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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)

Bar-On ES, Goldberg E, Hellmann S, Leibovici L

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TABLE OF CONTENTS

[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 optimising prevention. The World Health Organization (WHO) recommends that routine infant immunisation programmes include a vaccination against *Haemophilus influenzae* (*H. influenzae*) type B (HIB) in the combined diphtheria-tetanus-pertussis (DTP)-hepatitis B virus (HBV) vaccination. The effectiveness and safety of the combined vaccine should be carefully and systematically assessed to ensure its acceptability by the community.

Objectives

To compare the effectiveness of combined DTP-HBV-HIB vaccines versus combined DTP-HBV and separate HIB vaccinations.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to week 1, November 2011), EMBASE (January 1990 to November 2011) and www.clinicaltrials.gov (up to April 2011).

Selection criteria

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

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

Data for the primary outcome (prevention of disease) were lacking. We performed a meta-analysis to pool the results of 20 studies with 5874 participants in an immunogenicity analysis and 5232 participants in the reactogenicity analysis. There were no data on clinical outcomes for the primary outcome (prevention of disease) and all studies used immunogenicity and reactogenicity (adverse events). The number

of vaccine doses differed significantly between the studies. Heterogeneous interventions, study location, healthcare environment and combining research across disparate geographical locations, may have lead to bias. The risk of bias was unclear across most of the included studies. Comparisons found little heterogeneity. In two immunological responses the combined vaccine achieved lower responses than the separate vaccines for HIB and tetanus. No significant differences in immunogenicity were found for pertussis, diphtheria, polio and hepatitis B. Serious adverse events were comparable with mainly hospitalisation and acute bronchiolitis cases. Minor adverse events such as pain and redness were more common in children given the combined vaccine. Overall, the direction shown by the results is in favour of the DTPw (diptheria-tetanus-whole cell pertussis)-HBV-HIB vaccine rather than the DTPa (diptheria-tetanus-acellular pertussis)-HBV-HIB vaccine when compared to the separate vaccines (size of effect: risk ratio (RR) 1.43; 95% confidence interval (CI) 0.98 to 2.10, for 5269 participants).

Authors' conclusions

We could not conclude that the immune responses elicited by the combined vaccine were different from or equivalent to the separate vaccines. There was significantly less immunological response for HIB and tetanus 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 (ITT) 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 in healthy infants up to two years old

Childhood vaccinations provide an effective method of protection against diseases. The World Health Organization (WHO) recommends that routine infant immunisation programmes include a vaccination against *Haemophilus influenzae (H. influenza)* type B (HIB) in the combined diphtheria-tetanus-pertussis (DTP)-hepatitis B virus (HBV) vaccination. We compared the combined DTP-HBV-HIB vaccine with the separate DTP-HBV and HIB vaccines. Studies only reported on immunogenicity and reactogenicity.

We included 20 studies with 5874 participants in the immunogenicity analysis and 5232 in the reactogenicity analysis. In two immunological responses, the combined vaccine achieved lower responses than the separate vaccines for HIB and tetanus. We did not find any significant differences in immunogenicity for pertussis-diphtheria-polio and hepatitis B. Serious adverse events were comparable. Minor adverse events were more common with the combined vaccine. Overall, the level of evidence provided by the studies was low and we could not conclude that the immune responses with the combined vaccine were equivalent to the separate injections.

BACKGROUND

Description of the condition

Despite the availability of proven vaccination, hepatitis B virus (HBV) and *Haemophilus influenzae* (*H. influenzae*) type B (HIB) infections continue to be endemic in many parts of the world. The benefits of effective immunisation against HBV and HIB disease during the first year of life are known and in 1996, the World Health Organization (WHO) set an objective for the development of a vaccine combining HBV with the established diphtheria-tetanus-whole cell pertussis (DTPw) antigens (Ortega-Barria 2007). In 1998, the WHO further recommended the inclusion of HIB conjugate vaccines in infant immunisation programmes (WHO 1998).

Description of the intervention

Childhood vaccinations provide clinically-effective and cost-effective methods of protecting against many diseases. Combination vaccines have been widespread since the 1940s. Diphtheria-tetanus-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, optimising prevention and reducing operational costs. This might not be the case in some countries such as the United States (US), where combination vaccines are often more expensive than the separate components.

Assessment of the immune responses to combination vaccines has generally been based on randomised 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 titre (GMT) of antibodies elicited by the component (Ball 2001).

How the intervention might work

The WHO recommends that routine infant immunisation programmes include a vaccination against HIB in the combined DTP-HBV injection (WHO 1998). HIB is an important pathogen in both high-income and low-income countries. The DTP-HBV combination vaccine would make an ideal partner for combining with HIB vaccines, because the DTP vaccine is mandatory in most immunisation programmes and the HBV vaccination is already in widespread use (Santos 2002).

Why it is important to do this review

The strategy of combining the HBV vaccine with the DTP vaccine has already been adopted into immunisation programmes (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 Tritanrix-HBV/HIB in a variety of immunisation schedules and countries were reviewed for its suitability for use in national immunisation programmes (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 (defined as antibody concentration responses to infectious diseases) and reactogenicity (adverse events) of a combined DTP vaccine, (including both Pw (whole cell pertussis) and Pa (acellular pertussis) vaccines), HBV and conjugate HIB vaccine, (with or without three types of inactivated polio virus (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

Randomised controlled trials (RCTs) or quasi-RCTs.

Types of participants

Healthy male and female infants up to two years of age.

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 polio virus (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 identified trials tested the effectiveness of the combined DTP-HBV-conjugate HIB vaccine.

Types of outcome measures

Primary outcomes

- The incidence of diphtheria, tetanus, pertussis, hepatitis B and HIB post-vaccination.

Secondary outcomes

- Immunogenicity, defined as antibody responses to tetanus, diphtheria, pertussis, hepatitis B and HIB.
- Systemic and local adverse events, including fever, pain, redness, swelling, irritability, drowsiness, loss of appetite, vomiting and more generalised and severe signs, including potential adverse events which have been hypothesised in relation to the vaccination.

Search methods for identification of studies

Electronic searches

Previously we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 1); MEDLINE (January 1966 to March 2009); and EMBASE (January 1990 to March 2009).

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue

4, www.thecochranelibrary.com (accessed 11 November 2011)); MEDLINE (March 2009 to November week 1, 2011); EMBASE (March 2009 to November 2011); and www.clinicaltrials.gov (March 2008 to April 2011).

We used the terms in Appendix 1 to search CENTRAL and MEDLINE. We combined the search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) Ovid format (Lefebvre 2011). We modified these search terms and used a filter developed by Wong (Wong 2006) to fit the EMBASE.com interface (see Appendix 2). We imposed no language or publication restrictions.

Searching other resources

In addition, we scrutinised clinical practice guideline reference lists to identify additional 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 articles that we identified as potentially eligible. We scanned the bibliographies of all included studies and pertinent reviews 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 www.icaac.org/icaacarch.asp); European Congress of Clinical Microbiology and Infectious Diseases 2001 to 2006 (available at www.akm.ch); and the Annual Meeting of the Infectious Diseases Society of America (IDSA) 2001 to 2006 (available at www.idsociety.org/).

Data collection and analysis

Selection of studies

Three review authors (ESB, EG, SH) independently inspected references identified by the searches and evaluated them against our inclusion criteria. We resolved disagreements in the selection of relevant studies by consensus. Three review authors (ESB, EG, SH) independently inspected the full-text articles in cases of disagreement. We consulted a fourth review author (LL) in cases of continued disagreement. We have detailed the reasons for excluding studies.

Data extraction and management

Three review authors (EB, EG, SH) independently extracted data and assessed the methodological quality of each included trial. For each treatment group, we collected the following data.

1. Intervention characteristics: vaccination type, manufacturer, number of doses and schedule.
2. Characteristics of trial: publication year, start date, end date, study design, country where trial was preformed, data collection method, location of trial and date evaluated.
3. Quality assessment: blinding, unit of allocation, allocation generation and allocation concealment.
4. Case definitions - characteristics of participants: exclusion, inclusion, age and number randomised.
5. Outcomes:

- A. 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 haemagglutinin), PRN-pertactin, BPT-pertussis (PTox pertussis toxin), *Bordetella pertussis* (*B. pertussis*), HB-hepatitis B, D-diphtheria, T-tetanus, polio type 1, polio type 2, polio type 3.
- B. Reactogenicity - adverse events: number of vaccines, number of participants and number of events:
  - serious adverse events
  - pain
  - redness
  - swelling
  - fever (elevated temperature)
  - fussiness or restlessness
  - poor appetite
  - vomiting
  - irritability or tenderness
  - diarrhoea
  - unusual crying
  - sleeping more than usual.

Assessment of risk of bias in included studies

For this update, we used the recommended new 'Risk of bias' tool to assess methodological quality according to: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting and free of other bias (Higgins 2011). We used the categories 'high risk', 'low risk' and 'unclear risk' of bias to measure trial quality.

Measures of treatment effect

We analysed dichotomous (or binary) data, where each individual's outcome is one of only two possible categorical responses, by calculating the risk ratio (RR) for each trial with the uncertainty in each result expressed using 95% confidence intervals (CIs).

Unit of analysis issues

No studies reported on the main outcome, i.e. incidence of diphtheria, tetanus, pertussis, hepatitis B and HIB post-vaccination. All studies reported on immunogenicity, defined as antibody concentration responses to tetanus, diphtheria, pertussis, hepatitis B and HIB.

We performed a meta-analysis to pool the results of 20 studies. We analysed vaccine immunogenicity in subcategories, according to two types of pertussis vaccination: acellular pertussis (Pa) and whole cell pertussis (Pw).

We defined infants with no seroprotective antibody titres (with titres below the assay cut-off or without seroconversion) as events. Studies reported combined inactivated polio virus (IPV) in the DTP-HBV-HIB vaccine and oral polio vaccine (OPV) administered concurrently and therefore we included results of anti-polio types 1, 2 and 3.

We analysed reactogenicity (adverse events) by events of total symptom scores (incidence of any solicited local and systemic adverse events). Serious adverse events were reported by investigators and data completed upon our request. Incidence of any solicited local and systemic adverse events included pain, redness, swelling, fever (elevated temperature), fussiness or

restlessness, poor appetite, vomiting, irritability or tenderness, diarrhoea, unusual crying, or sleeping more than usual.

Dealing with missing data

Data of serious adverse events for some of the included trials are missing (although we did contact trial authors for additional information). We described missing participants due to drop-outs and whether intention-to-treat (ITT) analysis was conducted in the studies in the 'Risk of bias' tables under 'Incomplete outcome data (attrition bias)'.

Assessment of heterogeneity

We initially assessed heterogeneity in the results of the trials by inspection of graphical presentations and by calculating an estimate of heterogeneity (Chi^2 test and I^2 statistic).

Assessment of reporting biases

We examined the funnel plot, using the method described in Egger 1997 to estimate the precision of trials (the inverse of the standard error plotted against the RR), in order to estimate potential selection bias (publication or other).

Data synthesis

We used a random-effects model throughout the review because of heterogeneity. We pooled data, stratifying for number of doses received. We used a fixed-effect model in the sensitivity analysis.

Subgroup analysis and investigation of heterogeneity

An approximate guide to interpretation of the I^2 statistic is as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% represents considerable heterogeneity.

Different subgroups contain different amounts of information and thus have different abilities to detect effects. Therefore, we did not use other methods for investigating heterogeneity of effects in the meta-analysis.

Sensitivity analysis

We performed a post hoc sensitivity analysis for the anti-PRP (polyribosylribitolphoshate) comparison by excluding this study from the analysis. It was influenced by one study with a large number of events (Pichichero 1997), which used pure (and not conjugated) PRP vaccines.

