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Comparing *Haemophilus influenzae* type b Conjugate Vaccine Schedules: A Systematic Review and Meta-Analysis of Vaccine Trials

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Abstract

Background: The optimal schedule and the need for a booster dose are unclear for *Haemophilus influenzae* type b (Hib) conjugate vaccines. We systematically reviewed relative effects of Hib vaccine schedules.

Methods: We searched 21 databases to May 2010 or June 2012 and selected randomized controlled trials (RCTs) or quasi-RCTs that compared different Hib schedules (three primary doses with no booster dose [3p+0], 3p+1 and 2p+1) or different intervals in primary schedules and between primary and booster schedules. Outcomes were clinical efficacy, nasopharyngeal carriage and immunological response. Results were combined in random-effects meta-analysis.

Results: Twenty trials from 15 countries were included; 16 used vaccines conjugated to tetanus toxoid (PRP-T). No trials assessed clinical or carriage outcomes. Twenty trials examined immunological outcomes and found few relevant differences. Comparing PRP-T 3p+0 with 2p+0 there was no difference in seropositivity at the 1.0µg/ml threshold by six months after the last primary dose (combined risk difference -0.02, 95%CI -0.10, 0.06). Only small differences were seen between schedules starting at different ages, with different intervals between primary doses, or with different intervals between primary and booster doses. Individuals receiving a booster were more likely to be seropositive than those at the same age who did not.

Conclusions: There is no clear evidence from trials that any 2p+1, 3p+0 or 3p+1 schedule of Hib conjugate vaccine is likely to provide better protection against Hib disease than other schedules. Until more data become available, scheduling is likely to be determined by epidemiological and programmatic considerations in individual settings.

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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.[1] Nevertheless, there are still more than eight million cases of severe Hib disease worldwide annually in children under five years.[2] Conjugate vaccines in use in 2012 contained Hib capsular polysaccharide (polyribosylribitol phosphate, PRP) conjugated to diphtheria CRM197 protein, an oligosaccharide conjugate (PRP-HbOC), meningococcal outer membrane protein (PRP-OMP) or, most commonly tetanus toxoid (PRP-T).[1]

Countries are faced with decisions about optimal schedules for vaccines recommended for infants. The 2006 World Health Organization position paper on Hib conjugate vaccines, states that a three-dose schedule can be used with one to two months between doses, starting as young as six weeks.[3] The position paper does not explicitly recommend a booster dose, but states that if given it should be at 12-18 months of age. In 2012, most countries using Hib vaccine used a three-dose primary schedule with no booster dose (3p+0 schedule). Some countries, mainly in Europe and the Americas, added a booster dose to the three-dose primary schedule (3p+1 schedule) while other countries, mainly in Europe, used schedules with two primary doses and a booster (2p+1 schedule).[4] Variation in Hib vaccination schedules reflects not only differences in the historical scheduling of childhood vaccines, setting-specific epidemiology, existing health service infrastructure and co-administered vaccines, but also uncertainties about the optimal number of primary doses, the interval between doses in the primary schedule, and the need for a booster dose.[5] Whilst the clinical efficacy of Hib conjugate vaccines has been summarized,[6-9]

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there have been no systematic reviews summarizing immunological, carriage and clinical outcomes from trials making head-to-head comparisons of different Hib vaccine schedules. 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.

Methods

The review process followed a protocol, which was completed before starting the review (Supplementary text 1). Minor amendments were made after the review started and these are recorded in the protocol document. We report here results for the head-to-head comparisons of Hib conjugate vaccine schedules described in the protocol. Comparisons of Hib schedules to no Hib vaccination will be reported elsewhere.

Study identification

The literature search covered 21 electronic databases from the earliest citation until May 2010. There were five databases of published articles (AIM, Cochrane Library, LILACs, IndMED, Medline), three trial registries, 11 vaccine manufacturer databases and two regulatory authority websites. Search strategies included terms for “Hib” and “conjugate vaccine” adapted for each search engine (Supplementary text 2). In June 2012 the Medline search was updated, using a filter to identify RCTs (2012 search only), and the AIM, CENTRAL, LILACs, and IndMED searches were updated using the 2010 search strategy. Eligible trial registrations found in the 2010 search were also checked for new publications in June 2012.

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Study selection

Studies were considered eligible if they were randomized or quasi-randomized (e.g. allocated according to date of birth) and examined children vaccinated with PRP-T, PRP-OMP or PRP-HbOC at less than 6 years of age. Trials were eligible if they assigned participants to the following comparisons: 3p+0 vs. 2p+0; 3p+0 vs. 2p+1; 3p+1 vs. 2p+1; 3p+1 vs. 3p+0. We also included studies that compared different intervals between doses and different ages at the start of the primary schedule. We excluded studies where both the schedule and the PRP-conjugated molecule differed between available comparison groups so that no comparisons within the trial assessed the effect of schedule differences alone.

Outcomes included invasive Hib disease as a combined outcome or separate diagnoses of Hib meningitis; pneumonia due to any cause; Hib pneumonia; epiglottitis; nasopharyngeal carriage of Hib; seropositivity after vaccination or geometric mean concentration (GMC) of PRP antibody. 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.[10] Only systematically collected clinical outcomes were considered eligible.

Each title and abstract was screened for eligibility by independent two reviewers. The full texts of abstracts assessed by one or both reviewers to be potentially eligible were then screened for eligibility by two reviewers. Data were extracted on to a structured piloted form (available on request). Data were extracted by two independent reviewers and differences were resolved by consensus. Items extracted included trial characteristics, outcomes, potential sources of heterogeneity, and the risk of bias in individual trials.[11] The risk of bias was assessed by examining trial features including the adequacy of random sequence generation, adequacy of allocation concealment, the use of outcome assessor blinding, and the type of analysis.[12, 13]

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Analysis types included modified intention to treat (mITT), and per protocol (PP). Modified intention to treat is used to describe analyses that included all randomized (or assigned) participants who had outcome data available with the possible exclusion of those who received no doses of vaccine, and PP is used to describe those that additionally excluded individuals with other protocol violations. We did not contact authors to obtain additional information.

Analysis

We combined data statistically, where appropriate, using DerSimonian and Laird random-effects meta-analysis[14] in STATA version 12 (StataCorp LP, College Station, TX, USA). 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.[15] Where multiple intervention groups (or "trial arms") were available within a trial to make a comparison of two schedules, we compared the groups which were most similar except for the difference in schedule. The decision about intervention groups to compare was made by two senior reviewers (NL and PS) without reference to trial results. For immunological outcomes, and for both the 1.0ug/ml and 0.15ug/ml thresholds, we calculated the difference between groups in proportions seropositive (and 95% confidence intervals using the normal approximation to the sampling distribution of the difference) 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%). Immunogenicity data were stratified according to the conjugated molecule (PRP-HbOC, -OMP or -T). We report 1.0 µg/ml threshold data in figures in preference to 0.15µg/ml threshold data because risk differences were generally larger at the higher threshold. We report GMC data where seropositivity data were not available. We did not assess the

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presence of small trials biases using funnel plots or the Egger test because few trials were available for most analyses.

Results

The literature searches yielded a total of 4337 unique items; 4032 items from the 2010 database and 305 from reference lists or repeat database searches. Of these, 4299 items were excluded (Figure 1). The remaining 38 items referred to 20 randomized or quasi-randomized trials reporting on eligible comparisons and outcomes. Included studies are described in Table 1 and Supplementary Table 1.[16-34] The 20 trials were conducted in 15 countries in Africa, Asia, Europe, and North and South America. Sixteen trials used PRP-T, three used PRP-OMP, and two used PRP-HbOC. One trial used PRP-T in two trial groups and PRP-HbOC in two other groups (Chile1). Five trials did not report the number of individuals assigned to each intervention group. Where numbers were reported, a total of 6312 infants were assigned to intervention groups analyzed in this review: 661 infants to 2p+0 schedules, 1194 to 3p+0, 300 to 2p+1, and 4157 to 3p+1 schedules. The median number of participants in trials was 283 (range 54 - 1782).

Risk of bias in methods of included studies

Table 2 shows methodological features which could influence the risk of bias for the 20 trials. All trials individually assigned participants to intervention groups, and only one trial was judged to be quasi-randomized (USA3). Allocation concealment was assessed as adequate in two trials and inadequate in one trial. In 17 trials allocation concealment was not well enough described to be assessed. Outcome assessors (laboratory staff) were described as blinded in 11 of the 20 trials. Four trials reported mITT analyses (three of which also conducted PP analyses but only stated that results were similar to mITT results), nine reported PP analyses (two of which also

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conducted mITT analyses but only stated that results were similar to PP results) and for seven trials it was not clear which analysis was reported.

Head-to-head comparisons between schedules

There were no eligible clinical or carriage outcome data from trials that compared different schedules of Hib vaccination. Twenty trials examined eligible schedule comparisons and presented seropositivity or GMC data. Nine of these provided data for comparisons of schedules with different numbers of doses in the primary or booster schedules and 14 of these provided data for comparisons of schedules with the same number of doses but different timings. Supplementary Figures 1 and 2 show seropositivity (≥0.15μg/ml and ≥1.0μg/ml) for all trial arms used in eligible comparative analyses.

Number of doses in primary and booster schedules, immunological data

3p+0 vs. 2p+0 schedules

Seven trials provided data for this comparison (Chile1, Chile2, Guatemala, Netherlands, Niger, Sweden, USA2). Six examined PRP-T and two examined PRP-HbOC (one trial examined both). Six trials reported seropositivity (Chile1, Chile2, Guatemala, Netherlands, Niger, Sweden) and all trials reported GMC data.

Figure 2 shows the risk difference (≥ 1.0μg/ml) for seropositivity between groups receiving 3p+0 and 2p+0 schedules for trials where the interval between the last dose and blood draw was the same for both arms. In three trials examining PRP-T (Chile1, Niger, Sweden), neither the 2p nor the 3p schedule was consistently favored and heterogeneity was high (I^2 90% at the 1.0μg/ml threshold and 67% at the 0.15μg/ml threshold, shortly after the last primary dose). By six months after the last primary dose, there was no difference between the schedules at the 1.0μg/ml threshold (combined risk difference -0.02, 95%CI -0.10, 0.06) and no heterogeneity (I^2 0%).

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Heterogeneity remained high six months after the last primary dose at the 0.15μg/ml threshold (I^2 75%).

One trial (Chile1) examined PRP-HbOC and presented seropositivity data. Point estimates favored the 3p group but the confidence interval included the null effect. The trial which reported only GMC (USA2) 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 reported 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.

