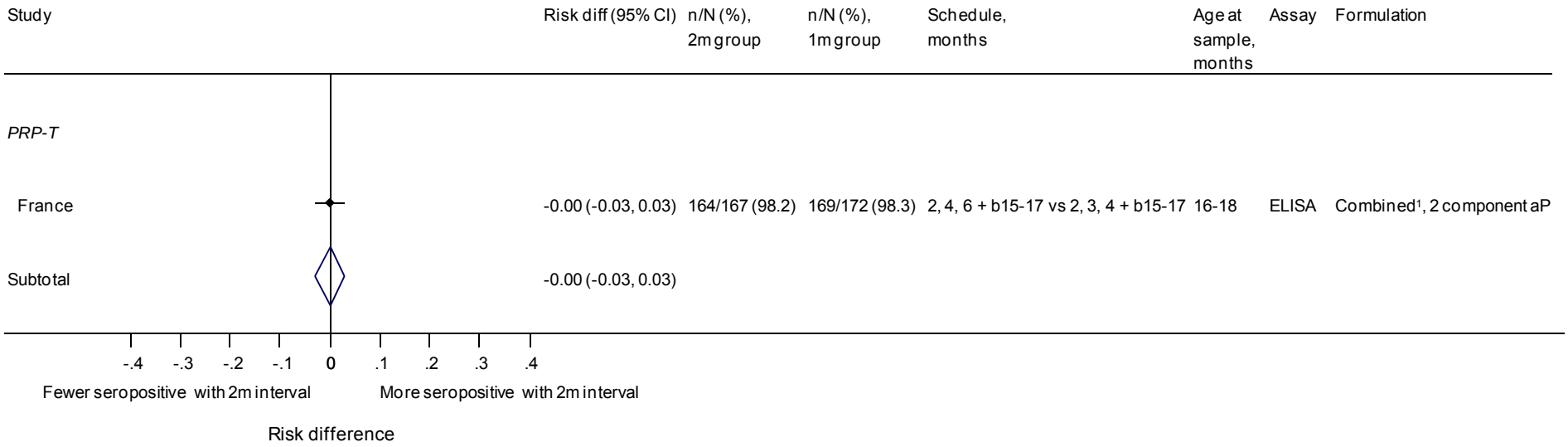

Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).
1 DTaP-hepB-IPV/Hib (2 component aP)

## Figure 27: 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 (2 component aP)

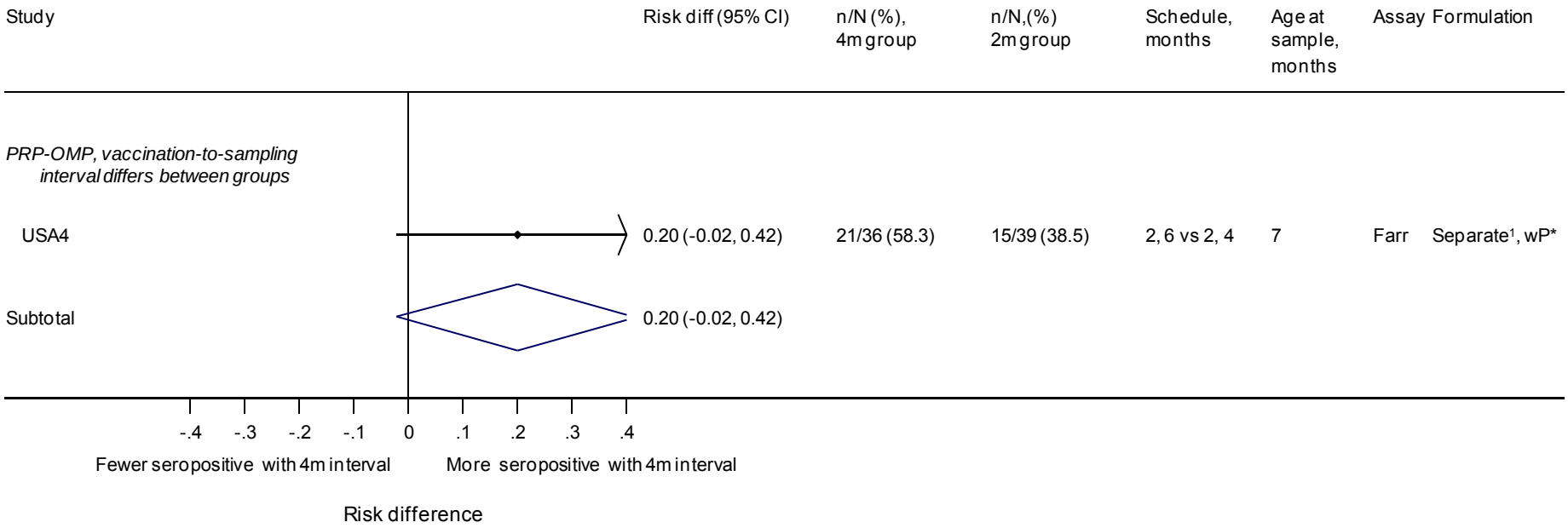
## Figure 28: 2m vs 1m interval in primary course, 1m post booster, 1.0µg/ml




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 (2 component aP)

# 4-month vs 2-month interval schedules

## Figure 29: 4-month vs 2-month interval, 1m post primary, 1.0µg/ml

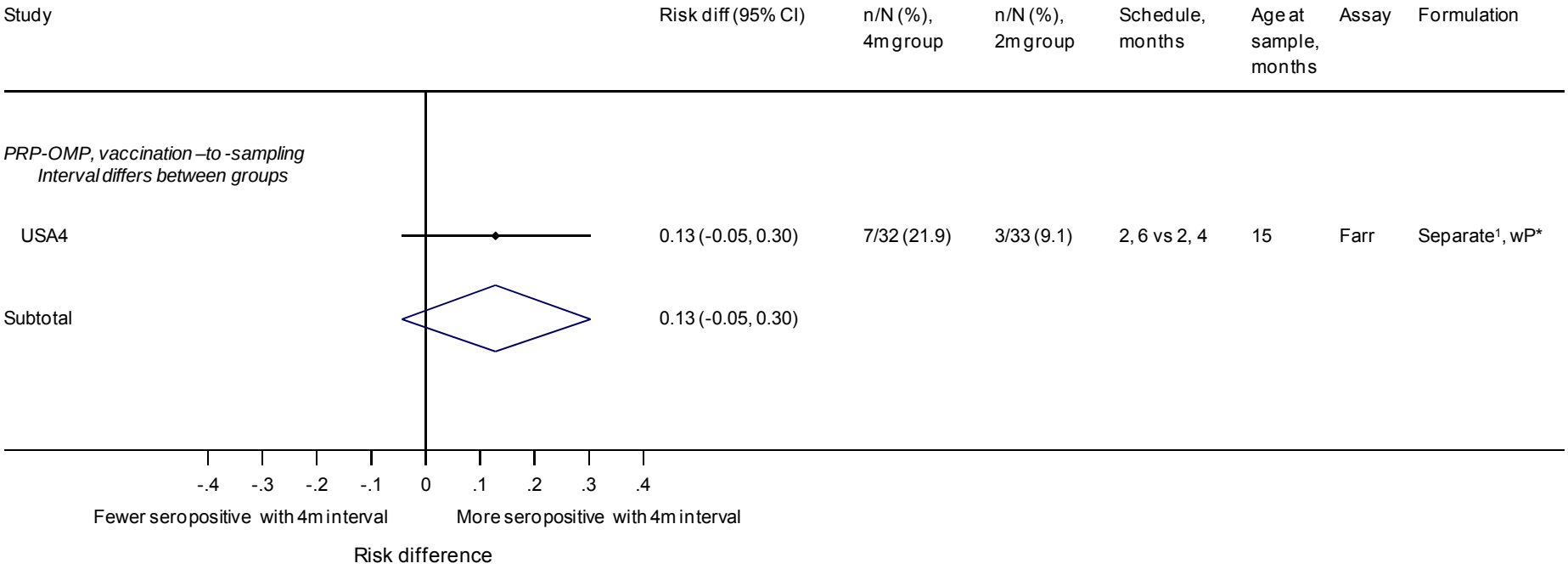



Combined – Hib vaccine mixed in same syringe as other vaccines; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).

* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted

1DTP, OPV, MMR given to both groups "according to published guidelines" . Not stated if aP or wP.

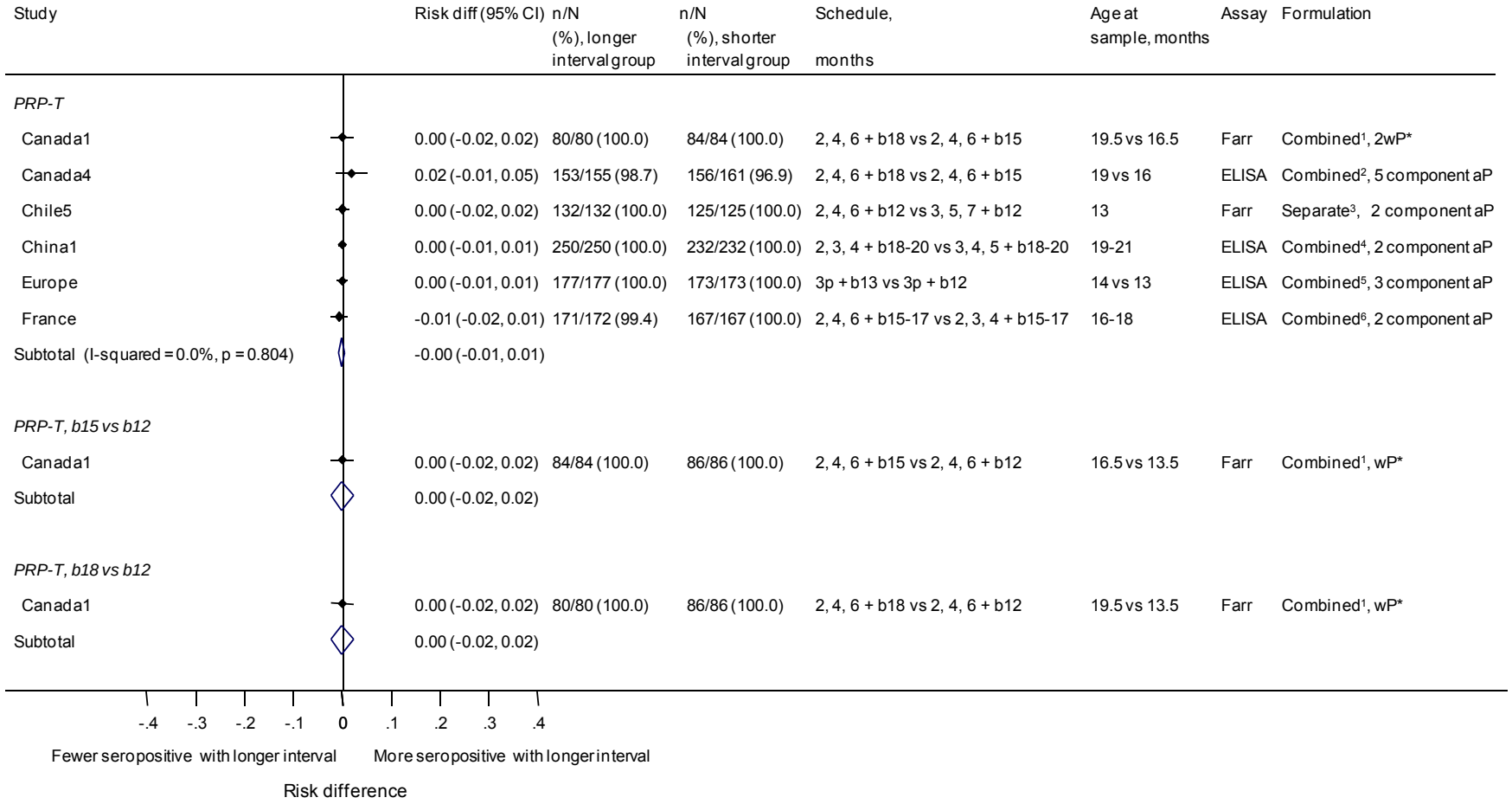
## Figure 30: 4-month vs 2-month interval, pre-booster, 1.0µg/ml




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).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
1DTP, OPV, MMR given to both groups "according to published guidelines". Not stated if aP or wP.

