# Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB) (Review)

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[Intervention Review]

# Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

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## ABSTRACT

### Background

Advantages to combining childhood vaccines include reducing the number of visits, injections and patient discomfort, increasing compliance, and optimizing prevention. The World Health Organization recommends that routine infant immunization programs include a vaccination against *Haemophilus influenza* type B (HIB) in the combined diphtheria, tetanus, pertussis (DTP)-hepatitis B (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure their acceptability by the community.

### Objectives

To compare the effectiveness of combined DTP-HBV-HIB vaccine with DTP-HBV and HIB vaccinations.

### Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 1) which contains the Acute Respiratory Infection Group's Specialized Register; MEDLINE (January 1966 to March 2009) and EMBASE (January 1990 to March 2009).

### Selection criteria

Randomized or quasi-randomized controlled trials comparing vaccination with any combined DTP-HBV-HIB vaccine, with or without three types of inactivated poliovirus (IPV) or concomitant oral polio vaccine (OPV) in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants aged up to two years.

### Data collection and analysis

Two review authors independently inspected references identified by the searches and evaluated them against the inclusion criteria, extracted data and assessed the methodological quality of included trials.

**Main results**

Meta-analysis was performed to pool the results of 18 studies. There were no data on clinical outcomes for the primary outcome and all studies used immunogenicity and reactogenicity (adverse events). In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and HBV. Comparison found little heterogeneity. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and tetanus. Serious adverse events were comparable. Minor adverse events were more common in children given the combined vaccine.

**Authors' conclusions**

We could not conclude that the immune responses elicited by the combined vaccine were different from, or equivalent to, the separate vaccines. Data for the primary outcome (prevention of disease) were lacking. There was significantly less immunological response for HIB and HBV, and more local reactions in the combined injections. However, these differences rely mostly on one study each. Studies did not use an intention-to-treat analysis and we were uncertain about the risk of bias in many of the studies. These results are therefore inconclusive. Studies addressing clinical end-points whenever possible, using correct methodology and a large enough sample size should be conducted.

## PLAIN LANGUAGE SUMMARY

**Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for prevention of diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* B in healthy infants up to two years of age**

Childhood vaccinations provide an effective method of protection against many diseases. There are multiple advantages to combining vaccines: reducing the number of visits, injections and patient discomfort, increasing compliance, and optimizing prevention. The World Health Organization recommends that routine infant immunization programs include a vaccination against *Haemophilus influenzae (H. influenza)* type B (HIB) in the combined diphtheria, tetanus, pertussis (DTP)-hepatitis B (HBV) vaccination. The effect of adding a conjugate HIB vaccination to the DTP-HBV vaccine, compared to a separate injection for preventing these diseases, has yet to be assessed.

The objective of this review was to compare the effectiveness of the combined DTP-HBV-HIB vaccine with the separate DTP-HBV and HIB vaccines. No data on clinical outcomes for the primary outcome was found. All included studies reported only on immunogenicity, defined as antibody concentration responses to tetanus, diphtheria, pertussis, hepatitis B and *H. influenzae* type B and reactogenicity, defined as systematic and local adverse events to vaccination.

Eighteen published randomized or quasi-randomized clinical trials, comparing vaccination with any combined DTP-HBV-HIB vaccine with or without three types of inactivated poliovirus (IPV) or concomitant oral polio vaccine (OPV) given in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants aged up to two years, were included. In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and HBV. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and tetanus. Serious adverse events were comparable. Minor adverse events were more common in children given the combined vaccine.

Overall, the level of evidence provided by the studies was low, and we could not conclude that the immune responses elicited by the combined vaccine are equivalent to the separate injections. The combined vaccine did not result in a significant increase in the incidence of serious adverse events, but caused more minor reactions.

## BACKGROUND

### Description of the intervention

Childhood vaccinations provide a clinically-effective and cost-ef-

fective method of protecting against many diseases. Combination vaccines have been in widespread use since the 1940s. Diphtheria, tetanus and pertussis (DTP) is one such vaccine and it is estimated that the DTP infant vaccine coverage exceeds 80% worldwide ( Faingezicht 2002). There are multiple advantages to combining vaccines, for example, reducing the number of visits and injections, increasing compliance, reducing patient discomfort, optimizing prevention and reducing operational costs. This might not be the case in some countries like in the United States where combination vaccines are often more expensive than the separate components. Assessment of the immune responses to combination vaccines has generally been based on randomized controlled comparative trials. The US Food and Drug Administration (FDA) recommends that clinical trials compare the immune responses elicited by the combination vaccine versus separate injections or other appropriate controls. End points commonly used for evaluating combination vaccines include the percentage of people responding to an antigen with a predefined antibody level and the geometric mean concentration (GMC) or geometric mean titer (GMT) of antibodies elicited by the component (Ball 2001).

### How the intervention might work

The World Health Organization (WHO) recommends that routine infant immunization programs include a vaccination against *Haemophilus influenzae* (*H. influenzae*) type B (HIB) in the combined DTP-HBV injection (WHO 1998). HIB is an important pathogen in both high and low income countries. The DTP-HBV combination vaccine would make an ideal partner for combining with HIB vaccines, because DTP is mandatory in most immunization programs, whereas the HB vaccine (HBV) is already in widespread use (Santos 2002).

### Why it is important to do this review

The strategy of combining hepatitis B vaccination (HBV) with the DTP vaccine has already been adopted into immunization programs (Riedemann 2002). The effectiveness and safety of adding a conjugate HIB vaccination to the DTP-HBV vaccine, compared with separate administrations, for preventing these diseases has yet to be systematically assessed. The immunogenicity and reactogenicity (adverse events) results of five published clinical trials involving Trinanrix-HB/HIB in a variety of immunization schedules and countries were reviewed for its suitability for use in national immunization programs (Aristegui 2003). Despite its use in accordance with the WHO recommendation in several countries, no systematic review of the effectiveness and safety of the combined vaccine is available.

## OBJECTIVES

The objective of the review is to assess the clinical protection, immunogenicity and reactogenicity (adverse events) of a combined DTP, applied to both DTPw (whole cell pertussis) and DTPa (acellular pertussis) vaccines, HBV and conjugate HIB vaccine, with or without three types of inactivated poliovirus (IPV) or concomitant oral polio vaccine (OPV), in comparison with separate vaccinations of DTP, HBV conjugate HIB, IPV and OPV, in infants up to two years of age.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials (RCTs) or quasi-RCTs.

#### Types of participants

Healthy male and female infants aged up to two years.

#### Types of interventions

The interventions were vaccination with any combined DTP (applied to both DTPw and DTPa vaccines) -HBV-conjugate HIB vaccine with or without three types of inactivated poliovirus (IPV) or concomitant oral polio vaccine (OPV) given in any dose, preparation or time schedule, compared with separate vaccines or placebo, administered to infants aged up to two years. All studies identified tested the effectiveness of combined DTP-HBV-conjugate HIB vaccine.

#### Types of outcome measures

##### Primary outcomes

Incidence of diphtheria, tetanus, pertussis, hepatitis B and *H. influenzae* type B post-vaccination.

##### Secondary outcomes

Immunogenicity, (defined as antibody responses to tetanus, diphtheria, pertussis, hepatitis B and *H. influenzae* type B).
Systemic and local adverse events, including fever, pain, redness, swelling, irritability, drowsiness, loss of appetite, vomiting and more generalized and severe signs, including potential adverse events which have been hypothesized related to the vaccination.

### Search methods for identification of studies

### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 1) which contains the Acute Respiratory Infection Group's Specialized Register; MEDLINE (January 1966 to March 2009) and EMBASE (January 1990 to March 2009).

The following terms were used to search CENTRAL and MEDLINE. The search strategy was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format (Lefebvre 2008). There were no language or publication restrictions.

**MEDLINE (OVID)**

1 Diphtheria-Tetanus-Pertussis Vaccine/
2 Diphtheria-Tetanus-acellular Pertussis Vaccines/
3 (diphtheria and tetanus and pertussis).mp.
4 (dtp* or dtap*).tw.
5 1 or 2 or 3 or 4
6 exp Haemophilus Vaccines/
7 exp Haemophilus influenzae type b/
8 exp HAEMOPHILUS/
9 (haemophilus or hemophilus).mp.
10 Hib.mp.
11 or/6-10
12 exp Hepatitis B Vaccines/
13 exp Hepatitis B/
14 (hepatitis b or HBV).mp.
15 or/12-14
16 5 and 11 and 15

### Searching other resources

We modified the above terms and filter developed by Wong (Wong 2006) to fit with the Embase.com interface (see Appendix 1). In addition, we scrutinized clinical practice guideline reference lists to identify further trials. We also checked relevant RCT references for additional studies. We looked for eligible titles and abstracts in electronic search results and obtained the full text of articles we identified as potentially eligible. The bibliographies of all included studies and pertinent reviews were scanned for additional references.

We searched the following conference proceedings for unpublished trials: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 1995 to 2006 (available at http://www.icaac.org/icaacarch.asp); European Congress of Clinical Microbiology and Infectious Diseases 2001 to 2006 (available at http://www.akm.ch); and the Annual Meeting of the Infectious Diseases Society of America (IDSA) 2001 to 2006 (available at http://www.idsociety.org/).

## Data collection and analysis

### Selection of studies

Two review authors (ESB, EG) independently inspected references identified by the searches and evaluated them against the inclusion criteria. Disagreements in the selection of relevant studies were resolved by consensus. For possible relevant articles, or in cases of disagreement between the two review authors, the full article was obtained and inspected independently by the two review authors. A third review author (LL) was consulted in cases of continued disagreement. The reasons for excluding studies are detailed.

### Data extraction and management

Two review authors (EB, EG) independently performed the data extraction and assessed the methodological quality of each included trial. Per each treatment group, the data collected was as follows:

- Intervention characteristics (vaccination type, manufacturer, number of doses, schedule);
- Characteristics of trial (publication year, start date, end date, study design, country where trial was preformed, data collection method, location of trial, date evaluated);
- Quality assessment (blinding, unit of allocation, allocation generation, allocation concealment);
- Case definitions - characteristics of participants (exclusion, inclusion, age, number randomized);
- Outcomes:

Immunogenicity - antibody concentrations by serological analysis
Number participated, exclusion (post-random = evaluated for serology), number with antibody concentrations above the assay cut-offs (PRP-polyribsylribitolphosphate, PRP-T (vaccine conjugated to tetanus toxoid), FHA -filamentous hemagglutinin, PRN - pertactin, BPT - Pertussis (PTox pertussis toxin, *Bordetella pertussis* (*B. pertussis*), HBs - Hepatitis B, D-Diphtheria, T-Tetanus, Polio type 1, Polio type 2, Polio type 3).
Reactogenicity - adverse events
Number of vaccines, number of participants and number of events (serious adverse events; pain; redness; swelling; fever (temperature); fussiness or restlessness; poor appetite; vomiting; irritability or tenderness; diarrhea; unusual crying; sleeping more than usual).

### Assessment of risk of bias in included studies

We used an individual component approach to quality assessment (Chalmers 1990) with the following variables: generation of the allocation sequence, allocation concealment and blinding and intention-to-treat analysis. Allocation concealment and generation have been graded as

A - adequate measures to conceal allocation (central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered sealed opaque envelopes; other convincing),
B - no report of allocation concealment or not A/C,

C - Inadequate concealment of allocation (non-concealed table, non-opaque envelopes),
A/B - sealed envelopes, opaque not mentioned.
Assessment of bias was performed through sensitivity analyses for allocation concealment, based on previous evidence showing overestimation of effects with inadequate allocation concealment ( Schulz 1955). Studies with a dropout rate above 30% were excluded unless an intention-to-treat analysis was possible for any outcome. Information was recorded in a pre-designed data extraction form.

### Unit of analysis issues

No studies were found reporting on the main outcome, i.e. incidence of diphtheria, tetanus, pertussis, hepatitis B and *H. influenzae* type post-vaccination. All studies reported on immunogenicity, defined as antibody concentration responses to tetanus, diphtheria, pertussis, hepatitis B and *H. influenzae* type B. Meta-analysis was performed to pool the results of 17 studies. Vaccine immunogenicity was analyzed in sub-categories, according to two types of pertussis vaccination: acellular pertussis (DTPa) and whole cell pertussis (DTPw).
Infants with no seroprotective antibody titers (with titers below the assay cutoff or without seroconversion) were defined as events.
Studies reported combined inactivated polio virus (IPV) in the DTP-HBV-HIB vaccine and oral poliovirus vaccine (OPV) administered concurrently, and therefore we included results of anti-polio type 1, 2 and 3. Reactogenicity (adverse events) were analyzed by events of total symptom scores (incidence of any solicited local and systemic adverse events). Serious adverse events reported by investigators included pain, redness, swelling, fever (temperature), fussiness or restlessness, poor appetite, vomiting, irritability or tenderness, diarrhea, unusual crying, or sleeping more than usual.

### Data synthesis

Dichotomous data were analyzed by calculating the relative risk (RR) for each trial with the uncertainty in each result expressed using 95% confidence intervals (CI). Heterogeneity in the results of the trials was initially assessed by inspection of graphical presentations and by calculating an estimate of heterogeneity (chi square, I-square ($I^2$) statistic). A random-effects model was used throughout the review. Data were pooled, stratifying for number of doses received. Sensitivity analysis was performed in order to assess the impact of possible sources of heterogeneity in the main results. A funnel plot estimating the precision of trials (the inverse of the standard error plotted against relative risk) was examined in order to estimate potential selection bias (publication or other). Asymmetry of the funnel plot has been formally expressed using the method described by Egger (Egger 1997).

## RESULTS

### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

#### Results of the search

We identified 199 studies and 52 of these were considered potentially eligible.

#### Included studies

Eighteen studies were included. Two different types of pertussis vaccination were used in the studies. Nine studies used acellular pertussis (DTPa) and nine studies used whole cell pertussis (DTPw). In five studies IPV was combined with DTP-HBV-HIB vaccine (Aristegui 2003; Avdicova 2002; Gabutti 2004; Mallet 2000; Schmitt 2000), while three studies reported oral poliovirus vaccine administered to all vaccinees in both groups concurrently (Nolan 2001; Omenaca 2001; Pichichero 1997).

#### Excluded studies

Thirty-four studies were excluded. Four studies were not true RCTs: one (Kalies 2004) was an observational study; one trial was a single group design (Lopez 2002), one was a presentation of data from investigations on the nature and function of anti-Hib antibodies (Poolman 2001) and one was a report of four primary and booster-based pediatric clinical trials (Denoel 2007).
Six trials compared two different types of combined vaccines ( Aristegui 2001; Gatchalian 2005; Gylca 2001; Scheifele 2006; Tichmann 2005; Tichmann-Schumann 2005).
Three trials compared combined DTP/HIB and separate DTP + HIB vaccination without HBV (Botet-Asensi 2003; Calbo 2002; Huang 1998).
One trial compared combined DTPa-HBV-IPV with separate DTPa-HBV and IPV vaccines (Meriste 2006).
Two trials compared combined DTPw-HepB-Hib vaccine with separately administered DTPw-Hib and hepatitis B vaccines ( Kanra 2006, Lim 2007)).
One trial compared between primary and booster combined vaccines (Hla 2006).
One trial compared the fourth dose of combined DTPa-IPV/PRP-T with the third dose of combined vaccine (Scheifele 2005).
One trial compared combined DTPa-HBV-IPV-Hib vaccine and PCV7 vaccine with DTPa-HBV-IPV-Hib (Knuf 2006).
One trial compared three lots of *H. influenzae* type B conjugate vaccines (Aristegui 1998).
One study compared Lot-to-Lot consistency of combined vaccines and not with separate vaccines (Lagos 2005).
One trial compared a new combined DTPw-HBV/HIB vaccine of HIB Lot 001A44 to HIB Lot 002A41 (Usonis 1999b).

One trial was a comparison between a five-component pertussis combination vaccine CPDT-IPV/PRP-T to that of whole cell pertussis combination vaccine DPT-IPV/PRP-T (Mills 1998).
One trial compared five-component vaccine DTPa-HepB-IPV-PCV-7 and Hib with separate vaccines concurrently or staggered (delayed) administration of PCV-7 (Pichichero 2007).
We excluded another two trials that compared novel and local licensed DTPw/HIB vaccines (Clemens 2003) and the reactogenicity (adverse events) and immunogenicity of four commercial HIB vaccines (Usonis 1999a). Another five trials that had no comparison between vaccines were excluded (Bavdekar 2007; Hogg 2003; Pichichero 1999; Trollfors 2005; Zepp 1997). Three additional trials were excluded: in the first trial only data of safety and reactogenicity (adverse events) were provided (Zepp 2004) and the second trial included the same trials reported elsewhere while only safety data was provided (Saenger 2005). In the third excluded study, only data on antibody persistence (immunogenicity) of plain PRP and conjugate PRP-T was provided (Nolan 2004).

## Risk of bias in included studies

### Allocation

#### Allocation concealment

Only two of the studies reported adequate allocation concealment (Mallet 2000; Nolan 2001). One study reported inadequate allocation concealment (Bravo 1998).