3p vs. 2p+1 schedules

One trial (Sweden) using PRP-T provided data for this comparison. 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 risk difference was -0.79 (95%CI -0.87, -0.71) at the 1.0μg/ml threshold, and -0.20 (95%CI -0.27, -0.13) at 0.15μg/ml, favoring the 2p+1 schedule.

3p+1 vs. 2p+1 schedules

Two trials using PRP-T provided data on seropositivity for this comparison (Netherlands, Sweden). Proportions seropositive one month after the booster vaccinations were high and similar in both groups. The combined risk difference was 0.01 (95%CI -0.03, 0.05) at the 1.0μg/ml threshold and 0.01 (95%CI -0.01, 0.02) at 0.15μg/ml, with moderate (I^2 56%) and low (I^2 24%) heterogeneity, respectively.

3p+1 vs. 3p schedules

Two trials examined PRP-T for this comparison (Canada2, Europe). One reported seropositivity data (Europe) and both reported GMC. 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

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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 (Canada2). Multiple intervention groups in this trial were available for comparison and not all are presented here. At 16 months of age the intervention 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, Canada2) 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, Canada2).

Age at start of primary schedule, immunological data

Eight trials compared schedules with the same number of doses, in which the first dose was given earlier or later (Belgium, Chile2, China1, China2, Gambia1, Gambia2, Netherlands, Turkey). Seven examined PRP-T, and one examined PRP-OMP (Gambia1). Seven trials reported seropositivity data and eight reported GMC. Seropositivity results at the 1.0µg/ml threshold are shown in Figure 3. Some schedule comparisons differed in both the age at first dose and in the interval between doses in the primary schedule. There were only small differences in seropositivity between schedules and heterogeneity was low. The combined risk difference one month after the last primary dose was 0.02 (95%CI -0.01, 0.05) at the 1.0µg/ml threshold, based on 3 trials (I^2 1%). It was 0.01 (95%CI 0.00, 0.02) at 0.15µg/ml based on 4 trials (I^2 0%).

The trial which reported only GMC (Gambia2) compared PRP-T doses at 2 and 4 months to doses at 1 and 3 months of age. One month after the last dose of vaccine, the GMC was 0.41µg/ml (95%CI 0.28, 0.61) in infants receiving the first dose at 2 months and 0.26µg/ml (95%CI 0.19, 0.35) in the group with the earlier start. One study comparing a birth dose of PRP-HbOC plus doses at 2, 4 and 6 months of age with doses at 2, 4 and 6 months (USA2) concluded that antibody levels were not higher after a birth dose.

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Interval between doses, immunological data

Longer vs. shorter interval in primary schedules

Five trials provided immunological data comparing longer and shorter intervals in the primary schedule (Belgium, France, Turkey, USA1, USA3). Four trials compared two-month intervals to one-month intervals (Belgium, France, Turkey, USA3); three used 3p schedules with PRP-T and reported both seropositivity and GMC data (Belgium, France, Turkey) and one used a 2p schedule with PRP-OMP and reported GMC data only (USA3). At the 1.0µg/ml threshold, neither the two-month nor the one-month interval schedule was consistently favored but results were heterogeneous (Figure 4). At the 0.15 µg/ml threshold, no difference was seen between the schedules and heterogeneity was low: the combined risk difference one month after the last primary dose was 0.00 (95%CI -0.02, 0.02), I^2 0%. The trial using PRP-OMP (USA3) was quasi-randomized, using alternation for assignment of interventions. The mean age at first vaccination was 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 vaccination 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. One trial compared 4-month intervals to two-month intervals using PRP-OMP (USA1), but results were difficult to interpret because the interval between vaccination and blood-sampling differed between the groups being compared.

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Longer vs. shorter interval between primary and booster schedules

Seven trials examined PRP-T and provided seropositivity and GMC data (Canada1, Canada2, Canada3, Chile2, China1, Europe, France). There were no differences in seropositivity one month after the booster dose and little between-study heterogeneity. The combined risk difference was 0.00 (95%CI -0.01, 0.01) at the 1.0μg/ml threshold (Figure 5) and 0.00 (95%CI -0.01, 0.01) at 0.15μg/ml, with I^2 14% and I^2 0%, respectively.

Discussion

Immunological data in this systematic review showed few differences that were both consistent and clinically relevant 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.

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. A limitation identified by this review was the paucity of data on several outcomes and comparisons of interest. We did not include data from observational studies because well-conducted RCTs are at lower risk of bias than observational study designs,[35, 36] and because observational studies have been summarized elsewhere.[37, 38] The potential for bias does remain in many of the included trials, with allocation concealment,

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blinding of outcome assessors and exclusions after randomization being key trial design features influencing the risk of bias within trials.[39] In particular, many trials in this review explicitly excluded some randomized individuals by conducting only a per protocol analysis. For some design features it is difficult to categorize the risk of bias if the design feature is poorly described. For example, an incomplete description of allocation concealment could be compatible with either a high or low risk of bias; if allocation was adequate, the risk of bias is low but if allocation concealment was not well conducted, bias might occur if it can be easily predicted which individuals are more or less likely to seroconvert. Incomplete descriptions for features such as blinding are less important when considering immunological results where outcomes are assessed by laboratory technicians. It is possible and even likely that outcome assessors were blinded, even if this was not reported. Even if the laboratory staff are not blinded, automated procedures are likely to reduce the risk of bias.

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. Available clinical data show good protection against invasive Hib disease with 2p+0 schedules using PRP-OMP,[40] and with 3p+0 schedules using PRP-T or PRP-HbOC,[40-44] when compared to no Hib vaccine and these data have been summarized several times.[6-9] However, estimates of VE from different trials cannot be compared directly as evidence of equivalence or superiority of one particular schedule and there are too few trials for a network meta-analysis, which would allow such a comparison.[45, 46]

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Two-month 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 immunological findings because the clinical relevance of Hib seropositivity levels and GMCs are not well established in general,[10] and also because of differences in the schedules compared within each study other than the difference of interest. Data from an observational review found no strong evidence from cohort or case-control studies that the choice of intended intervals of one or two months between doses affects vaccine effectiveness,[38] but differences between the intended and actual schedules and other factors such as herd immunity in the population again add complexity to interpretation.[5]

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.[10] This review was not designed to collect data about antibody persistence, and therefore caution should be taken when examining such data from this review. However, when data from individual groups in trials eligible for this review are plotted alongside each other (Supplementary figures 1 and 2), it can be seen that the proportion seropositive tends to be higher soon after a booster dose than

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soon after the last primary dose, or several months after the last primary dose, particularly at the 1.0μg/ml threshold. Trials that assessed seropositivity more than one month after the last primary dose showed generally lower proportions seropositive than those assessing seropositivity one month after the last primary dose. In the one trial with long follow up after a booster dose, a high proportion of individuals remained seropositive at the 0.15μg/ml threshold years after the booster dose and a much lower proportion at the 1.0μg/ml threshold. These trends are in general agreement with studies which have found sustained antibody persistence after a booster dose.[47,48] 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.[49] 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.[50, 51]

This review did not aim to examine the effects of co-administrated vaccines on Hib conjugate vaccine efficacy, which is best examined in trials comparing groups with different co-administered vaccines but with the same schedule. However, conclusions from our review about the relative effects of different schedules do not change when restricted to trials that co-administered aP or trials that co-administered wP. In analyses that included both trials in which whole cell pertussis vaccine (wP) was co-administered and trials in which acellular pertussis vaccine (aP) was co-administered, the relative effects of different schedules of Hib vaccine did not appear to change substantially between studies. However, owing to the limited availability of data in each analysis, this could not be formally assessed using statistical methods such as meta-regression. The observational review conducted simultaneously with our review found no strong

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evidence from cohort studies that co-administration with aP reduced vaccine effectiveness, but two case-control studies conducted in the UK provided some evidence of a reduction.[38, 51, 52] Further carefully conducted systematic reviews of RCTs, as well as observational data, could provide useful information about this and other questions about Hib vaccine scheduling.

Hib conjugate vaccine 2p+1, 3p+0 and 3p+1 schedules are all likely to provide protection against Hib disease and, until further data about the relative effects of different Hib vaccine schedules are available, the choice of schedule is likely to depend on the 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. 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 into 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.[53]

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Variation in the burden of disease, health infrastructure and scheduling of other vaccines create 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 is likely to provide better protection against Hib disease than other schedules. Until additional data about the relative effects of different Hib vaccine schedules are available, the choice of Hib vaccination schedule is likely to be determined by the epidemiological and programmatic conditions in individual settings.

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Figure legends

Figure 1: Flow diagram of studies

Legend:

The 4032 items found in initial database searches include duplicates that were retrieved in 2 or more databases.

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

Figure 2: Comparison of seropositivity after 3 or 2 primary doses of Hib conjugate vaccine, 1.0µg/ml

Additional data for this comparison are not shown on this plot because the interval between the last dose of vaccine and blood sampling differed between the groups being compared within each study, making the comparison unfair. These data came from Chile2 (at one or two months after the primary dose), Guatemala (at three or six months after the primary dose) and Netherlands (four or six months after the primary dose).

Legend:

Combined - Hib vaccine administered in the same syringe as pertussis containing vaccine; separate - Hib vaccine administered by itself, either at the same time as or at different time from other vaccines; aP - acellular pertussis vaccine ; wP - whole-cell pertussis vaccine

* not specified as whole cell pertussis vaccine but assumed to be whole cell due to the year in which the trial was conducted

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Figure 3: Comparison of seropositivity after late or early start of primary course of Hib conjugate vaccine, 1.0µg/ml

Additional data for this comparison are not shown on this plot because the interval between the last dose of vaccine and blood sampling differed between the groups being compared within each study, making the comparison unfair. These data came from China1 (at 13 or 14 months after the primary dose), Gambia1 (at 14 or 15 months after the primary dose) and Netherlands (four or six months after the primary dose).