RESULTS

Description of studies

Results of the search

We identified 246 studies (47 studies in this update), of which we considered 60 as potentially eligible, including eight studies in this update.

Included studies

We included 20 studies. Two different types of pertussis vaccination were used in the studies; 10 studies used acellular pertussis (DTPa) and 10 studies used whole cell pertussis (DTPw) (as part of the diptheria-tetanus-pertussis vaccine). In five studies inactivated polio virus (IPV) was combined with the DTP-HBV-HIB vaccine (Aristegui 2003; Avdicova 2002; Gabutti 2004; Mallet 2000; Schmitt 2000), while three studies reported oral polio vaccine (OPV) administered to all vaccinees in both groups concurrently (Nolan 2001; Omenaca 2001; Pichichero 1997).

Excluded studies

We excluded forty studies. Four studies were not true RCTs: one was an observational study (Kalies 2004); 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 paediatric 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 vaccination (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-HBV-HIB vaccine with separately administered DTPw-HIB and HBV vaccines (Kanra 2006; Lim 2007)).
- One trial compared 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 pneumococcal conjugate vaccine (PCV7) with DTPa-HBV-IPV-HIB vaccine (Knuf 2006).
- One trial compared three lots of HIB 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 a five-component vaccine DTPa-HBV-IPV-PCV7 and HIB with separate vaccines concurrently, or staggered (delayed) administration of PCV7 (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). We excluded another five trials that had no comparison between vaccines (Bavdekar 2007; Hogg 2003; Pichichero 1999; Trollfors 2005; Zepp 1997). We excluded three additional trials: in the first trial only data of safety and reactogenicity (adverse events) were provided (Zepp 2004); the second trial included the same trials reported elsewhere and only safety data was provided (Saenger 2005); and in the third excluded study, only data on antibody persistence (immunogenicity) of plain PRP and conjugate PRP-T was provided (Nolan 2004).

In this 2011 update, we excluded six more studies: two studies compared different formulas of combined vaccines (Diaz-Mitoma

2011; Madhi 2011) and three studies had no comparison between separate and combined vaccines (Gentile 2011; Halperin 2009; Kilpi 2009). One study compared DTPa-IPV-HBV-PRP-T vaccine with Pentaxim and Engerix B Pediatrico (HBV monovalent) vaccines in infants born to hepatitis B surface antigen seronegative mothers (Tregnaghi 2011).

Risk of bias in included studies

The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

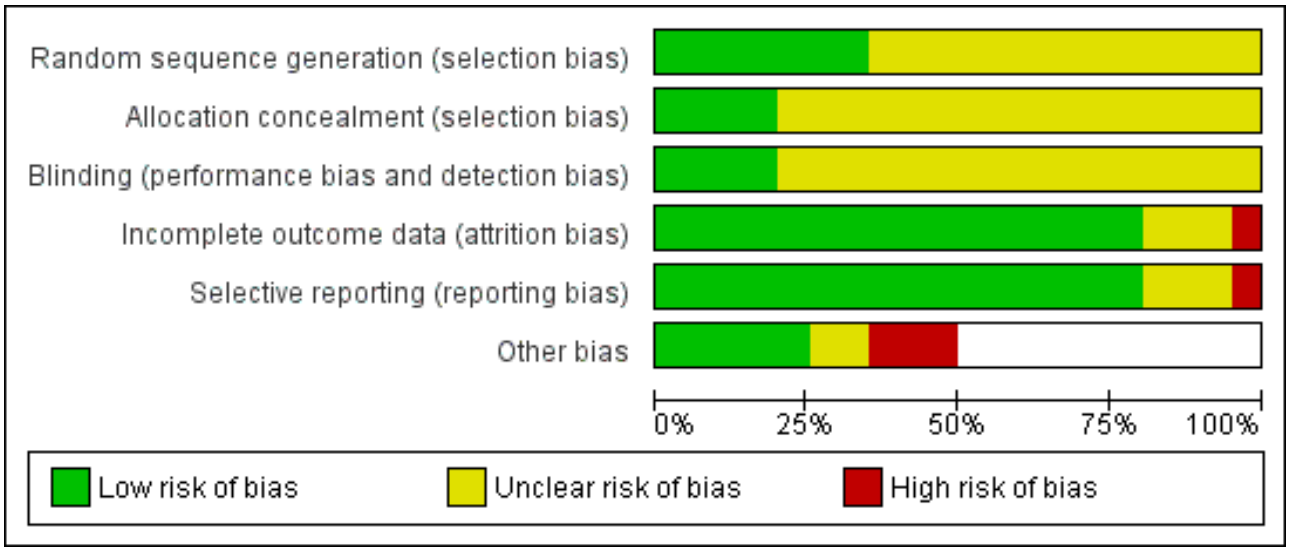


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Allocation concealment

Four of the studies reported adequate allocation concealment (Faingezicht 2002; Mallet 2000; Nolan 2001; Rao 2009). One study reported inadequate allocation concealment (Bravo 1998).

Random sequence generation

Seven studies reported random sequence generation (Aristegui 2003; Avdicova 2002; Faingezicht 2002; Mallet 2000; Nolan 2001; Rao 2009; Win 1997).

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 seven studies, blinding of assessors and/or laboratory personnel was reported (Faingezicht 2002; Greenberg 2000; Mallet 2000; Nolan 2001; Pichichero 1997; Rao 2009; 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.

Incomplete outcome data

Incomplete outcome data were reported in most studies. Unclear risk was determined in three studies with no data (Nolan 2001; Pichichero 1997; Ramkissoon 2001). High risk of bias was determined in one study (Aristegui 2003).

Selective reporting

Reporting bias was determined by the method of collecting data for reactogenicity since immunogenicity data are not subject to reporting bias.

Most studies reported that parents documented the reactions (adverse events) for four days and therefore the reporting bias in the review is low. In one study there were no details how the adverse events were evaluated (Gabutti 2005). Two studies had no details on reporting method (Nolan 2001; Pichichero 1997) and in one study, serious adverse events were reported generally with no specification per study arm (Marshall 2010).

Other potential sources of bias

Intention-to-treat (ITT) analysis

No study clearly mentioned that the ITT 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) titres below the assay cutoff 0.15 µg/ml

Four studies of DTPa-HBV-HIB vaccines and three studies of DTPw-HBV-HIB vaccines were estimated. Four studies of DTPa-HBV-HIB vaccines and four studies of DTPw-HBV-HIB vaccines reported no events. No significant difference was found between combined and separate DTPa-HBV-HIB vaccines and DTPw-HBV-HIB vaccines (RR 1.82; 95% CI 0.98 to 3.38) (Analysis 1.1). 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 between combined and separate DTPa-HBV-HIB vaccines (RR 2.60; 95% CI 1.33 to 5.08).

Exclusion of Pichichero 1997, which donated most of the outcomes, resulted in a point estimate still in favour of the separate vaccines but no longer significant in a random-effects model for the DTPa-HBV-HIB vaccines (RR 1.21; 95% CI 0.53 to 2.77). However, there is no significant heterogeneity for this comparison (Chi^2 test 0.46, df 2, P = 0.8; and I^2 statistic 0%) for the DTPa-HBV-HIB vaccines; and Chi^2 test 3.93, df 5, P = 0.56; and I^2 statistic 0% for all studies). Using a fixed-effect model, there was no significant difference with the exclusion of Pichichero 1997 for the DTPa-HBV-HIB vaccines (RR 2.17; 95% CI 0.79 to 6.00) and RR 1.22; 95% CI 0.57 to 2.62 for all studies.

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

Nine studies of DTPa-HBV-HIB vaccines and six studies of DTPw-HBV-HIB vaccines reported on this outcome. No significant difference was found between combined and separate vaccines (RR 1.43; 95% CI 0.98 to 2.10) (Analysis 1.2). No significant difference was found between combined and separate DTPw-HBV-HIB vaccines (RR 0.83; 95% CI 0.44 to 1.58). A significant difference was found between combined and separate DTPa-HBV-HIB vaccines (RR 2.14; 95% CI 1.48 to 3.10). For the DTPa-HBV-HIB comparison we found little heterogeneity, I^2 statistic -23%.

Exclusion of Pichichero 1997, which donated most of the outcomes, resulted in a point estimate still in favour of the separate vaccines in a random-effects model for the DTPa-HBV-HIB vaccines (RR 1.91; 95% CI 1.33 to 2.74). There was no significant heterogeneity for this comparison. Chi^2 test 6.5, df 6, P = 0.4; and I^2 statistic 8%) for the DTPa-HBV-HIB vaccines; and Chi^2 test 21.5, df 13, P = 0.06; and I^2 statistic 40% for all studies). Using a fixed-effect model, the difference was significant even with the exclusion of Pichichero 1997 (RR 1.94; 95% CI 1.43 to 2.64) for the DTPa-HBV-HIB vaccines; and RR 1.51; 95% CI 1.21 to 1.88 for all studies.

Anti-FHA (filamentous haemagglutinin) - no seroprotective titres

No significant difference was found between combined and separate DTPa-HBV-HIB vaccines (RR 0.94; 95% CI 0.20 to 4.36) (Analysis 1.3). Four studies of DTPa-HBV-HIB were estimated with total of five events. Four studies had no events (Avdicova 2002; Gabutti 2005; Gabutti 2004; Omenaca 2001).

Anti-PRN - no seroprotective titres

No significant difference was found between combined and separate DTPa-HBV-HIB vaccines (RR 0.71; 95% CI 0.34 to 1.50) (Analysis 1.4). Four studies of DTPa-HBV-HIB were estimated with total of 27 events. Four studies had no events (Gabutti 2004; Gabutti 2005; Omenaca 2001; Pichichero 1997).

Anti-BPT (pertussis) - no seroprotective titres

No significant difference (RR 1.01; 95% CI 0.80 to 1.28) (Analysis 1.6) between combined and separate DTPa-HBV-HIB vaccines (RR 0.97; 95% CI 0.75 to 1.25) and DTPw-HBV-HIB combined and separate vaccines (RR 1.33; 95% CI 0.69 to 2.57). Two studies of DTPa-HBV-HIB were included with a total of 117 events. Six studies of DTPw-HBV-HIB were estimated with a total of 10 events in the separate vaccines and 29 events in the combined vaccine. Three studies had no events (Ramkissoon 2001; Santos 2002; Win 1997).

Anti-D (diphtheria): titres below the assay cutoff

No significant difference (RR 0.91; 95% CI 0.59 to 1.38) (Analysis 1.7) between combined and separate DTPa-HBV-HIB vaccines (RR 0.91; 95% CI 0.73 to 1.14) and DTPw-HBV-HIB combined and separate vaccines (RR 0.87; 95% CI 0.39 to 1.91). Nine studies of DTPa-HBV-HIB and DTPw-HBV-HIB were estimated with a total of 193 events (Avdicova 2002; Aristegui 2003; Gabutti 2004; Omenaca 2001; Ortega-Barria 2007; Pichichero 1997; Ramkissoon 2001; Rao 2009; Schmitt 2000). There were no events in eight studies (Aristegui 2003; Avdicova 2002; Gabutti 2004; Gabutti 2005; Omenaca 2001; Pichichero 1997; Ramkissoon 2001; Schmitt 2000).

Anti-T (tetanus) titres below the assay cutoff

No significant difference (RR 0.56; 95% CI 0.04 to 8.95) (Analysis 1.8) between DTPa-HBV-HIB and DTPw-HBV-HIB combined and separate vaccines. There were significant differences (RR 2.22; 95% CI 1.21 to 4.06) between combined and separate DTPa-HBV-HIb vaccines. There was no significant difference (RR 0.20; 95% CI 0.00 to 9.94) between combined and separate DTPw-HBV-HIB vaccines. Three studies were included with a total of 28 events in the combined vaccine and 18 in the separate vaccines. Most events were contributed by one study with 27 events in the combined vaccine and 13 events in the separate vaccines (Marshall 2010) and one study with five events in the separate vaccines (Ortega-Barria 2007).