#### Allocation generation

Only three studies reported adequate generation allocation ( Faingezicht 2002; Nolan 2001; Omenaca 2001). One study reported randomization "in the order in which they enrolled between two groups", which was considered to be inadequate allocation generation (Bravo 1998).

#### Unit of allocation

All of the studies used infants or neonates as units of allocation.

### Blinding

In one study where the term "double blind" was used, it is not clear who was blinded (Nolan 2001). One study reported that three different production lots of the combined vaccine were used in a double blind manner but not for the control group (Tregnaghi 2006). In six studies blinding of assessors and/or laboratory personnel was reported (Faingezicht 2002; Greenberg 2000; Mallet 2000; Nolan 2001; Pichichero 1997; Win 1997). Blinding of parents may not be relevant in the case of the infant's vaccination. Measurement of outcomes may not be influenced by the lack of blinding.

### Other potential sources of bias

#### Intention-to-treat analysis

No study clearly mentioned that the intention-to-treat principle was used in the analysis. Most studies excluded participants from analysis if they were leaving the study area, were lost to follow up, had an unsatisfactory compliance or protocol violation, parental request or consent was withdrawn, or experienced unrelated medical problems or death.

## Effects of interventions

### Immunogenicity: antibody concentrations by serological analysis

Data were not stratified for number of doses received. Last dose of the vaccines was extracted, excluding a booster dose.

#### Anti-PRP (HIB) titers below the assay cutoff 0.15 µg/ml

Three studies of DTPa-HBV-HIB vaccines and three studies of DTPw-HBV-HIB vaccines were estimated. Four studies of DTPa-HBV-HIB and four studies of DTPw-HBV-HIB reported no events. No significant difference was found between combined and separate DTPa-HBV-HIB vaccines and DTPw-HBV-HIB vaccines (RR 1.35, 95% CI 0.55 to 3.32) . No significant difference was found between combined and separate DTPw-HBV-HIB vaccines (RR 0.42, 95% CI 0.10 to 1.70) . Significant difference was found (RR 2.73, 95% CI 1.19 to 6.22) between combined and separate DTPa-HBV-HIB vaccines.

#### Anti-PRP (HIB) titers below the assay cutoff 1.0 µg/ml

Eight studies of DTPa-HBV-HIB vaccines and five studies of DTPw-HBV-HIB vaccines reported on this outcome. No significant difference was found between combined and separate vaccines (RR 1.26, 95% CI 0.79 to 2.01). No significant difference was found between combined and separate DTPw-HBV-HIB vaccines (RR 0.77, 95% CI 0.39 to 1.52). A significant difference was found between combined and separate DTPa-HBV-HIB vaccines (RR 2.09, 95% CI 1.20 to 3.64). For the DTPa-HBV-HIB comparison we found little heterogeneity, $I^2$ = 33%.
Exclusion of Pichichero 1997, which donated most of the outcomes, resulted in a point estimate still in favor of the separate vaccines, but no longer significant in a random-effects model, RR 1.67, 95% CI 0.85 to 3.28 for the DTPa-HBV-HIB vaccines. However there is no significant heterogeneity for this comparison, ($\chi$2 =6.3, d.f.=5, P = 0.3; and $I^2$=21% for the DTPa-HBV-HIB vaccines; and $\chi$2=16.4, d.f.=10, P = 0.09; and $I^2$= 39% for all studies). Using a fixed-effect model, the difference is significant even with the exclusion of Pichichero 1997, RR 1.83, 95% CI

1.17 to 2.86 for the DTPa-HBV-HIB vaccines; and RR 1.34, 95% CI 1.04 to 1.73 for all studies.

#### Anti-FHA (filamentous hemagglutinin) - no seroprotective titers

No significant difference was found between combined and separate DTPa-HBV-HIB vaccines (RR 0.66, 95% CI 0.11 to 3.75). Three studies of DTPa-HBV-HIB were estimated with total of four events. Four studies had no events (Avdicova 2002; Gabutti 2005; Gabutti 2004; Omenaca 2001).

#### Anti-PRN - no seroprotective titers

No significant difference was found between combined and separate DTPa-HBV-HIB vaccines (RR 0.70, 95% CI 0.15 to 3.23). Three studies of DTPa-HBV-HIB were estimated with total of seven events. Four studies had no events (Gabutti 2004; Gabutti 2005; Omenaca 2001; Pichichero 1997).

#### Anti-BPT (Pertussis) - no seroprotective titers

No significant difference (RR 1.12, 95% CI 0.42 to 3.00) between combined and separate DTPa-HBV-HIB vaccines (RR 0.47, 95% CI 0.04 to 5.12) and DTPw-HBV-HIB combined and separate vaccines (RR 1.34, 95% CI 0.45 to 3.95). One study of DTPa-HBV-HIB was included with a total of three events. Five studies of DTPw-HBV-HIB were estimated with a total of three events in the separate vaccines and eleven events in the combined vaccine. Three studies had no events (Win 1997; Ramkissoon 2001; Santos 2002).

#### Anti-D (Diphtheria): titers below the assay cutoff

No significant difference (RR 0.96, 95% CI 0.42 to 2.20) between combined and separate DTPa-HBV-HIB vaccines (RR 3.05, 95% CI 0.13 to 74.15) and DTPw-HBV-HIB combined and separate vaccines (RR 0.89, 95% CI 0.37 to 2.16). Seven studies of DTPa-HBV-HIB and DTPw-HBV-HIB were estimated with a total of 61 events (Ortega-Barria 2007, Avdicova 2002; Aristegui 2003; Gabutti 2004; Ramkissoon 2001; Omenaca 2001; Pichichero 1997; Schmitt 2000). No events in eight studies (Aristegui 2003; Avdicova 2002; Gabutti 2004; Gabutti 2005; Omenaca 2001; Pichichero 1997; Ramkissoon 2001; Schmitt 2000).

#### Anti-T (Tetanus) titers below the assay cutoff

No events below the assay cutoff 0.1 IU/ml were found except in one study with five events in the separate vaccines (Ortega-Barria 2007).

#### Anti-HBV (Hepatitis B) titers concentrations below the assay cutoff

No significant difference was found (RR 1.27, 95% CI 0.72 to 2.25) between combined and separate DTPa-HBV-HIB vaccines (RR 1.83, 95% CI 0.75 to 4.46) and DTPw-HBV-HIB combined and separate vaccines (RR 0.92, 95% CI 0.36 to 2.38). Seven studies of DTPa-HBV-HIB were estimated with a total of 31 events. Seven studies of DTPw-HBV-HIB were estimated with a total of 163 events. Three studies had no events (Omenaca 2001, Ramkissoon 2001, Faingezicht 2002).
Results excluding one study (Nolan 2001) with a total of 26 events show no significant difference was found (RR 0.99, 95% CI 0.52 to 1.88) between combined and separate DTPa-HBV-HIB vaccines (RR 1.83, 95% CI 0.75 to 4.46) and DTPw-HBV-HIB combined and separate vaccines (RR 0.54, 95% CI 0.24 to 1.22).

#### Anti-polio type 1, 2 and 3 titers below the assay cutoff

No significant difference was found between combined and separate DTPa-HBV-HIB vaccines of anti polio type 1 (RR 1.22, 95% CI 0.20 to 7.56), of anti-polio type 2 (RR 1.84, 95% CI 0.66 to 5.12) and of anti-polio type 3 (RR 1.87, 95% CI 0.59 to 5.94). Four studies of DTPa-HBV-HIB were estimated. Three studies (Avdicova 2002; Gabutti 2004; Schmitt 2000) combined IPV vaccine with DTP-HBV-HIB vaccine and one study (Pichichero 1997) combined OPV vaccine with DTP-HBV-HIB vaccine.

### Reactogenicity (adverse events - number of reported events by number of vaccines given)

#### Serious adverse events - number of reported events by number of participants

Nine studies with a total of 4932 participants were estimated.
No significant difference between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 0.91, 95% CI 0.56 to 1.48). Three studies of DTPa-HBV-HIB were estimated with 18 events in the combined group and 24 events in the separate group. No significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 0.75, 95% CI 0.41 to 1.37). Five studies of DTPw-HBV-HIB were estimated with 22 events in the combined group and eight events in the separate group. No significant difference was found between combined and separate DTPw-HBV-HIB vaccines (RR 1.32, 95% CI 0.58 to 3.00).
See Table 1 and Table 2 for details.

**Table 1. Serious Adverse Events (DTPw): details**

| Combined group | Separate group | Not given |
|---|---|---|
| A few hours after the first vaccine dose, one child experienced seizures, which resolved spontaneously.<br>Two weeks after the first vaccine dose, another child was diagnosed with acute bronchiolitis and subsequently died due to respiratory distress (Faingezicht 2002). | One acute bronchiolitis case, due to respiratory syncytials virus infection, occurred three days after the first vaccination. The child recovered after treatment and hospitalization (Faingezicht 2002). | Five subjects were hospitalized or experienced a serious adverse event, including one subject who died as a secondary result of sudden infant death syndrome 52 days after the first dose vaccine (Greenberg 2000). |
| Three events: one hypotonic-hyporesponsiveness,<br>two seizures (Nolan 2001). | Three events of seizures (Nolan 2001). | |
| In one case four booster doses were followed by unsolicited grade '3' symptoms (pharyngitis and severe asthma) (Santos 2002). | | |
| Twelve serious adverse events were reported by 10 subjects (Tregnaghi 2006). | Two serious adverse events after the primary vaccination course were reported by two subjects (Tregnaghi 2006). | |
| Four serious adverse events occurred in subjects receiving DTPw-HBV/Hib 2.5 vaccine. Two hypotonic-hyporesponsive episodes (HHE) in Hib-078 and two cases of convulsions in Hib-079. All four subjects recovered (Ortega-Barria 2007). | Two events occurred following the administration of Tritanrix™-Hep B and Hiberix™ vaccines in Hib-078. One case of HHE and one case of viral meningoencephalitis (Ortega-Barria 2007). | |

**Table 2. Serious Adverse Events (DTPa): details**

| Combined group | Separate group | Not given |
|---|---|---|
| Seven SAEs were hospitalizations due to vaccination-related common childhood infections (Avdicova 2002).<br>Ten SAEs including one drop-out following a serious adverse event and another following a non-serious adverse event ( Gabutti 2004). One case of large, local reactions after the second and third injections (Mallet 2000). | Eleven SAEs were hospitalizations due to vaccination-related common childhood infections (one erythematous rash) (Avdicova 2002)<br>Ten SAEs including one drop-out following a serious adverse event (Gabutti 2004).<br>Three infants presented symptoms that were considered as a contradiction for further vaccination:inconsolable crying i.e. more than three hours after first dose (n = | Two episodes of "inconsolable crying" were reported within the context of multiple severe local reactions without further sequelae (Mallet 2000).<br>Four serious adverse events were reported ( Aristegui 2003).<br>Eight serious adverse events occurred ( Schmitt 2000). |

**Pain**

A total of 17,841 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. A significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-

HBV-HIB combined and separate vaccines (RR 1.09, 95% CI 1.02 to 1.17). Seven studies of DTPa-HBV-HIB were estimated with 788 events in the combined group and 449 events in the separate group. A significant difference between combined and separate DTPa-HBV-HIB vaccines was found (RR 1.20, 95% CI 1.06 to 1.37). Nine studies of DTPw-HBV-HIB were estimated with 2691 events in the combined group and 1597 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 1.05, 95% CI 0.98 to 1.12).

#### Redness

A total of 17,841 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. A significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.09, 95% CI 1.00 to 1.19). Seven studies of DTPa-HBV-HIB were estimated with 1289 events in the combined group and 824 events in the separate group. A significant difference between combined and separate DTPa-HBV-HIB vaccines was shown (RR 1.12, 95% CI 0.96 to 1.30). Nine studies of DTPw-HBV-HIB were estimated with 1646 events in the combined group and 975 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 1.06, 95% CI 0.95 to 1.18).

#### Swelling

No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.05, 95% CI 0.98 to 1.13). Seven studies of DTPa-HBV-HIB were estimated with 1015 events in the combined group and 711 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.06, 95% CI 0.94 to 1.21). Nine studies of DTPw-HBV-HIB were estimated with 1587 events in the combined group and 962 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 1.04, 95% CI 0.95 to 1.14).

#### Fever

A total of 15,901 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.02, 95% CI 0.95 to 1.08). Six studies of DTPa-HBV-HIB were estimated with 814 events in the combined group and 561 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.09, 95% CI 0.98 to 1.22). Six studies of DTPw-HBV-HIB were estimated with 1528 events in the combined group and 1009 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 0.98, 95% CI 0.92 to 1.05).

#### Fussiness or restlessness

A total of 11,112 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.03, 95% CI 0.95 to 1.12). Six studies of DTPa-HBV-HIB were estimated with 1255 events in the combined group and 844 events in the separate group. No significant difference between combined and separate DTPa-HBV-HIB vaccines was found (RR 1.03, 95% CI 0.91 to 1.15). Two studies of DTPw-HBV-HIB was estimated with 498 events in the combined group and 477 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 1.05, 95% CI 0.90 to 1.23).

#### Drowsiness

A total of 11,178 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 0.99, 95% CI 0.89 to 1.09). Six studies of DTPa-HBV-HIB were estimated with 756 events in the combined group and 717 events in the separate group. No significant difference between combined and separate DTPa-HBV-HIB vaccines was shown (RR 1.02, 95% CI 0.88 to 1.19). Four studies of DTPw-HBV-HIB were estimated with 880 events in the combined group and 354 events in the separate group. No significant difference was found between combined and separate DTPw-HBV-HIB vaccines (RR 0.91, 95% CI 0.82 to 1.00).

#### Poor appetite

A total of 12,851 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.01, 95% CI 0.94 to 1.09). Five studies of DTPa-HBV-HIB were estimated with 681 events in the combined group and 450 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.07, 95% CI 0.94 to 1.22). Five studies of DTPw-HBV-HIB were estimated with 1118 events in the combined group and 425 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 0.97, 95% CI 0.89 to 1.06).

#### Vomiting

A total of 7210 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. No significant difference was found between

DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.05, 95% CI 0.87 to 1.26). Three studies of DTPa-HBV-HIB were estimated with 267 events in the combined group and 148 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.05, 95% CI 0.85 to 1.29). Three studies of DTPw-HBV-HIB were estimated with 28 events in the combined group and 26 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 1.08, 95% CI 0.64 to 1.81).

#### Irritability or tenderness

A total of 7440 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 0.97, 95% CI 0.90 to 1.04). Two studies of DTPa-HBV-HIB were estimated with 255 events in the combined group and 242 events in the separate group. No significant difference between combined and separate DTPa-HBV-HIB vaccines was shown (RR 1.03, 95% CI 0.74 to 1.44). Six studies of DTPw-HBV-HIB were estimated with 1874 events in the combined group and 925 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 0.95, 95% CI 0.90 to 1.01).

#### Diarrhea

A total of 4690 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.16, 95% CI 0.93 to 1.44). Two studies of DTPa-HBV-HIB were estimated with 217 events in the combined group and 79 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.17, 95% CI 0.91 to 1.51). Three studies of DTPw-HBV-HIB were estimated with 34 events in the combined group and 30 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 1.11, 95% CI 0.69 to 1.77).

#### Unusual crying

A total of 3986 DTPa-HBV-HIB and DTPw-HBV-HIB vaccines were estimated. No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 0.88, 95% CI 0.71 to 1.09). One study of DTPa-HBV-HIB was estimated with three events in the combined group and no events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 6.99, 95% CI 0.36 to 135.16). Three studies of DTPw-HBV-HIB were estimated with 174 events in the combined group and 200 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 0.87, 95% CI 0.72 to 1.04).

#### Sleeping more than usual

A total of 5492 DTPa-HBV-HIB vaccines were estimated. Three studies were estimated with 530 events in the combined group and 243 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 0.99, 95% CI 0.86 to 1.14).

#### Sensitivity analysis

We could not perform sensitivity analysis to assess the impact of methods on the main results because only three studies had adequate allocation generation. We looked at the sub-groups according to the antibody concentrations above the assay cut-offs and found no difference between the sub-groups.

#### Selection bias

Two funnel plot graphs of studies for anti-PRP were examined and showed no significant selection bias (Figure 1; Figure 2).