Legend:

Combined - Hib vaccine administered in the same syringe as pertussis containing vaccine; separate - Hib vaccine administered by itself, either at the same time as or at different time from other vaccines; aP - acellular pertussis vaccine ; wP - whole-cell pertussis vaccine

* not specified as whole cell pertussis vaccine but assumed to be whole cell due to the year in which the trial was conducted

Figure 4: Comparison of seropositivity after 2 or 1 month intervals between doses in the primary course of Hib conjugate vaccine, 1.0µg/ml

Additional data for this comparison are not shown on this plot because the interval between the last dose of vaccine and blood sampling differed between the groups being compared within each study, making the comparison unfair. These data came from France (at nine or 11 months after the primary dose)

Legend:

Combined - Hib vaccine administered in the same syringe as pertussis containing vaccine; separate - Hib vaccine administered by itself, either at the same time as or at different time from other vaccines; aP - acellular pertussis vaccine ; wP - whole-cell pertussis vaccine

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* Data for this trial reported unclearly at this time point and for this definition of seropositivity

Figure 5: Comparison of seropositivity after long or short intervals between primary and booster doses of Hib conjugate vaccine, 1.0µg/ml

Legend:

Combined - Hib vaccine administered in the same syringe as pertussis containing vaccine; separate - Hib vaccine administered by itself, either at the same time as or at different times from other vaccines; aP - acellular pertussis vaccine ; wP - whole-cell pertussis vaccine

* not specified as whole cell pertussis vaccine but assumed to be whole cell due to the year in which the trial was conducted

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Legend of Supplemental Digital Content

Supplementary Text 1: Study protocol

Supplementary Text 2: Search strategy

Supplementary Table1: Trials included in Hib conjugate vaccine review, detailed information

Supplementary Figure 1: Seropositivity after 2p, 3p, 2p+1 and 3p+1 schedules, 0.15µg/ml

Supplementary Figure 2: Seropositivity after 2p, 3p, 2p+1 and 3p+1 schedules, 1.0µg/ml

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Table 1: Summary of included studies

Trial name and location	Conjugate vaccine	Allocation level	Schedules, age at administration in months		Number of participants randomized	Immunological outcomes reported
			Intended	Actual, mean (SD)		
Belgium[16]	PRP-T	Individual	3, 4, 5*	3.0 (0.1) 4.0 (0.1) 5.0 (0.2)	49†	Seropositivity GMC
			2, 4, 6*	2.1 (0.2) 4.0 (0.2) 5.9 (0.2)	54†	
Canada1[17]	PRP-T	Individual	2, 4, 6 + b18	NR‡	82	Seropositivity
			2, 4, 6 + b15		85	GMC
			2, 4, 6 + b12		86	
Canada2[18]	PRP-T	Individual	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		
Canada3[19]	PRP-T	Individual	2, 4, 6 +b18	18.3 (0.3)	167	Seropositivity
			2, 4, 6 +b15	15.3 (0.3)	168	GMC
				Primary: NR		
Chile1[20]	PRP-T	Individual	2, 4, 6	NR	78	Seropositivity
			4, 6		79	GMC
	PRP-HBOC		2, 4, 6		78	
			4, 6		78	

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Trial name and location	Conjugate vaccine	Allocation level	Schedules, age at administration in months		Number of participants randomized	Immunological outcomes reported
			Intended	Actual, mean (SD)		
Chile2[21]	PRP-T	Individual	3, 5, 7 + b12[§]	NR	710[¶]	Seropositivity
			2, 4, 6 + b12[§]			GMC
China1[22]	PRP-T	Individual	3, 4, 5 +b18-20[‖]	NR	264	Seropositivity
			2, 3, 4 +b18-20[‖]		264	GMC
China2[23]	PRP-T	Individual	3, 4, 5**	3.3 (0.3)	324	Seropositivity
			2, 3, 4**	2.3 (0.3)	330	GMC
				dose 2-3:NR		
Europe[24]	PRP-T	Individual	3p +b13[‡‡]	NR	220	Seropositivity
(Austria,	(booster)[††]		3p +b12[‡‡]	14.9 (3.2)	224	GMC
Germany,				primary NR		
Greece)						
France[25]	PRP-T	Individual	2, 4, 6 + b15-17	NR	258	Seropositivity
			2, 3, 4 + b15-17		258	GMC
Gambia1[26]	PRP-OMP	Individual	2, 4	NR[§§]	95	Seropositivity
			1, 3		99	GMC
Gambia2[27]	PRP-T	Individual	2, 4	NR	43	GMC
			1, 3		45	
Guatemala[28]	PRP-T	Individual	2, 4, 6	NR	325	Seropositivity
			7, 9		106	GMC
Netherlands[29]	PRP-T	Individual	3, 4, 5 + b11[¶¶]	NR	181	Seropositivity
			6, 7 + b13[¶¶]		182	GMC

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Trial name and location	Conjugate vaccine	Allocation level	Schedules, age at administration in months		Number of participants randomized	Immunological outcomes reported
			Intended	Actual, mean (SD)		
Niger[30]	PRP-T	Individual	1.5, 2.5, 3.5 2.5, 3.5	Over all groups, mean (range): 1.9 (0.9-2.8) 3.0 (2.1-5.1) 4.2 (3.0-6.8)	59 62	Seropositivity GMC
Sweden[31]	PRP-T	Individual	2, 4, 6 +b13 3, 5 +b12	NR‖‖	118 118	Seropositivity GMC
Turkey[16]	PRP-T	Individual	3, 4, 5* 2, 4, 6*	3.0 (0.1) 4.0 (0.2) 5.1 (0.3) 2.1 (0.2) 4.0 (0.3) 5.9 (0.3)	78† 81†	Seropositivity GMC
USA1[32]	PRP-OMP	Individual	2, 6 2, 4	NR	36*** 39***	Seropositivity GMC
USA2[33]	PRP-HbOC	Individual	2, 4, 6 0, 2, 4, 6	NR†††	150‡‡‡	GMC
USA3[34]	PRP-OMP	Individual	2-6, 4-8 2-6, 3-7	4.1 (1.6) 6.1 (1.6) 3.2 (1.3) 4.2 (1.3)	27 27	GMC (adjusted)

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Legend

All times are in months of age unless otherwise stated. One reference is supplied for each trial in this table. A complete list of references for each trial can be found in Supplementary Table 1.

3p – 3-dose primary schedule where intended ages at vaccination not specified; +b – booster dose given at number of months indicated

DTaP - diphtheria, tetanus, acellular pertussis vaccine; DTwP - diphtheria, tetanus, whole cell pertussis vaccine; Hib – Haemophilus influenzae type b vaccine; IPV - inactivated polio vaccine; IQR - inter-quartile range; Men A and C vaccines - conjugate or polysaccharide meningococcal A and C vaccines; NR not reported; OPV - oral polio vaccine; p - primary course; PRP - polyribosylribitol phosphate; PRP-HbOC - polyribosylribitol phosphate conjugated to diphtheria toxin CRM 197; PRP-OMP - polyribosylribitol phosphate conjugated to outer membrane protein of Neisseria meningitidis; PRP-T - polyribosylribitol phosphate conjugated to tetanus toxoid; SD - standard deviation.

* 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.

† Number receiving vaccine; number randomized not reported

‡ 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)”

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

¶ Number randomized to each group not reported. 710 infants randomized to five groups (not all included here)

‖ 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).

** 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.

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

‡‡ Multiple groups exist for the 3p + b12 schedule in this trial. Results presented 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.

§§ 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).”

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¶¶ 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 (not with PRP-T) 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

‖‖ 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"

*** Number analyzed; number of randomized or immunized children not reported

††† The group receiving 2, 4, 6 PRP-HbOC received the 3rd dose at a mean age of 6.7 months. Other groups and doses not reported.

‡‡‡Total recruited, randomized and immunized; numbers per group not reported

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Table 2: 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 (immunological outcomes)	Blinding of other persons	Modified Intention to treat or per protocol analyses, immunological outcomes
Belgium[16]	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	Yes	Unclear, not reported	mITT (PP performed and "similar")
Canada1[17]	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	Unclear, authors refer to "code-numbered samples", but no explicit description of blinding	Not reported	mITT
Canada2[18]	Unclear, not reported	Unclear, not reported	No, not possible due to schedule differences	Unclear, trial described as open-label	Unclear, trial described as open-label	PP (mITT performed and "similar")

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Study, vaccine (manufacturer)	Adequate randomization sequence generation	Adequate randomization allocation concealment	Blinding of patient or parent to exposure status	Blinding of outcome assessors (immunological outcomes)	Blinding of other persons	Modified Intention to treat or per protocol analyses, immunological outcomes
Canada3[19]	Unclear, not reported	Unclear, not reported	Parents partially blinded. Not blinded to age at vaccination	Unclear, not reported	Unclear, not reported	Unclear
Chile1[20]	Unclear not reported how "list of correlative numbers" generated	Unclear, not well reported	No, not possible due to schedule differences	Yes	Vaccinators not blinded	Unclear
Chile2[21]	Unclear, does not report how "list of ... study numbers, in blocks of 10" generated	Unclear, not reported	No, not possible due to schedule differences	Yes	Unclear, trial reported to be "open"	mITT (PP analysis conducted with "identical results")
China1[22]	Unclear, not reported	Unclear, not reported	No, not possible due to schedule differences	Yes	Unclear, trial reported to be "open"	Unclear

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Study, vaccine (manufacturer)	Adequate randomization sequence generation	Adequate randomization allocation concealment	Blinding of patient or parent to exposure status	Blinding of outcome assessors (immunological outcomes)	Blinding of other persons	Modified Intention to treat or per protocol analyses, immunological outcomes
China2[23]	Unclear, not reported	Unclear, not reported	No, not possible due to schedule differences	Unclear, trial reported to be "open"	Unclear, trial reported to be "open"	PP
Europe[24] (Austria, Germany, Greece)	Unclear, not reported	Unclear, not reported	No, not possible due to schedule differences	Unclear, trial reported to be "open"	Unclear, trial reported to be "open"	PP
France[25]	Unclear, not reported	Unclear, not reported	Unclear, but unlikely due to schedule differences	Unclear, trial reported to be "open"	Unclear, trial reported to be "open"	PP (mITT performed and reported to be 'consistent with PP)
Gambia1[26]	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	Yes	Field workers not blinded	PP

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Study, vaccine (manufacturer)	Adequate randomization sequence generation	Adequate randomization allocation concealment	Blinding of patient or parent to exposure status	Blinding of outcome assessors (immunological outcomes)	Blinding of other persons	Modified Intention to treat or per protocol analyses, immunological outcomes
Gambia2[27]	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	Yes, laboratory staff blinded	Unclear, not reported	Unclear
Guatemala[28]	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"	Unclear, trial reported to be "open"	Described as "open study"	Unclear
Netherlands[29]	Yes, computer generated list	Unclear, not reported	Unclear, not reported	Yes	Unclear, not reported	PP
Niger[30]	Unclear, not reported	Unclear, not reported	Unclear, not reported	Unclear, "assays were performed on coded specimens" but no additional description given.	Those who assess adverse events were blinded	Unclear

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Study, vaccine (manufacturer)	Adequate randomization sequence generation	Adequate randomization allocation concealment	Blinding of patient or parent to exposure status	Blinding of outcome assessors (immunological outcomes)	Blinding of other persons	Modified Intention to treat or per protocol analyses, immunological outcomes
Sweden[31]	Unclear, "randomly assigned, in blocks of 10", but sequence generation not reported	Unclear, not reported	No, not possible due to schedule differences	Yes	Unclear, trial reported as "open"	PP
Turkey[16]	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	Yes	Unclear, not reported	mITT (PP performed and "similar")
USA1[32]	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	Yes	"Investigators who enrolled, interviewed, or evaluated subjects or parents were blinded to study group assignment"	PP

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Study, vaccine (manufacturer)	Adequate randomization sequence generation	Adequate randomization allocation concealment	Blinding of patient or parent to exposure status	Blinding of outcome assessors (immunological outcomes)	Blinding of other persons	Modified Intention to treat or per protocol analyses, immunological outcomes
USA2[33]	Unclear, not reported*	Unclear, not reported	Yes	Yes	Vaccinators not blinded. Those assessing safety were blinded.	Unclear
USA3[34]	No, alternation	No, alternation	No, not possible due to schedule differences	Unclear, not reported	Unclear, not reported	PP

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Legend:

ITT - intention-to-treat analysis - analysis where no randomized individuals are excluded; mITT- modified intention-to- treat analysis - similar to an ITT 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

All assessments based on information contained in published articles or pre-publication manuscripts. Authors of individual trials were not contacted for information on methodological features. One reference is supplied for each trial in this table. A complete list of references for each trial can be found in Supplementary Table 1.