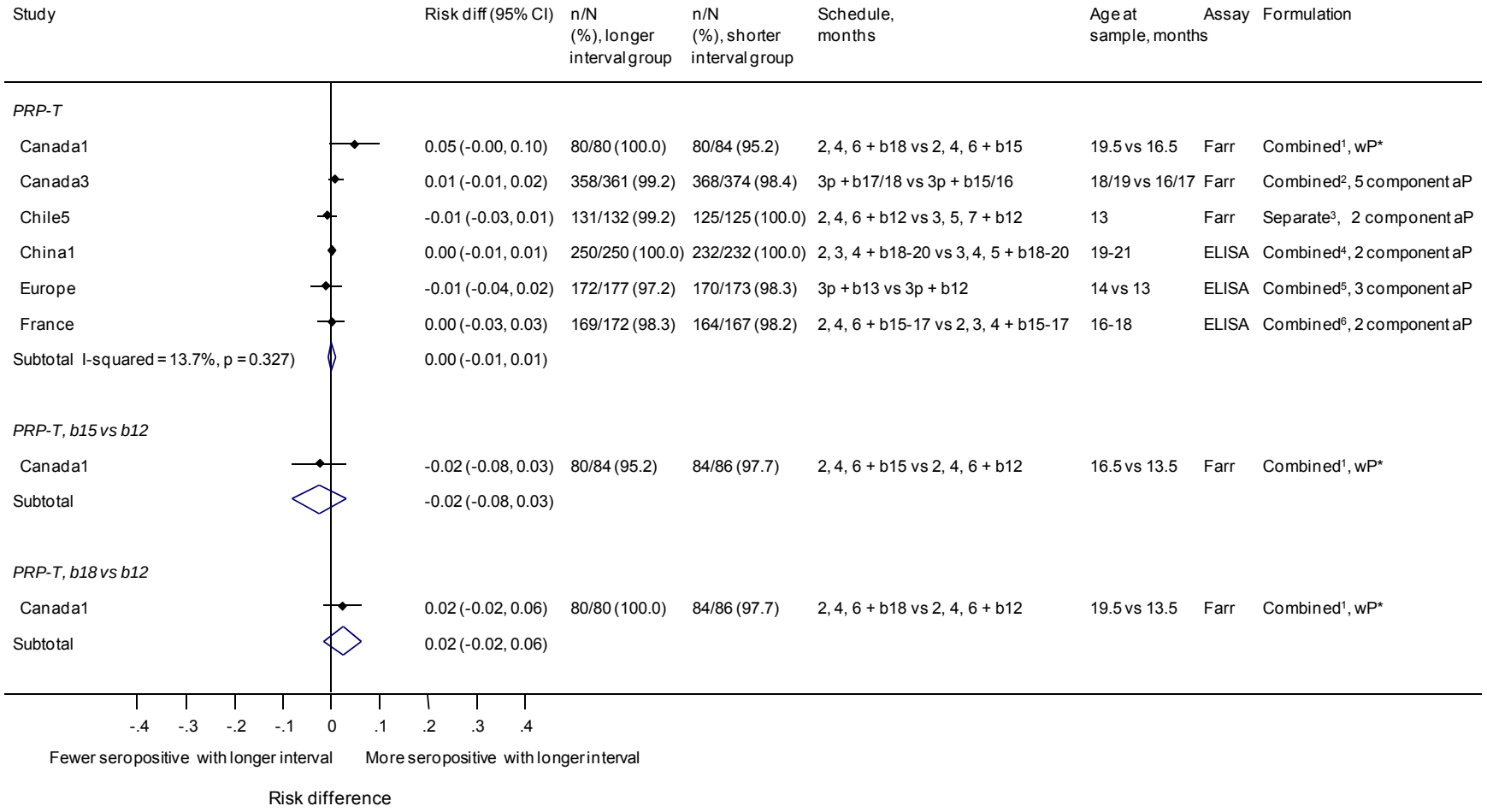
# Long vs short interval between primary and booster schedules

## Figure 31: 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).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
1 DTP-IPV/Hib. Not stated if aP or wP. MMR given separately at 12m
2 DTaP-IPV/Hib (5 component aP). PCV7 given at the same time but separate to other vaccines
3 DTaP 2, 4, 6 both groups (2 component aP)
4 DTaP-IPV/Hib (2 component aP)
5 DTaP-hepB-IPV/Hib (3 component aP) . Men ACWY at 12m in both groups
6 DTaP-hepB-IPV/Hib (2 component aP)

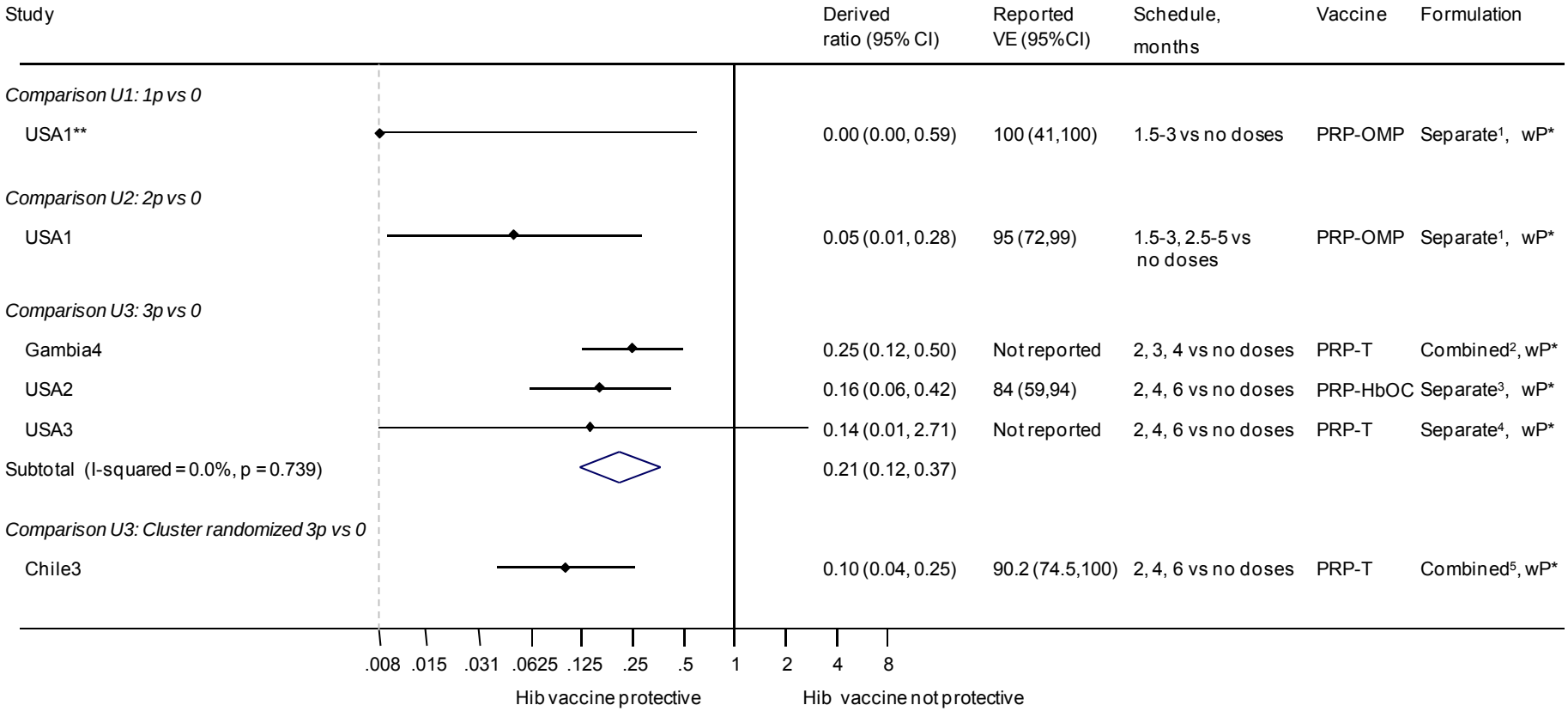
## Figure 32: Long vs short interval between primary and booster, 1m post-booster, 1.0µg/ml




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).
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
1 DTP-IPV/Hib. Not stated if aP or wP. MMR given separately at 12m
2 DTaP-IPV/Hib (5 component aP)
3 DTaP 2, 4, 6 both groups (2 component aP)
4 DTaP-IPV/Hib (2 component aP)
5 DTaP-hepB-IPV/Hib (3 component aP) . Men ACWY given at 12m in both groups
6 DTaP-hepB-IPV/Hib (2 component aP)

# Clinical data

## Figure 33: Invasive Hib disease, intention to treat analyses, all available schedules

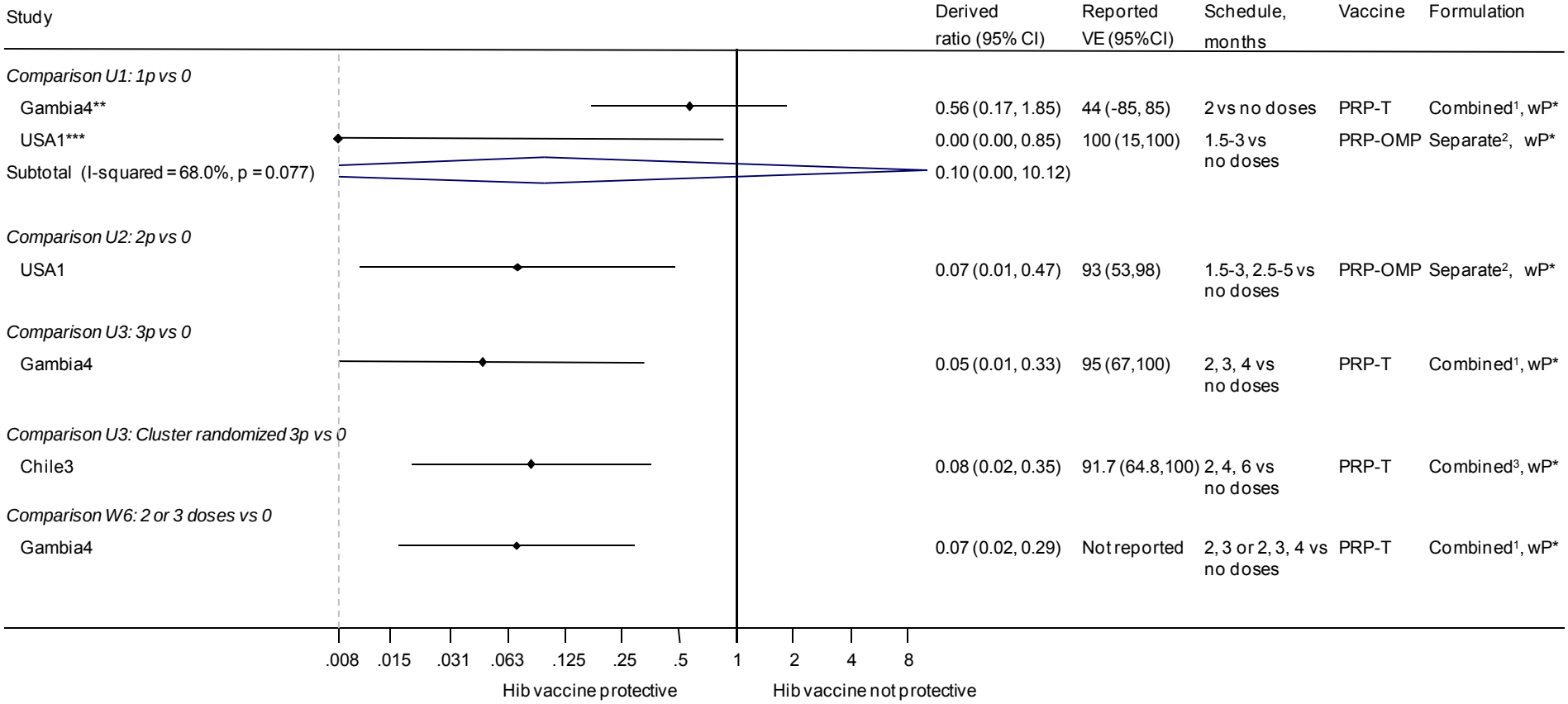



For the purposes of this graph, "intention to treat" is used to mean analyses where no individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – 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

* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted
** USA1 - onset before second dose