**Figure 1. Funnel plot of comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, outcome: 1.1 Anti PRP titres below the assay cutoff 0.15 µg/ml.**

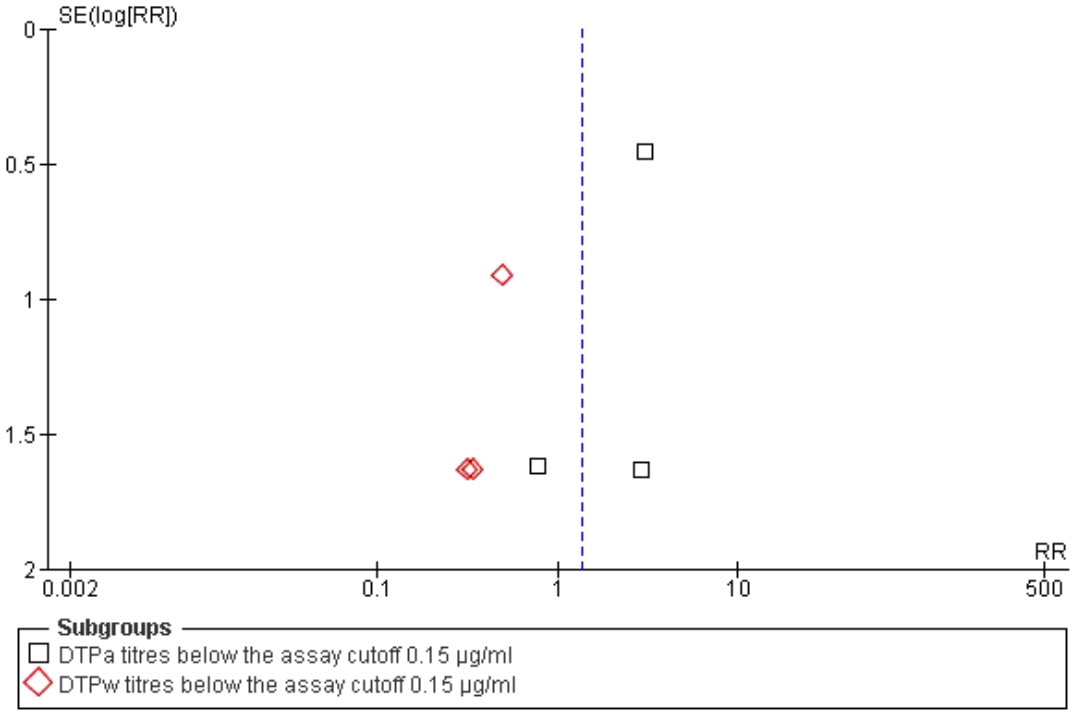
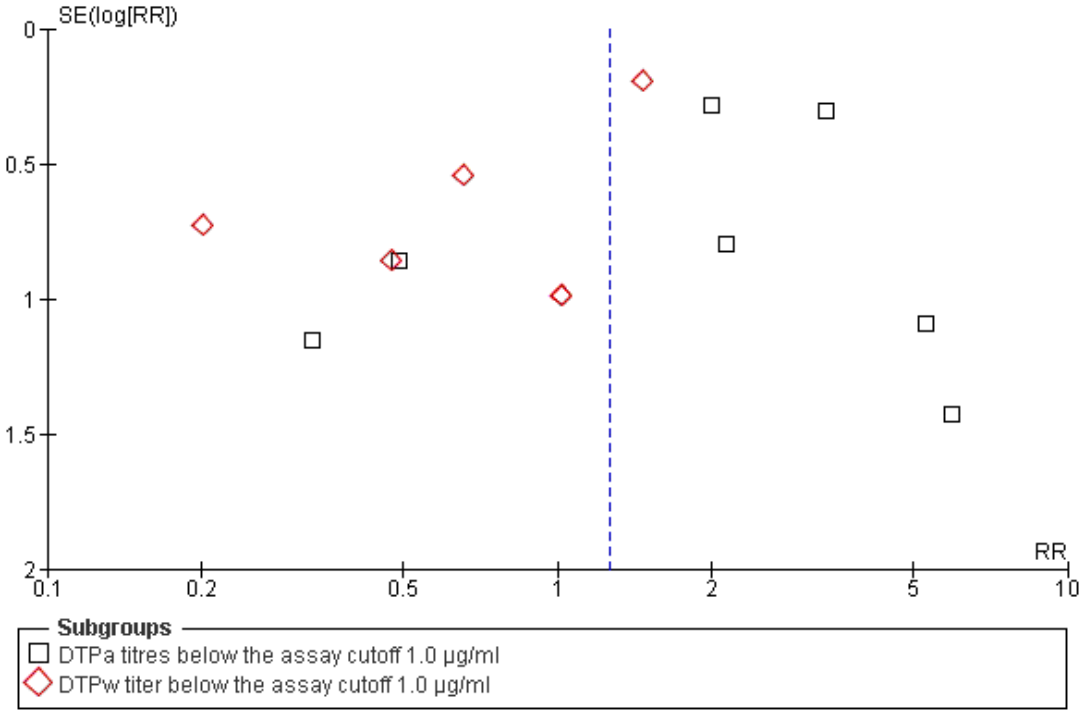


**Figure 2. Funnel plot of comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, outcome: 1.2 Anti PRP titres below the assay cutoff 1.0 µg/ml.**



## DISCUSSION

We found no studies that addressed clinical outcomes, i.e. incidence of diphtheria, tetanus, pertussis, hepatitis B and *H. influenzae* type B. For some of these diseases, past eradication programs were effective in almost-total eradication of the disease, and thus trials addressing clinical outcomes demand an unrealistic sample size and follow up. However, for some of them, for example, hepatitis B and *H. influenzae* type B clinical outcomes could be expected. The lack of such outcomes weakens conclusions that can be drawn from published studies.

### Immunogenicity

The number of vaccines doses differed significantly between the studies. We decided to extract data following the last dose of the vaccines, excluding a booster dose, because the sample size of booster groups differed significantly from the original groups.

In two immunological responses the combined vaccine achieved lower responses than the separate vaccines: anti-PRP (*H. influenzae* type B), both for the threshold of 0.15 mg/ml, and for the threshold of 1.0 $\mu$g/ml; and anti-hepatitis B. For the other responses no significant differences could be shown, but the number of events (response below the threshold) was so low that the confidence intervals are very large.

We should take note that the anti-PRP comparison was influenced by one study with a large number of events (Pichichero 1997), which used pure (and not conjugated) PRP vaccines (polyribosylribitolphoshate). The anti-hepatitis B comparison is influenced by one large study, with a high number of serological failures (Nolan 2001).

### Reactogenicity (adverse events)

We were unable to find data of serious adverse events for some of the included trials, (although trial authors were contacted for additional information). No difference was found between combined and separate vaccines. However, eight studies of a total of 4932 participants is a relatively small number upon which to base conclusions. A significant increase in pain and redness was observed in the patients given the combination vaccine.

### Limitations of the review

The quality of many of the studies included in the analysis is uncertain. The interventions are heterogeneous. While most of the studies were supported by the manufacturers Hiberix, GlaxoSmith\Kline Biologicals, Rixensart, Belgium and by Aventis Pasteur, Lyon, France, combined vaccines were prepared as investi-

gational formulations and reconstituted with different diluents. Therefore, the findings may not generalize to all DTP-HBV-HIB vaccines. Though studies included in the meta-analysis had similar vaccination schedules, immunogenicity was measured at different points of vaccination: after the first, second or third vaccination, and in some studies, after the booster vaccination. The meta-analysis included immunogenicity data after the third vaccinations, while the immunogenicity profile might differ after the booster vaccination. The study location, the healthcare environment, and combining research across disparate geographical locations, may lead to bias. The studies did not use an intention-to-treat analysis. However, the differences rely mostly on one study each. It is not clear whether the results can be generalized to all vaccines. The results of this review should be viewed with caution, mostly as an indication that high quality data are lacking.

## AUTHORS' CONCLUSIONS

### Implications for practice

Overall the level of evidence provided by the studies was low, and we could not conclude that the immune responses elicited by the combined vaccine are equivalent to the separate injections. The data showed significantly less immunological response for *H. influenza* and hepatitis B, and more local reactions to the injections.

### Implications for research

Studies addressing clinical end-points whenever possible, using correct methodology and a large enough sample size (and probably including DTPa components) should be conducted.

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* Clemens SC, Azevedo T, Homma A. Feasibility study of the immunogenicity and safety of a novel DTPw/Hib (PRP-T) Brazilian combination compared to a licensed vaccine in healthy children at 2, 4, and 6 months of age. *Revista da Sociedade Brasileira de Medicina Tropical* 2003;**36**(3):321–30.

**Denoel 2007** *{published data only}*

Denoel PA, Goldblatt D, de Vleeschauwer I, Jacquet JM, Pichichero ME, Poolman JT. Quality of the Haemophilus influenzae type b (Hib) antibody response induced by diphtheria-tetanus-acellular pertussis/Hib combination vaccines. *Clinical and Vaccine Immunology* 2007;**October 14**(10):1362–9.

**Gatchalian 2005** *{published data only}*

Gatchalian S, Reyes M, Bernal N, Lefevre I, David MP, Han HH, et al.A new DTPw-HBV/Hib vaccine is immunogenic and safe when administered according to the EPI (Expabded Programme for Immunization) schedule and following hepatitis B vaccination at birth. *Human Vaccines* 2005;**1**(5):198–203.

**Gylca 2001** *{published data only}*

* Gylca R, Gylca V, Benes O, Melnic A, Chicu V, Weisbecker C, et al.A new DTPa-HBV-IPV vaccine co-administered with Hib, compared to a commercially available DTPw-IPV/Hib vaccine co-ad-

ministered with HBV, given at 6, 10 and 14 weeks following HBV at birth. *Vaccine* 2001;**19**(7-8):825–33.

**Hla 2006** ***{published data only}***

Hla KH, Thein SA, Aye A, Han HH, Bock HL, David MP, et al.Reactogenicity and immunogenicity profiles of a novel pentavalent diphtheria-tetanus-whole cell pertussis-hepatitis B and Haemophilus influenzae type B vaccine: a randomized dose-ranging trial of the Hib tetanus-conjugate content. *Pediatric Infectious Disease Journal* 2006;**25**(8):706–12.

**Hogg 2003** ***{published data only}***

* Hogg K, Hogg G. The immunogenicity of oral poliomyelitis vaccine in a primary vaccination series at 2, 4 and 6 months given concurrently with Hib, hepatitis B and diphtheria, tetanus and whole-cell pertussis vaccines administered as three separate injections or as a combination pentavalent vaccine. *Vaccine* 2003;**21**(21-2):2906–10.

**Huang 1998** ***{published data only}***

* Huang LM, Chang PF, Lee PI, Chiu HH, Tsai SY, Lee CY. Immunogenicity and safety of Haemophilus influenzae type b conjugate vaccine (HibTITER) and a combination vaccine of diphtheria, tetanus, pertussis and HibTITER (TETRAMUNE) in two-month-old infants. *Journal of Microbiology, Immunology, and Infection* 1998; **31**(3):180–6.

**Kalies 2004** ***{published data only}***

* Kalies H, Verstraeten T, Grote V, Meyer N, Siedler A, Schmitt HJ, et al.Four and one-half-year follow-up of the effectiveness of diphtheria-tetanus toxoids-acellular pertussis/Haemophilus influenzae type b and diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus/H. influenzae type b combination vaccines in Germany. *Pediatric Infectious Disease Journal* 2004;**23**(10):944–50.

**Kanra 2006** ***{published data only}***

Kanra G, Kara A, Demiralp O, Contorni M, Hilbert AK, Spyr C, et al.Safety and immunogenicity of a new fully liquid DTPw-HepB-Hib combination vaccine in infants. *Human Vaccines* 2006;**2**(4): 155–60.

**Knuf 2006** ***{published data only}***

Knuf M, Habermehl P, Cimino C, Petersen G, Schmitt HJ, Habermehl P. Immunogenicity, reactogenicity and safety of a 7-valent pneumococcal conjugate vaccine (PCV7) concurrently administered with a DTPa-HBV-IPV/Hib combination vaccine in healthy infants. *Vaccine* 2006;**24**(22):4727–36.

**Lagos 2005** ***{published data only}***

Lagos R, Hoffenbach A, Scemama M, Dupuy M, Schodel F, Hessel L, et al.Lot-to-lot consistency of a combined hexavalent diptheria-tetanus-acellular-pertussis, hepatitis B, Inactivated polio and haemophilus B conjugate vaccine, administered to healthy Chilean infants at two, four and six months of age. *Human Vaccines* 2005;**1** (3):112–7.

**Lim 2007** ***{published data only}***

Lim FS, Han HH, Jacquet JM, Bock HL. Primary vaccination of infants against hepatitis B can be completed using a combined hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliomyelitis-Haemophilus influenzae type B vaccine. *Annals of the Academy of Medicine, Singapore* 2007;**Oct 36**(10):801–6.

**Lopez 2002** ***{published data only}***

Lopez P, Rubiano L, del Pilar Rubio M, David MP, Safary A. Immunogenicity and reactogenicity of DTPw-HB/Hib vaccine administered to Colombian infants after a birth dose of hepatitis B vaccine. *Expert Review of Vaccines* 2002;**1**(3):277–83.

**Meriste 2006** ***{published data only}***

Meriste S, Lutsar I, Tamm E, Willems P. Safety and immunogenicity of a primary course and booster dose of a combined diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated poliovirus vaccine. *Scandinavian Journal of Infectious Diseases* May;**38**(5):350–6.

**Mills 1998** ***{published data only}***

* Mills E, Gold R, Thipphawong J, Barreto L, Guasparini R, Meekison W, et al.Safety and immunogenicity of a combined five-component pertussis-diphtheria-tetanus-inactivated poliomyelitis-Haemophilus B conjugate vaccine administered to infants at two, four and six months of age. *Vaccine* 1998;**16**(6):576–85.

**Nolan 2004** ***{published data only}***

Nolan T, Altmann A, Skeljo M, Streeton C, Schuerman L. Antibody persistence, PRP-specific immune memory, and booster responses in infants immunised with a combination DTPa-HBV-IPV/Hib vaccine. *Vaccine* 2004;**23**(1):14–20.

**Pichichero 1999** ***{published data only}***

* Pichichero ME, Voloshen T, Zajac D, Passador S. Avidity maturation of antibody to Haemophilus influenzae type b (Hib) after immunization with diphtheria-tetanus-acellular pertussis-hib-hepatitis B combined vaccine in infants. *Journal of Infectious Diseases* 1999; **180**(4):1390–3.

**Pichichero 2007** ***{published data only}***

Pichichero ME, Bernstein H, Blatter MM, Schuerman L, Cheuvart B, Holmes SJ. Immunogenicity and safety of a combination diphtheria, tetanus toxoid, acellular pertussis, hepatitis B, and inactivated poliovirus vaccine co administered with a 7-valent pneumococcal conjugate vaccine and a *Haemophilus influenzae* type b conjugate vaccine. *Journal of Pediatrics* 2007;**151**(1):43–9;e1-2.

**Poolman 2001** ***{published data only}***

* Poolman J, Kaufhold A, De Grave D, Goldblatt D. Clinical Relevance of Lower Hib Response in DTPa-based Combination Vaccines. *Vaccine* 2001;**19**(17-9):2280–5.

**Saenger 2005** ***{published data only}***

Saenger R, Maechler G, Potreck M, Zepp F, Knuf M, Habermehl P, et al.Booster vaccination with hexavalent DTPa-HBV-IPV/Hib vaccine in the second year of life is as safe as concomitant DTPa-IPV/Hib + HBV administered separately. *Vaccine* 2005;**23**(9):1135–43.

**Scheifele 2005** ***{published data only}***

Scheifele DW, Halperin SA, Rubin E, Tapiero B, Guasparini R, Meekison W, et al.Safety and immunogenicity of a pentavalent combination vaccine (diphtheria, tetanus, accellular pertussis, polio and haemophilus influenzae type B conjugate) when administered as a fourth dose at 15 to 18 months of age. *Human Vaccines* 2005;**1**(5): 180–6.

**Scheifele 2006** ***{published data only}***

Scheifele DW, Halperin SA, Smith B, Ochnio J, Meloff K, Duarte-Monteiro D. Assessment of the compatibility of co-administered 7-valent pneumococcal conjugate, DTaP.IPV/PRP-T Hib and hepatitis

B vaccines in infants 2-7 months of age. *Vaccine* 2006;**24**(12):2057–64.

**Tichmann 2005** ***{published data only}***
Tichmann I, Preidel H, Grunert D, Habash S, Schult R, Maier R, et al.Comparison of the immunogenicity and reactogenicity of two commercially available hexavalent vaccines administered as a primary vaccination course at 2, 4 and 6 months of age. *Vaccine* 2005;**23**(25):3272–9.

**Tichmann-Schumann 2005** ***{published data only}***
Tichmann-Schumann I, Soemantri P, Behre U, Disselhoff J, Mahler H, Maechler G, et al.Immunogenicity and reactogenicity of four doses of diphtheria-tetanus-three-component acellular pertussis-hepatitis B-inactivated polio virus-Haemophilus influenzae type b vaccine coadministered with 7-valent pneumococcal conjugate vaccine. *Pediatric Infectious Disease Journal* 2005;**24**(1):70–7.

**Trollfors 2005** ***{published data only}***
* Trollfors B, Taranger J, Lagergard T, Sundh V. Reduced immunogenicity of diphtheria and tetanus toxoids when combined with pertussis toxoid. *Pediatric Infectious Disease Journal* 2005;**24**(1):85–6.

**Usonis 1999a** ***{published data only}***
Usonis V, Bakasenas V. Does concomitant injection of a combined diphtheria-tetanus-acellular pertussis - Hepatitis B virus - Inactivated polio virus vaccine influence the reactogenicity and immunogenicity of commercial Haemophilus influenzae type b conjugate vaccines?. *European Journal of Pediatrics* 1999;**158**(5):398–402.