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Supplemental Digital Content (Including Separate Legend)
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Supplementary Table 1: 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*	
						Mortality	*Immunological*
Belgium[1]							
Location: Belgium **Recruitment dates:** October 1994 to March 1995 **Hib vaccine:** PRP-T, Act-HIB, Pasteur Mérieux Connaught **Pertussis vaccine:** aP (2 compontent), brand name not stated, Pasteur Mérieux, Connaught **Funding:** Pasteur Mérieux Connaught	**Inclusion criteria:** healthy infants, Belgian, aged 2 months (22 weeks) with informed written consent from the parents or legal guardian **Exclusion criteria:** none reported	**A:** 3, 4, 5 +b12-14 **B:** 3, 4, 5 +b12-14 **C:** 2, 4, 6 **Additional information:** **A:** DTaP at 3, 4, 5, 12-14 combined **B:** DTaP at 3, 4, 5, 12-14m, separate **C:** DTaP at 2, 4, 6, separate	**N=**54* **Mean age at randomization (SD):** 2 (0.5) **Mean age at vaccination (SD):** 1st dose: 3.0 (0.1) 2nd dose: 4.0 (0.1) 3rd dose: 5.0 (0.2) Booster:14.0 (0.7) **Gender (M/F):** 32/22 (59% M)	**N=** 49* **Median age at randomization (SD):** 2 (0.5) **Mean age at vaccination (SD):** 1st dose: 3.0 (0.1) 2nd dose: 4.0 (0.1) 3rd dose: 5.0 (0.2) Booster: 13.8 (0.6) **Gender (M/F):** 27/25 (50% M)	**N=** 54* **Mean age at randomization (SD):** 2 (0.5) **Mean age at vaccination (SD):** 1st dose: 2.1 (0.2) 2nd dose: 4.0 (0.2) 3rd dose: 5.9 (0.2) No booster **Gender (M/F):** 22/32 (41% M)		✓
Canada1[2]							
Location: Canada **Recruitment dates:** Not stated **Hib vaccine (booster):** PRP-T, PENTA (combined DPT-IPV/PRP-T), Pasteur Mérieux Connaught **Pertussis vaccine:** Not stated if wP or aP, assume wP given trial date, PENTA, Pasteur Mérieux Connaught **Funding:** 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 **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 **B:** 2, 4, 6 + b15 **C:** 2, 4, 6 + b12 **Additional information:** 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 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR† **Gender (M/F):** NR	**N=** 85 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR† **Gender (M/F):** NR	**N=** 86 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR† **Gender (M/F):** NR		✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
Canada2[3-7]							
Location: Canada **Recruitment dates:** Study performed in 2000 to 2001 **Hib vaccine:** PRP-T, Act-HIB, Sanofi Pasteur **Pertussis vaccine:** aP (5 component) Quadracel, Sanofi Pasteur. **Funding:** 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 **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 **B:** 3p +b17 **C:** 3p +b16 **D:** 3p +b15 **Additional information:** 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 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** Primary: NR Booster: 18.3 (0.3) **Gender (M/F):** 213/225 (47% M) **Schedule D:** **N=** 445 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** Booster:15.4 (0.3) **Gender (M/F):** 215/230 (48% M)	**N=** 450 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** Primary: NR Booster:17.4 (0.3) **Gender (M/F):** 222/228 (49% M)	**N=** 449 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** Primary: NR Booster:16.4 (0.3) **Gender (M/F):** 211/238 (47% M)		✓
Canada3[8]							
Location: Canada **Recruitment dates:** 2003 **Hib vaccine:** PRP-T, Pentacel, Sanofi Pasteur **Pertussis vaccine:** aP (5 component) Pentacel, Sanofi Pasteur **Funding:** 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 **Exclusion criteria:** none stated.	**A:** 2, 4, 6 +b18 **B:** 2, 4, 6 +b15 **Additional information:** All received DTaP-IPV combined with Hib and offered routine MMR at 12 months. **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 **Mean age at randomization based on time beyond birthday (SD):** 6.3 (0.3) **Mean age at vaccination (SD):** Primary: NR Booster:18.3(0.3) **Gender (M/F):** 98/69 (59% M)	**N=** 168 **Median age at randomization based on time beyond birthday (SD):** 3.3 (0.3) **Mean age at vaccination (SD):** Primary: NR Booster**:** 15.3 (0.3) **Gender (M/F):** 100/68 (59.5% M)			✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
Chile1[9, 10]							
Location: Chile **Recruitment dates:** October to December, 1995 **Hib vaccine:** PRP-T, ActHib, Pasteur Mérieux Connaught PRP-HbOC, HibTiter, Wyeth-Lederle **Pertussis vaccine:** **Funding:** 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 **Exclusion criteria:** contraindication to receiving DTP vaccine, major chronic or congenital diseases, or known immunological disorders	**A:** 2, 4, 6 (PRP-T) **C:** 4, 6 (PRP-T) **B:** 2, 4, 6 (PRP-HbOC) **D:** 4, 6 (PRP-HbOC) **Additional information:** 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 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR **Schedule D:** **N=** 78 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR	**N=** 79 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):**NR **Gender (M/F):** NR	**N=** 78 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR		✓
Chile2[11]							
Location: Chile **Recruitment dates:** December 20, 1995 to April 2, 1996 **Hib vaccine:** PRP-T, ActHIB, Pasteur Mérieux Connaught **Pertussis vaccine:** aP (2 compontent), brand name not stated, Pasteur Mérieux Connaught **Funding:** Pasteur Mérieux Connaught	**Inclusion criteria:** healthy 2 month-old infants (±4 weeks) planning to receive primary care at the selected health centres for the complete study period, informed consent from parents or guardian **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 **B:** 3, 5, 7 +b12 **C:** 3, 5, 7 +b12 **D:** 2, 4, 6 +b12 (separate) **E:** 2, 4, 6 +b12 (combined) **Additional information:** All children received MMR and DTaP combined with Hib vaccine at 12 months. **A, B, C, D, E**: received DTaP at 2, 4, 6 **B, C, D, E:** received IPV at 2, 4, 6 (B separate, others combined with DTaP), OPV at 7, 13 **A:** OPV at 2, 4, 6, 13	**N=**NR(710 total in study)* **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR. **Schedule D:** **N=**NR(710 total in study)* **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR.	**N=**NR(710 total in study)* **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR. **Schedule E:** **N=**NR(710 total in study)* **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR.	**N=**NR(710 total in study)* **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR.	✓	✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
China1[12-14]							
Location: China **Recruitment dates:** NR **Hib vaccine:** PRP-T, Pentacel, Sanofi Pasteur **Pertussis vaccine:** aP (2 component) in combined schedules) Pentaxim, Sanofi Pasteur aP (1 component) in separate schedule, brand name not stated, Wuhan Institute of Biological Products **Funding:** Sanofi Pasteur	**Inclusion criteria:** children who had completed the primary vaccination study and had informed consent from parents or legal representatives **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) **B:** 3, 4, 5 +b18-20 (separate) **C:** 2, 3, 4 +b18-20 (combined) **Additional information:** **A and C:** DTaP-IPV combined with Hib **B:** DTaP, Hib, IPV separately 3, 4, 5, 18-20	**N=** 264 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall gender based on N=792 (M/F):** 393-444/348-399 (49.6–56% M).	**N=** 264 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall gender based on N=792 (M/F):** 393-444/348-399 (49.6–56% M).	**N=** 264 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall gender based on N=792 (M/F):** 393-444/348-399 (49.6–56% M).	✓	✓
China2[15, 16]							
Location: China **Recruitment dates:** Study period: March 24 to November 19, 2010 **Hib vaccine:** PRP-T, Infanrix-Hib or Infanrix-IPV+Hib, GlaxoSmithKline **Pertussis vaccine:** aP (3 component), Infanrix-Hib or Infanrix-IPV+Hib, GlaxoSmithKline **Funding:** 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 **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 (DTaP-IPV combined) **B:** 2, 3, 4 (DTaP-IPV combined) **C:** 2, 3, 4 (DTaP combined, IPV separate) **Additional information:**	**N=** 324 **Mean age at randomization (SD):** NR **Mean age vaccination (SD):** 3.3 (0.3) **Gender (M/F):** 147/177 (45.4% M).	**N=** 330 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** 2.3 (0.3) **Gender (M/F):** 155/175 (47% M).	**N=** 330 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** 2.3 (0.3) **Gender (M/F):** 141/189 (43% M).	✓	✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
Europe[17-22]							
Location: Austria, Germany, Greece **Recruitment dates:** August 2007 to October 2008 **Hib vaccine:** Booster: PRP-T, Infanrix-hexa; GlaxoSmithKline **Pertussis vaccine:** aP (3 component), Infanrix-hexa, GlaxoSmithKline **Funding:** 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 **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 **B:** 3p‡ +b12 **C:** 3p‡ +b12 (MenACWY-TT, separate at 12) **D:** 3p‡ **Additional information:** **A:** MenACWY-TT at 12 months. DTaP combined with Hib at 13 months **B:** MenACWY-TT at 13 months. DTaP combined with Hib at 12 months **C:** MenACWY-TT, separate at 12 months, DTaP combined with Hib at 12 months **D:** MenC conjugate at 12 months	**N=** 220 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** Booster dose: 15(3.3) **Gender (M/F):** 114/106 (51.8% M) **Schedule D:** **N=** 127 **Median age at randomization:** NR **Mean age at vaccination (SD):** Booster dose: 14.6(3.0) **Gender (M/F):** 66/61 (52% M)	**N=** 224 **Median age at randomization (SD):** NR **Mean age at vaccination (SD):** Booster dose: 14.9(3.17) **Gender (M/F):** 105/119 (46.9% M)	**N=** 224 **Median age at randomization (SD):** NR **Mean age at vaccination (SD):** Booster dose: 14.6(3.01) **Gender (M/F):** 113/109 (50.9% M)	✓	✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