Anti-HBV (hepatitis B) titres concentrations below the assay cutoff

No significant difference was found (RR 1.24; 95% CI 0.78 to 2.01) (Analysis 1.5) between combined and separate DTPa-HBV-HIB vaccines (RR 1.51; 95% CI 0.68 to 3.34) and DTPw-HBV-HIB combined and separate vaccines (RR 0.96, 95% CI 0.43 to 2.16). Eight studies of DTPa-HBV-HIB were estimated with a total of 36 events. Eight studies of DTPw-HBV-HIB were estimated with a total of 174 events. Three studies had no events (Faingezicht 2002; Omenaca 2001; Ramkissoon 2001).

Anti-polio type 1, 2 and 3 titres 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) (Analysis 1.9), of anti-polio type 2 (RR 1.84; 95% CI 0.66 to 5.12) (Analysis 1.10) and of anti-polio type 3 (RR 1.87; 95% CI 0.59 to 5.94) (Analysis 1.11). 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 combined OPV with DTP-HBV-HIB vaccine (Pichichero 1997).

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 5239 participants were estimated.
No significant difference between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 0.94; 95% CI 0.58 to 1.53) (Analysis 1.12). 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). Six studies of DTPw-HBV-HIB were estimated with 25 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 1.41; 95% CI 0.64 to 3.13). See Table 1 and Table 2 for details.

Pain

A total of 19,745 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 1.16) (Analysis 1.13). Eight studies of DTPa-HBV-HIB were estimated with 892 events in the combined group and 538 events in the separate group. A significant difference between combined and separate DTPa-HBV-HIB vaccines was found (RR 1.20; 95% CI 1.08 to 1.34). Ten studies of DTPw-HBV-HIB were estimated with 2889 events in the combined group and 1699 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 1.11).

Redness

A total of 19,745 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 1.01 to 1.18) (Analysis 1.14). Eight studies of DTPa-HBV-HIB were estimated with 1495 events in the combined group and 1013 events in the separate group. No significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.11; 95% CI 0.98 to 1.27). Ten studies of DTPw-HBV-HIB were estimated with 1751 events in the combined group and 1025 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 1.06; 95% CI 0.96 to 1.17).

Swelling

No significant difference was found between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.04; 95% CI 0.98 to 1.11) (Analysis 1.15). Eight studies of DTPa-HBV-HIB were estimated with 1050 events in the combined group and 837 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.06; 95% CI 0.95 to 1.18). Ten studies of DTPw-HBV-HIB were estimated with 1740 events in the combined group and 1047 events in the separate group. There was

no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 1.03; 95% CI 0.95 to 1.12).

Fever

A total of 17,805 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 0.96 to 1.09) (Analysis 1.16). Seven studies of DTPa-HBV-HIB were estimated with 891 events in the combined group and 621 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.11; 95% CI 1.00 to 1.24). Seven studies of DTPw-HBV-HIB were estimated with 1559 events in the combined group and 1028 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 1.04).

Fussiness or restlessness

A total of 12,183 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 1.09) (Analysis 1.17). Seven studies of DTPa-HBV-HIB were estimated with 1532 events in the combined group and 1138 events in the separate group. No significant difference between combined and separate DTPa-HBV-HIB vaccines was found (RR 1.01; 95% CI 0.92 to 1.11). 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 12,011 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) (Analysis 1.18). 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). Five studies of DTPw-HBV-HIB were estimated with 907 events in the combined group and 367 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 1.01).

Poor appetite

A total of 13,922 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 1.08) (Analysis 1.20). Six studies of DTPa-HBV-HIB were estimated with 756 events in the combined group and 531 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.05; 95% CI 0.94 to 1.18). 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 8281 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 0.90 to 1.23) (Analysis 1.21). Four studies of DTPa-HBV-HIB were estimated with 345 events in the combined group and 223 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.05; 95% CI 0.89 to 1.23). 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 8273 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 0.91 to 1.04) (Analysis 1.19). 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). Seven studies of DTPw-HBV-HIB were estimated with 1987 events in the combined group and 982 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).

Diarrhoea

A total of 5761 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 1.11; 95% CI 0.94 to 1.32) (Analysis 1.22). Three studies of DTPa-HBV-HIB were estimated with 308 events in the combined group and 166 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.12; 95% CI 0.93 to 1.34). 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 5890 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 0.72; 95% CI 0.49 to 1.05) (Analysis 1.23). Two studies of DTPa-HBV-HIB were estimated with 200 events in the combined group and 219 events in the separate group. There was no significant difference between combined and separate DTPa-HBV-HIB vaccines (RR 1.45; 95% CI 0.27 to 7.84). Four studies of DTPw-HBV-HIB were estimated with 205 events in the combined group and 267 events in the separate group. There was no significant difference between combined and separate DTPw-HBV-HIB vaccines (RR 0.64; 95% CI 0.37 to 1.10).

Sleeping more than usual

A total of 6563 DTPa-HBV-HIB vaccines were estimated. Four studies were estimated with 680 events in the combined group and 395 events in the separate group. There was no significant difference

between combined and separate DTPa-HBV-HIB vaccines (RR 0.99; 95% CI 0.89 to 1.11) (Analysis 1.24).

Sensitivity analysis

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

Selection bias

We examined two funnel plot graphs of studies for anti-PRP and they showed no significant selection bias (Figure 3; Figure 4).

Figure 3. 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 cut-off 0.15 µg/ml.

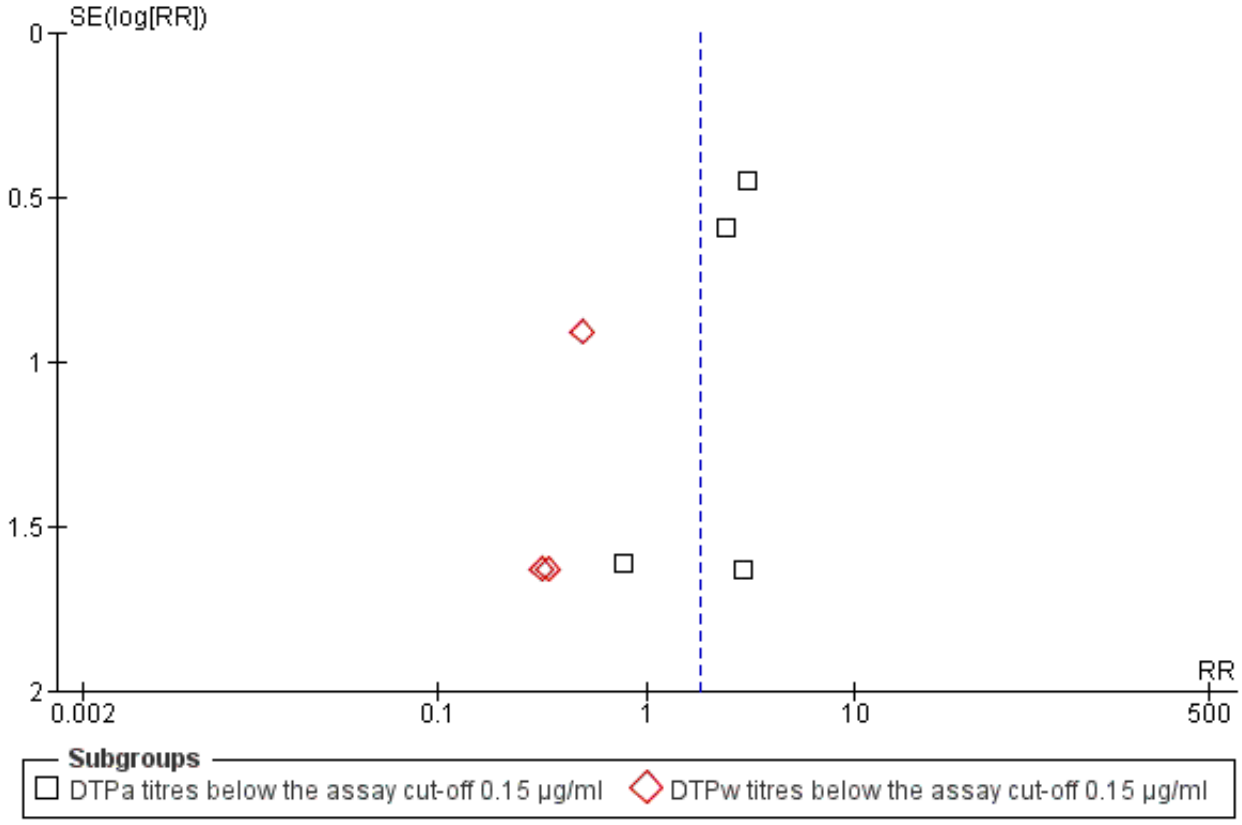
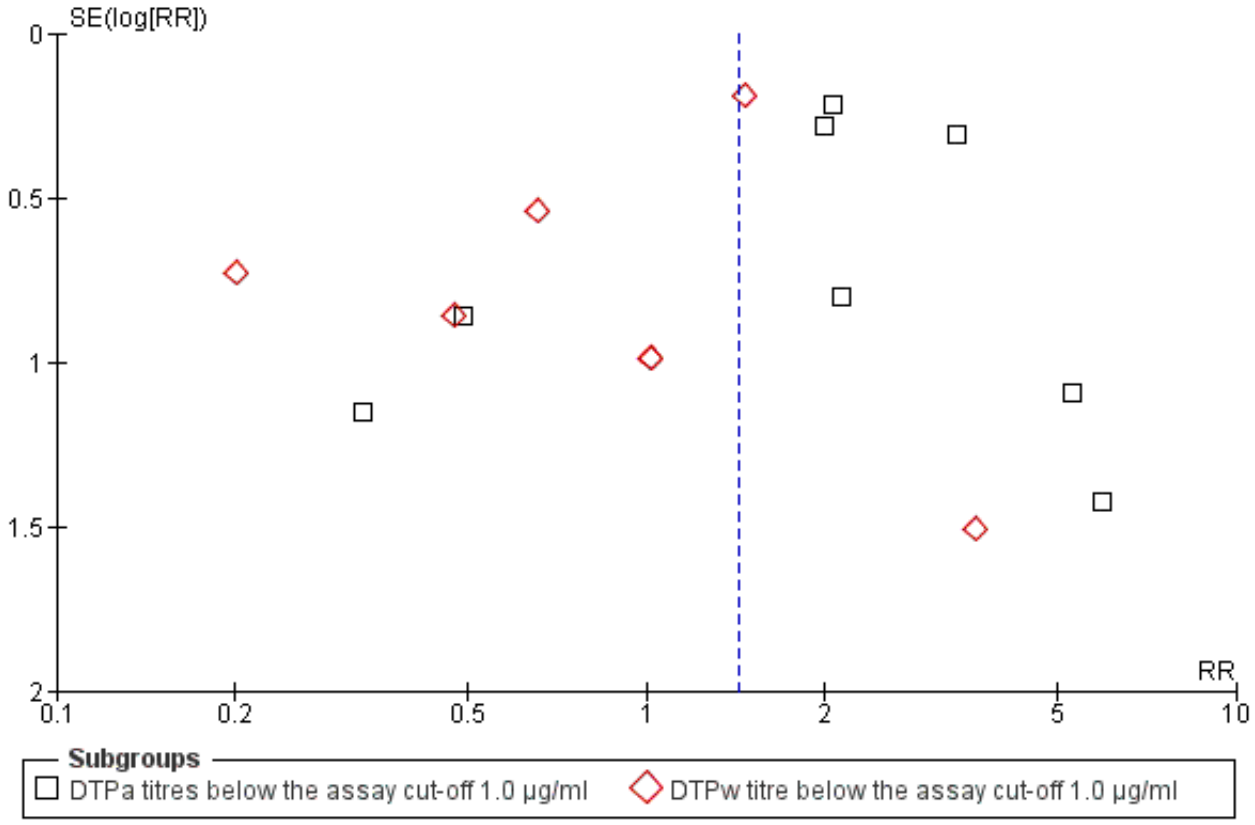


Figure 4. Funnel plot of comparison: 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, outcome: 1.2 Anti-PRP titres below the assay cut-off 1.0 µg/ml.