**Usonis 1999b** ***{published data only}***
* Usonis V, Bakasenas V. Evaluation of the immunogenicity and reactogenicity of a new combined diphtheria, tetanus, whole-cell Bordetella pertussis and Hepatitis B vaccine and Haemophilus influenzae type b vaccine in children at 3, 4.5 and 6 months of age. *Acta Medica Lituanica* 1999;**T6**:Nr 3.

**Zepp 1997** ***{published data only}***
* Zepp F, Schmitt HJ, Kaufhold A, Schuind A, Knuf M, Habermehl P, et al.Evidence for induction of polysaccharide specific B-cell-memory in the 1st year of life: plain Haemophilus influenzae type b-PRP (Hib) boosters children primed with a tetanus-conjugate Hib-DTPa-HBV combined vaccine. *European Journal of Pediatrics* 1997;**156**(1):18–24.

**Zepp 2004** ***{published data only}***
Zepp F, Knuf M, Heininger U, Jahn K, Collard A, Habermehl P, et al.Safety, reactogenicity and immunogenicity of a combined hexavalent tetanus, diphtheria, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and Haemophilus influenzae type b conjugate vaccine, for primary immunization of infants. *Vaccine* 2004;**22**(17-8):2226–33.

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**Ball 2001**
Ball LK, Falk LA, Horne D, Finn TM. Evaluating the immune response to combination vaccines. *Clinical Infectious Diseases* 2001;**33**(Suppl 4):299–305.

**Chalmers 1990**
Chalmers I, Adams M, Dickersin K, Hetherington J, Tarnow-Mordi W, Meinert C, et al.A cohort study of summary reports of controlled trials. *JAMA* 1990;**263**(10):1401–5.

**Egger 1997**
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

**Lefebvre 2008**
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley, 2008.

**Schulz 1955**
Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *The Journal of the American Medical Association* 1955;**273**(5):408–12.

**WHO 1998**
World Health Organization. Global Programme for Vaccines and Immunization: The WHO position paper on Haemophilus influenza type b conjugate vaccines. *Weekly Epidemiological Record* 1998;**73**(10):64–71.

**Wong 2006**
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association* 2006;**94**:41–47.

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Aristegui 2003**

| | |
|---|---|
| Methods | Open randomized, comparative phase IIIb multicenter trial |
| Participants | Healthy male and female infants age 8.7 (± 0.8) weeks |
| Interventions | Combined DTPa-HBV-IPV-Hib compared to separate DTPa-IPV/Hib + HBV in 3 doses at 2, 4 and 6 months of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Avdicova 2002**

| | |
|---|---|
| Methods | Open randomized trial |
| Participants | Healthy male and female infants age 13.2 weeks, range 8 to 12 weeks |
| Interventions | DTPa-HBV-IPV/Hib compared to DTPa-IPV/Hib and HBV in separate injections 3 doses between 11 and 17 weeks of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Bravo 1998**

| | |
|---|---|
| Methods | Open randomized clinical trial |
| Participants | Healthy male and female infants. No age reported |
| Interventions | DTPw-HBV-Hib and separate DTP-HBV and Hib when received hepatitis B at birth. 3 doses given at 6, 10 and 14 weeks of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | No | C - Inadequate |

**Faingezicht 2002**

| | |
|---|---|
| Methods | Phase III observed-blind prospective randomized controlled trial |
| Participants | Healthy male and female infants age 8.8 (SD = 0.9) weeks |
| Interventions | DTPw-HB/Hib pentavalent combination after extemporaneous mixing of the liquid DTPw-HB with the lyophilised Hib compared to DTPw-HB vaccine and Hib vaccine reconstituted with its own diluent. 3 doses given to 2, 4, and 6 months old and booster at 15 to 18 months old |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Gabutti 2004**

| | |
|---|---|
| Methods | Open, phase III, randomized, multicenter study |
| Participants | Healthy male and female infants age 13.3 weeks, range 9 to 17 weeks |

**Gabutti 2004** (*Continued*)

| | | |
|---|---|---|
| Interventions | DTPa-HBV-IPV/Hib compared to separate DTPa - HBV - IPV + Hib. 3 doses given to 3, 5 and 11 months old | |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity | |
| Notes | | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

**Gabutti 2005**

| | | |
|---|---|---|
| Methods | Open, randomized multicenter trial | |
| Participants | Healthy male and female infants age 13 and 13.1 weeks | |
| Interventions | DTaP-HBV-Hib compared with two separate or mixed injection. 3 doses given to 3, 5 and 11 months old | |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity | |
| Notes | | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

**Greenberg 2000**

| | |
|---|---|
| Methods | Randomization equally to three groups |
| Participants | Healthy male and female infants age 6 to 12 weeks at the time of the first vaccination |
| Interventions | DTaP, Hepatitis B (HepB) and PRP-T (Hib). Oral polio vaccine. was given concurrently. 3 doses given to 2, 4, 6 months old and booster combined vaccine to ages 11 to 15 months |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |

**Greenberg 2000** (*Continued*)

| | | |
|---|---|---|
| Notes | | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B - Unclear |

**Mallet 2000**

| | |
|---|---|
| Methods | Open label, multicenter prospective, comparative trial |
| Participants | Healthy male and female infants age 63 days ± 7 days |
| Interventions | DTPa-IPV-HBV-Hib compared to separate DTPa-IPV-Hib and HB vaccine. 3 doses given to 2, 4 and 6 months of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Yes | A - Adequate |

**Nolan 2001**

| | |
|---|---|
| Methods | Randomized double-blind series of three studies |
| Participants | Good health male and female infants. No age reported |
| Interventions | DTP-Hib (PRP-OMPC)-HB in three studies + OPV<br>DTP-liqHib-HB + placebo (group A). DTP-HB + liqHib (group B). HB-liqHib + DTP (group C). DTP+lyoHib+hepB (group D). Monovalent HB at birth and DTP-liqHib-HB (group E). 3 and 4 dozes (including booster) given to 2, 4, 6 and 18 months of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

| ***Risk of bias*** |
|---|

**Nolan 2001** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Omenaca 2001**

| | |
|---|---|
| Methods | Open, randomized, multicenter, comparative phase III clinical trial |
| Participants | Healthy male and female infants age 9.3 ± 1.4 weeks (range 5 to 16) |
| Interventions | DTPa-HBV-Hib and separate DTPa-HBV and Hib with OPV vaccine simultaneously. 3 doses given to 2, 4, 6 months of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Ortega-Barria 2007**

| | |
|---|---|
| Methods | Four separate phase III trials which assessed the immunogenicity and reactogenicity of DTPw-HBV/Hiv 2.5 in comparison with DTPw-HBV + Hiberix™ (10µg PRP) given as separate or mixed injections (3 trials) or with or without hepatitis B vaccine at birth (1 trial) |
| Participants | Healthy male and female infants age 2 to 14 weeks |
| Interventions | DTPw-HBV mixed with Hib 2.5 (lot A, lot B, lot C) compared with DTPw-HBV and Hiberix™ either given as separate injections (Hib-078) or as mixed injections (Hib-079, Hib-080) administered at either 2, 4 and 6 months of age (Hib-078, Hib-079); at 3, 4 and 5 months of age (Hib-080); or at 6, 10 and 14 weeks of age (Hib-081). |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Ortega-Barria 2007** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Pichichero 1997**

| | |
|---|---|
| Methods | Prospective randomized multicenter trial. Three to one to group 1 and 2 respectively comparing combined injections with three separate simultaneous injections |
| Participants | Healthy male and female infants age 6 to 12 weeks |
| Interventions | DTaP-HBV-PRP-T and booster of Hib. Oral poliovirus vaccine was administered to all vaccinees in both groups concurrently at 2, 4, and 6 months of age. 3 doses given to 2, 4, 6 months of age and booster of PRP conjugate vaccine to group 1 (combined) with low levels of antibody at 9 to 13 months of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Ramkissoon 2001**

| | |
|---|---|
| Methods | Open, randomized comparative study |
| Participants | Healthy male and female infants age of 6 weeks (not reported) |
| Interventions | DTPw-HBV mixed with Hib compared with DTPw-HBV and Hib separate. 3 doses given to 6, 10, 14 weeks of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Riedemann 2002**

| | |
|---|---|
| Methods | Open randomized parallel-group design randomized study |
| Participants | Healthy male and female infants age 9.9 weeks |
| Interventions | DTPw-HB/Hib compared with DTPw-HB and Hib separate in opposite deltoids. 3 doses given to 2, 4, 6 months old and booster at 18 months of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Santos 2002**

| | |
|---|---|
| Methods | Open, multicenter randomized (1:1), parallel-group design |
| Participants | Healthy male and female infants age 8 to 15 weeks |
| Interventions | DTPw-HB mixed with Hib compared with DTPw-HB and Hib separate in opposite thighs. 3 doses given to 2, 4, 6 months and booster at 18 months of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Schmitt 2000**

| | |
|---|---|
| Methods | Open, multicenter, randomized trial |
| Participants | Healthy male and female infants age 8 to 16 weeks |
| Interventions | DTPa-HBV-IPV/Hib compared to separate DTPa - HBV - IPV + Hib. 3 doses given to 2, 4 and 6 months of age |

**Schmitt 2000** (*Continued*)

| | |
|---|---|
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Tregnaghi 2006**

| | |
|---|---|
| Methods | Double blind design of three different production lots in the studies |
| Participants | Healthy infants age 8 ± 1.8 weeks with a male:female ratio of 1:1 |
| Interventions | DTPw-HB/Hib compared with separate vaccines |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Win 1997**

| | |
|---|---|
| Methods | Open, randomized and controlled with two groups of healthy neonates |
| Participants | Healthy male and female infants age 5 to 8 weeks |
| Interventions | DTPw-HBV-Hib and separate DTPw-HBV and Hib. 3 doses given to 1.5, 3 and 5 months of age |
| Outcomes | Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Win 1997** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

SD: standard deviation

## Characteristics of excluded studies *[ordered by study ID]*

| | |
|---|---|
| Aristegui 1998 | Comparison of three lots of Haemophilus influenzae type B conjugate (Hib): DTPa-HBV (lot no. 16707B2) + Hib (002A44), DTPa-HBV (16708B2) + Hib (001A41) and DTPa-HBV (16710A2) + Hib (003A41) |
| Aristegui 2001 | Compares DTPa/Hib with DTPw + Hib as booster. No HBV. Reactogenicity and safety only |
| Bavdekar 2007 | Evaluates the immunogenicity of the Hepatitis B and Haemophilus influenzae type b components and the overall safety and reactogenicity of the DTPw-HBV/Hib vaccine. No comparison of combined and separate vaccines |
| Botet-Asensi 2003 | DTwP/Hib vaccine compared to separate injections of DTwP+ Hib. No HBV |
| Calbo 2002 | Comparative trial to assess the reactogenicity of the DTPa vaccine + Hib and DTPw + Hib administered in single injection as a booster dose. No HBV |
| Clemens 2003 | Immunogenicity and safety of a novel DTPw/Hib Brazilian combination compared to a licensed DTPw/Hib European combination |
| Denoel 2007 | Not an RCT: Report of primary and booster-based pediatric clinical trials |
| Gatchalian 2005 | Compares two combined vaccines: DTPw-HBV/Hib containing 2.5 micro PRP compared to GSK Biologicals' licensed Tritanrix HepB/Hiberix containing 10 micro PRP |
| Gylca 2001 | DTPa-HBV-IPV + Hib vaccine compared to DTPw-IPV/Hib + HBV vaccine (diphtheria, tetanus, polioviruses, HBsAg, PRP antigens) |
| Hla 2006 | A randomized, dose-ranging trial to asses the combined vaccine content (no comparison to separate vaccines) |
| Hogg 2003 | Assesses the immunogenicity of oral poliomyelitis vaccine under current and possible new conditions (different objective) |
| Huang 1998 | Combined DTP/Hib and separate DTP + Hib vaccination without HBV |
| Kalies 2004 | No RCT: follow up of case surveillance and vaccine uptake |

(*Continued*)

| | |
|---|---|
| Kanra 2006 | Combined DTPw-Hepb-Hib compared with separately administered DTPw-Hib and hepatitis B vaccines |
| Knuf 2006 | Hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio virus-H. influenzae type b vaccine concomitantly with PCV7 (DTPa-HBV-IPV-Hib and PCV7) compared with DTPa-HBV-IPV/Hib |
| Lagos 2005 | Comparison of Lot-to-Lot consistency of combined vaccine and not comparison of combined and separate vaccines |
| Lim 2007 | Comparison of combined DTPa-IPV/Hib + HBV vaccines with DTPa-HBV-IPV/Hib vaccine |
| Lopez 2002 | Not an RCT: no control group |
| Meriste 2006 | Comparison of combined DTPa-HBV-IPV with DTPa-HBV and IPV separate vaccines |
| Mills 1998 | Comparison between a five-component pertussis combination vaccine (CPDT-IPV/PRP-T) to that of whole cell pertussis combination vaccine (DPT-IPV/PRP-T) |
| Nolan 2004 | Only data on antibody persistence (immunogenicity) of plain PRP and conjugate PRP-T was provided |
| Pichichero 1999 | Avidity maturation of antibody to Hib after immunization with DTPa/Hib/HBV |
| Pichichero 2007 | Compares the DTaP-Hepb-IPV vaccine co-administered with pneumococcal 7-valent conjugate vaccine (PCV-7) and Hib vaccine to separate vaccines concurrently or staggered (delayed) administration of PCV-7 vaccine |
| Poolman 2001 | Not RCT: Two studies in Germany and USA reported to show that the nature and function of the antibody are the same in combined and separate DTPa-HBV-IPV/Hib vaccination |
| Saenger 2005 | Two studies reported elsewhere while only data of safety is provided |
| Scheifele 2005 | Evaluation of a fourth dose of DTPa-IPV/PRP-T and not compared with separate vaccines |
| Scheifele 2006 | Concurrently administered PCV7, DTaP-IPV/PRP-T and HB compared with separate injections |
| Tichmann 2005 | Comparison of two combined vaccines |
| Tichmann-Schumann 2005 | DTPa-HBV-IPV/Hib vaccine and 7vPn conjugate vaccine compared with the administration of the hexavalent DTPa-HBV-IPV/Hib vaccine given alone |
| Trollfors 2005 | Study of the effect of pertussis toxoid on the immunogenicity of diphtheria and tetanus toxoids (DT) during a trial of an acellular pertussis vaccine |

(*Continued*)

| | |
|---|---|
| Usonis 1999a | The target is to ensure that separate, concomitant vaccination does not interfere with the PRP response nor negatively influence the reactogenicity profiles of the vaccines when used with an acellular pertussis based combination. In the trial Hib immunization performed concomitantly with a candidate DTPa-HBV-IPV in order to compare the local reactogenicity and immunogenicity of four commercial Hib vaccines |
| Usonis 1999b | Evaluation of the immunogenicity and reactogenicity of a new combined DTPw-HBV/Hib. Comparison of Hib Lot 001A44 to Hib Lot 002A41 |
| Zepp 1997 | A study of memory B-cell induction and the immune response to the combined DTPa-HBV-Hib vaccine (no comparison) |
| Zepp 2004 | Two studies report of safety and reactogenicity of infant primary immunization with the simultaneous administration of six vaccines in a single injection (DTPa-IPV/HIB) to the administration of the same vaccine-antigens given as two separate injections with widely used licensed products |