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

## Figure 34: Invasive Hib disease, 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

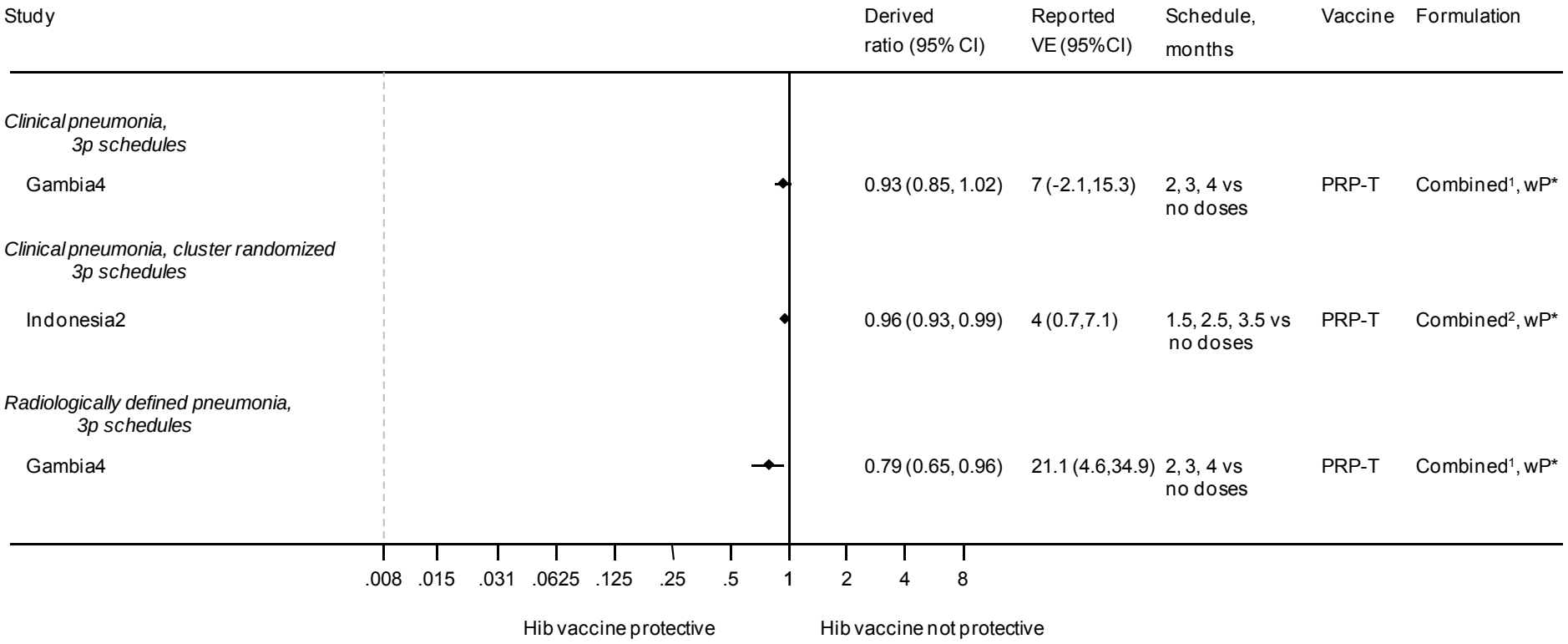
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted

**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 Not stated if aP or wP; 3 DTP/Hib. Not stated if aP or wP. OPV at same time.

## Figure 35: Pneumonia, intention to treat analyses, all available schedules

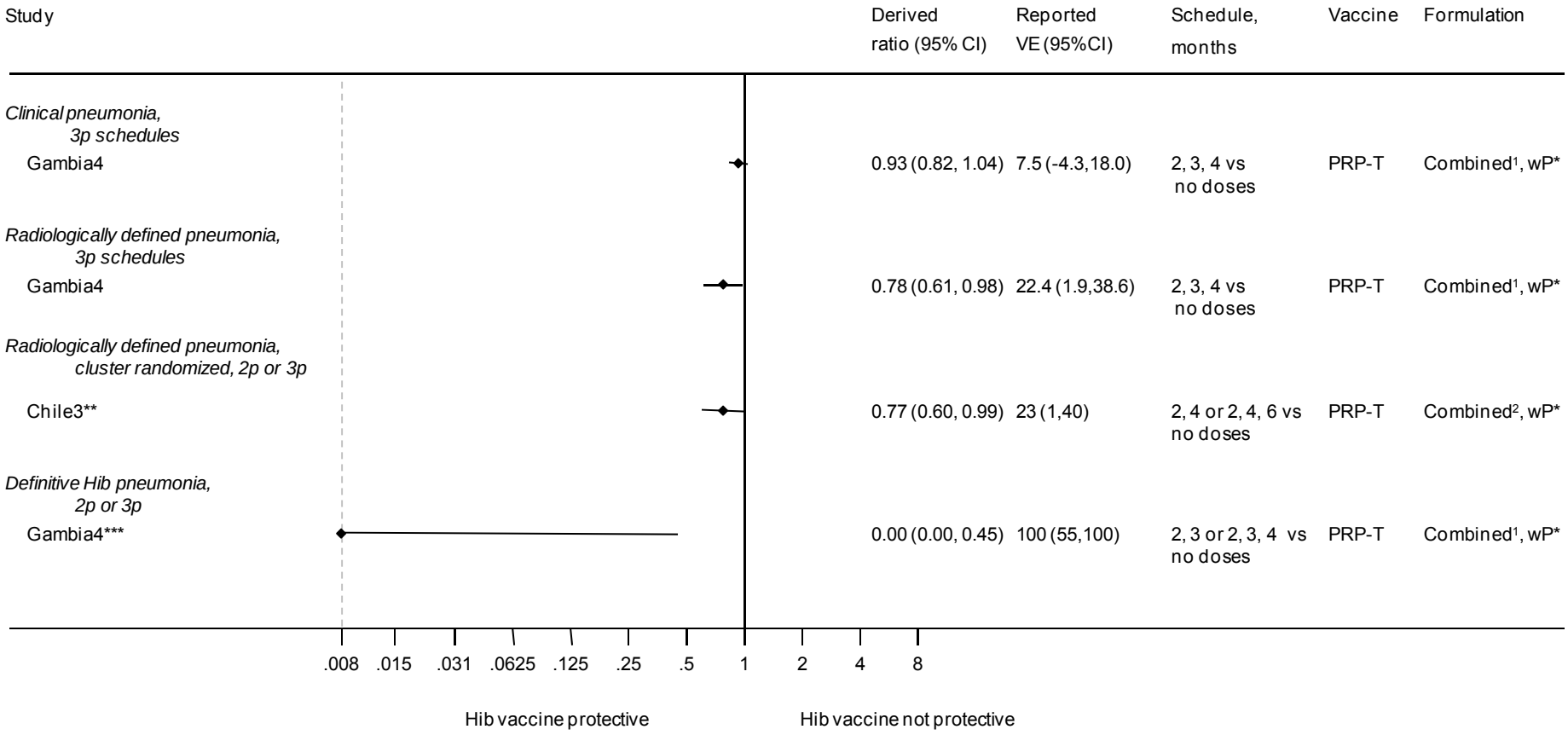



For the purposes of this graph, "intention to treat" is used to mean analyses where no individuals with available outcome data are excluded. Dashed grey line indicates VE approaching 100%. Solid black line indicates VE of 0%. Combined – Hib vaccine mixed in same syringe as other vaccines; separate – 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

* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted

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

## Figure 36: 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

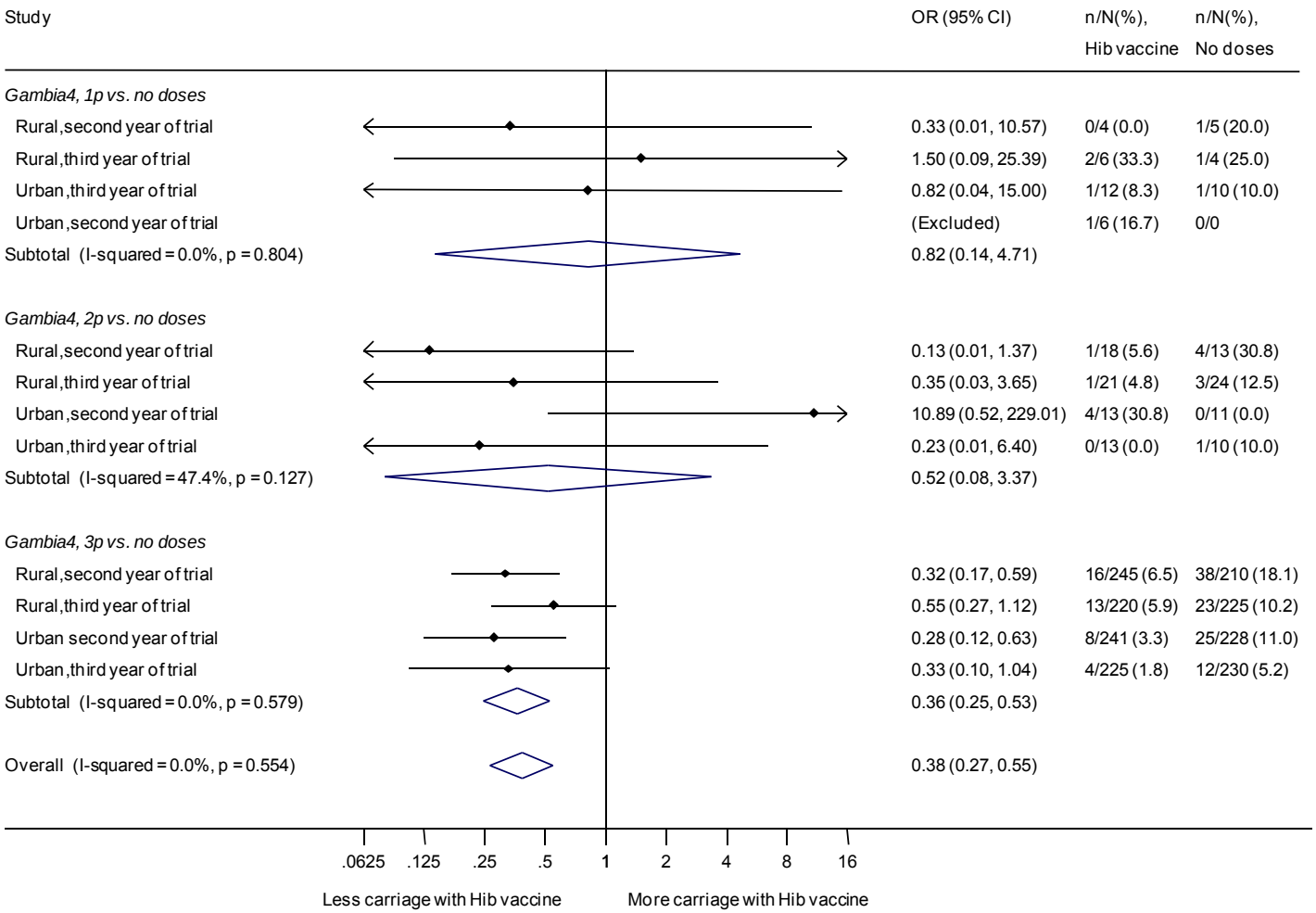
* Not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted

** 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 37: 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. Assumed to be whole cell due to year trial conducted

# Appendix 1: Search strategy

2010 searches conducted May 18th 2010, 2012 searches conducted June 21st 2012

1. **Medline**

Searches conducted in Ovid

2010 search

1 exp Haemophilus Vaccines/
2 exp Haemophilus Influenzae type b/
3 exp haemophilus influenzae type b.ab,ti
4 exp hemophilus influenzae type b.ab,ti
5 exp haemophilus influenza type b.ab,ti
6 exp hemophilus influenzae type b.ab,ti
7 2 or 3 or 4 or 5 or 6
8 exp *vaccines/
9 immunization/ or vaccination/
10 exp Immunization Programs/
11 8 or 9 or 10
12 7 and 11
13 1 or 12

2012 search (restricted to trials and to publications 2009 onwards)

1 exp Haemophilus Vaccines/
2 exp haemophilus influenzae type b/
3 haemophilus influenzae type b.ab,ti.
4 hemophilus influenzae type b.ab,ti.
5 haemophilus influenza type b.ab,ti.
6 hemophilus influenza type b.ab,ti.
7 2 or 3 or 4 or 5 or 6
8 exp *vaccines/
9 immunization/ or vaccination/
10 exp immunization Programs/
11 8 or 9 or 10
12 7 and 11
13 1 or 12
14 randomi?ed controlled trial.pt.
15 controlled clinical trial.pt.
16 randomi?ed.ab.
17 placebo.ab.
18 drug therapy.fs.
19 randomly.ab.
20 trial.ab.
21 groups.ab.
22 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 exp animals/ not humans.sh.
24 22 not 23
25 13 and 24
26 limit 25 to yr="2009 -Current"150

**2. Cochrane library**

2010 search
1 MeSH descriptor Haemophilus Vaccines explode all trees
2 (haemophilus influenzae):ti,ab,kw OR (hemophilus influenzae):ti,ab,kw OR (hib):ti,ab,kw
3 (vaccin*):ti,ab,kw OR (immuniz*):ti,ab,kw OR (immunis*):ti,ab,kw
4 (#2 AND #3)
5 (#1 OR #4)

2012 search
1 MeSH descriptor Haemophilus Vaccines explode all trees
2 (haemophilus influenzae):ti,ab,kw OR (hemophilus influenzae):ti,ab,kw OR (hib):ti,ab,kw
3 (vaccin*):ti,ab,kw OR (immuniz*):ti,ab,kw OR (immunis*):ti,ab,kw
4 (#2 AND #3)
5 (#1 OR #4), from 2009 to 2012

In both searches clinical trials, Cochrane reviews and other reviews were exported for eligibility screening

**3. World Health Organization International Clinical Trials Registry Platform**

2010 search
1 Haemophilus influenzae AND vaccin*
2 Hib AND vaccin*
3 Haemophilus influenzae AND immuni*
4 Hib AND immuni*

Searches manually combined and deduplicated

#### 7.1.1.1 The Data Providers of the ICTRP Search Portal were:

- Australian New Zealand Clinical Trials Registry (ANZCTR)
- Chinese Clinical Trial Register (ChiCTR)
- Clinical Research Information Service (CRiS), Republic of Korea
- ClinicalTrials.gov
- Clinical Trials Registry - India (CTRI)
- Cuban Public Registry of Clinical Trials (RPCEC)
- EU Clinical Trials Register (EU-CTR)
- German Clinical Trials Register (DRKS)
- Iranian Registry of Clinical Trials (IRCT)
- ISRCTN.org
- Japan Primary Registries Network (JPRN)
- Pan African Clinical Trial Registry (PACTR)
- Sri Lanka Clinical Trials Registry (SLCTR)
- The Netherlands National Trial Register (NTR)

In June 2012 eligible trial registrations found in the 2010 search were checked for new publications.