DISCUSSION

We found no studies that addressed clinical outcomes, i.e. incidence of diphtheria, tetanus, pertussis, hepatitis B virus (HBV) and *H. influenzae* type B (HIB). For some of these diseases, past eradication programmes 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, HBV, tetanus and HIB, clinical outcomes could be expected. The lack of such outcomes weakens conclusions that can be drawn from published studies.

Immunogenicity

The number of vaccine 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 (HIB) and anti-T (tetanus). These results changed slightly by the update when we added two studies to the meta-analysis. The direction shown by the results is in favour of the DTPw-HBV-HIB vaccine rather than the DTPa-HBV-HIB vaccine when compared to the separate vaccines (size of effect: RR 1.43; 95% CI 0.98 to 2.10 for 5269 participants). For the other responses, no significant differences could be shown but the number of events (response below the threshold) was so low that the CIs 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-T comparison is influenced by one study added in the update with a high number of serological failures (Marshall 2010).

Reactogenicity (adverse events)

We were unable to find data of serious adverse events for some of the included trials, although we did contact trial authors for additional information. We did not find any difference between combined and separate vaccines. However, nine studies with a total of 5232 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 GlaxoSmith \Kline Biologicals, Rixensart (Belgium) and by Aventis Pasteur (Lyon, France), combined vaccines were prepared as investigational formulations and reconstituted with different dilutents. Therefore, the findings may not generalise 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 ITT analysis (excluding one study included at the update) (Rao 2009).

Summary of main results

Immunogenicity, defined as antibody concentration responses by serological analysis of diphtheria, tetanus, pertussis, HBV and HIB reported no significant difference between combined and separate vaccines. However, for anti-PRP (HIB) below the assay cut-off of 1.0 µg/ml, in nine studies of DTPa-HBV-HIB vaccines, we found a significant difference between combined and separate vaccines (RR 2.14; 95% CI 1.48 to 3.10). This cut-off refers to the long-term protection and that, according to many authors, a significant difference on this specific point is not clinically relevant. In six studies of DTPw-HBV-HIB vaccines we did not find a significant difference between combined and separate vaccines (RR 0.83; 95% CI 0.44 to 1.58).

We did not find a significant difference (RR 0.56; 95% CI 0.04 to 8.95) between DTPa-HBV-HIB and DTPw-HBV-HIB combined and separate vaccines in anti-T (tetanus) immunological response. However, we did find a significant difference (RR 2.22; 95% CI 1.21 to 4.06) between combined and separate DTPa-HBV-HIB vaccines. Most events were due to one study added to the meta-analysis.

Reactogenicity (adverse events) defined as incidence of any solicited local and systemic adverse event showed no difference between combined and separate vaccines. However, for pain, we found a significant difference between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.09; 95% CI 1.02 to 1.16). We found a significant difference between DTPa-HBV-HIB combined and separate vaccines and DTPw-HBV-HIB combined and separate vaccines (RR 1.09; 95% CI 1.01 to 1.18) for redness.

Overall completeness and applicability of evidence

The objective of the review was to assess the clinical protection, immunogenicity and reactogenicity (adverse events) of a combined DTP, applied to both DTPw (diptheria-tetanus-whole cell pertussis) and DTPa (diptheria-tetanus-acellular pertussis) vaccines, HBV and conjugate HIB vaccines, with or without three types of inactivated polio virus (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.

We found no studies that addressed clinical outcomes, i.e. incidence of diphtheria, tetanus, pertussis, HBV and HIB. For some of these diseases, past eradication programmes 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, HBV, tetanus and HIB, clinical outcomes could be expected. The lack of such outcomes weakens conclusions that can be drawn from published studies.

The number of vaccine 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.

Updating the review we included two more studies and the new data showed significantly less immunological response for HIB and tetanus and more local reactions to the injections with DTPa-HBV-HIB vaccines rather than DTPw-HBV-HIB vaccines.

The quality of many of the studies included in the analysis is uncertain and we could not conclude that the immune responses elicited by the combined vaccine are equivalent to the separate injections. However, the differences rely mostly on one study each; it is not clear whether the results can be generalised to all vaccines. The results of this review should be viewed with caution, mostly as an indication that high quality data are lacking.

Quality of the evidence

We included 20 studies in the meta-analysis with 5874 participants in the immunogenicity analysis and 5232 participants in the reactogenicity analysis. 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 HIB and tetanus and more local reactions to the injections. However, the differences rely mostly on one study each; it is not clear whether the results can be generalised to all vaccines. The results of this review should be viewed with caution, mostly as an indication that high quality data are lacking.

Potential biases in the review process

We identified all relevant studies but we could not obtain all relevant data. The number of vaccine doses which differed significantly between the studies, heterogeneous interventions, study location, healthcare environment and combining research across disparate geographical locations, may lead to bias.

Agreements and disagreements with other studies or reviews

We included no other studies.

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 vaccines. The data showed significantly less immunological response for HIB and tetanus and more local reactions to the injections. However, the differences rely mostly on one study each. In the case of HIB, the less immunological response is related to a cut-off of 1.0 µg/ml, whose clinical relevance is questionable. It is not clear whether the results can be generalised to all vaccines. The results of this review should be viewed with caution, mostly as an indication that high quality data are lacking.

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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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aristegui 2003

Methods	Open, randomised, comparative phase IIIb, multi-centre 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	Study supported by a grant from SmithKline Beecham SA, Madrid, Spain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study was conducted in full-term healthy infants recruited in 9 Spanish centres
Allocation concealment (selection bias)	Unclear risk	Randomised trial - two groups of healthy infants no details of randomisation method
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	High risk	71 out of 241 completed
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days
Other bias	High risk	The limited number of subjects (71 out of 235) from whom immunogenicity data are available does not allow any conclusions to be drawn

Avdicova 2002

Methods	Open, randomised 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	The study was supported by a grant from GlaskoSmithKline Biologicals, Rixensart, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study was conducted in healthy infants in 8 regions in Slovakia
Allocation concealment (selection bias)	Unclear risk	Randomised study without details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	309 out of 312 completed
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days
Other bias	Low risk	

Bravo 1998

Methods	Open, randomised 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 vaccine 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	Funding for this study was provided by SmithKline Beecham Biologicals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was conducted in healthy infants with an Apgar score of 7 or higher at birth

Bravo 1998 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Randomised trial - no details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 8 out of 148 did not complete
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days
Other bias	Low risk	

Faingezicht 2002

Methods	Phase III, observed-blind, prospective RCT
Participants	Healthy male and female infants; age 8.8 (SD = 0.9) weeks
Interventions	DTPw-HBV/HIB pentavalent combination after extemporaneous mixing of the liquid DTPw-HBV with lyoHIB compared to DTPw-HBV vaccine and HIB vaccine reconstituted with its own diluent. 3 doses given at 2, 4 and 6 months of age and booster at 15 to 18 months old
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	This study was funded by GlaskoSmithKline Biologicals, Rixensart, Belgium

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The study was conducted in healthy infants in a single vaccination centre in Costa Rica
Allocation concealment (selection bias)	Low risk	RCT detailed
Blinding (performance bias and detection bias) All outcomes	Low risk	Observer-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 out of 207 not completed
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days
Other bias	Low risk	

Gabutti 2004

Methods	Open, phase III, randomised, multi-centre study
Participants	Healthy male and female infants mean age 13.3 weeks, range 9 to 17 weeks
Interventions	DTPa-HBV-IPV/HIB compared to separate DTPa - HBV - IPV + HIB. 3 doses given at 3, 5 and 11 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	This research was supported by a grant from GSK Biologicals, Rixensart, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was conducted in healthy infants in 24 centres in Germany and Italy - no details
Allocation concealment (selection bias)	Unclear risk	Randomised study - children were randomly allocate (1:1 ratio) to the 2 study groups
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	26 out 440 did not complete the study
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days

Gabutti 2005

Methods	Open, randomised, multi-centre trial
Participants	Healthy male and female infants aged 13 and 13.1 weeks
Interventions	DTPa-HBV-HIB compared with two separate or mixed injection. 3 doses given at 3, 5 and 11 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	This study was supported by a grand from GSK Biologicals, Rixensart, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was conducted in healthy infants in 12 Italian centres - no details
Allocation concealment (selection bias)	Unclear risk	Randomised to two study groups

Gabutti 2005 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 out 360 did not complete the study
Selective reporting (reporting bias)	Unclear risk	No details how the adverse events were evaluated
Other bias	Low risk	

Greenberg 2000

Methods	Randomisation equally to 3 groups
Participants	Healthy male and female infants; age 6 to 12 weeks at the time of the first vaccination
Interventions	DTPa, HBV and PRP-T (HIB). OPV was given concurrently. 3 doses given at 2, 4, 6 months of age and booster combined vaccine to ages 11 to 15 months
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	This study was supported by a grant from SmithKline Beecham Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Healthy infants were recruited from two Kaiser Permanente, Southern California Region medical centres
Allocation concealment (selection bias)	Unclear risk	Randomised equally to three groups
Blinding (performance bias and detection bias) All outcomes	Low risk	Parents and study personnel were not blinded. Laboratory personnel were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	54 out of 405 did not complete the study
Selective reporting (reporting bias)	Low risk	Parents mailed the completed diary cards to office. Reserch personnel collected severe adverse event data from parents by telephone 1 and 3 days after each immunisation and from parents and medical records at each visit

Mallet 2000

Methods	Open-label, multi-centre, prospective, comparative trial
Participants	Healthy male and female infants; age 63 days ± 7 days

Mallet 2000 *(Continued)*

Interventions	DTPa-IPV-HBV-HIB compared to separate DTPa-IPV-HIB and HBV vaccine. 3 doses given at 2, 4 and 6 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	This study was supported by a grant from Avintis Pasteur MSD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study was conducted in healthy infants born after 36 weeks of pregnancy with birth weight of > 2500 g by 70 paediatricians located in the Haute-Normandie, Provence-Alpes-Cote d'azur and Rhone-Alpes regions of France
Allocation concealment (selection bias)	Low risk	Randomly allocated according to a centralised list
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	166 out of 833 did not complete the study
Selective reporting (reporting bias)	Low risk	The reactogenicity profile was determined by describing the rates of immediate reactions, the rates of local and systemic adverse events within 15 min to 72 hours and the frequency of adverse events requiring a medical visit within 1 month of vaccination

Marshall 2010

Methods	Open-label, randomised comparative trial
Participants	Healthy infants of either sex aged 2, 4 and 6 months of age
Interventions	Combined DTPa-HBV/HIB or separate injections of DTPa-HBV and HIB in opposite thighs at 2, 4 and 6 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	This study was supported by a grant from GlaskoSmithKline Biologicals, Rixensart, Belgium Conflict of interest statement reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was conducted in healthy infants in two centres in Australia - no details
Allocation concealment (selection bias)	Unclear risk	Randomised to two study groups - no details