## DATA AND ANALYSES

**Comparison 1. DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Anti PRP titres below the assay cutoff 0.15 µg/ml | 14 | 3944 | Risk Ratio (M-H, Random, 95% CI) | 1.35 [0.55, 3.32] |
| 1.1 DTPa titres below the assay cutoff 0.15 µg/ml | 7 | 1740 | Risk Ratio (M-H, Random, 95% CI) | 2.73 [1.19, 6.22] |
| 1.2 DTPw titres below the assay cutoff 0.15 µg/ml | 7 | 2204 | Risk Ratio (M-H, Random, 95% CI) | 0.42 [0.10, 1.70] |
| 2 Anti PRP titres below the assay cutoff 1.0 µg/ml | 13 | 4670 | Risk Ratio (M-H, Random, 95% CI) | 1.26 [0.79, 2.01] |
| 2.1 DTPa titres below the assay cutoff 1.0 µg/ml | 7 | 1732 | Risk Ratio (M-H, Random, 95% CI) | 2.09 [1.20, 3.64] |
| 2.2 DTPw titer below the assay cutoff 1.0 µg/ml | 6 | 2938 | Risk Ratio (M-H, Random, 95% CI) | 0.77 [0.39, 1.52] |
| 3 Anti-FHA (Filamentous haemagglutinin) | 7 | 1706 | Risk Ratio (M-H, Random, 95% CI) | 0.66 [0.11, 3.75] |
| 3.1 DTPa - immunogenicity failure | 7 | 1706 | Risk Ratio (M-H, Random, 95% CI) | 0.66 [0.11, 3.75] |
| 4 Anti-PRN (Pertactin) | 7 | 1713 | Risk Ratio (M-H, Random, 95% CI) | 0.70 [0.15, 3.23] |
| 4.1 DTPa - immunogenicity failure | 7 | 1713 | Risk Ratio (M-H, Random, 95% CI) | 0.70 [0.15, 3.23] |
| 5 Anti-HBV (Hepatitis B) | 17 | 5275 | Risk Ratio (M-H, Random, 95% CI) | 1.27 [0.72, 2.25] |
| 5.1 DTPa - immunogenicity failure | 8 | 1972 | Risk Ratio (M-H, Random, 95% CI) | 1.83 [0.75, 4.46] |
| 5.2 DTPw - immunogenicity failure | 9 | 3303 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.36, 2.38] |
| 6 Anti-BPT (Pertussis) | 9 | 2440 | Risk Ratio (M-H, Random, 95% CI) | 1.12 [0.42, 3.00] |
| 6.1 DTPa - immunogenicity failure | 1 | 262 | Risk Ratio (M-H, Random, 95% CI) | 0.47 [0.04, 5.12] |
| 6.2 DTPw - immunogenicity failure | 8 | 2178 | Risk Ratio (M-H, Random, 95% CI) | 1.34 [0.45, 3.95] |
| 7 Anti-D (Diphtheria) | 15 | 4073 | Risk Ratio (M-H, Random, 95% CI) | 0.96 [0.42, 2.20] |
| 7.1 DTPa - immunogenicity failure | 8 | 1956 | Risk Ratio (M-H, Random, 95% CI) | 3.05 [0.13, 74.15] |
| 7.2 DTPw - immunogenicity failure | 7 | 2117 | Risk Ratio (M-H, Random, 95% CI) | 0.89 [0.37, 2.16] |
| 8 Anti-T (Tetanus) | 16 | 4156 | Risk Ratio (M-H, Random, 95% CI) | 0.03 [0.00, 0.54] |
| 8.1 DTPa - immunogenicity failure | 8 | 1956 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 8.2 DTPw - immunogenicity failure | 8 | 2200 | Risk Ratio (M-H, Random, 95% CI) | 0.03 [0.00, 0.54] |
| 9 DTPa Anti-polio type 1 below the assay cutoff 1:8 IU/mL | 5 | 1236 | Risk Ratio (M-H, Random, 95% CI) | 1.22 [0.20, 7.56] |

| | | | | |
|---|---|---|---|---|
| 10 DTPa Anti-polio type 2 below the assay cutoff 1:8 IU/mL | 5 | 1228 | Risk Ratio (M-H, Random, 95% CI) | 1.84 [0.66, 5.12] |
| 11 DTPa Anti-polio type 3 below the assay cutoff 1:8 IU/mL | 5 | 1233 | Risk Ratio (M-H, Random, 95% CI) | 1.87 [0.59, 5.94] |
| 12 Serious adverse events | 8 | 4932 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.56, 1.48] |
| 12.1 DTPa | 3 | 1298 | Risk Ratio (M-H, Random, 95% CI) | 0.75 [0.41, 1.37] |
| 12.2 DTPw | 5 | 3634 | Risk Ratio (M-H, Random, 95% CI) | 1.32 [0.58, 3.00] |
| 13 Pain | 16 | 17841 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [1.02, 1.17] |
| 13.1 DTPa | 7 | 9445 | Risk Ratio (M-H, Random, 95% CI) | 1.20 [1.06, 1.37] |
| 13.2 DTPw | 9 | 8396 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.98, 1.12] |
| 14 Redness | 16 | 17841 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [1.00, 1.19] |
| 14.1 DTPa | 7 | 9445 | Risk Ratio (M-H, Random, 95% CI) | 1.12 [0.96, 1.30] |
| 14.2 DTPw | 9 | 8396 | Risk Ratio (M-H, Random, 95% CI) | 1.06 [0.95, 1.18] |
| 15 Swelling | 16 | 17841 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.98, 1.13] |
| 15.1 DTPa | 7 | 9445 | Risk Ratio (M-H, Random, 95% CI) | 1.06 [0.94, 1.21] |
| 15.2 DTPw | 9 | 8396 | Risk Ratio (M-H, Random, 95% CI) | 1.04 [0.95, 1.14] |
| 16 Fever | 12 | 15901 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.95, 1.08] |
| 16.1 DTPa | 6 | 8740 | Risk Ratio (M-H, Random, 95% CI) | 1.09 [0.98, 1.22] |
| 16.2 DTPw | 6 | 7161 | Risk Ratio (M-H, Random, 95% CI) | 0.98 [0.92, 1.05] |
| 17 Fussiness or restlessness | 8 | 11112 | Risk Ratio (M-H, Random, 95% CI) | 1.03 [0.95, 1.12] |
| 17.1 DTPa | 6 | 8740 | Risk Ratio (M-H, Random, 95% CI) | 1.03 [0.91, 1.15] |
| 17.2 DTPw | 2 | 2372 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.90, 1.23] |
| 18 Drowsiness | 10 | 11178 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.89, 1.09] |
| 18.1 DTPa | 6 | 6830 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.88, 1.19] |
| 18.2 DTPw | 4 | 4348 | Risk Ratio (M-H, Random, 95% CI) | 0.91 [0.82, 1.00] |
| 19 Irritability or tenderness | 8 | 7440 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.90, 1.04] |
| 19.1 DTPa | 2 | 1761 | Risk Ratio (M-H, Random, 95% CI) | 1.03 [0.74, 1.44] |
| 19.2 DTPw | 6 | 5679 | Risk Ratio (M-H, Random, 95% CI) | 0.95 [0.90, 1.01] |
| 20 Poor appetite | 10 | 12851 | Risk Ratio (M-H, Random, 95% CI) | 1.01 [0.94, 1.09] |
| 20.1 DTPa | 5 | 8158 | Risk Ratio (M-H, Random, 95% CI) | 1.07 [0.94, 1.22] |
| 20.2 DTPw | 5 | 4693 | Risk Ratio (M-H, Random, 95% CI) | 0.97 [0.89, 1.06] |
| 21 Vomiting | 6 | 7210 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.87, 1.26] |
| 21.1 DTPa | 3 | 6191 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.85, 1.29] |
| 21.2 DTPw | 3 | 1019 | Risk Ratio (M-H, Random, 95% CI) | 1.08 [0.64, 1.81] |
| 22 Diarrhea | 5 | 4690 | Risk Ratio (M-H, Random, 95% CI) | 1.16 [0.93, 1.44] |
| 22.1 DTPa | 2 | 3671 | Risk Ratio (M-H, Random, 95% CI) | 1.17 [0.91, 1.51] |
| 22.2 DTPw | 3 | 1019 | Risk Ratio (M-H, Random, 95% CI) | 1.11 [0.69, 1.77] |
| 23 Unusual crying | 4 | 3986 | Risk Ratio (M-H, Random, 95% CI) | 0.88 [0.71, 1.09] |
| 23.1 DTPa | 1 | 2520 | Risk Ratio (M-H, Random, 95% CI) | 6.99 [0.36, 135.16] |
| 23.2 DTPw | 3 | 1466 | Risk Ratio (M-H, Random, 95% CI) | 0.87 [0.72, 1.04] |
| 24 Sleeping more than usual | 3 | 5492 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.86, 1.14] |
| 24.1 DTPa | 3 | 5492 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.86, 1.14] |

## Analysis 1.1. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 1 Anti PRP titres below the assay cutoff 0.15 µg/ml.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 1 Anti PRP titres below the assay cutoff 0.15 g/ml

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 DTPa titres below the assay cutoff 0.15 g/ml | | | | |
| Aristegui 2003 | 0/40 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Avdicova 2002 | 0/141 | 0/138 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2004 | 0/177 | 0/175 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2005 | 0/164 | 0/172 | | 0.0 [ 0.0, 0.0 ] |
| Omenaca 2001 | 1/69 | 0/17 | | 0.77 [ 0.03, 18.15 ] |
| Pichichero 1997 | 47/251 | 5/80 | | 3.00 [ 1.23, 7.27 ] |
| Schmitt 2000 | 1/145 | 0/140 | | 2.90 [ 0.12, 70.53 ] |
| **Subtotal (95% CI)** | **987** | **753** | | **2.73 [ 1.19, 6.22 ]** |
| Total events: 49 (Combined), 5 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.66$, df = 2 (P = 0.72); $I^2 = 0.0\%$ | | | | |
| Test for overall effect: Z = 2.38 (P = 0.017) | | | | |
| 2 DTPw titres below the assay cutoff 0.15 g/ml | | | | |
| Bravo 1998 | 0/50 | 0/45 | | 0.0 [ 0.0, 0.0 ] |
| Ortega-Barria 2007 | 3/543 | 2/178 | | 0.49 [ 0.08, 2.92 ] |
| Ramkissoon 2001 | 0/49 | 0/48 | | 0.0 [ 0.0, 0.0 ] |
| Riedemann 2002 | 0/41 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Santos 2002 | 0/181 | 1/171 | | 0.32 [ 0.01, 7.68 ] |
| Tregnaghi 2006 | 0/524 | 0/177 | | 0.0 [ 0.0, 0.0 ] |
| Win 1997 | 0/78 | 1/79 | | 0.34 [ 0.01, 8.16 ] |
| **Subtotal (95% CI)** | **1466** | **738** | | **0.42 [ 0.10, 1.70 ]** |
| Total events: 3 (Combined), 4 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.08$, df = 2 (P = 0.96); $I^2 = 0.0\%$ | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | |
| **Total (95% CI)** | **2453** | **1491** | | **1.35 [ 0.55, 3.32 ]** |
| Total events: 52 (Combined), 9 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 5.89$, df = 5 (P = 0.32); $I^2 = 15\%$ | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | |

## Analysis 1.2. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 2 Anti PRP titres below the assay cutoff 1.0 µg/ml.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 2 Anti PRP titres below the assay cutoff 1.0 g/ml

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa titres below the assay cutoff 1.0 g/ml | | | | | |
| Aristegui 2003 | 5/34 | 2/29 | | 6.1 % | 2.13 [ 0.45, 10.18 ] |
| Avdicova 2002 | 2/141 | 4/138 | | 5.5 % | 0.49 [ 0.09, 2.63 ] |
| Gabutti 2004 | 1/177 | 3/175 | | 3.5 % | 0.33 [ 0.03, 3.14 ] |
| Gabutti 2005 | 5/164 | 1/172 | | 3.8 % | 5.24 [ 0.62, 44.41 ] |
| Omenaca 2001 | 11/69 | 0/17 | | 2.5 % | 5.91 [ 0.37, 95.68 ] |
| Pichichero 1997 | 105/251 | 10/80 | | 14.8 % | 3.35 [ 1.84, 6.08 ] |
| Schmitt 2000 | 33/145 | 16/140 | | 15.3 % | 1.99 [ 1.15, 3.45 ] |
| **Subtotal (95% CI)** | **981** | **751** | | **51.6 %** | **2.09 [ 1.20, 3.64 ]** |
| Total events: 162 (Combined), 36 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.16; $Chi^2$ = 8.95, df = 6 (P = 0.18); $I^2$ =33% | | | | | |
| Test for overall effect: Z = 2.59 (P = 0.0096) | | | | | |
| 2 DTPw titer below the assay cutoff 1.0 g/ml | | | | | |
| Faingezicht 2002 | 2/78 | 2/79 | | 4.5 % | 1.01 [ 0.15, 7.01 ] |
| Nolan 2001 | 58/417 | 41/433 | | 17.3 % | 1.47 [ 1.01, 2.14 ] |
| Ortega-Barria 2007 | 10/543 | 5/178 | | 9.7 % | 0.66 [ 0.23, 1.89 ] |
| Santos 2002 | 2/181 | 4/171 | | 5.5 % | 0.47 [ 0.09, 2.55 ] |
| Tregnaghi 2006 | 3/524 | 5/177 | | 6.9 % | 0.20 [ 0.05, 0.84 ] |
| Win 1997 | 2/78 | 2/79 | | 4.5 % | 1.01 [ 0.15, 7.01 ] |
| **Subtotal (95% CI)** | **1821** | **1117** | | **48.4 %** | **0.77 [ 0.39, 1.52 ]** |
| Total events: 77 (Combined), 59 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.31; $Chi^2$ = 9.55, df = 5 (P = 0.09); $I^2$ =48% | | | | | |
| Test for overall effect: Z = 0.76 (P = 0.44) | | | | | |
| **Total (95% CI)** | **2802** | **1868** | | **100.0 %** | **1.26 [ 0.79, 2.01 ]** |
| Total events: 239 (Combined), 95 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.29; $Chi^2$ = 25.98, df = 12 (P = 0.01); $I^2$ =54% | | | | | |
| Test for overall effect: Z = 0.98 (P = 0.33) | | | | | |

## Analysis 1.3. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 3 Anti-FHA (Filamentous haemagglutinin).

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 3 Anti-FHA (Filamentous haemagglutinin)

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 DTPa - immunogenicity failure | | | | |
| Aristegui 2003 | 0/40 | 1/31 | | 0.26 [ 0.01, 6.18 ] |
| Avdicova 2002 | 0/141 | 0/138 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2004 | 0/177 | 0/175 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2005 | 0/162 | 0/172 | | 0.0 [ 0.0, 0.0 ] |
| Omenaca 2001 | 0/64 | 0/16 | | 0.0 [ 0.0, 0.0 ] |
| Pichichero 1997 | 1/251 | 0/80 | | 0.96 [ 0.04, 23.44 ] |
| Schmitt 2000 | 1/130 | 1/129 | | 0.99 [ 0.06, 15.70 ] |
| **Total (95% CI)** | **965** | **741** | | **0.66 [ 0.11, 3.75 ]** |
| Total events: 2 (Combined), 2 (Separate) | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.47, df = 2 (P = 0.79); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.47 (P = 0.64) | | | | |

## Analysis 1.4. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 4 Anti-PRN (Pertactin).

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 4 Anti-PRN (Pertactin)

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 DTPa - immunogenicity failure | | | | |
| Aristegui 2003 | 1/40 | 1/31 | | 0.78 [ 0.05, 11.90 ] |
| Avdicova 2002 | 1/141 | 0/138 | | 2.94 [ 0.12, 71.47 ] |
| Gabutti 2004 | 0/177 | 0/175 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2005 | 0/164 | 0/172 | | 0.0 [ 0.0, 0.0 ] |
| Omenaca 2001 | 0/64 | 0/16 | | 0.0 [ 0.0, 0.0 ] |
| Pichichero 1997 | 0/251 | 0/80 | | 0.0 [ 0.0, 0.0 ] |
| Schmitt 2000 | 1/134 | 3/130 | | 0.32 [ 0.03, 3.07 ] |
| **Total (95% CI)** | **971** | **742** | | **0.70 [ 0.15, 3.23 ]** |
| Total events: 3 (Combined), 4 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.23$, df = 2 (P = 0.54); $I^2 = 0.0\%$ | | | | |
| Test for overall effect: Z = 0.45 (P = 0.65) | | | | |

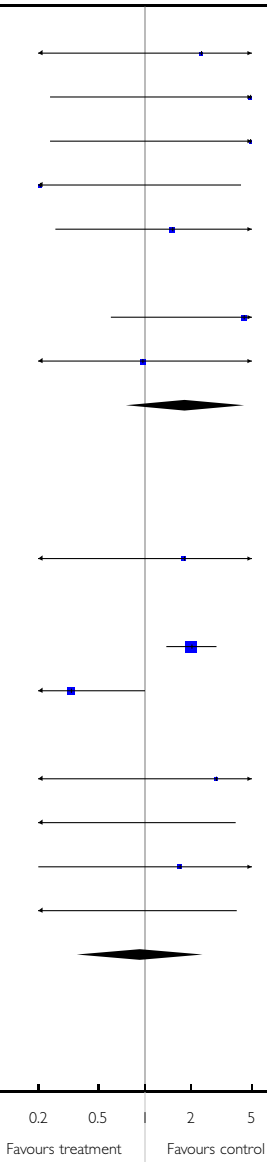
## Analysis 1.5. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 5 Anti-HBV (Hepatitis B).