4. **Current Controlled Trials metaRegister of Controlled Trials (mRCT), active registers**

2010 search only
Hib OR haemophilus influenzae OR hemophilus influenzae

5. **Current Controlled Trials metaRegister of Controlled Trials (mRCT), archived registers**

2010 search only
Hib OR haemophilus influenzae OR hemophilus influenzae

6. **US Food and Drug Agency (FDA)**

2010 search only
Manual search for Hib containing vaccines

7. **European Medicines Agency (EMEA)**

2010 search only
Manual search of EPARS for Hib containing vaccines

8. **African Index Medicus (AIM)**

2010 and 2012 searches
1 Haemophilus AND influenzae
2 Hemophilus AND influenzae
3 Hib
4 Haemophilus
5 Hemophilus

Searches manually combined and deduplicated

9. **Latin American and Caribbean Health Sciences Literature (LILACS)**

2010 and 2012 searches
(Haemophilus influenzae OR Hib) AND (vacc$ or vacun$ or immuniz$ or immunis$) [Words]
OR Haemophilus vaccines [Subject descriptor]

10. **INDMED**

2010 and 2012 searches
(haemophilus influenzae) or (Hib) or (hemophilus influenzae

**Manufacturers**

2010 search

11. **GSK**
Manual search for Hib containing vaccines

**12. Wyeth/Pfizer**
Manual search of both Wyeth and Pfizer websites for Hib containing vaccines

**13. Novartis**
Manual search for Hib containing vaccines

**14. Sanofi Pasteur**
Manual search for Hib containing vaccines

**15. Merck**
Manual search for Hib containing vaccines

**16. Panacea Biotech**
Manual search for Hib containing vaccines

**17. Serum institute India:**
Manual search for Hib containing vaccines

**18. Bio-Manguinhos**
Manual search for Hib containing vaccines

**19. Bharat Biotech**
Manual search for Hib containing vaccines

**20. Biological E**
Manual search for Hib containing vaccines

**21. Shantha Biotech**
Manual search for Hib containing vaccines

# Appendix 2: Trials included in Hib conjugate vaccine review, detailed information

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Belgium1**[25] | | | | | | | | | | |
| **Location**: Belgium<br>**Recruitment dates:** October 1990 to September 1991<br>**Hib vaccine:**<br>PRP-T, Act-HIB, Pasteur Mérieux Connaught<br>**Pertussis vaccine:**<br>wP, Triamer, Pasteur Mérieux, Connaught<br>**Funding:**<br>Pasteur Mérieux Connaught | **Inclusion criteria:** healthy infants in daycare centers, 12±16 weeks of age, afebrile, born at term, minimum birth weight of 2500g<br>**Exclusion criteria:** history of seizures or other neurologic disorders, family history of sudden infant death syndrome (SIDS), receipt of medication likely to alter the immune response | **A:** 3, 4, 5 + b14<br>**B:** b14<br>**Additional information:**<br>**A:**<br>Primary: DTwP at 3, 4, 5, combined<br>Booster: DTwP at 14, combined<br>**B:**<br>Primary: Placebo<br>Booster: DTwP/Placebo at 14, combined | **N=** 46<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Primary: NR<br>Booster: 13.4 (0.6)<br>**Gender (M/F):**<br>41/44; (48% M) | **N=** 45<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD) :**<br>Primary: NR<br>Booster: 13.5 (0.6)<br>**Gender (M/F):**<br>48/35; (58% M) | | | | | | ✓ |
| **Belgium2**[26] | | | | | | | | | | |
| **Location**: Belgium<br>**Recruitment dates:** October 1994 to March 1995<br>**Hib vaccine:**<br>PRP-T, Act-HIB, Pasteur Mérieux Connaught<br>**Pertussis vaccine:**<br>aP (2 component), brand name not stated, Pasteur Mérieux, Connaught<br>**Funding:**<br>Pasteur Mérieux Connaught | **Inclusion criteria:** healthy infants, Belgian, aged 2 months (22 weeks) with informed written consent from the parents or legal guardian<br>**Exclusion criteria:** none reported | **A:** 3, 4, 5 +b12-14<br>**B:** 3, 4, 5 +b12-14<br>**C:** 2, 4, 6<br>**Additional information:**<br>**A:** DTaP at 3, 4, 5, 12-14 combined<br>**B:** DTaP at 3, 4, 5, 12-14m, separate<br>**C:** DTaP at 2, 4, 6, separate | **N=**54*<br>**Mean age at randomization (SD):** 2 (0.5)<br>**Mean age at vaccination (SD):**<br>1st dose: 3.0 (0.1)<br>2nd dose: 4.0 (0.1)<br>3rd dose: 5.0 (0.2)<br>Booster:14.0 (0.7)<br>**Gender (M/F):**<br>32/22 (59% M) | **N=** 49*<br>**Median age at randomization (SD):** 2 (0.5)<br>**Mean age at vaccination (SD):**<br>1st dose: 3.0 (0.1)<br>2nd dose: 4.0 (0.1)<br>3rd dose: 5.0 (0.2)<br>Booster: 13.8 (0.6)<br>**Gender (M/F):**<br>27/25 (50% M) | **N=** 54*<br>**Mean age at randomization (SD):** 2 (0.5)<br>**Mean age at vaccination (SD):**<br>1st dose: 2.1 (0.2)<br>2nd dose: 4.0 (0.2)<br>3rd dose: 5.9 (0.2)<br>No booster<br>**Gender (M/F):**<br>22/32 (41% M) | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Canada1**[27] | | | | | | | | | | |
| **Location**: Canada<br>**Recruitment dates:** Not stated<br>**Hib vaccine (booster):**<br>PRP-T, PENTA (combined DPT-IPV/PRP-T), Pasteur Mérieux Connaught<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date, PENTA, Pasteur Mérieux Connaught<br>**Funding:**<br>Pasteur Mérieux Connaught | **Inclusion criteria:** healthy children, written consent from a parent or legal guardian, completed a study of primary immunization with a DPT-IPV/PRP-T combination vaccine<br>**Exclusion criteria:** any contraindication to receipt of PENTA or MMR vaccines, impairment of immune responsiveness, prior infection with any of the agents targeted by PENTA or MMR vaccines; receipt of any other DPT, polio or Hib vaccine apart from in the earlier study; receipt of blood products within 3 months, receipt of any other vaccine within 2 weeks | **A:** 2, 4, 6 + b18<br>**B:** 2, 4, 6 + b15<br>**C:** 2, 4, 6 + b12<br>**Additional information:**<br>All children had previously received 3 doses of PENTA (combined DPT-IPV/PRP-T) at 2, 4, 6 months and received a PENTA booster in this study. All received MMR vaccine at 12 months. | **N=** 82<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR†<br>**Gender (M/F):** NR | **N=** 85<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR†<br>**Gender (M/F):** NR | **N=** 86<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR†<br>**Gender (M/F):** NR | | | | | ✓ |
| **Canada2**[28, 63] | | | | | | | | | | |
| **Location**: Canada<br>**Recruitment dates:** Not stated.<br>**Hib vaccine:**<br>PRP-T, Act-HIB, Pasteur Mérieux Connaught<br>**Pertussis vaccine:**<br>aP (components not described), Quadracel, Pasteur Mérieux Connaught<br>wP,Quadracel, Pasteur Mérieux Connaught<br>**Funding:**<br>Pasteur Mérieux Connaught | **Inclusion criteria:** children 4 to 5 years of age who had taken part in studies of primary and booster immunization, continuing good health, absence of contraindications to receive the planned vaccines, and absence of documented Hib infection<br>**Exclusion criteria:** none stated | **A:** 2, 4, 6 +b18, b48-60<br>**B:** 2, 4, 6 +b18<br>**Additional information:**<br>All children received DTwP-IPV at 2, 4, 6, 18 (separately or combined). Children received either aP or wP at 48-60 months (combined with PRP-T in schedule A). | **N=** 106*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Primary: NR<br>Booster: NR<br>**Gender (M/F):** NR | **N=** 106*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Primary: NR<br>Booster: NR.<br>**Gender (M/F):** NR | | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Canada3**[29, 64-67] | | | | | | | | | | |
| **Location**: Canada<br>**Recruitment dates:** Study performed in 2000 to 2001<br>**Hib vaccine:**<br>PRP-T, Act-HIB, Sanofi Pasteur<br>**Pertussis vaccine:**<br>aP (5 component) Quadracel, Sanofi Pasteur.<br>**Funding:**<br>Sanofi Pasteur | **Inclusion criteria:** healthy toddlers, 12 months of age, who had completed a routine three-dose primary series with DTaP-IPV//PRP-T combination vaccine (Pentacel) by eight months of age<br>**Exclusion criteria:** history of neurologic disorder, confirmed pertussis, chronic underlying disorder; known or suspected hypersensitivity to any component of the study vaccine; impaired immunologic function or receipt of immunosuppressive therapy or immunoglobulins; and prior immunization with a fourth dose of diphtheria, tetanus, pertussis, H. influenza type b conjugate, or poliovirus vaccine) | **A:** 3p +b18<br>**B:** 3p +b17<br>**C:** 3p +b16<br>**D:** 3p +b15<br>**Additional information:**<br>Primary and booster doses were combined DTaP-IPV and PRP-T vaccines. Varicella and MMR vaccines offered upon study entry at 12 months of age to those who had not received them. | **N=** 438<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Primary: NR<br>Booster: 18.3 (0.3)<br>**Gender (M/F):**<br>213/225 (47% M)<br>**Schedule D:**<br>**N=** 445<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Booster:15.4 (0.3)<br>**Gender (M/F):**<br>215/230 (48% M) | **N=** 450<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Primary: NR<br>Booster:17.4 (0.3)<br>**Gender (M/F):**<br>222/228 (49% M) | **N=** 449<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Primary: NR<br>Booster:16.4 (0.3)<br>**Gender (M/F):**<br>211/238 (47% M) | | | | | ✓ |
| **Canada4**[30] | | | | | | | | | | |
| **Location**: Canada<br>**Recruitment dates:** 2003<br>**Hib vaccine:**<br>PRP-T, Pentacel, Sanofi Pasteur<br>**Pertussis vaccine:**<br>aP (5 component) Pentacel, Sanofi Pasteur<br>**Funding:**<br>Wyeth Pharmaceuticals | **Inclusion criteria:** healthy children who had completed a study of 3-dose primary PCV7 vaccination, with a final blood sample for serology obtained at 7–8 months of age, informed consent from parents<br>**Exclusion criteria:** none stated. | **A:** 2, 4, 6 +b18<br>**B:** 2, 4, 6 +b15<br>**Additional information:**<br>All received DTaP-IPV combined with Hib and offered routine MMR at 12 months.<br>**A and B:** primary PCV doses either 2, 4, 6 or 3, 5, 7. Booster doses of PCV given at the same time but separately from Hib. | **N=** 167<br>**Mean age at randomization** based **on** time beyond birthday **(SD):** 6.3 (0.3)<br>**Mean age at vaccination (SD):**<br>Primary: NR<br>Booster:18.3(0.3)<br>**Gender (M/F):**<br>98/69 (59% M) | **N=** 168<br>**Median age at randomization based on time beyond birthday (SD):** 3.3 (0.3)<br>**Mean age at vaccination (SD):**<br>Primary: NR<br>Booster**:** 15.3 (0.3)<br>**Gender (M/F):**<br>100/68 (59.5% M) | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Chile1**[31, 68-70] | | | | | | | | | | |
| **Location**: Chile<br>**Recruitment dates:** June 20 to August 4, 1989<br>**Hib vaccine:**<br>PRP-T, brand name not stated, Pasteur Mérieux<br>**Pertussis vaccine:**<br>wP, brand name not stated, Pasteur Mérieux<br>**Funding:**<br>Ministry of Health of Chile, Servicio de Salud, Area Norte, Pasteur Merieux | **Inclusion criteria:** children 6 to 12 weeks old, informed consent from parents or guardians.<br>**Exclusion criteria:** serious congenital defect or chronic illness, >38°C, history of neurologic disorders, need for daily medication, receipt of a dose of any vaccine within 2 weeks of visit | **A:** 2, 4, 6<br>(DTwP combined)<br>**B:** 2, 4, 6<br>(DTwP separate)<br>**C:** No doses<br>**Additional information:** | **N=** 94<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>1st dose**:** 2.1 (0.1)<br>2nd dose: NR<br>3rd dose: NR<br>**Gender (M/F):** 45/49 (48%M) | **N=** 93<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>1st dose**:** 2.1 (0.1)<br>2nd dose: NR<br>3rd dose: NR<br>**Gender (M/F):** 47/46 (51% M) | **N=** 93<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>no Hib<br>**Gender based on N=91 (M/F):** 46/45 (51% M) | | | ✓ | | ✓ |
| **Chile2**[32, 70] | | | | | | | | | | |
| **Location**: Chile<br>**Recruitment dates:** NR<br>**Hib vaccine:**<br>PRP-T, brand name not stated, Pasteur Mérieux<br>**Pertussis vaccine:**<br>wP, brand name not stated, Connaught Laboratories<br>**Funding:**<br>Ministry of Health of Chile, Servicio de Salud, Area Norte, Pasteur Merieux | **Inclusion criteria:** infants 2 months of age were recruited during their routine well baby visit to the community health center, using eligibility criteria and informed consent procedures described previously (not clear where)<br>**Exclusion criteria:** none stated | **A:** 2,4,6<br>(DTwP, combined)<br>**B:** 2,4,6<br>(DTwP, separate)<br>**C:** No doses<br>**Additional information:** | **N=** 94<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 92<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 91<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** no Hib<br>**Gender (M/F):** NR | | | ✓ | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Chile3**[33, 70-72] | | | | | | | | | | |
| **Location**: Chile<br>**Recruitment dates:**<br>November 1, 1992 to October 31, 1993<br>**Hib vaccine:**<br>PRP-T, Act-HIB, Pasteur Mérieux<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date, brand name not stated, Pasteur Mérieux<br>**Funding:**<br>Ministerio de Salud, Chile; NIAID, Pasteur Mérieux (vaccines) | **Inclusion criteria:** not explicitly stated<br>**Exclusion criteria:** not explicitly stated | **A:** 2, 4, 6<br>**B:** No doses<br>**Additional information:**<br>OPV given to children in both groups at 2, 4, 6.<br>**A:** DTP combined with Hib vaccine | **N=**38829<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR. | **N=**37704<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** no Hib<br>**Gender (M/F):** NR. | | ✓ | ✓ | | | |
| **Chile4**[34, 73] | | | | | | | | | | |
| **Location**: Chile<br>**Recruitment dates:**<br>October to December, 1995<br>**Hib vaccine:**<br>PRP-T, ActHib, Pasteur Mérieux Connaught<br>PRP-HbOC, HibTiter, Wyeth-Lederle<br>**Pertussis vaccine:**<br>**Funding:**<br>Children's Vaccine Initiative (WHO, Geneva, Switzerland), National Institute of Allergy and Infectious Disease | **Inclusion criteria:** healthy infants born at full term with a birth weight of 2500 g or more, written, informed consent from parent or guardian<br>**Exclusion criteria:** contraindication to receiving DTP vaccine, major chronic or congenital diseases, or known immunological disorders | **A:** 2, 4, 6<br>(PRP-T)<br>**C:** 4, 6<br>(PRP-T)<br>**B:** 2, 4, 6<br>(PRP-HbOC)<br>**D:** 4, 6<br>(PRP-HbOC)<br>**Additional information:**<br>PRP given to all at 12 months of age (results after PRP not eligible for this review. Fractional dose groups also not eligible | **N=** 78<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR<br>**Schedule D:**<br>**N=** 78<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 79<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR<br>.<br>. | **N=** 78<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Chile5**[35] | | | | | | | | | | |
| **Location**: Chile<br>**Recruitment dates:** December 20, 1995 to April 2, 1996<br>**Hib vaccine:**<br>PRP-T, ActHIB, Pasteur Mérieux Connaught<br>**Pertussis vaccine:**<br>aP (2 component), brand name not stated, Pasteur Mérieux Connaught<br>**Funding:**<br>Pasteur Mérieux Connaught | **Inclusion criteria:** healthy 2 month-old infants (±4 weeks) planning to receive primary care at the selected health centers for the complete study period, informed consent from parents or guardian<br>**Exclusion criteria:** known or suspected disease; previous vaccination against diphtheria, tetanus, pertussis, Hib or polio; <37 weeks of gestation; birth weight <2500g; known contraindication to receiving DTP, PRP-T or IPV vaccines | **A:** 3, 5, 7 +b12<br>**B:** 3, 5, 7 +b12<br>**C:** 3, 5, 7 +b12<br>**D:** 2, 4, 6 +b12 (separate)<br>**E:** 2, 4, 6 +b12 (combined)<br>**Additional information:**<br>All children received MMR and DTaP combined with Hib vaccine at 12 months.<br>**A, B, C, D, E**: received DTaP at 2, 4, 6<br>**B, C, D, E:** received eIPV at 2, 4, 6 (B separate, others combined with DTaP), OPV at 7, 13<br>**A:** OPV at 2, 4, 6, 13 | **N=**NR(710 total in study)*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR.<br>**Schedule D:**<br>**N=**NR(710 total in study)*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR. | **N=**NR(710 total in study)*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR.<br>**Schedule D:**<br>**N=**NR(710 total in study)*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR. | **N=**NR(710 total in study)*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR. | | | ✓ | | ✓ |
| **China1**[36, 74, 75] | | | | | | | | | | |
| **Location**: China<br>**Recruitment dates:** NR<br>**Hib vaccine:**<br>PRP-T, Pentacel, Sanofi Pasteur<br>**Pertussis vaccine:**<br>aP (2 component) in combined schedules) Pentaxim, Sanofi Pasteur<br>aP (1 component) in separate schedule, brand name not stated, Wuhan Institute of Biological Products<br>**Funding:**<br>Sanofi Pasteur | **Inclusion criteria:** children who had completed the primary vaccination study and had informed consent from parents or legal representatives<br>**Exclusion criteria:** participation in another clinical trial in the 4 weeks preceding the trial inclusion, immunodeficiency, immunosuppressive therapy, hypersensitivity to vaccine components, chronic illness; receipt of blood products | **A:** 3, 4, 5 +b18-20 (combined)<br>**B:** 3, 4, 5 +b18-20 (separate)<br>**C:** 2, 3, 4 +b18-20 (combined)<br>**Additional information:**<br>**A and C:** DTaP-IPV combined with Hib<br>**B:** DTaP, Hib, IPV separately 3, 4, 5, 18-20 | **N=** 264<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall gender based on N=792 (M/F):** 393-444/348-399 (49.6–56% M). | **N=** 264<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall gender based on N=792 (M/F):** 393-444/348-399 (49.6–56% M). | **N=** 264<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall gender based on N=792 (M/F):** 393-444/348-399 (49.6–56% M). | | | ✓ | | ✓ |