Marshall 2010 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 out of 328 were excluded from the according-to-protocol (APT) analyses
Selective reporting (reporting bias)	High risk	Serious adverse events reported generally with no specification per study arm

Nolan 2001

Methods	Randomised, double-blind series of 3 studies
Participants	Male and female infants in good health from community maternal and child health clinics in greater Melbourne and from the maternity service of the Royal Women's Hospital in Melbourne, Australia No age reported
Interventions	DTP-HIB (PRP-OMPC)-HBV in three studies + OPV DTP-liqHIB-HBV + placebo (group A). DTP-HBV + liqHIB (group B). HBV-liqHIB + DTP (group C). DTP+lyoHIB+HBV (group D). Monovalent HBV at birth and DTP-liqHIB-HBV (group E). 3 and 4 doses (including booster) given at 2, 4, 6 and 18 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	This study was supported by a grant to the Royal Children's Hospital Research Foundation from CSL Ltd. and Merck and Co., Inc. PRP-OMPC : the *Haemophilus influenzae* capsular polysaccharide-outer membrane protein conjugate, PRP-OMPC (PedvaxHIB)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Infants in good health were recruited through community maternal and child health clinics in greater Melbourne and from the maternity service of the Royal Women's Hospital in Melbourne
Allocation concealment (selection bias)	Low risk	The principal study was randomised. Computer-generated with stratification by consent for immunogenicity testing and blocks of varying size
Blinding (performance bias and detection bias) All outcomes	Low risk	For the principal study, all study staff and parents/guardians were blinded to the vaccine administered for the duration of the study. The control group was an open study but parents were not aware of which vaccines were being administered in particular limbs. The third study was an open study with regard to administration of the pentavalent vaccine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	No details

Omenaca 2001

Methods	Open, randomised, multi-centre, 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 simultaneously. 3 doses given at 2, 4 and 6 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	Study supported by a grant from GlaskoSmithKline Biologicals, Rixensart, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Healthy infants were recruited in 11 centres from Greece, Spain and Switzerland
Allocation concealment (selection bias)	Unclear risk	The randomizations was made using an algorithm of pseudo-random numbers. Subjects were allocated to the two groups according to a 3:1 ratio
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	30 out of 885 did not complete the full vaccination course
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days
Other bias	High risk	The immunogenicity subset comprised 95 infants. The limited sample size of the immunogenicity results places a limitation on the conclusions that can be drawn

Ortega-Barria 2007

Methods	4 separate phase III trials which assessed the immunogenicity and reactogenicity of DTPw-HBV/HIB 2.5 in comparison with DTPw-HBV + Hiberix™ (10µg PRP) given as separate or mixed injections (3 trials) or with or without HBV 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	These studies were supported by grants from GSK Biologicals, Rixensart, Belgium

Ortega-Barria 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Healthy infants born after a normal gestation period
Allocation concealment (selection bias)	Unclear risk	Randomised trials, Phase III. Groups within studies were well matched for age and gender distribution
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	144 out of 1803 completed
Selective reporting (reporting bias)	Low risk	Diary cards completed during the 4-day follow-up period after each vaccination

Pichichero 1997

Methods	Prospective, randomised multi-centre trial. 3 to 1 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	DTPa-HBV-PRP-T and booster of HIB. OPV was administered to all vaccinees in both groups concurrently at 2, 4 and 6 months of age. 3 doses given at 2, 4 and 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	This work was supported by SmithKline Beecham Biologicals (Philadelphia) and the National Institute of Health (AI45248)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Healthy infants were recruited for a multi-centre (3 groups in NY, Pittsburgh and VA), prospective, randomised trial
Allocation concealment (selection bias)	Unclear risk	Infants were randomised three to one to groups 1 and 2 respectively
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data

Pichichero 1997 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No data

Ramkissoon 2001

Methods	Open, randomised comparative study
Participants	Healthy male and female infants; aged 6 weeks (not reported) in Durban, South Africa
Interventions	DTPw-HBV mixed with HIB compared with DTPw-HBV and HIB separate. 3 doses given at 6, 10 and 14 weeks of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	No support reported. SmithKline Beecham Biologicals, Belgium address given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Healthy male and female infants were enrolled - no details
Allocation concealment (selection bias)	Unclear risk	Participants were randomised into two groups
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days

Rao 2009

Methods	10 centres across India recruited participants for a single-blind, randomised, comparative, non-inferiority 3-arm study
Participants	Healthy infants in the age group 6 to 8 weeks, born to mothers proven seronegative for HBV after a normal gestation period between 36 and 42 weeks
Interventions	DTPw-HBV-HIB tetanus toxoid conjugate liquid pentavalent combination vaccine - group 1, DTPw-HBV-HIB Pentavalent combination vaccine liquid form - group 2, TritanrixHB^{TM} + Hibrix^{TM} Pentavalent combination vaccine (Liquid + Lyophilised) - group 3
Outcomes	Immune response and safety of DTPw-HBV-HIB tetanus toxoid conjugate vaccine when administered according to a 6-10-14 week Expanded Program on Immunization (EPI) Schedule compared to Easy five and TritanrixHB^{TM} = Hiberix^{TM}

Rao 2009 *(Continued)*

Notes	This work was funded by Shantha Biotechnics Limited Competing interests reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	10 centres across India recruited healthy infants in the age group 6 to 8 weeks, born to mothers proven seronegative for HBV after a normal gestation period between 36 and 42 weeks
Allocation concealment (selection bias)	Low risk	Randomly assigned to one of the three study groups in a 2:1:1 ratio. The randomizations code was generated using the SAS version 8.2 software package
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	35 out of 365 were excluded from efficacy analysis
Selective reporting (reporting bias)	Low risk	Parents/guardians recorded adverse events on diary cards for 3 days and 30 days respectively following vaccination
Other bias	Low risk	Safety analysis was based on ITT population

Riedemann 2002

Methods	Open randomised, parallel-group design, randomised study
Participants	Healthy male and female infants; age 9.9 weeks. No country reported
Interventions	DTPw-HBV/HIB compared with DTPw-HBV and HIB separate in opposite deltoids. 3 doses given at 2, 4 and 6 months old and booster at 18 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	The research described is this manuscript was funded by GlaskoSmithKline Biologicals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Healthy male and female infants, aged 6 to 12 weeks
Allocation concealment (selection bias)	Unclear risk	RCT. Participants were randomly allocated to one of two groups in a ratio of 1:1
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open

Riedemann 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	19 out of 101 were not included in the analysis
Selective reporting (reporting bias)	Low risk	The study nurses used diary cards to record local and systemic signs and symptoms for the day of each vaccination and the 3 following days. At each subsequent visit the investigator transcribed information from the diary cards onto the Case Report Form and asked about any other adverse experiences that occurred after the period covered by the diary card
Other bias	Unclear risk	The results of this study cannot be generalised to combinations other than that of Hiberix with Trianrix HBV which are both (including the combination), WHO approved

Santos 2002

Methods	Open, multi-centre, randomised (1:1), parallel-group design
Participants	Healthy male and female infants; age 8 to 15 weeks
Interventions	DTPw-HBV mixed with HIB compared with DTPw-HBV and HIB separate in opposite thighs. 3 doses given at 2, 4 and 6 months and booster at 18 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	This study was funded by SmithKline Beecham Biologicals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Healthy male and female infants from centres in Mexico, Brazil, Panama, Venezuela and the Dominician Republic
Allocation concealment (selection bias)	Unclear risk	Randomised (1:1), parallel-group design
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	382 out of 400 completed the primary vaccination phase
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days. At each subsequent visit the investigator transcribed information from the diary cards onto the Case Report Form and asked about any other adverse experiences that occurred after the period covered by the diary card

Schmitt 2000

Methods	Open, multi-centre, randomised trial

Schmitt 2000 *(Continued)*

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
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	Supported by SmithKline Biologicals, Rixensart, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Healthy infants from 12 private paediatric offices in Kiel, Germany
Allocation concealment (selection bias)	Unclear risk	Randomised
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 out of 359 failed to complete the study
Selective reporting (reporting bias)	Low risk	Parents documented the reactions for 4 days

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-HBV/HIB compared with separate vaccines
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	No support reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Healthy infants from 4 centres in Central and Latin America: Argentina, Columbia, the Dominican Republic and Nicaragua
Allocation concealment (selection bias)	Unclear risk	Randomised in a balanced 1:1:1 allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Three different production lots of the combined DTPw-HBV/HIB vaccine were used in a double-blind manner. The control group received 2 separate injections; blinding could not be maintained

Tregnaghi 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	76 out of 1000 did not complete the primary vaccination study
Selective reporting (reporting bias)	Low risk	Details of adverse events were collected on diary cards. Reactogenicity data were collected during a 4-day follow-up period after each vaccination
Other bias	Unclear risk	The use of the new DTPw-HBV/HIB vaccine in 'field' conditions was not assessed in this trial

Win 1997

Methods	Open, randomised and controlled with 2 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 at 1.5, 3 and 5 months of age
Outcomes	Immunogenicity (antibody concentrations by serological analysis) and adverse events - reactogenicity
Notes	Clinical Research and Development, SmithKline Beecham Biologicals, Rixensart, Belgium address reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Healthy neonates from Central Women's Hospital, Yangon, Myanmar. Neonates with an Apgar score of 7 or higher 5 minutes after birth and who had no concomitant administration of immunoglobulins were enrolled
Allocation concealment (selection bias)	Unclear risk	Randomly assigned to one of two groups
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open
Incomplete outcome data (attrition bias) All outcomes	Low risk	37 out of 286 did not complete the full vaccination course
Selective reporting (reporting bias)	Low risk	Demographic and reactogenicity data were collected from diary cards completed by parents or a study nurse on the day of vaccination and during the 3 days following each dose and transferred to a Standad Case Report Form by the investigator
Other bias	High risk	Recommendation should not be generalised, however, as the data from this study apply only to the 2 specified vaccines, Tritanrix™ and Hiberix™ alternative vaccines should be investigated with regards to non-interference before use as syringe mixes

DTPw: diphtheria, tetanus, whole cell pertussis
HBV: hepatitis B virus
HIB: *H. influenzae* type B

IPV: inactivated polio virus
ITT: intention-to-treat
liqHIB: liquid *H. influenzae* type B
lyoHIB: lyophilised HIB
OPV: oral polio vaccine
PRP-T: polyribsylribitolphosphate, (vaccine conjugated to tetanus toxoid)
RCT: randomised controlled trial
SD: standard deviation
WHO: World Health Organization

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

Study	Reason for exclusion
Aristegui 1998	Comparison of three lots of 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 HBV and HIB components and the overall safety and reactogenicity of the DTPw-HBV/HIB vaccine. No comparison of combined and separate vaccines
Botet-Asensi 2003	DTPw/HIB vaccine compared to separate injections of DTPw+ 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 a RCT: report of primary and booster-based paediatric clinical trials
Diaz-Mitoma 2011	Compares different formulas of combined vaccines: diptheria-tetanus-pertussis-polio-HIB + HBV vaccine compared to 1 of 3 double-blind investigational formulations
Gatchalian 2005	Compares 2 combined vaccines: DTPw-HBV/HIB containing 2.5 micro PRP compared to GSK Biologicals' licensed Tritanrix HepB/Hiberix containing 10 micro PRP
Gentile 2011	Assesses DTPw-HBV-HIB combination vaccine in infants who had or had not received a birth dose of HBV vaccine
Gylca 2001	DTPa-HBV-IPV + HIB vaccine compared to DTPw-IPV/HIB + HBV vaccine (diphtheria, tetanus, pertussis, polioviruses, PRP antigens + HBsAg (HBV) vaccine)
Halperin 2009	Compared 4 formulations of a liquid, hexavalent DTPa-IPV-HIB-HBV vaccine
Hla 2006	A randomised, 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
Kanra 2006	Combined DTPw-HBV-HIB compared with separately administered DTPw-HIB and HBV vaccines