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 5 Anti-HBV (Hepatitis B)

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 DTPa - immunogenicity failure | | | | |
| Aristegui 2003 | 1/40 | 0/31 | | 2.34 [ 0.10, 55.58 ] |
| Avdicova 2002 | 2/141 | 0/138 | | 4.89 [ 0.24, 101.03 ] |
| Gabutti 2004 | 2/177 | 0/175 | | 4.94 [ 0.24, 102.24 ] |
| Gabutti 2005 | 0/165 | 2/170 | | 0.21 [ 0.01, 4.26 ] |
| Greenberg 2000 | 3/115 | 2/117 | | 1.53 [ 0.26, 8.96 ] |
| Omenaca 2001 | 0/69 | 0/17 | | 0.0 [ 0.0, 0.0 ] |
| Pichichero 1997 | 14/251 | 1/80 | | 4.46 [ 0.60, 33.41 ] |
| Schmitt 2000 | 2/145 | 2/141 | | 0.97 [ 0.14, 6.81 ] |
| **Subtotal (95% CI)** | **1103** | **869** | | **1.83 [ 0.75, 4.46 ]** |
| Total events: 24 (Combined), 7 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.06$, df = 6 (P = 0.67); $I^2 = 0.0\%$ | | | | |
| Test for overall effect: Z = 1.32 (P = 0.19) | | | | |
| 2 DTPw - immunogenicity failure | | | | |
| Bravo 1998 | 2/50 | 1/45 | | 1.80 [ 0.17, 19.19 ] |
| Faingezicht 2002 | 0/78 | 0/79 | | 0.0 [ 0.0, 0.0 ] |
| Nolan 2001 | 70/417 | 36/433 | | 2.02 [ 1.38, 2.95 ] |
| Ortega-Barria 2007 | 6/543 | 6/178 | | 0.33 [ 0.11, 1.00 ] |
| Ramkissoon 2001 | 0/49 | 0/48 | | 0.0 [ 0.0, 0.0 ] |
| Riedemann 2002 | 1/41 | 0/40 | | 2.93 [ 0.12, 69.83 ] |
| Santos 2002 | 0/181 | 2/171 | | 0.19 [ 0.01, 3.91 ] |
| Tregnaghi 2006 | 5/524 | 1/177 | | 1.69 [ 0.20, 14.36 ] |
| Win 1997 | 0/127 | 2/122 | | 0.19 [ 0.01, 3.96 ] |
| **Subtotal (95% CI)** | **2010** | **1293** | | **0.92 [ 0.36, 2.38 ]** |
| Total events: 84 (Combined), 48 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.70$; $Chi^2 = 13.14$, df = 6 (P = 0.04); $I^2 = 54\%$ | | | | |
| Test for overall effect: Z = 0.16 (P = 0.87) | | | | |

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| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| **Total (95% CI)** | **3113** | **2162** | | **1.27 [ 0.72, 2.25 ]** |
| Total events: 108 (Combined), 55 (Separate) | | | | |
| Heterogeneity: $Tau^2$ = 0.24; $Chi^2$ = 17.23, df = 13 (P = 0.19); $I^2$ =25% | | | | |
| Test for overall effect: Z = 0.83 (P = 0.41) | | | | |


## Analysis 1.6. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 6 Anti-BPT (Pertussis).

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 6 Anti-BPT (Pertussis)

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 DTPa - immunogenicity failure | | | | |
| Schmitt 2000 | 1/135 | 2/127 | | 0.47 [ 0.04, 5.12 ] |
| **Subtotal (95% CI)** | **135** | **127** | | **0.47 [ 0.04, 5.12 ]** |
| Total events: 1 (Combined), 2 (Separate) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.62 (P = 0.54) | | | | |
| 2 DTPw - immunogenicity failure | | | | |
| Bravo 1998 | 2/49 | 0/45 | | 4.60 [ 0.23, 93.31 ] |
| Faingezicht 2002 | 1/78 | 0/79 | | 3.04 [ 0.13, 73.45 ] |
| Ortega-Barria 2007 | 3/543 | 1/178 | | 0.98 [ 0.10, 9.39 ] |
| Ramkissoon 2001 | 0/49 | 0/48 | | 0.0 [ 0.0, 0.0 ] |
| Riedemann 2002 | 1/41 | 0/40 | | 2.93 [ 0.12, 69.83 ] |
| Santos 2002 | 0/50 | 0/49 | | 0.0 [ 0.0, 0.0 ] |
| Tregnaghi 2006 | 4/507 | 2/174 | | 0.69 [ 0.13, 3.71 ] |
| Win 1997 | 0/126 | 0/122 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **1443** | **735** | | **1.34 [ 0.45, 3.95 ]** |


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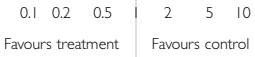
| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Total events: 11 (Combined), 3 (Separate) | | | | |
| Heterogeneity: Tau² = 0.0; Chi² = 1.84, df = 4 (P = 0.76); I² =0.0% | | | | |
| Test for overall effect: Z = 0.53 (P = 0.60) | | | | |
| **Total (95% CI)** | **1578** | **862** | | **1.12 [ 0.42, 3.00 ]** |
| Total events: 12 (Combined), 5 (Separate) | | | | |
| Heterogeneity: Tau² = 0.0; Chi² = 2.45, df = 5 (P = 0.78); I² =0.0% | | | | |
| Test for overall effect: Z = 0.23 (P = 0.82) | | | | |



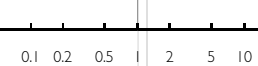

## Analysis 1.7. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 7 Anti-D (Diphtheria).

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 7 Anti-D (Diphtheria)

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 DTPa - immunogenicity failure | | | | |
| Aristegui 2003 | 0/40 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Avdicova 2002 | 0/141 | 0/138 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2004 | 0/177 | 0/175 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2005 | 0/164 | 0/172 | | 0.0 [ 0.0, 0.0 ] |
| Greenberg 2000 | 1/115 | 0/117 | | 3.05 [ 0.13, 74.15 ] |
| Omenaca 2001 | 0/64 | 0/16 | | 0.0 [ 0.0, 0.0 ] |
| Pichichero 1997 | 0/251 | 0/80 | | 0.0 [ 0.0, 0.0 ] |
| Schmitt 2000 | 0/141 | 0/134 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **1093** | **863** | | **3.05 [ 0.13, 74.15 ]** |
| Total events: 1 (Combined), 0 (Separate) | | | | |
| Heterogeneity: Tau² = 0.0; Chi² = 0.0, df = 0 (P = 1.00); I² =0.0% | | | | |
| Test for overall effect: Z = 0.69 (P = 0.49) | | | | |
| 2 DTPw - immunogenicity failure | | | | |

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| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Bravo 1998 | 3/50 | 3/45 | | 0.90 [ 0.19, 4.24 ] |
| Faingezicht 2002 | 1/78 | 2/79 | | 0.51 [ 0.05, 5.47 ] |
| Ortega-Barria 2007 | 20/543 | 11/178 | | 0.60 [ 0.29, 1.22 ] |
| Ramkissoon 2001 | 0/49 | 0/48 | | 0.0 [ 0.0, 0.0 ] |
| Santos 2002 | 1/50 | 1/49 | | 0.98 [ 0.06, 15.23 ] |
| Tregnaghi 2006 | 1/525 | 2/177 | | 0.17 [ 0.02, 1.85 ] |
| Win 1997 | 13/126 | 3/120 | | 4.13 [ 1.21, 14.12 ] |
| **Subtotal (95% CI)** | **1421** | **696** | | **0.89 [ 0.37, 2.16 ]** |
| Total events: 39 (Combined), 22 (Separate) | | | | |
| Heterogeneity: $Tau^2$ = 0.52; $Chi^2$ = 9.44, df = 5 (P = 0.09); $I^2$ =47% | | | | |
| Test for overall effect: Z = 0.26 (P = 0.80) | | | | |
| **Total (95% CI)** | **2514** | **1559** | | **0.96 [ 0.42, 2.20 ]** |
| Total events: 40 (Combined), 22 (Separate) | | | | |
| Heterogeneity: $Tau^2$ = 0.45; $Chi^2$ = 10.05, df = 6 (P = 0.12); $I^2$ =40% | | | | |
| Test for overall effect: Z = 0.09 (P = 0.92) | | | | |

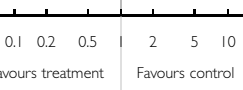
## Analysis 1.8. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 8 Anti-T (Tetanus).

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 8 Anti-T (Tetanus)

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| 1 DTPa - immunogenicity failure | | | | |
| Aristegui 2003 | 0/40 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Avdicova 2002 | 0/141 | 0/138 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2004 | 0/177 | 0/175 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2005 | 0/164 | 0/172 | | 0.0 [ 0.0, 0.0 ] |
| Greenberg 2000 | 0/115 | 0/117 | | 0.0 [ 0.0, 0.0 ] |
| Omenaca 2001 | 0/64 | 0/16 | | 0.0 [ 0.0, 0.0 ] |
| Pichichero 1997 | 0/251 | 0/80 | | 0.0 [ 0.0, 0.0 ] |
| Schmitt 2000 | 0/141 | 0/134 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **1093** | **863** | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Combined), 0 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P<0.00001); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | |
| 2 DTPw - immunogenicity failure | | | | |
| Bravo 1998 | 0/50 | 0/45 | | 0.0 [ 0.0, 0.0 ] |
| Faingezicht 2002 | 0/78 | 0/79 | | 0.0 [ 0.0, 0.0 ] |
| Ortega-Barria 2007 | 0/543 | 5/178 | ← | 0.03 [ 0.00, 0.54 ] |
| Ramkissoon 2001 | 0/49 | 0/48 | | 0.0 [ 0.0, 0.0 ] |
| Riedemann 2002 | 0/41 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Santos 2002 | 0/50 | 0/49 | | 0.0 [ 0.0, 0.0 ] |
| Tregnaghi 2006 | 0/525 | 0/176 | | 0.0 [ 0.0, 0.0 ] |
| Win 1997 | 0/127 | 0/122 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **1463** | **737** | ◢ | **0.03 [ 0.00, 0.54 ]** |
| Total events: 0 (Combined), 5 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 2.38 (P = 0.017) | | | | |
| **Total (95% CI)** | **2556** | **1600** | ◢ | **0.03 [ 0.00, 0.54 ]** |
| Total events: 0 (Combined), 5 (Separate) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 2.38 (P = 0.017) | | | | |



### Analysis 1.9. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 9 DTPa Anti-polio type 1 below the assay cutoff 1:8 IU/mL.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 9 DTPa Anti-polio type 1 below the assay cutoff 1:8 IU/mL

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Aristegui 2003 | 6/40 | 2/31 | | 2.33 [ 0.50, 10.74 ] |
| Avdicova 2002 | 0/141 | 0/138 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2004 | 0/177 | 0/175 | | 0.0 [ 0.0, 0.0 ] |
| Pichichero 1997 | 1/251 | 1/80 | | 0.32 [ 0.02, 5.04 ] |
| Schmitt 2000 | 0/104 | 0/99 | | 0.0 [ 0.0, 0.0 ] |
| **Total (95% CI)** | **713** | **523** | | **1.22 [ 0.20, 7.56 ]** |

Total events: 7 (Combined), 3 (Separate)

Heterogeneity: $Tau^2 = 0.68$; $Chi^2 = 1.53$, df = 1 (P = 0.22); $I^2 = 34\%$

Test for overall effect: Z = 0.21 (P = 0.83)

## Analysis 1.10. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 10 DTPa Anti-polio type 2 below the assay cutoff 1:8 IU/mL.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 10 DTPa Anti-polio type 2 below the assay cutoff 1:8 IU/mL

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Aristegui 2003 | 9/40 | 4/31 | | 1.74 [ 0.59, 5.14 ] |
| Avdicova 2002 | 0/141 | 0/138 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2004 | 0/177 | 0/175 | | 0.0 [ 0.0, 0.0 ] |
| Pichichero 1997 | 0/251 | 0/80 | | 0.0 [ 0.0, 0.0 ] |
| Schmitt 2000 | 1/98 | 0/97 | | 2.97 [ 0.12, 72.01 ] |
| **Total (95% CI)** | **707** | **521** | | **1.84 [ 0.66, 5.12 ]** |

Total events: 10 (Combined), 4 (Separate)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 1.17 (P = 0.24)

## Analysis 1.11. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 11 DTPa Anti-polio type 3 below the assay cutoff 1:8 IU/mL.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 11 DTPa Anti-polio type 3 below the assay cutoff 1:8 IU/mL

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Aristegui 2003 | 8/40 | 3/31 | | 2.07 [ 0.60, 7.15 ] |
| Avdicova 2002 | 0/141 | 0/138 | | 0.0 [ 0.0, 0.0 ] |
| Gabutti 2004 | 0/177 | 0/175 | | 0.0 [ 0.0, 0.0 ] |
| Pichichero 1997 | 1/251 | 0/80 | | 0.96 [ 0.04, 23.44 ] |
| Schmitt 2000 | 0/102 | 0/98 | | 0.0 [ 0.0, 0.0 ] |
| **Total (95% CI)** | **711** | **522** | | **1.87 [ 0.59, 5.94 ]** |

Total events: 9 (Combined), 3 (Separate)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 1.06 (P = 0.29)

## Analysis 1.12. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 12 Serious adverse events.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 12 Serious adverse events

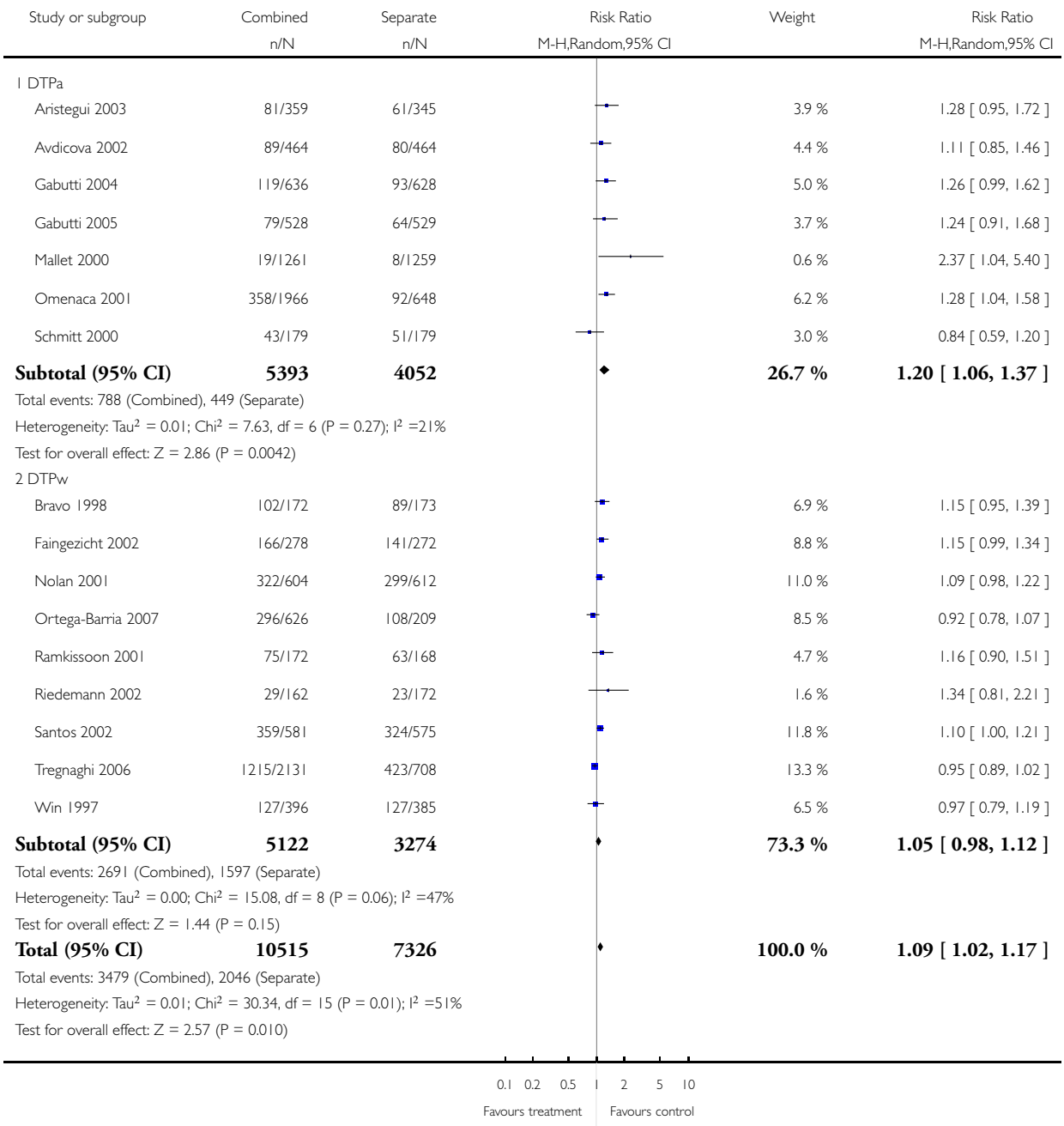
| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa | | | | | |
| Avdicova 2002 | 7/141 | 11/138 | | 28.1 % | 0.62 [ 0.25, 1.56 ] |
| Gabutti 2004 | 10/177 | 10/175 | | 32.6 % | 0.99 [ 0.42, 2.32 ] |
| Mallet 2000 | 1/334 | 3/333 | | 4.6 % | 0.33 [ 0.03, 3.18 ] |
| **Subtotal (95% CI)** | **652** | **646** | | **65.3 %** | **0.75 [ 0.41, 1.37 ]** |
| Total events: 18 (Combined), 24 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.06$, df = 2 (P = 0.59); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.94 (P = 0.35) | | | | | |
| 2 DTPw | | | | | |
| Faingezicht 2002 | 2/96 | 1/95 | | 4.2 % | 1.98 [ 0.18, 21.46 ] |
| Nolan 2001 | 3/604 | 3/612 | | 9.3 % | 1.01 [ 0.21, 5.00 ] |
| Ortega-Barria 2007 | 4/626 | 2/209 | | 8.3 % | 0.67 [ 0.12, 3.62 ] |
| Santos 2002 | 1/197 | 0/195 | | 2.3 % | 2.97 [ 0.12, 72.46 ] |
| Tregnaghi 2006 | 12/750 | 2/250 | | 10.6 % | 2.00 [ 0.45, 8.87 ] |
| **Subtotal (95% CI)** | **2273** | **1361** | | **34.7 %** | **1.32 [ 0.58, 3.00 ]** |
| Total events: 22 (Combined), 8 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.40$, df = 4 (P = 0.84); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.51) | | | | | |
| **Total (95% CI)** | **2925** | **2007** | | **100.0 %** | **0.91 [ 0.56, 1.48 ]** |
| Total events: 40 (Combined), 32 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.62$, df = 7 (P = 0.82); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.37 (P = 0.71) | | | | | |