| Study details | Participant characteristics | Schedule A / schedule B / schedule C | Schedule A population characteristics | Schedule B population characteristics | Schedule C population characteristics | Outcomes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Invasive Hib (any entity) | Pneumonia | Death | Carriage | Immuno-logical |
| **China2[37, 76]** | | | | | | | | | | |
| **Location**: China<br>**Recruitment dates:**<br>Study period: March 24 to November 19, 2010<br>**Hib vaccine:**<br>PRP-T, Infanrix-Hib or Infanrix-IPV+Hib, GlaxoSmithKline<br>**Pertussis vaccine:**<br>aP (3 component), Infanrix-Hib or Infanrix-IPV+Hib, GlaxoSmithKline<br>**Funding:**<br>GlaxoSmithKline | **Inclusion criteria:** healthy infants 60-90 days old, born after a gestation period of 36 to 42 weeks, written informed consent from the parents<br>**Exclusion criteria:** previous or intercurrent diphtheria, tetanus, pertussis, poliomyelitis and/or Hib disease or vaccination, current febrile illness or axillary temperature > 37.0°C or other moderate to severe illness within 24 hours of study vaccine administration | **A:** 3, 4, 5<br>(DTaP-IPV combined)<br>**B:** 2, 3, 4<br>(DTaP-IPV combined)<br>**C:** 2, 3, 4<br>(DTaP combined, IPV separate)<br>**Additional information:** | **N=** 324<br>**Mean age at randomization (SD):** NR<br>**Mean age vaccination (SD):** 3.3 (0.3)<br>**Gender (M/F):**<br>147/177 (45.4% M). | **N=** 330<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** 2.3 (0.3)<br>**Gender (M/F):**<br>155/175 (47% M). | **N=** 330<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** 2.3 (0.3)<br>**Gender (M/F):**<br>141/189 (43% M). | | | ✓ | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Europe**[38, 77-82] | | | | | | | | | | |
| **Location**: Austria, Germany, Greece<br>**Recruitment dates:** August 2007 to October 2008<br>**Hib vaccine:**<br>Booster: PRP-T, Infanrix-hexa; GlaxoSmithKline<br>**Pertussis vaccine:**<br>aP (3 component), Infanrix-hexa, GlaxoSmithKline<br>**Funding:**<br>GlaxoSmithKline | **Inclusion criteria:** healthy children between 12 and 23 months, documented evidence of 3-dose primary vaccination with DTaP, hepatitis B, IPV and Hib vaccines completed at least 180 days previously<br>**Exclusion criteria:** immunosuppression, previous receipt of any meningococcal vaccine or booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis or Hib, a past history of disease due to meningococcus, or receipt of blood products | **A:** 3p‡ +b13<br>**B:** 3p‡ +b12<br>**C:** 3p‡ +b12 (MenACWY-TT, separate at 12)<br>**D:** 3p‡<br>**Additional information:**<br>**A:** MenACWY-TT at 12 months. DTaP combined with Hib at 13 months<br>**B:** MenACWY-TT at 13 months. DTaP combined with Hib at 12 months<br>**C:** MenACWY-TT, separate at 12 months, DTaP combined with Hib at 12 months<br>**D:** MenC conjugate at 12 months | **N=** 220<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Booster dose: 15(3.3)<br>**Gender (M/F):**<br>114/106 (51.8% M)<br>**Schedule D:**<br>**N=** 127<br>**Median age at randomization:** NR<br>**Mean age at vaccination (SD):**<br>Booster dose: 14.6(3.0)<br>**Gender (M/F):** 66/61 (52% M) | **N=** 224<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Booster dose: 14.9(3.17)<br>**Gender (M/F):**<br>105/119 (46.9% M) | **N=** 224<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Booster dose: 14.6(3.01)<br>**Gender (M/F):**<br>Based on N=222: 113/109 (50.9% M) | | | ✓ | | ✓ |
| **France**[39, 83] | | | | | | | | | | |
| **Location**: France<br>**Recruitment dates:** 1995 to 1996<br>**Hib vaccine:**<br>PRP-T, Hexavac, Aventis Pasteur<br>**Pertussis vaccine:**<br>aP (2 component), Hexavac, Aventis Pasteur.<br>**Funding:**<br>Not stated, likely Aventis Pasteur | **Inclusion criteria:** healthy Infants already enrolled in the trial initiated for the investigational vaccine and who had received primary immunization under schedules 2, 4, 6 and 2, 3, 4 in the study<br>**Exclusion criteria:** none stated | **A:** 2, 4, 6 + b15-17<br>**B:** 2, 3, 4 + b15-17<br>**Additional information:**<br>DTaP-HepB-IPV combined with Hib at each dose | **N=** 258<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 258<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Gambia1**[40, 84-86] | | | | | | | | | | |
| **Location**: The Gambia<br>**Recruitment dates:** January 1 to December 31, 1985<br>**Hib vaccine:**<br>PRP-OMP, PedvaxHib, Merck Sharp & Dohme<br>**Pertussis vaccine:**<br>Not given as part of trial. Not stated if wP or aP, assume wP given trial date. No brand name or manufacturer stated<br>**Funding:**<br>Merck Sharp & Dohme | **Inclusion criteria:** children living in the area of the health center, informed consent from mothers<br>**Exclusion criteria:** none stated | **A:** 2, 4<br>**B:** 1, 3<br>**C:** No doses<br>**Additional information:**<br>Other routine EPI vaccinations received but not as part of study.BCG and oral polio vaccines at 1 month of age and DTP and oral polio vaccines at 2, 3, and 4 months. Assume DTP given separately from Hib<br>**C:** No control vaccine | **N=** 95<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 99<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 90<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** no Hib<br>**Gender (M/F):** NR | | | | | ✓ |
| **Gambia2** [41] | | | | | | | | | | |
| **Location**: The Gambia<br>**Recruitment dates:** 1990<br>**Hib vaccine:**<br>PRP-T, ActHib, Pasteur Mérieux<br>**Pertussis vaccine:**<br>Not given as part of trial. Not stated if wP or aP, assume wP given trial date. No brand name or manufacturer stated<br>**Funding:**<br>Pasteur Mérieux | **Inclusion criteria:** Not stated<br>**Exclusion criteria:** none stated | **A:** 2, 4<br>**B:** 1, 3<br>**C:** No doses<br>**Additional information:**<br>All children had EPI routine vaccination (not specified). Assume DTP separate from Hib | **N=** 43<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 45<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 40<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** no Hib<br>**Gender (M/F):** NR | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Gambia3**[42, 87] | | | | | | | | | | |
| **Location**: The Gambia<br>**Recruitment dates:**<br>**Hib vaccine:**<br>PRP-HbOC, brand name not stated, Lederle Praxis<br>**Pertussis vaccine:**<br>Not given as part of trial. Not stated if wP or aP, assume wP given trial date. No brand name or manufacturer stated<br>**Funding:**<br>Vaccine by Lederle Praxis, National Institute of Allergy and Infectious Diseases, National Institutes of Health | **Inclusion criteria:** infants younger than 7 weeks old<br>**Exclusion criteria:** age more than 12 weeks, acute febrile illness; under nutrition, severe chronic illness, known maternal HIV infection | **A:** 2, 3, 4<br>**B:** No doses<br>(PCV5 at 2, 3, 4)<br>**C:** No doses<br>(PCV5 at 2, 4)<br>**Additional information:**<br>All children received BCG when first seen, DTP (separate from Hib) at 2, 3, 4 months, OPV when first seen, and 2, 3, 4 months, HepB when first seen and 2, 4 months; and measles and yellow fever at 9 months. | **N=** 29<br>**Overall mean age recruitment:** approx. 2<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 30<br>**Overall mean age recruitment:** approx. 2<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 30<br>**Overall mean age recruitment:** approx. 2<br>**Mean age at vaccination (SD):** no Hib<br>**Gender (M/F):** NR | | | ✓ | | ✓ |
| **Gambia4**[43, 88-97] | | | | | | | | | | |
| **Location**: The Gambia<br>**Recruitment dates:** March 1993 to October 1995<br>**Hib vaccine:**<br>PRP-T, ActHIB, Pasteur Mérieux<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date. No brand name stated, Pasteur Mérieux<br>**Funding:**<br>United States Agency for International Development, WHO, UNICEF, Children's Vaccine Initiative, United Nations Development Programme, US National Institute for Allergy and Infectious Diseases. Vaccines from Pasteur | **Inclusion criteria:** healthy infants presenting at health centers for routine vaccination, informed consent from parents<br>**Exclusion criteria:** previous receipt of DTP from another health centre | **A:** 2, 3, 4<br>**B:** No doses<br>**Additional information:**<br>Routine vaccinations: BCG at birth or soon after, DTP combined with Hib at 2, 3, 4 months, OPV at birth or soon after, and 2, 3, 4, and 9 months, Hep B at birth or soon after, 2, 4, and measles and yellow fever at 9 months.<br>**B:** DTP combined with dextrose Placebo | **N=** 21490<br>**Mean age at randomization:** NR<br>**Median age at vaccination (IQR range):**<br>1st dose:<br>2.6(2.2-3.1)<br>2nd dose:<br>4.1(3.5-5.03)<br>3rd dose:<br>5.6 (4.8-6.9)<br>**Gender (M/F):** NR | **N=** 21358<br>**Mean age at randomization:** NR<br>**Median age at vaccination (IQR range):** no Hib<br>**Gender (M/F):** NR | | ✓ | ✓† | ✓ | ✓ | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Guatemala**[44] | | | | | | | | | | |
| **Location**: Guatemala<br>**Recruitment dates:** March 1998 to August 1999<br>**Hib vaccine:**<br>PRP-T, Hiberix, GlaxoSmithKline<br>**Pertussis vaccine:**<br>wP (combined schedule), Tritanrix, GlaxoSmithKline<br>wP (separate schedule), Brand name and manufacturer not clearly stated<br>**Funding:**<br>GlaxoSmithKline | **Inclusion criteria:** healthy infants ≥6 weeks of age<br>**Exclusion criteria:** known allergic reaction to any of the vaccine components, immunodeficiency, major congenital defects, serious illness, seizure disorders, history of blood product transfusions, or previous immunizations (except oral polio or Bacillus Calmette-Guerin vaccine) | **A:** 2, 4, 6<br>**B:** 7, 9 (+b12)<br>**Additional information:**<br>All children had OPV at 2, 4, 6 and MMR at 9-12.<br>**A:** Hib combined with DTwP and HepB<br>**B:** DTwP at 2, 4, 6months. HepB given separately from Hib at 7, 9 months. Also received Hib and HepB vaccines at 12 months but no data provided after 12 month dose | **N=**325[§]<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** 238/176 (57.5% M) | **N=**106[§]<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** 56/50 (53% M) | | | | | | ✓ |
| **Indonesia1**[45] | | | | | | | | | | |
| **Location**: Indonesia<br>**Recruitment dates:** January 1995 to November 1996.<br>**Hib vaccine:**<br>PRP-T, DTaP-PRP-T, Swiss Serum and Vaccine Institute<br>**Pertussis vaccine:**<br>aP (2 component), brand name not stated, Swiss Serum and Vaccine Institute<br>wP, brand name not stated, Swiss Serum and Vaccine Institute<br>**Funding:**<br>Not reported | **Inclusion criteria:** healthy infants, written informed consent from parents, with: weight >4 kg, temperature <37.58C<br>**Exclusion criteria:** history of prior immunization with a DTP or Hib vaccine, history of neurological or developmental disorders, history of a significant systemic illness, prior treatment with immunosuppressant drugs, blood products or investigational drugs, immunodeficiency in either the infant or mother, history of allergies and a normal physical examination at the time of immunization | **A:** 2, 4, 6 +b15-18<br>(DTaP combined)<br>**B:** 2, 4, 6 +b15-18<br>(DtwP combined)<br>**C:** 15-18m<br>(DTaP combined)<br>**Additional information:**<br>**A:** DTaP combined at 2, 4, 6, 15-18<br>**B:** DTwP combined at 2, 4, 6; DTaP or DTwP combined with Hib at 15-18m.<br>**C:**DTaP alone at 2, 4, 6. DTaP combined with Hib at 15-18 | **N=** 357*<br>**Mean age at randomization (SD):** NR<br>**Overall mean age at vaccination (SD):**[¶]<br>1st dose: 3.3<br>2nd dose: 4.9<br>3rd dose: 6.7<br>**Gender (M/F):** NR | **N=** 360*<br>**Median age at randomization (SD):** NR<br>**Overall mean age at vaccination (SD):**[¶]<br>1st dose: 3.3<br>2nd dose: 4.9<br>3rd dose: 6.7<br>**Gender (M/F):** NR | **N=** 172*<br>**Median age at randomization (SD):** NR<br>**Overall mean age at vaccination (SD):**[¶]<br>1st dose: 3.3<br>2nd dose: 4.9<br>3rd dose: 6.7<br>**Gender (M/F):** NR | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Indonesia2**[46, 98] | | | | | | | | | | |
| **Location**: Indonesia<br>**Recruitment dates:** 1998 to 2002<br>**Hib vaccine:**<br>PRP-T, brand name not reported, Aventis Pasteur<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date, brand name not reported, Aventis Pasteur<br>**Funding:**<br>Funded in part by Aventis Pasteur | **Inclusion criteria:** not explicitly described: children <2 yrs living in hamlets in proximity to study area with health status not mentioned, who had not already received three doses of DPT<br>**Exclusion criteria:** previous immunization with 3 doses of DTP | **A:** 1.5, 2.5, 3.5<br>**B:** No doses<br>**Additional information:**<br>**A:** DTP and PRP-T combined at 1.5, 2.5, 3.5<br>**B:** DTP at 1.5, 2.5, 3.5 | **N=** 28147*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (range):**<br>1st: 2.6<br>2nd: 3.5<br>3rd: 4.7<br>**Gender (M/F):** 14576/13571 (52% M) | **N=** 26926*<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**no Hib<br>**Gender (M/F):**<br>14025/12901 (52% M) | | ✓ | ✓ | ✓[f3] | | ✓ |
| **Lithuania[47]** | | | | | | | | | | |
| **Location**: Lithuania<br>**Recruitment dates:** Study started in March 4, 1994 and completed in July8, 1997.<br>**Hib vaccine:**<br>PRP-T, Hiberix, GlaxoSmithKline<br>PRP-T, ActHIB, Aventis Pasteur<br>PRP-OMP, PedvaxHIB, Merck Sharp & Dohme<br>PRP-HbOC, HibTITER, Wyeth-Lederle<br>**Pertussis vaccine:**<br>aP (3 component)Pediarix, GlaxoSmithKline.<br>**Funding:**<br>GlaxoSmithKline | **Inclusion Criteria:** 12-16 weeks of age, free of obvious health problems, written informed consent<br>**Exclusion Criteria:** Allergic disease, previous diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and/or *H. influenzae* type b vaccination or disease, acute febrile illness, major congenital defects or serious chronic illness, progressive neurological disease, any immunosuppressive condition or therapy, administration of any other experimental drug, immunoglobulin therapy, adverse events after previous DTP vaccination | **A:** 3, 4.5, 6<br>(PRP-T, Hiberix or ActHIB)<br>**B:** 3, 4.5, 6<br>(PRP-HbOC)<br>**C:** 3, 6<br>(PRP-OMP)<br>**Additional information:**<br>**A:** DTaP-HepB-IPV at same time as Hib in separate injection | **N=** 329<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 110<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 110<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Mali**[48, 99, 100] | | | | | | | | | | |
| **Location**: Mali<br>**Recruitment dates:** May to June 2006 and July to August 2006 extended follow up: November/December 2007 to January 2008<br>**Hib vaccine:**<br>PRP-T, Hiberix, GlaxoSmithKline<br>**Pertussis vaccine:**<br>Not part of trial<br>**Funding:**<br>National Institute of Allergy and Infectious Diseases, National Institutes of Health | **Inclusion criteria:** healthy children 2-3 years old living in the study area, available for the initial duration of the trial, normal screening labs and physical examination<br>**Exclusion criteria:** participation in another drug trial, history of severe allergic reaction or asthma, known immunodeficiency, recent use of immunosuppressive drugs, recent receipt of a licensed vaccine or blood transfusion, history of splenectomy, bleeding disorder, any other clinically significant disease or condition which might confound the interpretation of study results | **A:** 24-36, 25-37<br>**B:** No doses<br>**Additional information:**<br>**B:** AMA1-C1 Malaria vaccine. | **N=** 120<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):**<br>63/57(52.7% M) | **N=** 120<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR **Gender (M/F):**<br>68/52 (56.7% M) | | | | ✓ | | |
| **Netherlands**[49] | | | | | | | | | | |
| **Location**: The Netherlands<br>**Recruitment dates:**<br>March 1993 to September 2, 1994<br>**Hib vaccine:**<br>PRP-T, brand name not stated, Pasteur Mérieux<br>**Pertussis vaccine:**<br>wP, brand name not stated, Pasteur Mérieux<br>**Funding:**<br>Chief Inspectorate of Health Care, Netherlands | **Inclusion criteria:** children born in February and March 1993, living in the Rotterdam cluster or in Apeldoom, written informed consent by the parents<br>**Exclusion criteria:** None stated | **A:** 3, 4, 5 +b11<br>(DTwP-IPV combined)<br>**B:** 3, 4, 5 +b11<br>(DTwP-IPV separate)<br>**C:** 6, 7+b13<br>**Additional information:**<br>All children had MMR at 14 months.**A:** DTwP-IPV at 3, 4, 5, 11 in a combined injection.<br>**B, C:** DTwP-IPV at 3, 4, 5, 11 as a separate injection. | **N=**180<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):**<br>94/86 (52% M) | **N=**181<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):**<br>102/79 (56% M) | **N=**182<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):**<br>104/78 (57% M) | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Niger1**[50] | | | | | | | | | | |
| **Location**: Niger<br>**Recruitment dates:** January to November 1995<br>**Hib vaccine:**<br>PRP-T, brand name not stated, Pasteur Mérieux<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date. Brand name not stated, Pasteur Mérieux<br>**Funding:**<br>Supported by the French Ministry of Cooperation and the WHO Global Program on Vaccines | **Inclusion criteria: c**hildren between the ages of four and twelve weeks, informed consent from the parents<br>**Exclusion criteria:** none stated | **A:** 1.5, 2.5, 3.5<br>**B:** 2.5, 3.5<br>**C:** No doses<br>**Additional information:**<br>All children had BCG and OPV at birth, DTP (combined with Hib when Hib given) and OPV at 1.5, 2.5, 3.5; measles and yellow fever at 9 months.<br>**C:** Men A/C polysaccharide vaccine at 1.5, 3.5 months | **N=** 59<br>**Mean age at randomization:** NR<br>**Overall mean age at vaccination (range):**<br>1st visit:1.9(0.9-2.8)<br>2nd visit:3.0(2.1-5.1)<br>3rd visit: 4.2(3.0-6.8)<br>**Overall gender (M/F):** 93/87 (52% M). | **N=** 62<br>**Mean age at randomization:** NR<br>**Overall mean age at vaccination (range):**<br>11st visit:1.9(0.9-2.8)<br>2nd visit:3.0(2.1-5.1)<br>3rd visit: 4.2(3.0-6.8)<br>**Overall gender (M/F):** 93/87 (52% M). | **N=** 59<br>**Mean age at randomization:** NR<br>**Overall mean age at vaccination (range):**<br>No Hib<br>**Overall gender (M/F):** 93/87 (52% M). | | | | | ✓ |
| **Niger2**[51] | | | | | | | | | | |
| **Location**: Niger<br>**Recruitment dates:** January 1996 to March 1997.<br>**Hib vaccine:**<br>PRP-T, Act-HIB, Pasteur Mérieux Connaught<br>**Pertussis vaccine:**<br>Not stated if wP or aP. No brand names or manufacturers given.<br>**Funding:**<br>French Ministry of Cooperation and the WHO Global Program on Vaccines | **Inclusion criteria:** healthy children between five and nine weeks of age<br>**Exclusion criteria:** none stated | **A:** 1.5, 2.5, 3.5<br>**B:** No doses<br>**Additional information:**<br>All children had: BCG and OPV at birth, DTP+OPV at 1.5, 2.5, 3.5; measles and yellow fever at 9.<br>**B.** four groups were combined for group B. These groups received combinations of placebo and meningococcal vaccines | **N=** 37<br>**Overall mean age at randomization (SD):**<br>1.5 (0.19)<br>**Overall, mean age at vaccination (SD):**<br>1st dose: 1.59 (0.2)<br>2nd dose: NR<br>3rd dose: NR<br>**Overall gender based on N=180 enrolled children at inclusion (M/F):** 89/91 (49.4% M) | **N=** 143<br>**Overall mean age at randomization (SD):**<br>1.5 (0.19)<br>**Overall, mean age at vaccination (SD):**<br>no Hib<br>**Overall gender based on N=180 enrolled children at inclusion (M/F):** 89/91 (49.4% M) | | | ✓ | | |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Spain**[52, 101-105] | | | | | | | | | | |
| **Location:** Spain<br>**Recruitment dates:** 2004<br>**Hib vaccine:**<br>PRP-MenC-T (booster), Mentorix, GSK Biologicals<br>**Pertussis vaccine:**<br>None given at booster. Not stated which aP vaccine given in primary series<br>**Funding:**<br>GlaxoSmithKline | **Inclusion criteria:** healthy 13 to 14 month-old toddlers who had been routinely primed (at 2, 4, 6m) with Hib-TT and MenCCRM197 conjugate vaccines<br>**Exclusion criteria:** use of any investigational or non-registered product within 30 days preceding the study vaccine, previous vaccination against or history of: H. influenzae type b, meningococcal C disease, measles, mumps or rubella. Any immunodeficient condition, history of any neurologic disorders or seizures; history of allergic disease | **A:** 2, 4, 6 +b13-14<br>(MMR at booster)<br>**B:** 2, 4, 6 +b13-14<br>(no MMR at booster)<br>**C:** 2, 4, 6<br>(MMR 13-14)<br>**Additional information:**<br>All children had been primed with DTaP-Hib +MenC-CRM197 at 2, 4, 6 | **N=** 102<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Booster: 13.4 (0.5)<br>Primary: NR<br>**Gender (M/F):** 61/41 (60% M) | **N=** 104<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>Booster: 13.4 (0.5)<br>Primary: NR<br>**Gender (M/F):** 55/49 (53% M) | **N=** 91<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):**<br>No booster<br>Primary: NR<br>**Gender (M/F):** 49/42 (54% M) | | | ✓ | | ✓ |
| **Sweden**[53, 106] | | | | | | | | | | |
| **Location**: Sweden<br>**Recruitment dates:** November 19, 1994 to April, 1995<br>**Hib vaccine:**<br>PRP-T, ActHIB, Pasteur Mérieux Connaught<br>**Pertussis vaccine:**<br>aP (2 component), brand name not stated, Pasteur Mérieux Connaught<br>**Funding:**<br>Pasteur Mérieux Connaught, Göteborg Medical Society, the Medical Faculty of Göteborg University; the County Hospital of Norra Älvsborg | **Inclusion criteria:** healthy term infants, with a birth weight of at least 2500 g, who were recruited with written informed consent of parents at the age of 2m +/- 2 weeks at routine visits to Child Health Centers (CHC)<br>**Exclusion criteria:** none stated. | **A:** 2, 4, 6 +b13<br>**B:** 3, 5 +b12<br>**Additional information:** Both groups received DTaP-IPV in combination with Act-HIB in one injection. | **N=**118<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR but 98.8% of doses given within range stipulated in protocol<br>**Gender (M/F):** NR | **N=**118<br>**Median age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR but 98.8% of doses given within range stipulated in protocol<br>**Gender (M/F):** NR | | | | ✓ | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **Thailand**[54] | | | | | | | | | | |
| **Location**: Thailand<br>**Recruitment dates:** February 1994 to December 1995<br>**Hib vaccine:**<br>PRP-T (as DTP-Hib), Swiss Serum and Vaccine Institute<br>PRP-OMP, PedvaxHIB, Merck Sharp & Dohme<br>**Pertussis vaccine:**<br>Not stated if wP or aP. Swiss Serum and Vaccine Institute Group A: Brand name not stated, Group B: Berna<br>**Funding:**<br>Swiss Serum and Vaccine Institute, Berne, Switzerland | **Inclusion criteria:** healthy 2-month-old infants (1.4-2.9 months of age) with no prior history of immunization against diphtheria, tetanus, pertussis or Hib<br>**Exclusion criteria:** acute febrile illness, neurological or developmental disorder, allergies, treatment with immunosuppressive drugs, immunodeficiency syndrome, significant systemic illness, immunoglobulin therapy, plasma or whole blood transfusion since birth and participation in another clinical trial | **A:** 2, 4, 6 (PRP-T)<br>**B:** 2, 4 (PRP-OMP)<br>**Additional information:**<br>**A:** DTP combined with Hib at 2, 4, 6<br>**B:** DTP separately at 2, 4, 6 | **N=** 140<br>**Mean age at randomization:** NR.<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | **N=** 66<br>**Median age at randomization:** NR<br>**Mean age at vaccination (SD):** NR<br>**Gender (M/F):** NR | | | | | | ✓ |
| **Turkey**[26] | | | | | | | | | | |
| **Location**: Turkey<br>**Recruitment dates:** October 1994 to March 1995<br>**Hib vaccine:**<br>PRP-T, Act-HIB, Pasteur Mérieux Connaught.<br>**Pertussis vaccine:**<br>aP, brand name not stated, Pasteur Mérieux, Connaught<br>**Funding:**<br>Pasteur Mérieux Connaught | **Inclusion criteria:** healthy infants, Belgian, aged 2 months with informed written consent was obtained from the parents or legal guardian of each child<br>**Exclusion criteria:** none reported | **A:** 3, 4, 5 +b12-14 (DTaP combined)<br>**B:** 3, 4, 5 +b12-14 (DTaP separate)<br>**C:** 2, 4, 6 (DTaP separate)<br>**Additional information:**<br>**A:** DTaP at 3, 4, 5, 12-14,combined<br>**B:** DTaP at 3, 4, 5, 12-14, separate syringe.<br>**C:** DTaP at 2, 4, 6 in a separate syringe. | **N=** 74*<br>**Mean age at randomization:** 2 (0.5)<br>**Mean age at vaccination (SD):**<br>1st dose: 3.0 (0.2)<br>2nd dose: 4.1 (0.3)<br>3rd dose: 5.1 (0.3)<br>Booster: 13.4 (1.1)<br>**Gender (M/F):**<br>50/34 (60% M) | **N=** 78*<br>**Median age at randomization:** 2 (0.5)<br>**Mean age at vaccination (SD):**<br>1st dose: 3.0 (0.1)<br>2nd dose: 4.0 (0.2)<br>3rd dose: 5.1 (0.4)<br>Booster: 13.5 (1.1)<br>**Gender (M/F):**<br>41/42 (49% M) | **N=** 81*<br>**Median age at randomization:** 2 (0.5)<br>**Mean age at vaccination (SD):**<br>1st dose: 2.1 (0.2)<br>2nd dose: 4.0 (0.3)<br>3rd dose: 5.9 (0.3)<br>No booster<br>**Gender (M/F):**<br>51/32 (61% M) | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **USA1**[55, 107-114] | | | | | | | | | | |
| **Location**: USA<br>**Recruitment dates:** July 1, 1988 to August 2, 1990.<br>**Hib vaccine:**<br>PRP-OMP, PedvaxHIB Merck Sharp & Dohme<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date. No brand names or manufacturers given<br>**Funding:**<br>Merck Sharp & Dohme | **Inclusion criteria:** Navajo or Hopi infants living on the Navajo Indian Reservation with informed consent from parents or guardians<br>**Exclusion criteria:** known or suspected immunodeficiency disease, history of vaccination with any other H. influenzae vaccine, or history of contraindicating routine immunization with DPT vaccine or the oral polio vaccine | **A:** 1.5-3, 2.5-5<br>**B:** No doses<br>**Additional information:**<br>All children given DTP and OPV at same time but separately from Hib or placebo<br>Children were given PRP-D vaccine at 18m, or PR-D or PRP-HbOC at 15m (children not followed up beyond a booster dose)<br>**B:** Placebo | **N=** 2588<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (range):**<br>1st dose: 1.82 (1.17-3.5)<br>2nd dose: NR<br>**Gender (M/F):** 1305/1283 (50.4% M) | **N=** 2602<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (range):**<br>no Hib<br>**Gender (M/F):** 1320/1282 (49.3% M) | | ✓ | | ✓ | | ✓ |
| **USA2**[56, 115-119] | | | | | | | | | | |
| **Location**: USA<br>**Recruitment dates:**<br>7 centers from February, 1988 to June, 1990 and expanded to 16 centers in September, 1988<br>**Hib vaccine:**<br>PRP-HbOC, HibTITER, Praxis Biologics<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date. No brand names or manufacturers given<br>**Funding:**<br>Vaccine and grant from Praxis Biologics | **Inclusion criteria:** Children 6 weeks to 1 year of age at Kaiser Permanente Medical Care Program, at least one well-care visit at a medical center. informed consent from parents or legal guardians<br>**Exclusion criteria:** known immunodeficiency | **A:** 2, 4, 6<br>**B:** No doses<br>**Additional information:**<br>**A, B:** DTP and OPV usually given at 2, 4, 6 (assume DTP given separately from Hib) | **N=** 30400*<br>**Mean age at randomization (SD):** NR<br>**Overall mean age at vaccination range:**<br>Not well reported. 83.7% of 3rd doses given by 8 m of age.<br>**Gender (M/F):** NR | **N=** 30680*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (range):**<br>No Hib.<br>**Gender (M/F):** NR | | ✓ | Other outcomes reported but not eligible (non-randomized comparisons) | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **USA3**[57, 120, 121] | | | | | | | | | | |
| **Location**: USA<br>**Recruitment dates:** August 28, 1989 to October 12, 1990<br>**Hib vaccine:**<br>PRP-T, Act-Hib, Pasteur Mérieux<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date, half received Connaught, and half the Lederle vaccines (brand names not stated)<br>**Funding:**<br>Institute Pasteur Mérieux | **Inclusion criteria:** Children between 6 and 15 weeks of age Kaiser Permanente Health Plan outpatient clinics. Parental written consent. Enrollment deferred for children with acute febrile illnesses<br>**Exclusion criteria:** progressive neurologic disease, unexplained seizures, altered immune function, receipt of blood products within 2 months of enrollment; exposure to hepatitis B; anticipated medical care at non-study clinics | **A:** 2, 4, 6<br>**B:** No doses<br>**Additional information:**<br>**All:** OPV at 2, 4, 15-18 (optional at 6 months) DTP at 2, 4, 6, separately.<br>**B:** Hep B at 2, 4, 6 | **N=** 5208<br>**Overall mean age at randomization (SD):**<br>2.2(0.5)<br>**Mean age at vaccination:**<br>1st dose: 2.2<br>2nd dose: 4.6<br>3rd dose: 6.9<br>**Overall gender (M/F):** 2697/2507 (52% M) | **N=** 5109<br>**Overall mean age at randomization (SD):**<br>2.2(0.5)<br>**Mean age vaccination:**<br>no Hib<br>**Overall gender (M/F):** 2697/2507 (52% M) | | ✓ | | ✓ | | ✓ |
| **USA4[58]** | | | | | | | | | | |
| **Location**: USA<br>**Recruitment dates:** August 8, 1991 to June 19, 1992<br>**Hib vaccine:**<br>PRP-OMP, VaxHib, Merck & Co.<br>PRP-HbOC, HibTiter, Praxis Biologics<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date. Brand name and manufacturer not stated<br>**Funding:**<br>National Institute of Allergy and Infectious Diseases | **Inclusion criteria:** healthy two month old infants with informed consent of parent or guardian and scheduled to receive routine immunization<br>**Exclusion criteria:** none stated | **A:** 2 (PRP-OMP), 4, 6 (HbOC)<br>**B:** 2 (HbOC), 4, 6 (PRP-OMP)<br>**C:** 2, 4, 6 (HbOC)<br>**D:** 2, 6 (PRP-OMP)<br>**E:** 2, 4 (PRP-OMP)<br>**Additional information:**<br>DTP, OPV and MMR given to all groups "according to published guidelines". All children received unconjugated PRP vaccine at 15m.<br>**D:** Placebo at 4m<br>**E:** Placebo at 6m | **N=**36‖<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall gender (M/F):** 140/117 (55% M)<br>**Schedule D:**<br>**N=**36<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall gender (M/F):** 140/117 (55% M) | **N=**35‖<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall gender (M/F):** 140/117 (55% M)<br>**Schedule E:**<br>**N=**39<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall gender (M/F):** 140/117 (55% M) | **N=**96‖<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall gender (M/F):** 140/117 (55% M) | | | | | ✓ |