Study	Reason for exclusion
Kilpi 2009	Evaluates 2 commercial DTPa-HBV-IPV/HIB combination 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 a RCT: no control group
Madhi 2011	Compares DTPa-IPV-HBV-PRP-T with DTPw-HIB, HBV and OPV or DTPa-IPV-HBV-PRP-T vaccine with HBV vaccine at birth
Meriste 2006	Comparison of combined DTPa-HBV-IPV with DTPa-HBV and IPV separate vaccines
Mills 1998	Comparison between a 5-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 immunisation with DTPa/HIB/HBV
Pichichero 2007	Compares the DTPa-HBV-IPV vaccine co-administered with PCV7 and HIB vaccine to separate vaccines concurrently or staggered (delayed) administration of PCV7 vaccine
Poolman 2001	Not RCT: 2 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	2 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, DTPa-IPV/PRP-T and HBV compared with separate injections
Tichmann 2005	Comparison of 2 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
Tregnaghi 2011	Compares DTPa-IPV-HBV-PRP-T vaccine with Pentaxim and Engerix B Pediatrico (HBV monovalent) vaccine in infants born to HBV surface antigen seronegative mothers
Trollfors 2005	Study of the effect of pertussis toxoid on the immunogenicity of DT during a trial of an Pa vaccine
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 Pa based combination. In the trial, HIB immunisation performed concomitantly with a candidate DT-Pa-HBV-IPV in order to compare the local reactogenicity and immunogenicity of 4 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

Study	Reason for exclusion
Zepp 1997	A study of memory B-cell induction and the immune response to the combined DTPa-HBV-HIB vaccine (no comparison)
Zepp 2004	2 studies report of safety and reactogenicity of infant primary immunisation with the simultaneous administration of six vaccines in a single injection (DTPa-IPV/HIB) to the administration of the same vaccine-antigens given as 2 separate injections with widely used licensed products

DT: diphtheria and tetanus toxoids
DTPa: diphtheria, tetanus, acellular pertussis
DTPw: diphtheria, tetanus, whole cell pertussis
HBV: hepatitis B virus
HIB: *H. influenzae* type B
IPV: inactivated polio virus
Pa: acellular pertussis
PCV7: pneumococcal 7-valent conjugate vaccine
PRP: polyribsylribitolphosphate
PRP-T: polyribsylribitolphosphate vaccine conjugated to tetanus toxoid
RCT: randomised controlled trial
7vPn: pneumococcal 7-valent conjugate vaccine

Characteristics of ongoing studies *[ordered by study ID]*

Sanofi-Aventis 2011

Trial name or title	PENTAXIM™ Vaccine Versus TETRAXIM™ Vaccine Given With ACTHIB™ Vaccine in South Korean Infants
Methods	
Participants	This study is currently recruiting participants
Interventions	Immunogenicity and safety of the Sanofi Pasteur's DTacP-IPV//PRP˜T combined vaccine (PENTAXIM™) versus Sanofi Pasteur's DTacP-IPV combined vaccine (TETRAXIM™) given simultaneously at separate sites with PRP˜T conjugate vaccine (ACTHIB™) as a three-dose primary vaccination at 2, 4 and 6 months of age in South Korean infants
Outcomes	
Starting date	October 1, 2010
Contact information	Public Registry Sanofi Pasteur RegistryContactUs@sanofipasteur.com
Notes	This study is designed to assess the immunogenicity and safety of PENTAXIM™ combined vaccine versus TETRAXIM™ vaccine to support registration of PENTAXIM™ in South Korea

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 cut-off 0.15 µg/ml	15	4272	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.98, 3.38]
1.1 DTPa titres below the assay cut-off 0.15 µg/ml	8	2068	Risk Ratio (M-H, Random, 95% CI)	2.60 [1.33, 5.08]
1.2 DTPw titres below the assay cut-off 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 cut-off 1.0 µg/ml	15	5269	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.98, 2.10]
2.1 DTPa titres below the assay cut-off 1.0 µg/ml	8	2060	Risk Ratio (M-H, Random, 95% CI)	2.14 [1.48, 3.10]
2.2 DTPw titre below the assay cut-off 1.0 µg/ml	7	3209	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.44, 1.58]
3 Anti-FHA (Filamentous haemagglutinin)	8	1915	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.20, 4.36]
3.1 DTPa - immunogenicity failure	8	1915	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.20, 4.36]
4 Anti-PRN (Pertactin)	8	1931	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.34, 1.50]
4.1 DTPa - immunogenicity failure	8	1931	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.34, 1.50]
5 Anti-HBV (Hepatitis B)	19	5874	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.76, 2.01]
5.1 DTPa - immunogenicity failure	9	2300	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.68, 3.34]
5.2 DTPw - immunogenicity failure	10	3574	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.43, 2.16]
6 Anti-BPT (Pertussis)	11	2928	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.80, 1.28]
6.1 DTPa - immunogenicity failure	2	479	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.75, 1.25]
6.2 DTPw - immunogenicity failure	9	2449	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.69, 2.57]
7 Anti-D (Diphtheria)	17	4560	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.59, 1.38]
7.1 DTPa - immunogenicity failure	9	2172	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.73, 1.14]
7.2 DTPw - immunogenicity failure	8	2388	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.39, 1.91]

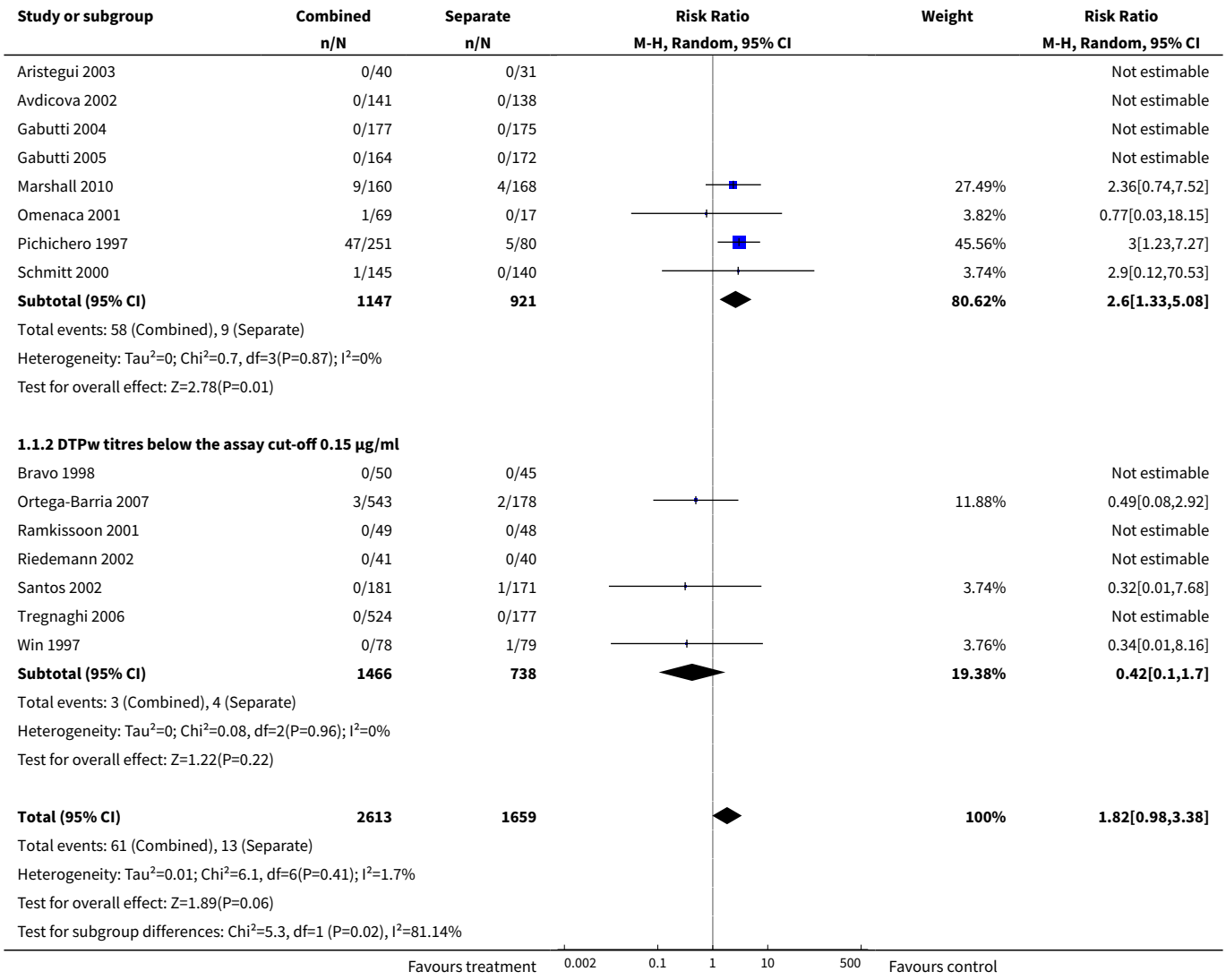
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Anti-T (Tetanus)	18	4644	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.04, 8.95]
8.1 DTPa - immunogenicity failure	9	2173	Risk Ratio (M-H, Random, 95% CI)	2.22 [1.21, 4.06]
8.2 DTPw - immunogenicity failure	9	2471	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.00, 9.94]
9 DTPa Anti-polio type 1 below the assay cut-off 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 cut-off 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 cut-off 1:8 IU/mL	5	1233	Risk Ratio (M-H, Random, 95% CI)	1.87 [0.59, 5.94]
12 Serious adverse events	9	5232	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.58, 1.53]
12.1 DTPa	3	1298	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.41, 1.37]
12.2 DTPw	6	3934	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.64, 3.13]
13 Pain	18	19745	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.02, 1.16]
13.1 DTPa	8	10516	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.08, 1.34]
13.2 DTPw	10	9229	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.98, 1.11]
14 Redness	18	19745	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.01, 1.18]
14.1 DTPa	8	10516	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.98, 1.27]
14.2 DTPw	10	9229	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.17]
15 Swelling	18	19745	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.98, 1.11]
15.1 DTPa	8	10516	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.95, 1.18]
15.2 DTPw	10	9229	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.95, 1.12]
16 Fever	14	17805	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.09]
16.1 DTPa	7	9811	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.00, 1.24]
16.2 DTPw	7	7994	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.04]
17 Fussiness or restlessness	9	12183	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.95, 1.09]
17.1 DTPa	7	9811	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.2 DTPw	2	2372	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.90, 1.23]
18 Drowsiness	11	12011	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	5	5181	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.01]
19 Irritability or tenderness	9	8273	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.04]
19.1 DTPa	2	1761	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.74, 1.44]
19.2 DTPw	7	6512	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.90, 1.01]
20 Poor appetite	11	13922	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.08]
20.1 DTPa	6	9229	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.94, 1.18]
20.2 DTPw	5	4693	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.06]
21 Vomiting	7	8281	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.90, 1.23]
21.1 DTPa	4	7262	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.23]
21.2 DTPw	3	1019	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.64, 1.81]
22 Diarrhoea	6	5761	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.94, 1.32]
22.1 DTPa	3	4742	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.93, 1.34]
22.2 DTPw	3	1019	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.69, 1.77]
23 Unusual crying	6	5890	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.05]
23.1 DTPa	2	3591	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.27, 7.84]
23.2 DTPw	4	2299	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.37, 1.10]
24 Sleeping more than usual	4	6563	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.11]
24.1 DTPa	4	6563	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.11]