## Analysis 1.13. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 13 Pain.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 13 Pain



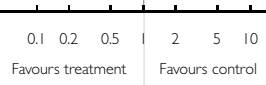
## Analysis 1.14. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 14 Redness.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 14 Redness

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa | | | | | |
| Aristegui 2003 | 109/359 | 82/345 | | 5.9 % | 1.28 [ 1.00, 1.63 ] |
| Avdicova 2002 | 148/464 | 142/464 | | 7.1 % | 1.04 [ 0.86, 1.26 ] |
| Gabutti 2004 | 168/636 | 141/628 | | 7.0 % | 1.18 [ 0.97, 1.43 ] |
| Gabutti 2005 | 101/528 | 111/529 | | 6.0 % | 0.91 [ 0.72, 1.16 ] |
| Mallet 2000 | 153/1261 | 86/1259 | | 5.7 % | 1.78 [ 1.38, 2.29 ] |
| Omenaca 2001 | 533/1966 | 178/648 | | 8.3 % | 0.99 [ 0.85, 1.14 ] |
| Schmitt 2000 | 77/179 | 84/179 | | 6.2 % | 0.92 [ 0.73, 1.15 ] |
| **Subtotal (95% CI)** | **5393** | **4052** | | **46.3 %** | **1.12 [ 0.96, 1.30 ]** |
| Total events: 1289 (Combined), 824 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.03; $Chi^2$ = 23.12, df = 6 (P = 0.00076); $I^2$ =74% | | | | | |
| Test for overall effect: Z = 1.40 (P = 0.16) | | | | | |
| 2 DTPw | | | | | |
| Bravo 1998 | 77/172 | 56/173 | | 5.3 % | 1.38 [ 1.05, 1.82 ] |
| Faingezicht 2002 | 165/278 | 146/272 | | 8.2 % | 1.11 [ 0.95, 1.28 ] |
| Nolan 2001 | 102/604 | 88/612 | | 5.5 % | 1.17 [ 0.90, 1.53 ] |
| Ortega-Barria 2007 | 179/626 | 58/209 | | 5.7 % | 1.03 [ 0.80, 1.32 ] |
| Ramkissoon 2001 | 55/172 | 56/168 | | 4.7 % | 0.96 [ 0.71, 1.30 ] |
| Riedemann 2002 | 20/162 | 7/172 | | 1.0 % | 3.03 [ 1.32, 6.98 ] |
| Santos 2002 | 191/581 | 183/575 | | 7.7 % | 1.03 [ 0.87, 1.22 ] |
| Tregnaghi 2006 | 754/2131 | 271/708 | | 9.2 % | 0.92 [ 0.83, 1.03 ] |
| Win 1997 | 103/396 | 110/385 | | 6.2 % | 0.91 [ 0.72, 1.14 ] |
| **Subtotal (95% CI)** | **5122** | **3274** | | **53.7 %** | **1.06 [ 0.95, 1.18 ]** |
| Total events: 1646 (Combined), 975 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.01; $Chi^2$ = 17.86, df = 8 (P = 0.02); $I^2$ =55% | | | | | |

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| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z = 1.07 (P = 0.28) | | | | | |
| **Total (95% CI)** | **10515** | **7326** | ◆ | **100.0 %** | **1.09 [ 1.00, 1.19 ]** |
| Total events: 2935 (Combined), 1799 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.02; $Chi^2$ = 42.45, df = 15 (P = 0.00019); $I^2$ =65% | | | | | |
| Test for overall effect: Z = 1.87 (P = 0.062) | | | | | |


## Analysis 1.15. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 15 Swelling.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 15 Swelling

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa | | | | | |
| Aristegui 2003 | 81/359 | 57/345 | | 4.2 % | 1.37 [ 1.01, 1.85 ] |
| Avdicova 2002 | 81/464 | 71/464 | | 4.5 % | 1.14 [ 0.85, 1.53 ] |
| Gabutti 2004 | 142/636 | 106/628 | | 6.3 % | 1.32 [ 1.06, 1.66 ] |
| Gabutti 2005 | 88/528 | 95/529 | | 5.2 % | 0.93 [ 0.71, 1.21 ] |
| Mallet 2000 | 183/1261 | 174/1259 | | 7.6 % | 1.05 [ 0.87, 1.27 ] |
| Omenaca 2001 | 374/1966 | 137/648 | | 8.5 % | 0.90 [ 0.76, 1.07 ] |
| Schmitt 2000 | 66/179 | 71/179 | | 5.2 % | 0.93 [ 0.71, 1.21 ] |
| **Subtotal (95% CI)** | **5393** | **4052** | ◆ | **41.5 %** | **1.06 [ 0.94, 1.21 ]** |
| Total events: 1015 (Combined), 711 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.01; $Chi^2$ = 11.86, df = 6 (P = 0.07); $I^2$ =49% | | | | | |
| Test for overall effect: Z = 0.95 (P = 0.34) | | | | | |
| 2 DTPw | | | | | |
| Bravo 1998 | 85/172 | 91/173 | | 7.0 % | 0.94 [ 0.76, 1.16 ] |
| Faingezicht 2002 | 130/278 | 115/272 | | 7.9 % | 1.11 [ 0.92, 1.33 ] |


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| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Nolan 2001 | 120/604 | 95/612 | | 5.7 % | 1.28 [ 1.00, 1.63 ] |
| Ortega-Barria 2007 | 170/626 | 52/209 | | 5.1 % | 1.09 [ 0.83, 1.43 ] |
| Ramkissoon 2001 | 78/172 | 66/168 | | 5.6 % | 1.15 [ 0.90, 1.48 ] |
| Riedemann 2002 | 16/162 | 12/172 | | 1.0 % | 1.42 [ 0.69, 2.90 ] |
| Santos 2002 | 181/581 | 161/575 | | 8.3 % | 1.11 [ 0.93, 1.33 ] |
| Tregnaghi 2006 | 702/2131 | 259/708 | | 11.8 % | 0.90 [ 0.80, 1.01 ] |
| Win 1997 | 105/396 | 111/385 | | 6.3 % | 0.92 [ 0.73, 1.15 ] |
| **Subtotal (95% CI)** | **5122** | **3274** | | **58.5 %** | **1.04 [ 0.95, 1.14 ]** |
| Total events: 1587 (Combined), 962 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.01; $Chi^2$ = 12.93, df = 8 (P = 0.11); $I^2$ =38% | | | | | |
| Test for overall effect: Z = 0.87 (P = 0.39) | | | | | |
| **Total (95% CI)** | **10515** | **7326** | | **100.0 %** | **1.05 [ 0.98, 1.13 ]** |
| Total events: 2602 (Combined), 1673 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.01; $Chi^2$ = 25.14, df = 15 (P = 0.05); $I^2$ =40% | | | | | |
| Test for overall effect: Z = 1.32 (P = 0.19) | | | | | |

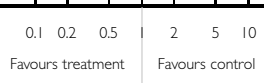
## Analysis 1.16. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 16 Fever.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 16 Fever

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa | | | | | |
| Avdicova 2002 | 51/464 | 42/464 | | 2.6 % | 1.21 [ 0.82, 1.79 ] |
| Gabutti 2004 | 186/635 | 147/628 | | 8.9 % | 1.25 [ 1.04, 1.51 ] |
| Gabutti 2005 | 59/528 | 71/529 | | 3.6 % | 0.83 [ 0.60, 1.15 ] |
| Mallet 2000 | 185/1261 | 183/1259 | | 8.7 % | 1.01 [ 0.84, 1.22 ] |
| Omenaca 2001 | 301/1966 | 87/648 | | 6.8 % | 1.14 [ 0.91, 1.42 ] |
| Schmitt 2000 | 32/179 | 31/179 | | 2.0 % | 1.03 [ 0.66, 1.62 ] |
| **Subtotal (95% CI)** | **5033** | **3707** | | **32.5 %** | **1.09 [ 0.98, 1.22 ]** |
| Total events: 814 (Combined), 561 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.00; $Chi^2$ = 5.92, df = 5 (P = 0.31); $I^2$ =16% | | | | | |
| Test for overall effect: Z = 1.53 (P = 0.13) | | | | | |
| 2 DTPw | | | | | |
| Nolan 2001 | 161/604 | 154/612 | | 8.6 % | 1.06 [ 0.88, 1.28 ] |
| Ortega-Barria 2007 | 322/626 | 104/209 | | 11.4 % | 1.03 [ 0.88, 1.21 ] |
| Riedemann 2002 | 52/162 | 68/172 | | 4.3 % | 0.81 [ 0.61, 1.09 ] |
| Santos 2002 | 290/581 | 307/575 | | 16.9 % | 0.93 [ 0.84, 1.05 ] |
| Tregnaghi 2006 | 484/2131 | 175/708 | | 12.0 % | 0.92 [ 0.79, 1.07 ] |
| Win 1997 | 219/396 | 201/385 | | 14.3 % | 1.06 [ 0.93, 1.21 ] |
| **Subtotal (95% CI)** | **4500** | **2661** | | **67.5 %** | **0.98 [ 0.92, 1.05 ]** |
| Total events: 1528 (Combined), 1009 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.00; $Chi^2$ = 5.48, df = 5 (P = 0.36); $I^2$ =9% | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.55) | | | | | |
| **Total (95% CI)** | **9533** | **6368** | | **100.0 %** | **1.02 [ 0.95, 1.08 ]** |
| Total events: 2342 (Combined), 1570 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.00; $Chi^2$ = 14.90, df = 11 (P = 0.19); $I^2$ =26% | | | | | |
| Test for overall effect: Z = 0.46 (P = 0.64) | | | | | |



## Analysis 1.17. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 17 Fussiness or restlessness.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 17 Fussiness or restlessness

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa | | | | | |
| Avdicova 2002 | 81/464 | 65/464 | | 5.9 % | 1.25 [ 0.92, 1.68 ] |
| Gabutti 2004 | 189/635 | 198/628 | | 14.4 % | 0.94 [ 0.80, 1.11 ] |
| Gabutti 2005 | 49/528 | 67/529 | | 4.6 % | 0.73 [ 0.52, 1.04 ] |
| Mallet 2000 | 339/1261 | 298/1259 | | 18.5 % | 1.14 [ 0.99, 1.30 ] |
| Omenaca 2001 | 563/1966 | 187/648 | | 17.7 % | 0.99 [ 0.86, 1.14 ] |
| Schmitt 2000 | 34/179 | 29/179 | | 2.9 % | 1.17 [ 0.75, 1.84 ] |
| **Subtotal (95% CI)** | **5033** | **3707** | | **64.0 %** | **1.03 [ 0.91, 1.15 ]** |
| Total events: 1255 (Combined), 844 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.90$, df = 5 (P = 0.11); $I^2 = 44\%$ | | | | | |
| Test for overall effect: Z = 0.43 (P = 0.67) | | | | | |
| 2 DTPw | | | | | |
| Nolan 2001 | 130/604 | 112/612 | | 9.3 % | 1.18 [ 0.94, 1.47 ] |
| Santos 2002 | 368/581 | 365/575 | | 26.7 % | 1.00 [ 0.91, 1.09 ] |
| **Subtotal (95% CI)** | **1185** | **1187** | | **36.0 %** | **1.05 [ 0.90, 1.23 ]** |
| Total events: 498 (Combined), 477 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.98$, df = 1 (P = 0.16); $I^2 = 49\%$ | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | |
| **Total (95% CI)** | **6218** | **4894** | | **100.0 %** | **1.03 [ 0.95, 1.12 ]** |
| Total events: 1753 (Combined), 1321 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.79$, df = 7 (P = 0.15); $I^2 = 35\%$ | | | | | |
| Test for overall effect: Z = 0.79 (P = 0.43) | | | | | |

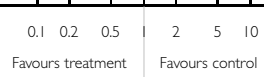
## Analysis 1.18. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 18 Drowsiness.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 18 Drowsiness

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa | | | | | |
| Aristegui 2003 | 99/359 | 100/345 | | 11.4 % | 0.95 [ 0.75, 1.20 ] |
| Avdicova 2002 | 67/464 | 62/464 | | 7.7 % | 1.08 [ 0.78, 1.49 ] |
| Gabutti 2004 | 164/635 | 157/628 | | 14.3 % | 1.03 [ 0.86, 1.25 ] |
| Gabutti 2005 | 46/528 | 71/529 | | 6.7 % | 0.65 [ 0.46, 0.92 ] |
| Mallet 2000 | 339/1261 | 298/1259 | | 18.5 % | 1.14 [ 0.99, 1.30 ] |
| Schmitt 2000 | 41/179 | 29/179 | | 4.9 % | 1.41 [ 0.92, 2.17 ] |
| **Subtotal (95% CI)** | **3426** | **3404** | | **63.7 %** | **1.02 [ 0.88, 1.19 ]** |
| Total events: 756 (Combined), 717 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.02; $Chi^2$ = 11.13, df = 5 (P = 0.05); $I^2$ =55% | | | | | |
| Test for overall effect: Z = 0.28 (P = 0.78) | | | | | |
| 2 DTPw | | | | | |
| Ortega-Barria 2007 | 160/626 | 54/209 | | 9.9 % | 0.99 [ 0.76, 1.29 ] |
| Ramkissoon 2001 | 17/172 | 20/168 | | 2.7 % | 0.83 [ 0.45, 1.53 ] |
| Riedemann 2002 | 24/162 | 27/172 | | 3.7 % | 0.94 [ 0.57, 1.57 ] |
| Tregnaghi 2006 | 679/2131 | 253/708 | | 20.0 % | 0.89 [ 0.79, 1.00 ] |
| **Subtotal (95% CI)** | **3091** | **1257** | | **36.3 %** | **0.91 [ 0.82, 1.00 ]** |
| Total events: 880 (Combined), 354 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.60, df = 3 (P = 0.90); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.88 (P = 0.060) | | | | | |
| **Total (95% CI)** | **6517** | **4661** | | **100.0 %** | **0.99 [ 0.89, 1.09 ]** |
| Total events: 1636 (Combined), 1071 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.01; $Chi^2$ = 16.25, df = 9 (P = 0.06); $I^2$ =45% | | | | | |
| Test for overall effect: Z = 0.27 (P = 0.78) | | | | | |



## Analysis 1.19. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 19 Irritability or tenderness.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 19 Irritability or tenderness

| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa | | | | | |
| Aristegui 2003 | 143/359 | 113/345 | | 10.3 % | 1.22 [ 1.00, 1.48 ] |
| Gabutti 2005 | 112/528 | 129/529 | | 8.5 % | 0.87 [ 0.70, 1.09 ] |
| **Subtotal (95% CI)** | **887** | **874** | | **18.7 %** | **1.03 [ 0.74, 1.44 ]** |
| Total events: 255 (Combined), 242 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 4.91$, df = 1 (P = 0.03); $I^2 = 80\%$ | | | | | |
| Test for overall effect: Z = 0.19 (P = 0.85) | | | | | |
| 2 DTPw | | | | | |
| Faingezicht 2002 | 153/278 | 142/272 | | 14.6 % | 1.05 [ 0.90, 1.23 ] |
| Ortega-Barria 2007 | 304/626 | 103/209 | | 14.1 % | 0.99 [ 0.84, 1.16 ] |
| Ramkissoon 2001 | 47/172 | 52/168 | | 4.2 % | 0.88 [ 0.63, 1.23 ] |
| Riedemann 2002 | 49/162 | 63/172 | | 4.9 % | 0.83 [ 0.61, 1.12 ] |
| Tregnaghi 2006 | 1185/2131 | 417/708 | | 32.1 % | 0.94 [ 0.88, 1.01 ] |
| Win 1997 | 136/396 | 148/385 | | 11.3 % | 0.89 [ 0.74, 1.08 ] |
| **Subtotal (95% CI)** | **3765** | **1914** | | **81.3 %** | **0.95 [ 0.90, 1.01 ]** |
| Total events: 1874 (Combined), 925 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.38$, df = 5 (P = 0.64); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 1.73 (P = 0.083) | | | | | |
| **Total (95% CI)** | **4652** | **2788** | | **100.0 %** | **0.97 [ 0.90, 1.04 ]** |
| Total events: 2129 (Combined), 1167 (Separate) | | | | | |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.69$, df = 7 (P = 0.21); $I^2 = 28\%$ | | | | | |
| Test for overall effect: Z = 0.88 (P = 0.38) | | | | | |

## Analysis 1.20. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 20 Poor appetite.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 20 Poor appetite