| Study details | Participant characteristics | Schedule A / schedule B / schedule C | Schedule A population characteristics | Schedule B population characteristics | Schedule C population characteristics | Outcomes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Invasive Hib (any entity) | Pneumonia | Death | Carriage | Immuno-logical |
| **USA5**[59] | | | | | | | | | | |
| **Location**: USA<br>**Recruitment dates:** NR<br>**Hib vaccine:**<br>PRP-T, ActHib, Pasteur Merieux<br>HbOC, HibTiter, Lederle-Praxis Biologics<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date. Brand name and manufacturer not stated<br>**Funding:**<br>National Institutes of Health and Connaught Laboratories | **Inclusion criteria:** healthy infants, 0 months of age with signed informed consent from a parent<br>**Exclusion criteria:** infants of a gestational age of less than 37 weeks, receipt of any blood product, known or suspected impairment of neurologic function, acute febrile illness, severe congenital defect or major organ dysfunction, known maternal immunodeficiency or human immunodeficiency virus infection | **A:** 2, 4, 6 (PRP-T)<br>**B:** 2, 4, 6 (HbOC)<br>**C:** 0, 2, 4, 6 (HbOC)<br>**Additional information:**<br>All children received regularly scheduled childhood immunizations including HepB, DTP, and OPV concurrently as separate injections at 2, 4, 6.<br>**A and B:** DT at birth | **N=**NR (total in all groups 150)*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall, gender (M/F):** 49% M | **N=**NR (total in all groups 150)*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** 3rd:6.7<br>Other doses NR<br>**Overall, gender (M/F):** overall 49% M | **N=**NR (total in all groups 150)*<br>**Mean age at randomization (SD):** NR<br>**Mean age at vaccination (SD):** NR<br>**Overall, gender (M/F):** overall 49% M | | | | ✓ |
| **USA6**[60] | | | | | | | | | | |
| **Location**: USA<br>**Recruitment dates:** NR.<br>**Hib vaccine:**<br>PRP-T, Act-Hib, Pasteur Mérieux Connaught<br>PRP-OMP, PedvaxHib, Merck Sharp & Dohme<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date. Brand name not stated, Connaught<br>**Funding:**<br>Connaught Laboratories, Pasteur Mérieux, and Merck, Sharpe & Dohme | **Inclusion criteria:** healthy infants about 2 months old from the practice of the Rothschild Pediatric Group in suburban New Orleans with informed consent<br>**Exclusion criteria:** none stated | **A:** 2 (PRP-OMP), 4, 6 (PRP-T)<br>**B:** 2, 4, 6<br>(PRP-T)<br>**C:** 2, 4<br>(PRP-OMP)<br>**Additional information:**<br>All children received DTP at 2, 4, 6 and OPV at 2, 4. | **N=** 34<br>**Mean age at randomization (SD):** NR.<br>**Overall, mean age at vaccination (SD):**<br>2.1 (0.3)<br>4.2 (0.3)<br>6.4 (0.4)<br>**Overall, gender at study entry and based on four randomized groups (M/F):** 72/68 (51.4% M) | **N=** 35<br>**Mean age at randomization (SD):** NR.<br>**Overall, mean age at vaccination (SD):**<br>2.1 (0.3)<br>4.2 (0.3)<br>6.4 (0.4)<br>**Overall, gender at study entry and based on four randomized groups (M/F):** 72/68 (51.4% M) | **N=** 35<br>**Mean age at randomization (SD):** NR.<br>**Overall, mean age at vaccination (SD):**<br>2.1 (0.3)<br>4.2 (0.3)<br>6.4 (0.4)<br>**Overall, gender at study entry and based on four randomized groups (M/F):** 72/68 (51.4% M) | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **USA7**[60] | | | | | | | | | | |
| **Location**: USA<br>**Recruitment dates:** NR.<br>**Hib vaccine:**<br>PRP-T, Act-Hib, Pasteur Mérieux Connaught<br>PRP-OMP, PedvaxHib, Merck Sharp & Dohme<br>**Pertussis vaccine:**<br>Not stated if wP or aP, assume wP given trial date. Brand name not stated, Connaught<br>**Funding:**<br>Connaught Laboratories, Pasteur Mérieux, and Merck, Sharpe & Dohme | **Inclusion criteria:** healthy infants about 2 months old suburban Chicago with informed consent<br>**Exclusion criteria:** none stated | **A:** 2, 4, 6 (PRP-T)<br>**B:** 2, 4 (PRP-OMP, PRP-T)<br>**C:** 2, 4 (PRP-OMP)<br>**Additional information:**<br>All children received DTP at 2, 4, 6 and OPV at 2, 4. | **N=** 58<br>**Mean age at randomization (SD):** NR.<br>**Overall, mean age at vaccination (SD):**<br>2.2 (0.3)<br>4.4 (0.4)<br>6.5 (0.5)<br>**Overall gender at study entry (M/F):** 106/75 (58.6% M) | **N=** 62<br>**Mean age at randomization (SD):** NR.<br>**Overall, mean age at vaccination (SD):**<br>2.2 (0.3)<br>4.4 (0.4)<br>6.5 (0.5)<br>**Overall gender at study entry (M/F):** 106/75 (58.6% M) | **N=** 61<br>**Mean age at randomization (SD):** NR.<br>**Overall, mean age at vaccination (SD):**<br>2.2 (0.3)<br>4.4 (0.4)<br>6.5 (0.5)<br>**Overall gender at study entry (M/F):** 106/75 (58.6% M) | | | | | ✓ |
| **USA8**[61, 122] | | | | | | | | | | |
| **Location**: USA<br>**Recruitment dates:** NR<br>**Hib vaccine:**<br>PRP-OMP, PedvaxHIB, Merck Sharp & Dohme<br>**Pertussis vaccine:**<br>Not described<br>**Funding:**<br>Supported, in part, by National Institute of Allergy and Infectious Diseases, National Institutes of Health, Connaught Laboratories, Inc. and Merck Sharp & Dohme | **Inclusion criteria:** healthy children from paediatric clinics in Missouri and Illinois with informed parental consent and with a physical examination performed prior to each immunization<br>**Exclusion criteria:** history of a serious reaction to any previous vaccination, suspicion of underlying immunodeficiency. Vaccination deferred if history of fever within the previous 72 hours vaccination within the previous week | **A:** 2-6, 4-8<br>**B:** 2-6, 3-7<br>**Additional information:**<br>No other vaccines described. | **N=** 27<br>**Mean age at randomization (SD):**<br>1st dose: 4.1 (1.6)<br>2nd dose: 6.1 (1.6)<br>**Overall mean age at vaccination (SD):** 3.6(1.5)<br>**Overall gender** at **randomization (M/F):** : 33/21 (61% M) | **N=** 27<br>**Median age at randomization (SD):**<br>1st dose: 3.2 (1.3)<br>2nd dose: 4.2 (1.3)<br>**Overall mean age at vaccination (SD):** 5.1(1.8)<br>**Overall gender at randomization (M/F):** 33/21 (61% M) | | | | | | ✓ |