France[23, 24]							
Location: France **Recruitment dates:** 1995 to 1996 **Hib vaccine:** PRP-T, Hexavac, Aventis Pasteur **Pertussis vaccine:** aP (2 component), Hexavac, Aventis Pasteur. **Funding:** Not stated, likely Aventis Pasteur	**Inclusion criteria:** healthy Infants already enrolled in the trial initiated for the investigational vaccine and who had received primary immunisation under schedules 2, 4, 6 and 2, 3, 4 in the study **Exclusion criteria:** none stated	**A:** 2, 4, 6 + b15-17 **B:** 2, 3, 4 + b15-17 **Additional information:** DTaP-HepB-IPV combined with Hib at each dose	**N=** 258 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR	**N=** 258 **Median age at randomization (SD):** NR **Mean age at vaccination (SD):**NR **Gender (M/F):** NR			✓
Gambia1[25-28]							
Location: The Gambia **Recruitment dates:** January 1 to December 31, 1985 **Hib vaccine:** PRP-OMP, PedvaxHib, Merck Sharp & Dohme **Pertussis vaccine:** Not given as part of trial. Not stated if wP or aP, assume wP given trial date. No brand name or manufacturer stated **Funding:** Merck Sharp & Dohme	**Inclusion criteria:** children living in the area of the health center, informed consent from mothers **Exclusion criteria:** none stated	**A:** 2, 4 **B:** 1, 3 **C:** No doses **Additional information:** 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 **C:** No control vaccine	**N=** 95 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR	**N=** 99 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR	**N=** 90 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** no Hib **Gender (M/F):** NR		✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
Gambia2 [29]							
Location: The Gambia **Recruitment dates:** 1990 **Hib vaccine:** PRP-T, ActHib, Pasteur Mérieux **Pertussis vaccine:** Not given as part of trial. Not stated if wP or aP, assume wP given trial date. No brand name or manufacturer stated **Funding:** Pasteur Mérieux	**Inclusion criteria:** Not stated **Exclusion criteria:** none stated	**A:** 2, 4 **B:** 1, 3 **C:** No doses **Additional information:** All children had EPI routine vaccination (not specified). Assume DTP separate from Hib	**N=** 43 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR	**N=** 45 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR	**N=** 40 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** NR		✓
Guatemala [30]							
Location: Guatemala **Recruitment dates:** March 1998 to August 1999 **Hib vaccine:** PRP-T, Hiberix, GlaxoSmithKline **Pertussis vaccine:** wP (combined schedule), Tritanrix, GlaxoSmithKline wP (separate schedule), Brand name and manufacturer not clearly stated **Funding:** GlaxoSmithKline	**Inclusion criteria:** healthy infants ≥6 weeks of age **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 **B:** 7, 9 (+b12) **Additional information:** All children had OPV at 2, 4, 6 and MMR at 9-12. **A:** Hib combined with DTwP and HepB **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[§] **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** 238/176 (57.5% M)	**N=**106[§] **Median age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** 56/50 (53% M)		✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
Netherlands[31]							
Location: The Netherlands **Recruitment dates:** March 1993 to September 2, 1994 **Hib vaccine:** PRP-T, brand name not stated, Pasteur Mérieux **Pertussis vaccine:** wP, brand name not stated, Pasteur Mérieux **Funding:** 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 **Exclusion criteria:** None stated	**A:** 3, 4, 5 +b11 (DTwP-IPV combined) **B:** 3, 4, 5 +b11 (DTwP-IPV separate) **C:** 6, 7+b13 **Additional information:** All children had MMR at 14 months.**A:** DTwP-IPV at 3, 4, 5, 11 in a combined injection. **B, C:** DTwP-IPV at 3, 4, 5, 11 as a separate injection.	**N=**180 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** 94/86 (52% M)	**N=**181 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** 102/79 (56% M)	**N=**182 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Gender (M/F):** 104/78 (57% M)		✓
Niger[32]							
Location: Niger **Recruitment dates:** January to November 1995 **Hib vaccine:** PRP-T, brand name not stated, Pasteur Mérieux **Pertussis vaccine:** Not stated if wP or aP, assume wP given trial date. Brand name not stated, Pasteur Mérieux **Funding:** 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 **Exclusion criteria:** none stated	**A:** 1.5, 2.5, 3.5 **B:** 2.5, 3.5 **C:** No doses **Additional information:** 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. **C:** Men A/C polysaccharide vaccine at 1.5, 3.5 months	**N=** 59 **Mean age at randomization:** NR **Overall mean age at vaccination (range):** 1st visit:1.9(0.9-2.8) 2nd visit:3.0(2.1-5.1) 3rd visit: 4.2(3.0-6.8) **Overal gender (M/F):** 93/87 (52% M).	**N=** 62 **Mean age at randomization:** NR **Overall mean age at vaccination (range):** 11st visit:1.9(0.9-2.8) 2nd visit:3.0(2.1-5.1) 3rd visit: 4.2(3.0-6.8) **Overal gender (M/F):** 93/87 (52% M).	**N=** 59 **Mean age at randomization:** NR **Overall mean age at vaccination (range):** No Hib **Overal gender (M/F):** 93/87 (52% M).		✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
Sweden[33, 34]							
Location: Sweden **Recruitment dates:** November 19, 1994 to April, 1995 **Hib vaccine:** PRP-T, ActHIB, Pasteur Mérieux Connaught **Pertussis vaccine:** aP (2 component), brand name not stated, Pasteur Mérieux Connaught **Funding:** 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) **Exclusion criteria:** none stated.	**A:** 2, 4, 6 +b13 **B:** 3, 5 +b12 **Additional information:** Both groups received DTaP-IPV in combination with Act-HIB in one injection.	**N=**118 **Median age at randomization (SD):** NR **Mean age at vaccination (SD):** NR but 98.8% of doses given within range stipulated in protocol **Gender (M/F):** NR	**N=**118 **Median age at randomization (SD):** NR **Mean age at vaccination (SD):** NR but 98.8% of doses given within range stipulated in protocol **Gender (M/F):** NR		✓	✓
Turkey[1]							
Location: Turkey **Recruitment dates:** October 1994 to March 1995 **Hib vaccine:** PRP-T, Act-HIB, Pasteur Mérieux Connaught. **Pertussis vaccine:** aP, brand name not stated, Pasteur Mérieux, Connaught **Funding:** 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 **Exclusion criteria:** none reported	**A:** 3, 4, 5 +b12-14 (DTaP combined) **B:** 3, 4, 5 +b12-14 (DTaP separate) **C:** 2, 4, 6 (DTaP separate) **Additional information:** **A:** DTaP at 3, 4, 5, 12-14,combined **B:** DTaP at 3, 4, 5, 12-14, separate syringe. **C:** DTaP at 2, 4, 6 in a separate syringe.	**N=** 74* **Mean age at randomization:** 2 (0.5) **Mean age at vaccination (SD):** 1st dose: 3.0 (0.2) 2nd dose: 4.1 (0.3) 3rd dose: 5.1 (0.3) Booster: 13.4 (1.1) **Gender (M/F):** 50/34 (60% M)	**N=** 78* **Median age at randomization:** 2 (0.5) **Mean age at vaccination (SD):** 1st dose: 3.0 (0.1) 2nd dose: 4.0 (0.2) 3rd dose: 5.1 (0.4) Booster: 13.5 (1.1) **Gender (M/F):** 41/42 (49% M)	**N=** 81* **Median age at randomization:** 2 (0.5) **Mean age at vaccination (SD):** 1st dose: 2.1 (0.2) 2nd dose: 4.0 (0.3) 3rd dose: 5.9 (0.3) No booster **Gender (M/F):** 51/32 (61% M)		✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
USA1[35]							
Location: USA **Recruitment dates:** August 8, 1991 to June 19, 1992 **Hib vaccine:** PRP-OMP, VaxHib, Merck & Co. PRP-HbOC, HibTiter, Praxis Biologics **Pertussis vaccine:** Not stated if wP or aP, assume wP given trial date. Brand name and manufacturer not stated **Funding:** 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 **Exclusion criteria:** none stated	**A:** 2 (PRP-OMP), 4, 6 (HbOC) **B:** 2 (HbOC), 4, 6 (PRP-OMP) **C:** 2, 4, 6 (HbOC) **D:** 2, 6 (PRP-OMP) **E:** 2, 4 (PRP-OMP) **Additional information:** DTP, OPV and MMR given to all groups "according to published guidelines". All children received unconjugated PRP vaccine at 15m. **D:** Placebo at 4m **E:** Placebo at 6m	**N=**36¶ **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall gender (M/F):** 140/117 (55% M) **Schedule D:** **N=**36 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall gender (M/F):** 140/117 (55% M)	**N=**35¶ **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall gender (M/F):** 140/117 (55% M) **Schedule E:** **N=**39 **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall gender (M/F):** 140/117 (55% M)	**N=**96¶ **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall gender (M/F):** 140/117 (55% M)		✓
USA2 [36]							
Location: USA **Recruitment dates:** NR **Hib vaccine:** PRP-T, ActHib, Pasteur Merieux HbOC, HibTiter, Lederle-Praxis Biologics **Pertussis vaccine:** Not stated if wP or aP, assume wP given trial date. Brand name and manufacturer not stated **Funding:** National Institutes of Health and Connaught Laboratories	**Inclusion criteria:** healthy infants, 0 months of age with signed informed consent from a parent **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) **B:** 2, 4, 6 (HbOC) **C:** 0, 2, 4, 6 (HbOC) **Additional information:** All children received regularly scheduled childhood immunizations including HepB, DTP, and OPV concurrently as separate injections at 2, 4, 6. **A and B:** DT at birth	**N=**NR (total in all groups 150)* **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall, gender (M/F):** 49% M	**N=**NR (total in all groups 150)* **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** 3rd:6.7 Other doses NR **Overall, gender (M/F):** overall 49% M	**N=**NR (total in all groups 150)* **Mean age at randomization (SD):** NR **Mean age at vaccination (SD):** NR **Overall, gender (M/F):** overall 49% M		✓