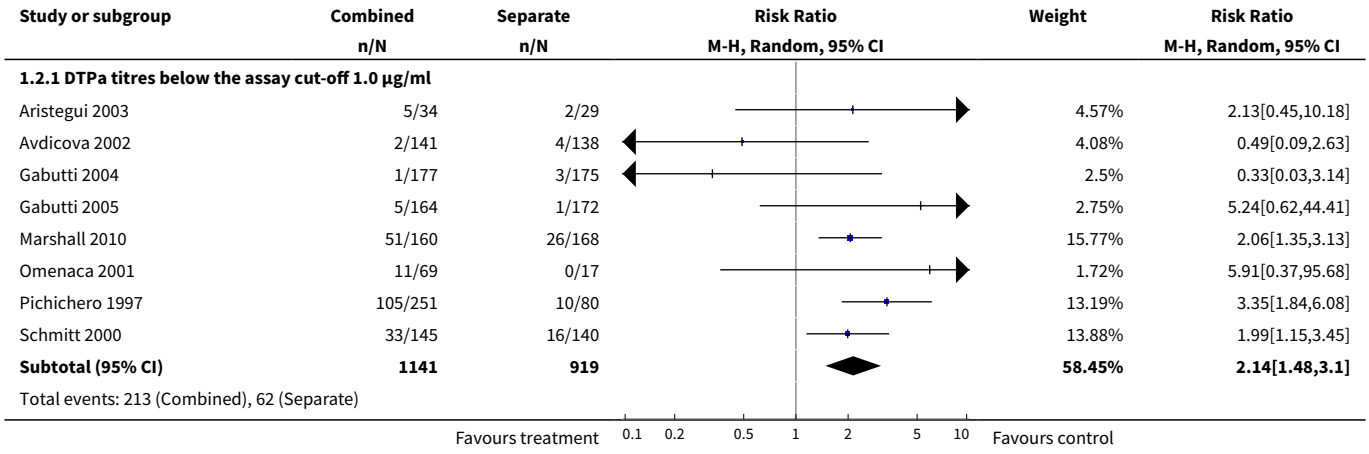
Analysis 1.1. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 1 Anti-PRP titres below the assay cut-off 0.15 µg/ml.

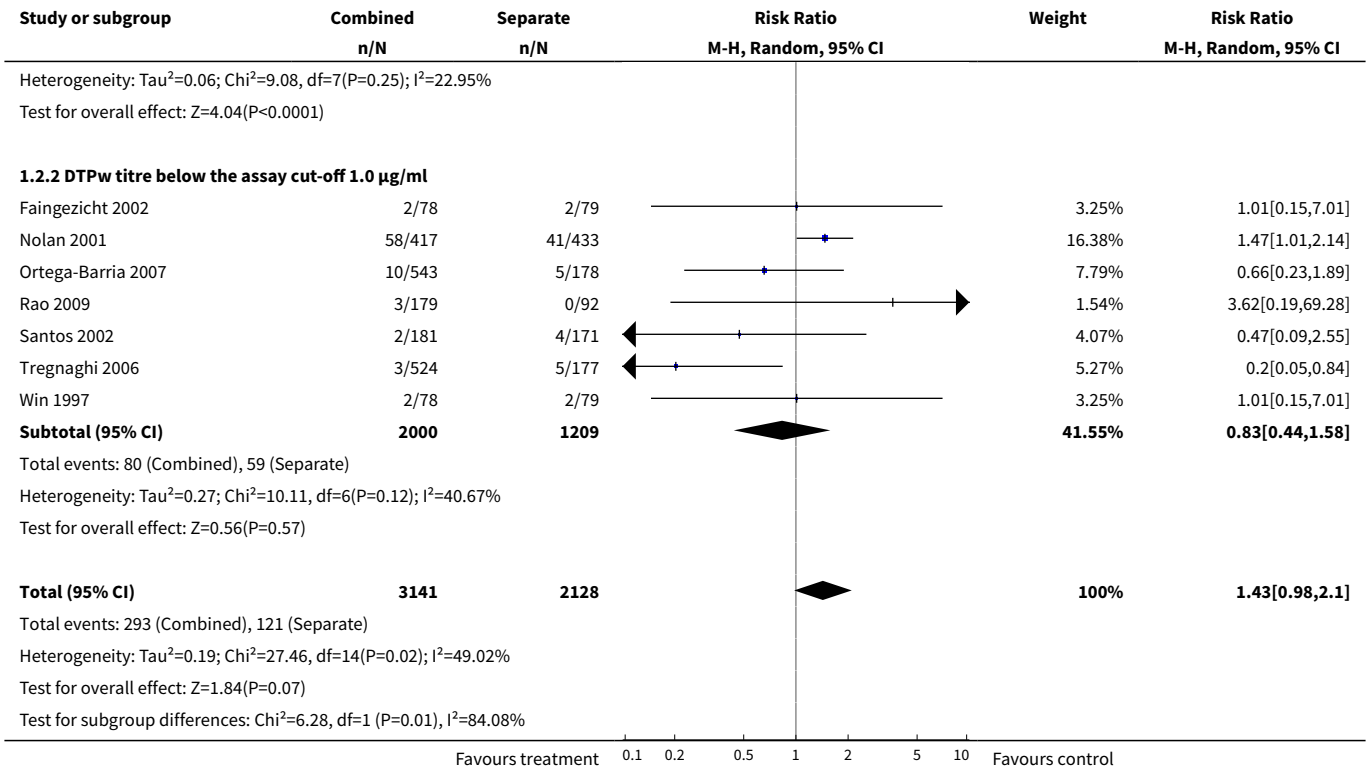
Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 DTPa titres below the assay cut-off 0.15 µg/ml					

Favours treatment 0.002 0.1 1 10 500 Favours control

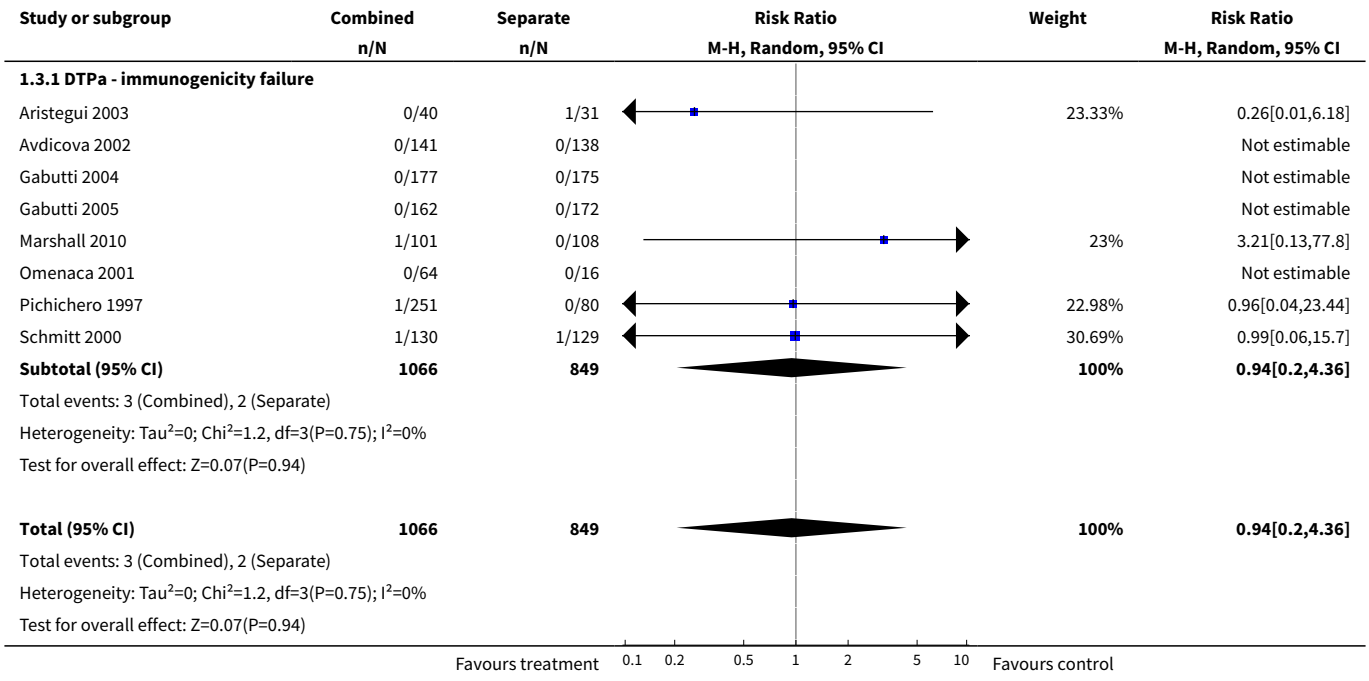


Analysis 1.2. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 2 Anti-PRP titres below the assay cut-off 1.0 µg/ml.



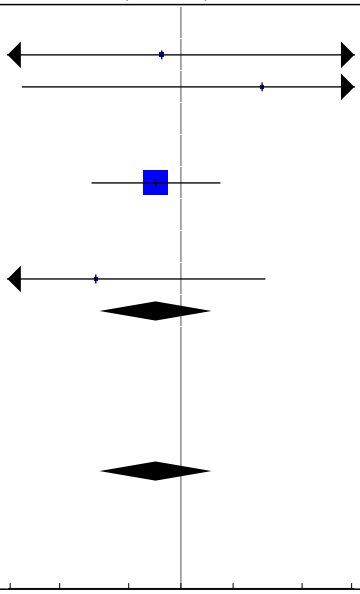


Analysis 1.3. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 3 Anti-FHA (Filamentous haemagglutinin).



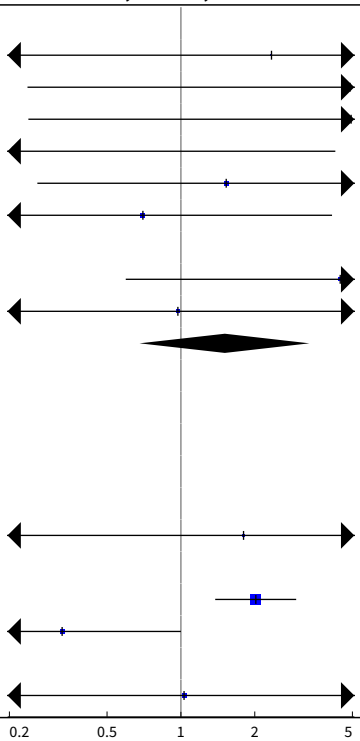
Analysis 1.4. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 4 Anti-PRN (Pertactin).