| *Study details* | *Participant characteristics* | *Schedule A / schedule B / schedule C* | *Schedule A population characteristics* | *Schedule B population characteristics* | *Schedule C population characteristics* | *Outcomes* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Invasive Hib (any entity)* | *Pneumonia* | *Death* | *Carriage* | *Immuno-logical* |
| **West Africa**[62, 123, 124] | | | | | | | | | | |
| **Location**: The Gambia, Mali<br>**Recruitment dates:** September 18 to November 6, 2006<br>**Hib vaccine:**<br>PRP-T, Hiberix, GlaxoSmithKline<br>**Pertussis vaccine:**<br>Not described<br>**Funding:**<br>Vaccines by GlaxoSmithKline (Mencevax) and the Serum Institute of India (all other vaccines). Meningitis Vaccine Project through a grant from the Bill and Melinda Gates Foundation | I**nclusion criteria:** healthy children between 12 and 23 in Bamako, Mali, and Basse, Gambia; free of obvious health problems as; guardian willing to bring their child or to receive home visits for all follow-up visits; residence in the study area; fully vaccinated according to local EPI schedule<br><br>**Exclusion criteria:** history of vaccination against Neisseria meningitidis within the preceding 6 years, known exposure to N. meningitidis within the preceding 3 months, allergy after any vaccination | **A:** 3p +b12-23 +b22-34<br>**B:** 3p +b22-34<br>**C:** 3p +b12-23<br>**D:** 3p<br>**Additional information:**<br>There were a total of 9 groups each receiving vaccines at 12-23 months and 22-34 months. Three vaccines were used (Hib and two Meningococcal A vaccines). Groups represented each possible permutation of administration of these vaccines after 12 months of age. | **N=** 66*<br>**Mean age at randomization (SD):** NR<br>**Median age at vaccination (range):**<br>Booster: 18 (12-23), 28 (20-32)<br>**Gender (M/F):** NR<br>**Schedule D:**<br>**N=** 260*<br>**Median age at randomization (SD):** NR<br>**Median age at vaccination (range):**<br>Primary: NR<br>**Gender (M/F):** NR | **N=** 134*<br>**Mean age at randomization (SD):** NR<br>**Median age at vaccination (range):**<br>Booster: 25 (20-32)<br>**Gender (M/F):** NR | **N=** 129*<br>**Mean age at randomization (SD):** NR<br>**Median age at vaccination (range):**<br>Booster: 18 (12-23)<br>**Gender (M/F):** NR | | | ✓ | | |