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Study details	*Participant characteristics*	*Schedule A / schedule B / schedule C*	*Schedule A population characteristics*	*Schedule B population characteristics*	*Schedule C population characteristics*	*Outcomes*	
						Mortality	*Immunological*
USA3[37, 38]							
Location: USA **Recruitment dates:** NR **Hib vaccine:** PRP-OMP, PedvaxHIB, Merck Sharp & Dohme **Pertussis vaccine:** Not described **Funding:** 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 **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 **B:** 2-6, 3-7 **Additional information:** No other vaccines described.	**N=** 27 **Mean age at randomization (SD):** 1st dose: 4.1 (1.6) 2nd dose: 6.1 (1.6) **Overall mean age at vaccination (SD):** 3.6(1.5) **Overall gender** at **randomization (M/F):** 33/21 (61% M)	**N=** 27 **Median age at randomization (SD):** 1st dose: 3.2 (1.3) 2nd dose: 4.2 (1.3) **Overall mean age at vaccination (SD):** 5.1(1.8) **Overall gender at randomization (M/F):** 33/21 (61% M)			✓

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; 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

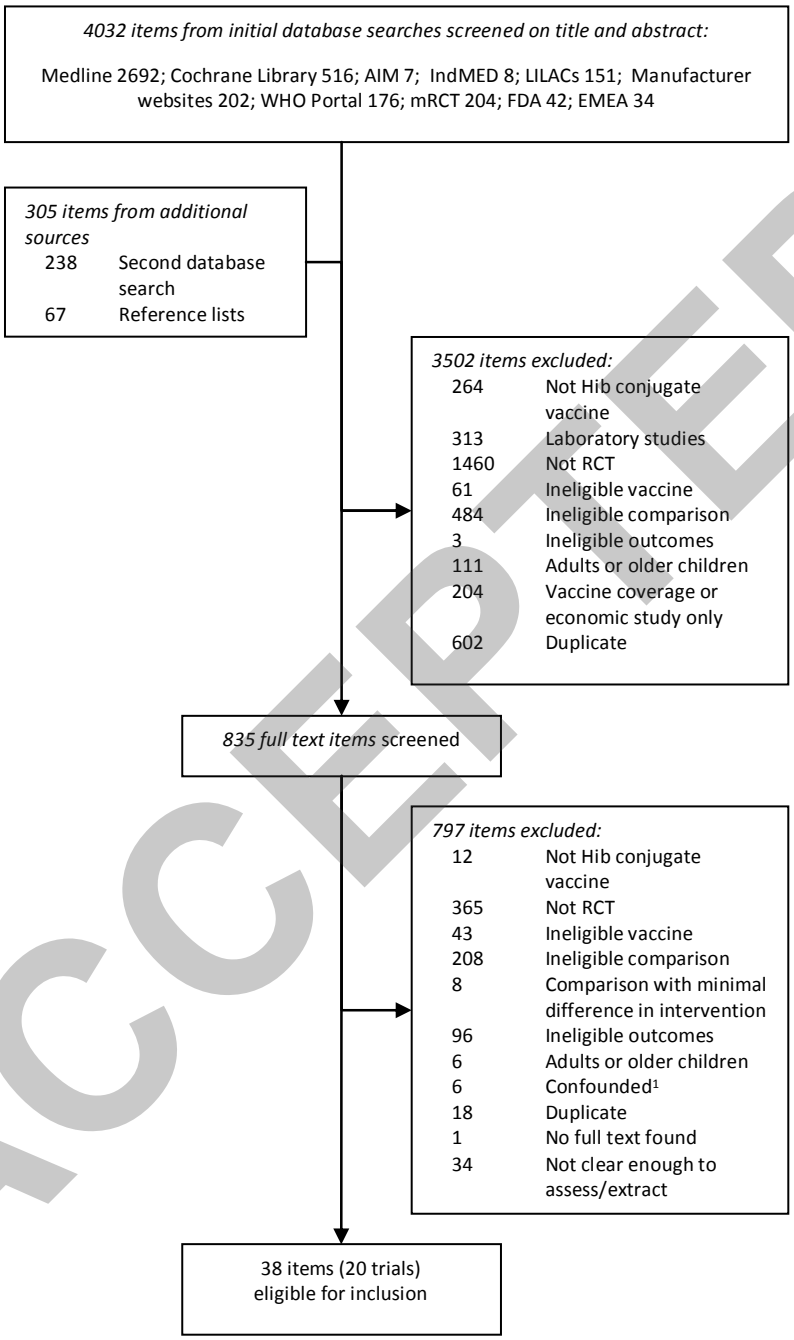
‡Type of conjugate vaccine in primary schedule (3p) not specified.

§ Group A includes 164 Ladino and 161 Native Indian participants; Group B includes 47 Ladino and59 Native Indian participants.

¶ Number of children followed-up. Numbers randomized to each group not reported. Total number randomized 497