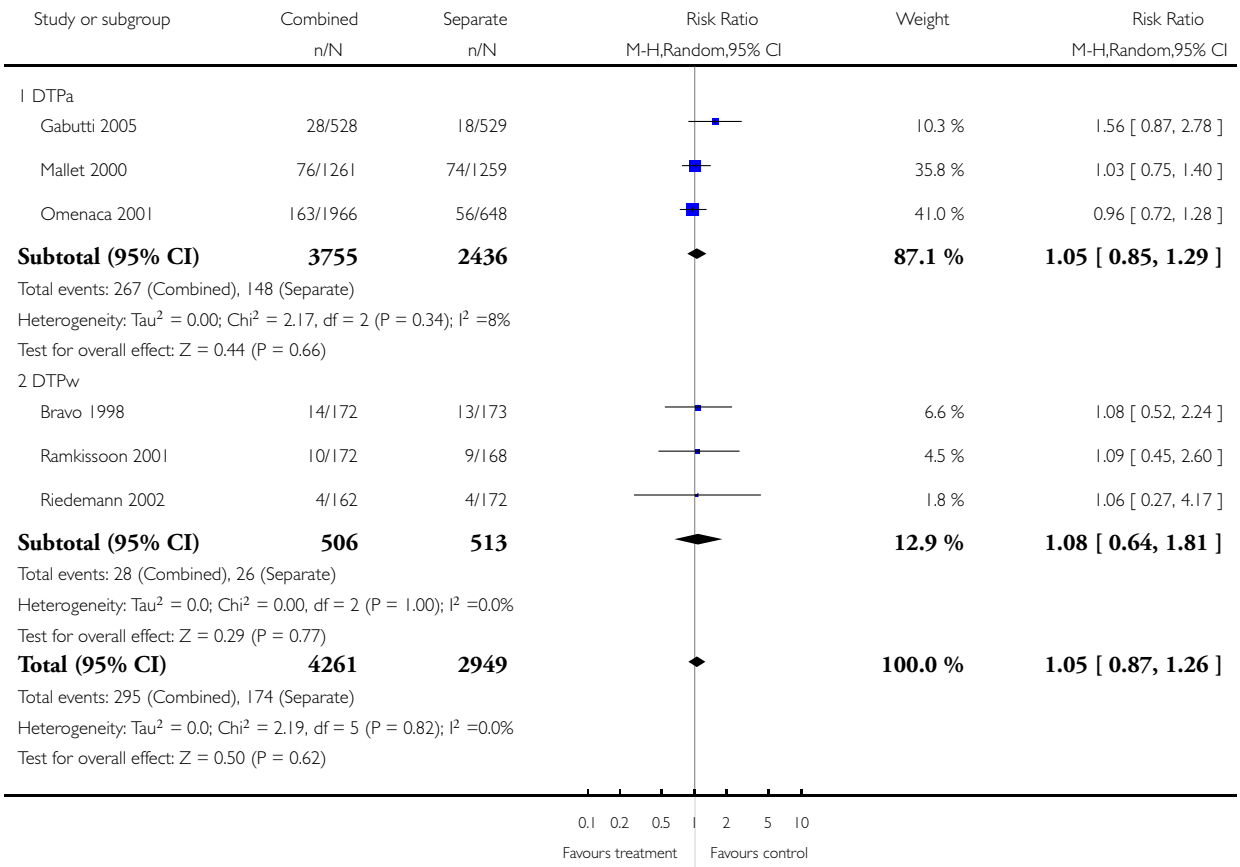
| Study or subgroup | Combined n/N | Separate n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 DTPa | | | | | |
| Aristegui 2003 | 91/359 | 74/345 | | 7.0 % | 1.18 [ 0.90, 1.55 ] |
| Gabutti 2004 | 115/635 | 115/628 | | 9.3 % | 0.99 [ 0.78, 1.25 ] |
| Gabutti 2005 | 61/528 | 74/529 | | 5.1 % | 0.83 [ 0.60, 1.13 ] |
| Mallet 2000 | 117/1261 | 108/1259 | | 8.2 % | 1.08 [ 0.84, 1.39 ] |
| Omenaca 2001 | 297/1966 | 79/648 | | 9.4 % | 1.24 [ 0.98, 1.56 ] |
| **Subtotal (95% CI)** | **4749** | **3409** | | **39.0 %** | **1.07 [ 0.94, 1.22 ]** |
| Total events: 681 (Combined), 450 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.00; $Chi^2$ = 5.07, df = 4 (P = 0.28); $I^2$ =21% | | | | | |
| Test for overall effect: Z = 1.03 (P = 0.30) | | | | | |
| 2 DTPw | | | | | |
| Bravo 1998 | 26/172 | 28/173 | | 2.1 % | 0.93 [ 0.57, 1.53 ] |
| Ortega-Barria 2007 | 130/626 | 46/209 | | 5.8 % | 0.94 [ 0.70, 1.27 ] |
| Ramkissoon 2001 | 30/172 | 21/168 | | 1.9 % | 1.40 [ 0.83, 2.34 ] |
| Riedemann 2002 | 11/162 | 15/172 | | 0.9 % | 0.78 [ 0.37, 1.64 ] |
| Tregnaghi 2006 | 921/2131 | 315/708 | | 50.2 % | 0.97 [ 0.88, 1.07 ] |
| **Subtotal (95% CI)** | **3263** | **1430** | | **61.0 %** | **0.97 [ 0.89, 1.06 ]** |
| Total events: 1118 (Combined), 425 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 2.29, df = 4 (P = 0.68); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | |
| **Total (95% CI)** | **8012** | **4839** | | **100.0 %** | **1.01 [ 0.94, 1.09 ]** |
| Total events: 1799 (Combined), 875 (Separate) | | | | | |
| Heterogeneity: $Tau^2$ = 0.00; $Chi^2$ = 9.17, df = 9 (P = 0.42); $I^2$ =2% | | | | | |
| Test for overall effect: Z = 0.34 (P = 0.74) | | | | | |

## Analysis 1.21. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 21 Vomiting.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 21 Vomiting

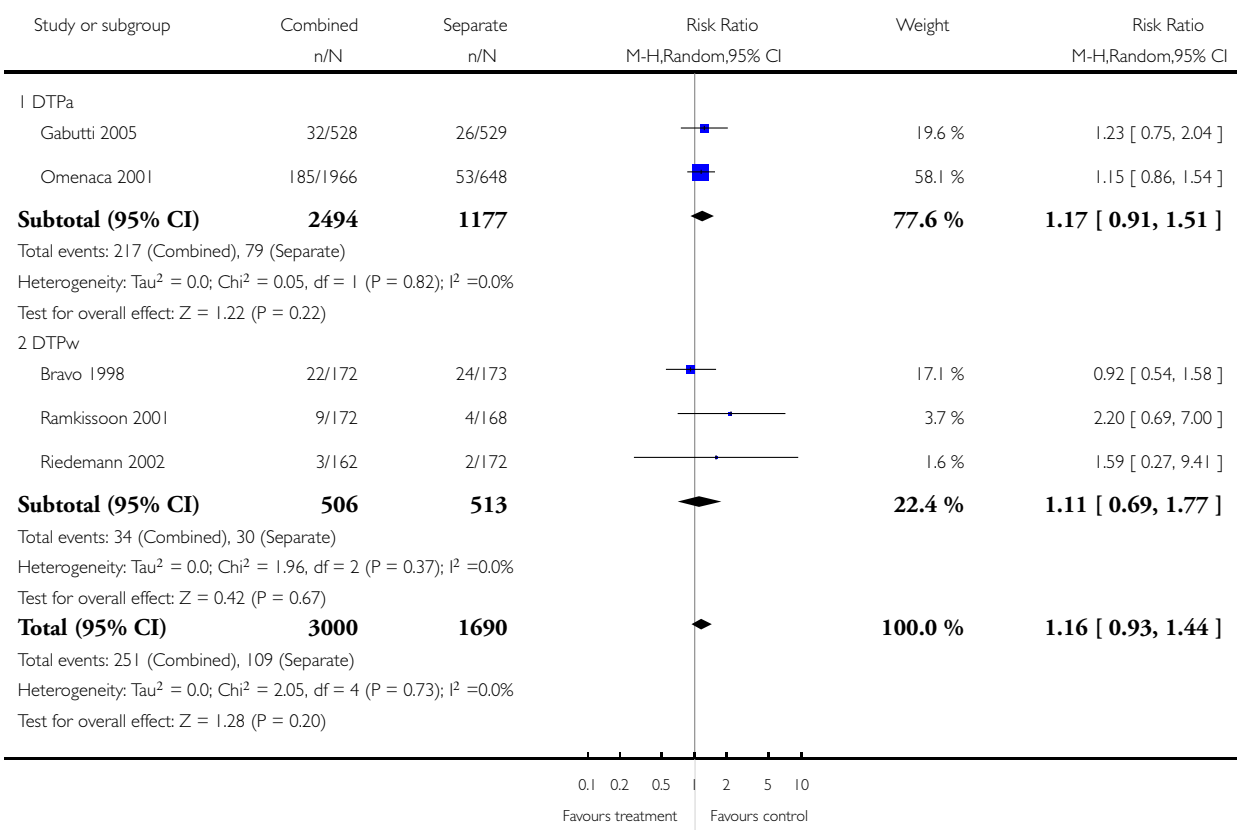


## Analysis 1.22. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 22 Diarrhea.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 22 Diarrhea

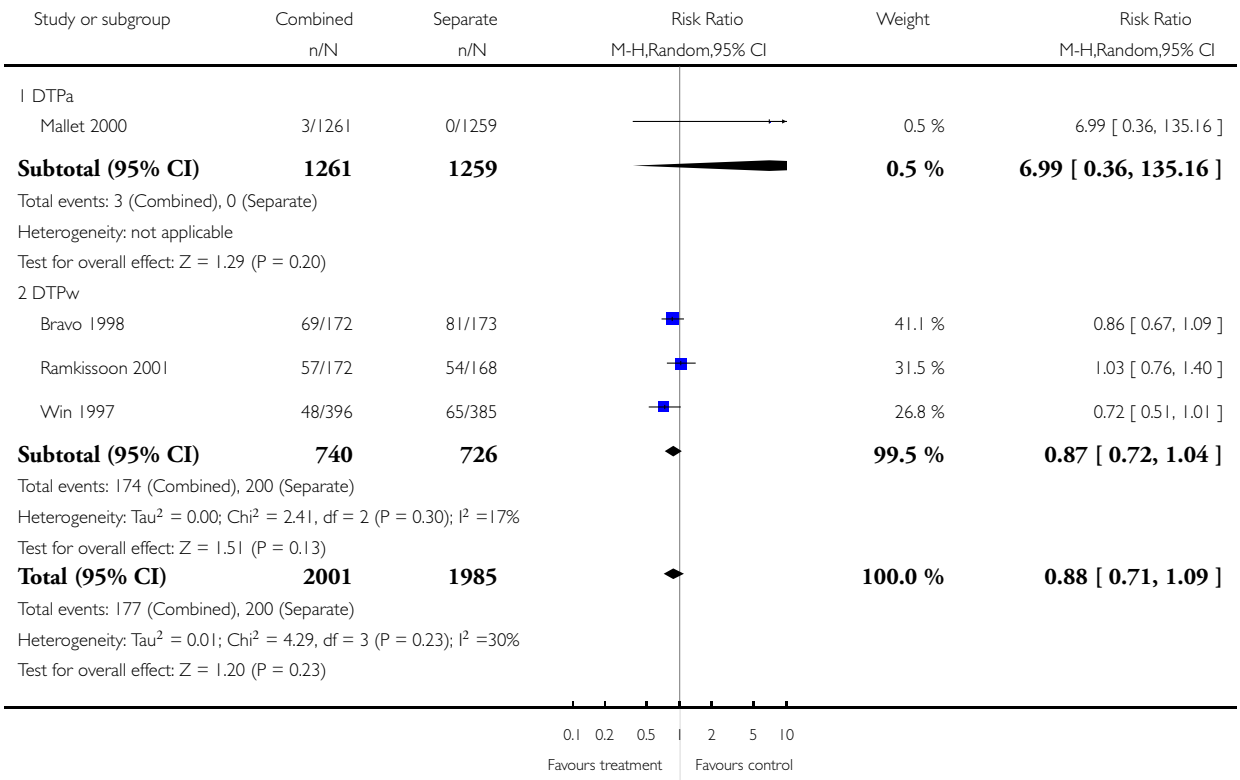


## Analysis 1.23. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 23 Unusual crying.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 23 Unusual crying

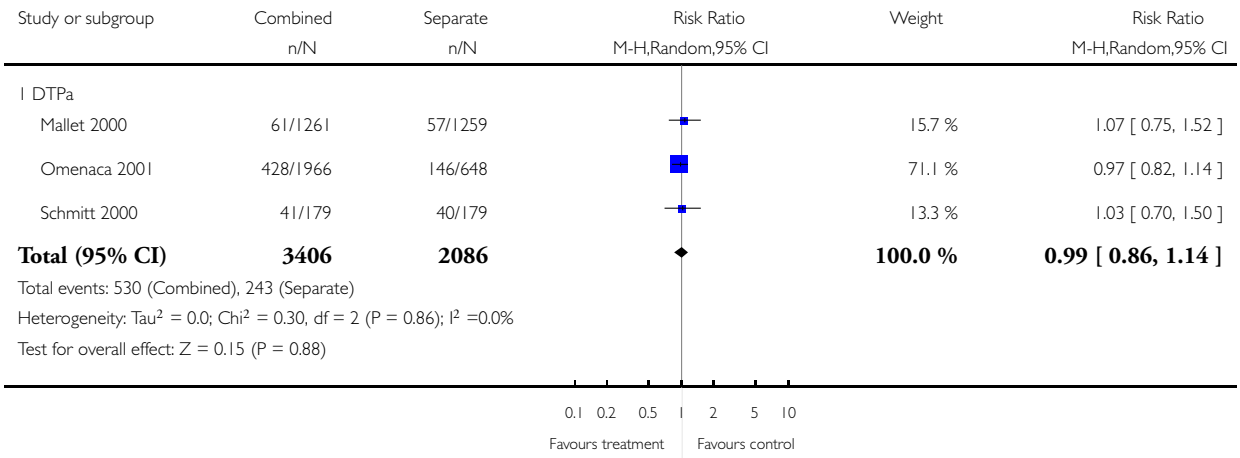


### Analysis 1.24. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 24 Sleeping more than usual.

Review: Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB)

Comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines

Outcome: 24 Sleeping more than usual




## APPENDICES

## Appendix 1. EMBASE.COM

1. 'diphtheria pertussis tetanus haemophilus influenzae type b hepatitis b vaccine'/exp AND [embase]/li
m AND [2005-2009]/py
2. 'diphtheria pertussis tetanus vaccine'/exp AND [embase]/lim AND [2005-2009]/py
3. diphtheria:ti,ab AND pertussis:ti,ab AND tetanus:ti,ab AND [embase]/lim AND [2005-2009]/py
4. dtp:ti,ab OR dpt:ti,ab OR dtap:ti,ab AND [embase]/lim AND [2005-2009]/py
5. #2 OR #3 OR #4
6. 'haemophilus vaccine'/exp AND [embase]/lim AND [2005-2009]/py
7. 'haemophilus influenzae type b'/exp AND [embase]/im AND [2005-2009]/py
8. 'haemophilus influenzae type b vaccine'/exp AND [embase]/lim AND [2005-2009]/py
9. haemophilus:ti,ab OR hemophilus:ti,ab OR hib:ti,ab AND [embase]/lim AND [2005-2009]/py
10. #6 OR #7 OR #8 OR #9
11. 'hepatitis b vaccine'/exp AND [embase]/lim AND [2005-2009]/py
12. 'hepatitis b'/exp AND [embase]/lim AND [2005-2009]/py
13. 'hepatitis b':ti,ab OR hbv:ti,ab AND [embase]/lim AND [2005-2009]/py
14. #11 OR #12 OR #13
15. #5 AND #10 AND #14
16. #1 OR #15
17. random*:ti,ab OR placebo*:ti,ab OR 'double blind':ti,ab OR 'double blinded':ti,ab OR 'double blinding':ti,ab AND [embase]/lim
AND [2005-2009]/py
18. #16 AND #17
19. #18 AND [embase]/lim AND [01-02-2008]/sd NOT [05-0 16 05 Mar 2009
3-2009]/sd AND [2005-2009]/py

## HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 3, 2009

| | | |
|---|---|---|
| 8 July 2008 | Amended | Converted to new review format. |

## CONTRIBUTIONS OF AUTHORS

Edna Bar-On (EB): was responsible for the reference searches, article retrieval, study inclusion and exclusion, data extraction, analysis, interpretation of results and writing of the review.

Abigail Fraser (AF): assisted with writing the protocol.

Sarah Hellmann (SH): has assisted with writing the protocol.

Goldberg Elad (GE): was responsible for the reference searches, article retrieval, study inclusion and exclusion, data extraction, analysis and interpretation of results.

Liat Vidal (LV): assisted with the search terms for the protocol.

Leonard Leibovici (LL): was responsible for study inclusion and exclusion, analysis, interpretation of results and writing of the review.

## DECLARATIONS OF INTEREST

None to declare


## SOURCES OF SUPPORT

### Internal sources

- Rabin Medical Center, Beilinson Campus, Israel.

### External sources

- The National Institute for Health Policy and Health Services Research, Israel.


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The separate vaccine immunogenicity analysis of two types of pertussis vaccination: acellular pertussis (DTPa) and whole cell pertussis (DTPw) was added after the protocol was written.