**Legend:**

aP - acellular pertussis vaccine; BCG - Calmette-Guérin Bacillus; combined – Hib vaccine mixed in same syringe as other vaccines; DTP - diphtheria, tetanus, pertussis vaccine; DTaP - diphtheria, tetanus, acellular pertussis vaccine; DTwP - diphtheria, tetanus, whole cell pertussis vaccine; EPI: Expanded Program on Immunization; FHA - filamentous hemagglutinin; FIM - fimbriae; Hib – Haemophilus influenzae type b vaccine; m - months; MenACWY-PsACWY - quadrivalent meningococcal polysaccharide (groups A, C, Y, and W135) conjugate vaccine; MenA-TT-PsA-TT - MenA meningococcal conjugate vaccine; MMR - measles, mumps, rubella vaccine MMRV - measles, mumps, rubella, varicella vaccine; NR - Not reported; OPV - oral polio vaccine; p - primary course; PCV5: 5 valent pneumococcal conjugate vaccine; PCV7: 7-valent 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; PT - pertusis toxoid; wP - whole cell pertussis vaccine; separate – Hib vaccine not given in same syringe as other vaccines (other vaccines given at same or different time from Hib vaccine).

* Number of children vaccinated. Number of randomized children not reported.
† Authors state the intended schedule immunization was met for each child with only 2 single exceptions
‡Type of conjugate vaccine in primary schedule (3p) not specified.
§ Group A includes 164 Ladino and 161 Native Indian participants; Group B includes 47 Ladino and59 Native Indian participants.
¶ Authors state there was no significant difference in the mean age at the time of any immunization between the 3 vaccine groups.
‖ Number of children followed-up. Numbers randomized to each group not reported. Total number randomized 497

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