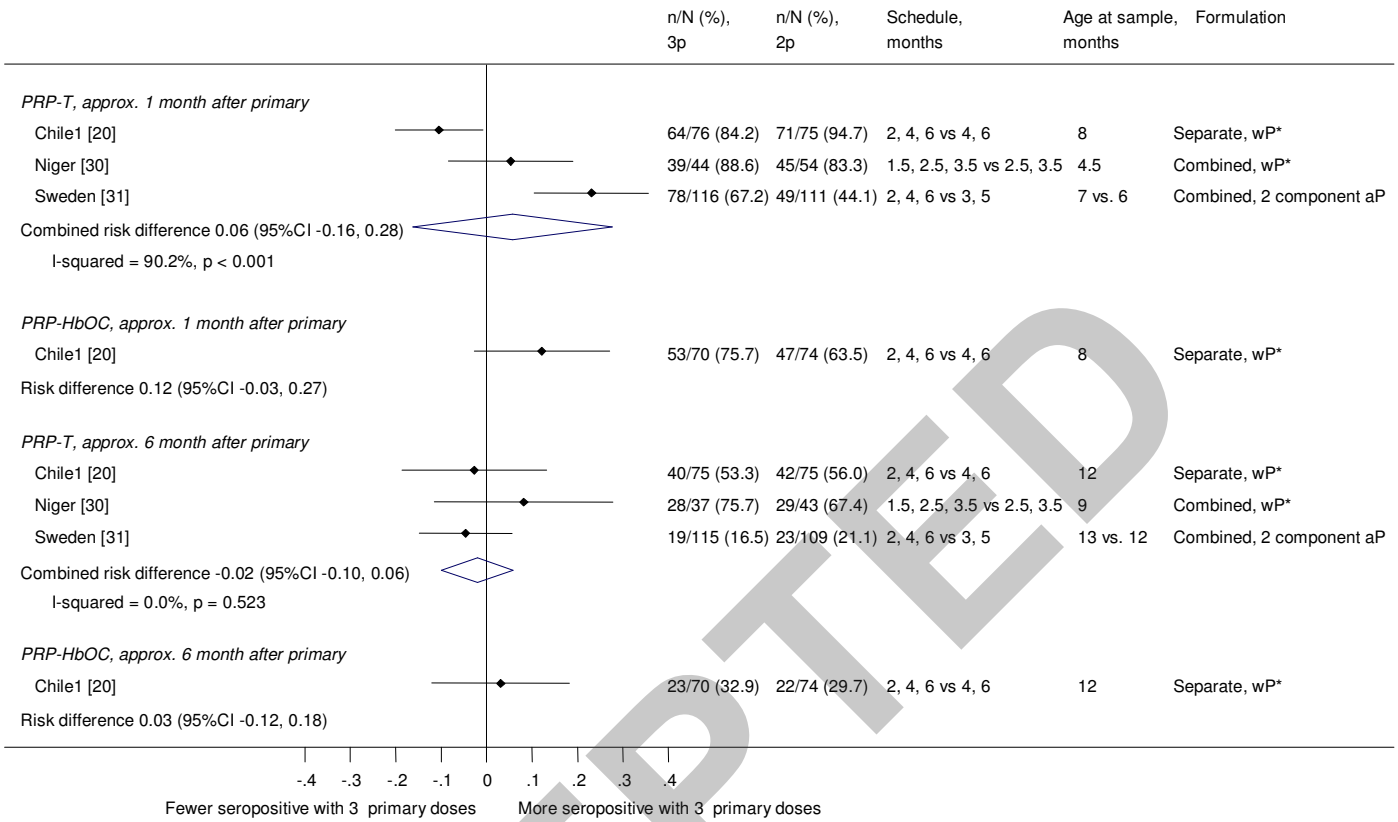
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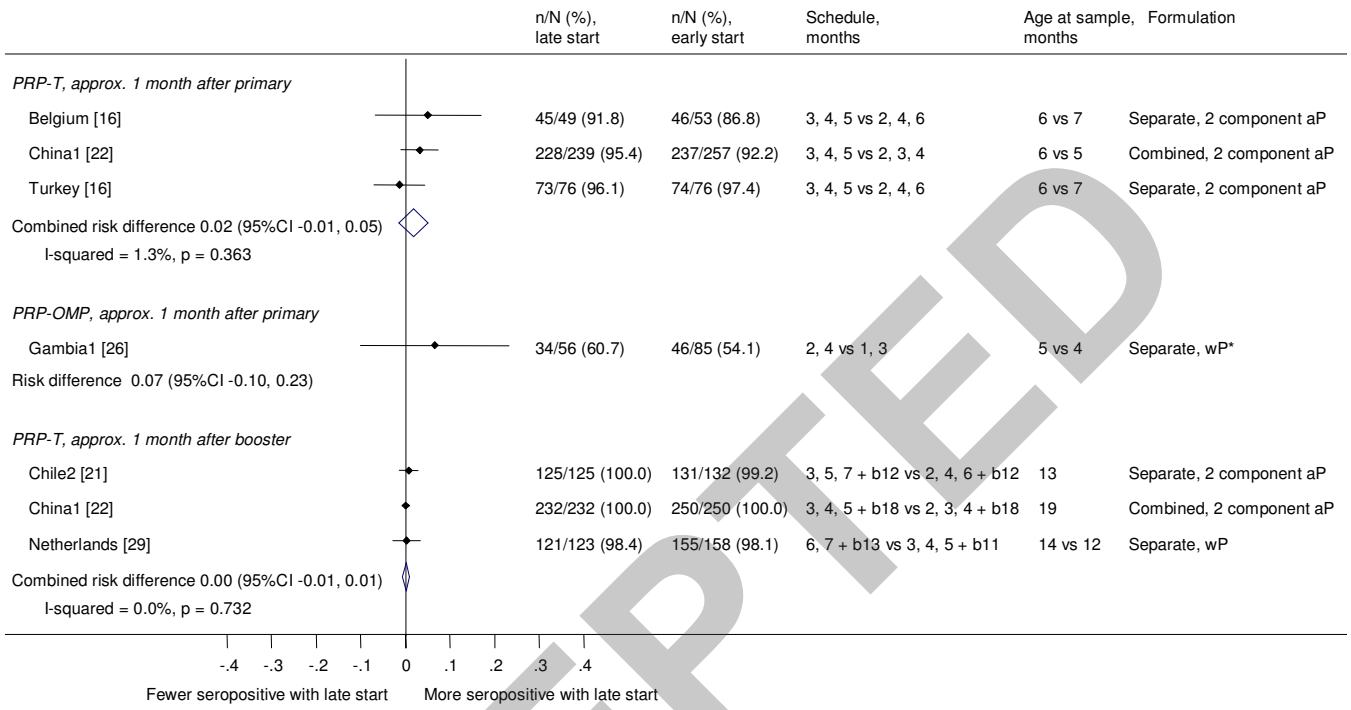
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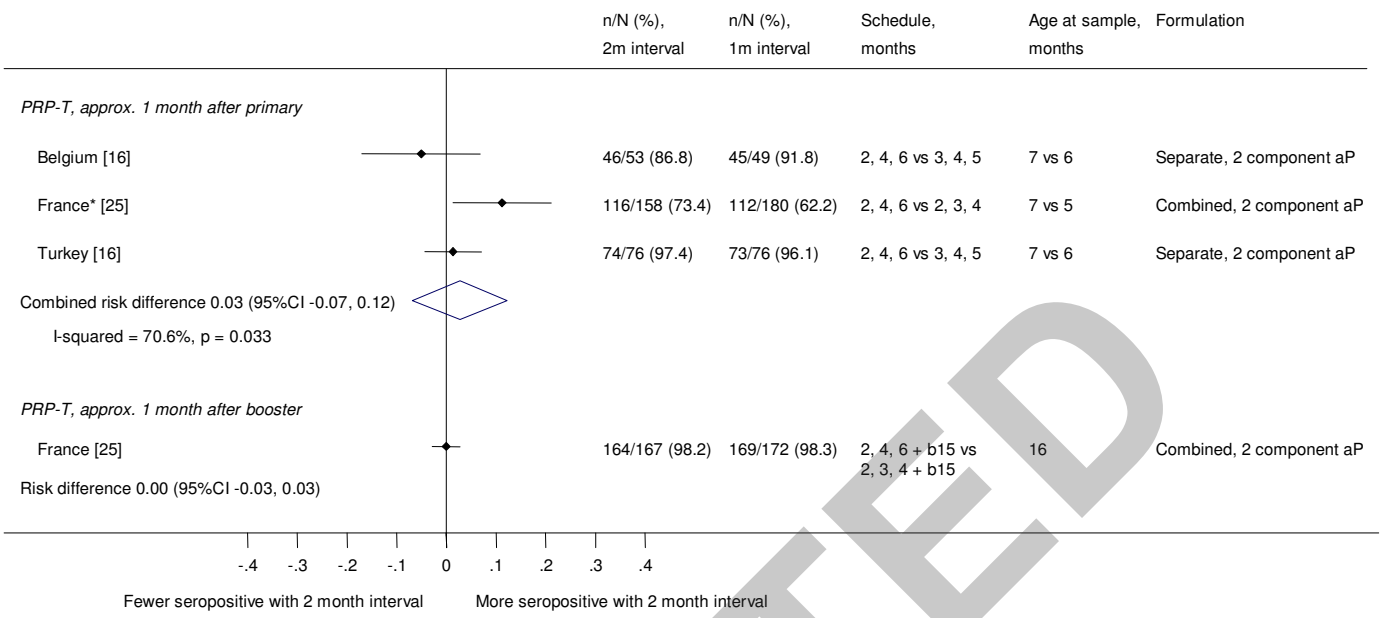
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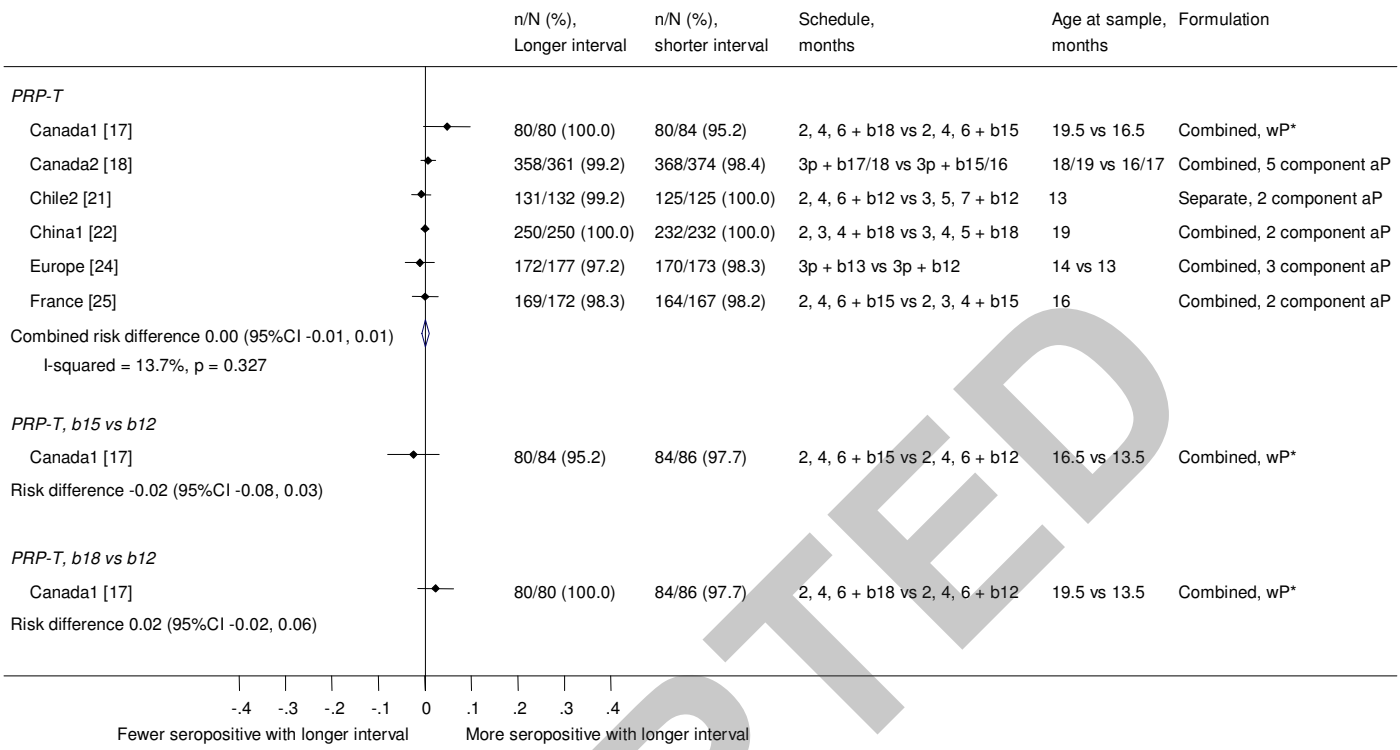
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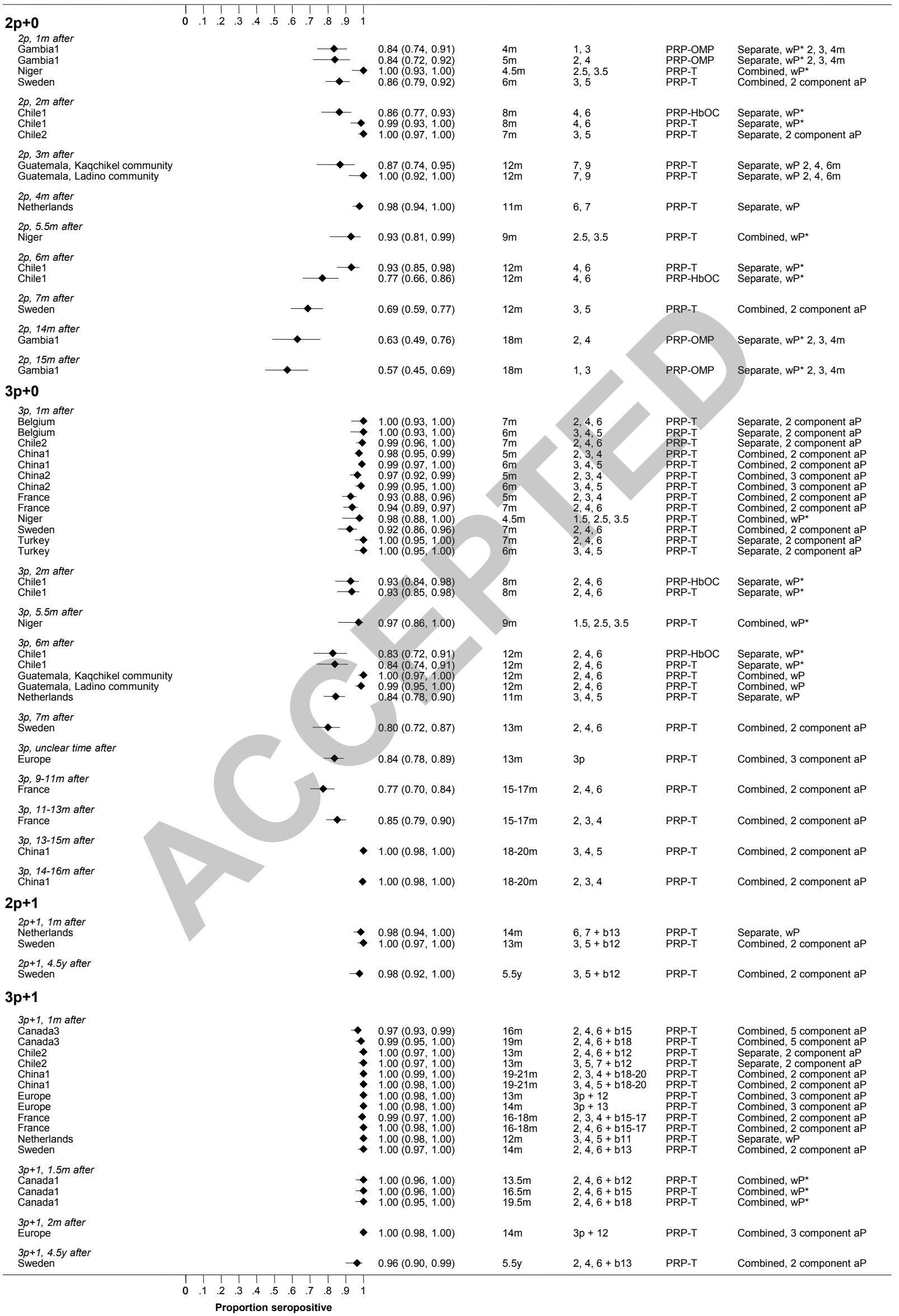
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Supplementary figure 1: Seropositivity after 2p, 3p, 2p+1 and 3p+1 schedules, 0.15µg/ml



Combined - Hib vaccine administered in the same syringe as pertussis containing vaccine; separate - Hib vaccine administered by itself, either at the same time as or at different time from other vaccines; aP - acellular pertussis vaccine ; wP - whole-cell pertussis vaccine

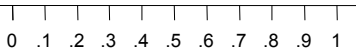
* not specified as whole cell pertussis vaccine but assumed to be whole cell due to year trial conducted

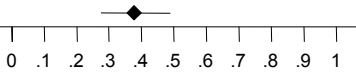
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Supplementary figure 2: Seropositivity after 2p, 3p, 2p+1 and 3p+1 schedules, 1.0µg/ml

Study, schedule and time since vaccination	Proportion seropositive (95%CI)	Age at blood draw	Intended schedule	Conjugate	Formulation
2p+0					
2p, 1m after					
Gambia1	0.54 (0.43, 0.65)	4m	1, 3	PRP-OMP	Separate, wP* 2, 3, 4m
Gambia1	0.61 (0.47, 0.74)	5m	2, 4	PRP-OMP	Separate, wP* 2, 3, 4m
Niger	0.83 (0.71, 0.92)	4.5m	2.5, 3.5	PRP-T	Combined, wP*
Sweden	0.44 (0.35, 0.54)	6m	3, 5	PRP-T	Combined, 2 component aP
USA1	0.58 (0.41, 0.74)	7m	2, 6	PRP-OMP	Separate, wP* according to guidelines
2p, 2m after					
Chile1	0.64 (0.52, 0.74)	8m	4, 6	PRP-HbOC	Separate, wP*
Chile1	0.95 (0.87, 0.99)	8m	4, 6	PRP-T	Separate, wP*
Chile2	0.95 (0.89, 0.98)	7m	3, 5	PRP-T	Separate, 2 component aP
2p, 3m after					
Guatemala, Kaqchikel community	0.87 (0.74, 0.95)	12m	7, 9	PRP-T	Separate, wP 2, 4, 6m
Guatemala, Ladino community	1.00 (0.92, 1.00)	12m	7, 9	PRP-T	Separate, wP 2, 4, 6m
USA1	0.38 (0.23, 0.55)	7m	2, 4	PRP-OMP	Separate, wP* according to guidelines
2p, 4m after					
Netherlands	0.81 (0.73, 0.87)	11m	6, 7	PRP-T	Separate, wP
2p, 5.5m after					
Niger	0.67 (0.51, 0.81)	9m	2.5, 3.5	PRP-T	Combined, wP*
2p, 6m after					
Chile1	0.56 (0.44, 0.67)	12m	4, 6	PRP-T	Separate, wP*
Chile1	0.30 (0.20, 0.41)	12m	4, 6	PRP-HbOC	Separate, wP*
2p, 7m after					
Sweden	0.21 (0.14, 0.30)	12m	3, 5	PRP-T	Combined, 2 component aP
2p, 9m after					
USA1	0.22 (0.09, 0.40)	15m	2, 6	PRP-OMP	Separate, wP* according to guidelines
2p, 11m after					
USA1	0.09 (0.02, 0.24)	15m	2, 4	PRP-OMP	Separate, wP* according to guidelines
2p, 14m after					
Gambia1	0.26 (0.15, 0.40)	18m	2, 4	PRP-OMP	Separate, wP* 2, 3, 4m
2p, 15m after					
Gambia1	0.27 (0.17, 0.39)	18m	1, 3	PRP-OMP	Separate, wP* 2, 3, 4m
3p+0					
3p, 1m after					
Belgium	0.87 (0.75, 0.95)	7m	2, 4, 6	PRP-T	Separate, 2 component aP
Belgium	0.92 (0.80, 0.98)	6m	3, 4, 5	PRP-T	Separate, 2 component aP
Chile2	0.96 (0.92, 0.99)	7m	2, 4, 6	PRP-T	Separate, 2 component aP
China1	0.92 (0.88, 0.95)	5m	2, 3, 4	PRP-T	Combined, 2 component aP
China1	0.95 (0.92, 0.99)	6m	3, 4, 5	PRP-T	Combined, 2 component aP
France	0.62 (0.55, 0.69)	5m	2, 3, 4	PRP-T	Combined, 2 component aP
France	0.73 (0.66, 0.80)	7m	2, 4, 6	PRP-T	Combined, 2 component aP
Niger	0.89 (0.75, 0.96)	4.5m	1.5, 2.5, 3.5	PRP-T	Combined, wP*
Sweden	0.67 (0.58, 0.76)	7m	2, 4, 6	PRP-T	Combined, 2 component aP
Turkey	0.97 (0.91, 1.00)	7m	2, 4, 6	PRP-T	Separate, 2 component aP
Turkey	0.96 (0.89, 0.99)	6m	3, 4, 5	PRP-T	Separate, 2 component aP
3p, 2m after					
Chile1	0.84 (0.74, 0.92)	8m	2, 4, 6	PRP-T	Separate, wP*
Chile1	0.76 (0.64, 0.85)	8m	2, 4, 6	PRP-HbOC	Separate, wP*
3p, 5.5m after					
Niger	0.76 (0.59, 0.88)	9m	1.5, 2.5, 3.5	PRP-T	Combined, wP*
3p, 6m after					
Chile1	0.53 (0.41, 0.65)	12m	2, 4, 6	PRP-T	Separate, wP*
Chile1	0.33 (0.22, 0.45)	12m	2, 4, 6	PRP-HbOC	Separate, wP*
Guatemala, Kaqchikel community	0.95 (0.90, 0.98)	12m	2, 4, 6	PRP-T	Combined, wP
Guatemala, Ladino community	0.89 (0.82, 0.93)	12m	2, 4, 6	PRP-T	Combined, wP
Netherlands	0.40 (0.32, 0.48)	11m	3, 4, 5	PRP-T	Separate, wP
3p, 7m after					
Sweden	0.17 (0.10, 0.25)	13m	2, 4, 6	PRP-T	Combined, 2 component aP
3p, unclear time after					
Europe	0.39 (0.32, 0.47)	13m	3p	PRP-T	Combined, 3 component aP
3p, 9-11m after					
France	0.26 (0.19, 0.33)	15-17m	2, 4, 6	PRP-T	Combined, 2 component aP
3p, 11-13m after					
France	0.40 (0.32, 0.48)	15-17m	2, 3, 4	PRP-T	Combined, 2 component aP
3p, 13-15m after					
China1	0.75 (0.69, 0.80)	18-20m	3, 4, 5	PRP-T	Combined, 2 component aP
3p, 14-16m after					
China1	0.74 (0.68, 0.79)	18-20m	2, 3, 4	PRP-T	Combined, 2 component aP
2p+1					
2p+1, 1m after					
Netherlands	0.98 (0.94, 1.00)	14m	6, 7 + b13	PRP-T	Separate, wP
Sweden	0.95 (0.90, 0.98)	13m	3, 5 + b12	PRP-T	Combined, 2 component aP
2p+1, 4.5y after					
Sweden	0.44 (0.33, 0.55)	5.5y	3, 5 + b12	PRP-T	Combined, 2 component aP
3p+1					
3p+1, 1m after					
Canada2	0.98 (0.97, 0.99)	17/18m	3p + b16/17	PRP-T	Combined, 5 component aP
Canada2	0.99 (0.98, 1.00)	18/19m	3p + b17/18	PRP-T	Combined, 5 component aP
Chile2	0.99 (0.96, 1.00)	13m	2, 4, 6 + b12	PRP-T	Separate, 2 component aP
Chile2	1.00 (0.97, 1.00)	13m	3, 5, 7 + b12	PRP-T	Separate, 2 component aP
China1	1.00 (0.99, 1.00)	19-21m	2, 3, 4 + b18-20	PRP-T	Combined, 2 component aP
China1	1.00 (0.98, 1.00)	19-21m	3, 4, 5 + b18-20	PRP-T	Combined, 2 component aP
Europe	0.98 (0.95, 1.00)	13m	3p + 12	PRP-T	Combined, 3 component aP
Europe	0.97 (0.94, 0.99)	14m	3p + 13	PRP-T	Combined, 3 component aP
France	0.98 (0.95, 1.00)	16-18m	2, 3, 4 + b15-17	PRP-T	Combined, 2 component aP
France	0.98 (0.95, 1.00)	16-18m	2, 4, 6 + b15-17	PRP-T	Combined, 2 component aP
Netherlands	0.98 (0.95, 1.00)	12m	3, 4, 5 + b11	PRP-T	Separate, wP
Sweden	0.99 (0.95, 1.00)	14m	2, 4, 6 + b13	PRP-T	Combined, 2 component aP
3p+1, 1.5m after					
Canada1	0.98 (0.92, 1.00)	13.5m	2, 4, 6 + b12	PRP-T	Combined, wP*
Canada1	0.95 (0.88, 0.99)	16.5m	2, 4, 6 + b15	PRP-T	Combined, wP*
Canada1	1.00 (0.95, 1.00)	19.5m	2, 4, 6 + b18	PRP-T	Combined, wP*
3p+1, 2m after					
Europe	0.97 (0.93, 0.99)	14m	3p + 12	PRP-T	Combined, 3 component aP
3p+1, 4.5y after					
Sweden	0.38 (0.27, 0.49)	5.5y	2, 4, 6 + b13	PRP-T	Combined, 2 component aP





Combined - Hib vaccine administered in the same syringe as pertussis containing vaccine; separate - Hib vaccine administered by itself, either at the same time as or at different time from other vaccines; aP - acellular pertussis vaccine ; wP - whole-cell pertussis vaccine

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

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