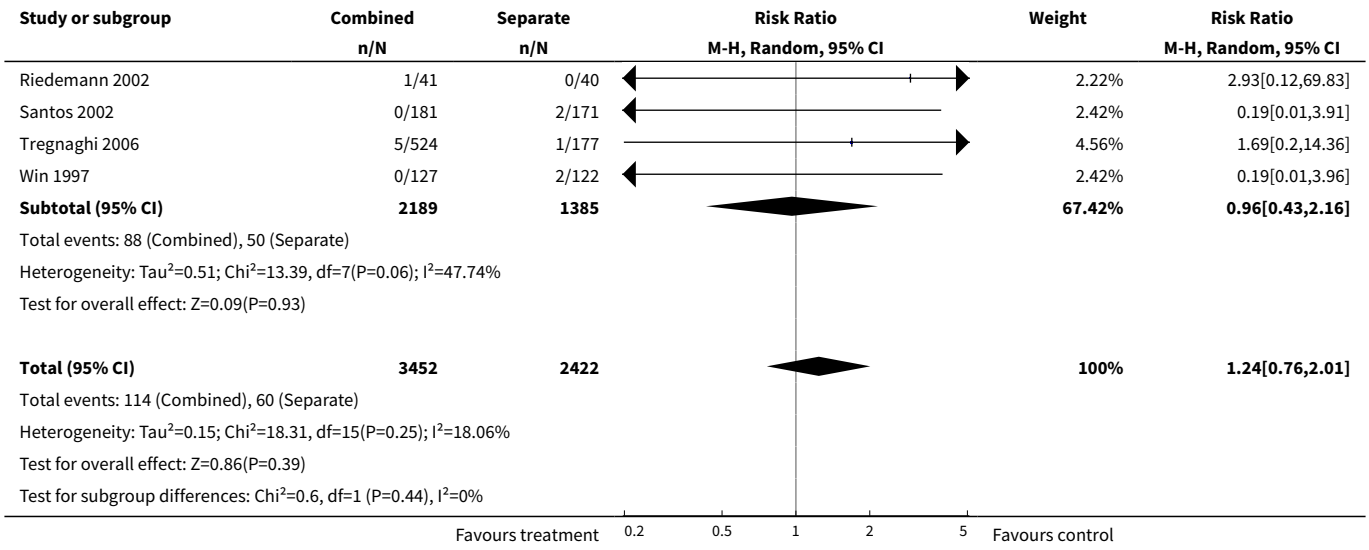
Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 DTPa - immunogenicity failure					
Aristegui 2003	1/40	1/31		7.44%	0.78[0.05,11.9]
Avdicova 2002	1/141	0/138		5.45%	2.94[0.12,71.47]
Gabutti 2004	0/177	0/175			Not estimable
Gabutti 2005	0/164	0/172			Not estimable
Marshall 2010	8/105	12/113		76.13%	0.72[0.31,1.69]
Omenaca 2001	0/64	0/16			Not estimable
Pichichero 1997	0/251	0/80			Not estimable
Schmitt 2000	1/134	3/130		10.97%	0.32[0.03,3.07]
Subtotal (95% CI)	**1076**	**855**		**100%**	**0.71[0.34,1.5]**
Total events: 11 (Combined), 16 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=1.23, df=3(P=0.74); I^2=0%					
Test for overall effect: Z=0.89(P=0.38)					
Total (95% CI)	**1076**	**855**		**100%**	**0.71[0.34,1.5]**
Total events: 11 (Combined), 16 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=1.23, df=3(P=0.74); I^2=0%					
Test for overall effect: Z=0.89(P=0.38)					



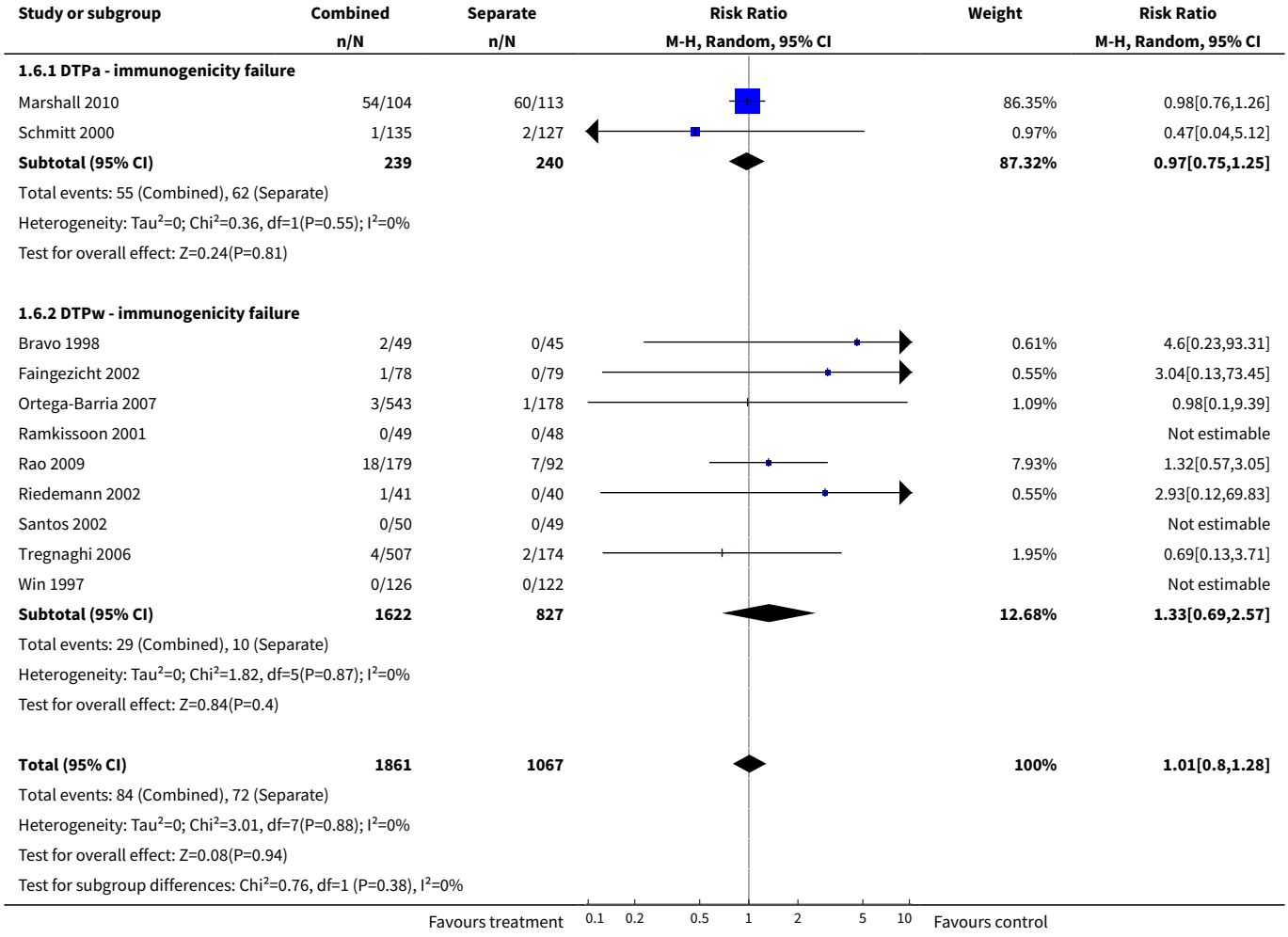
Analysis 1.5. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 5 Anti-HBV (Hepatitis B).

Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 DTPa - immunogenicity failure					
Aristegui 2003	1/40	0/31		2.22%	2.34[0.1,55.58]
Avdicova 2002	2/141	0/138		2.42%	4.89[0.24,101.03]
Gabutti 2004	2/177	0/175		2.42%	4.94[0.24,102.24]
Gabutti 2005	0/165	2/170		2.42%	0.21[0.01,4.26]
Greenberg 2000	3/115	2/117		6.33%	1.53[0.26,8.96]
Marshall 2010	2/160	3/168		6.3%	0.7[0.12,4.13]
Omenaca 2001	0/69	0/17			Not estimable
Pichichero 1997	14/251	1/80		5.08%	4.46[0.6,33.41]
Schmitt 2000	2/145	2/141		5.39%	0.97[0.14,6.81]
Subtotal (95% CI)	**1263**	**1037**		**32.58%**	**1.51[0.68,3.34]**
Total events: 26 (Combined), 10 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=4.98, df=7(P=0.66); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					
1.5.2 DTPw - immunogenicity failure					
Bravo 1998	2/50	1/45		3.81%	1.8[0.17,19.19]
Faingezicht 2002	0/78	0/79			Not estimable
Nolan 2001	70/417	36/433		32.25%	2.02[1.38,2.95]
Ortega-Barria 2007	6/543	6/178		12.82%	0.33[0.11,1]
Ramkissoon 2001	0/49	0/48			Not estimable
Rao 2009	4/179	2/92		6.92%	1.03[0.19,5.51]

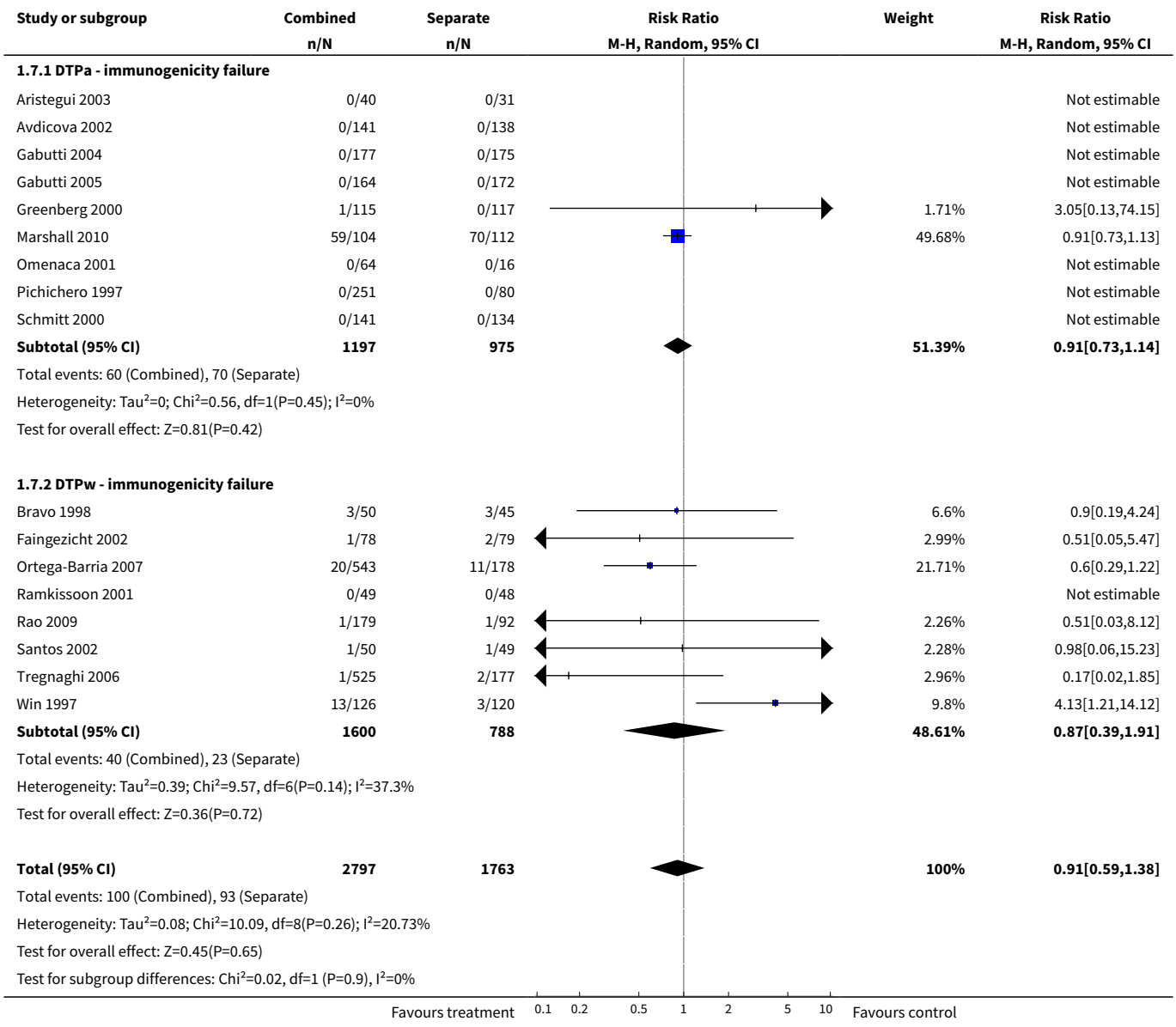




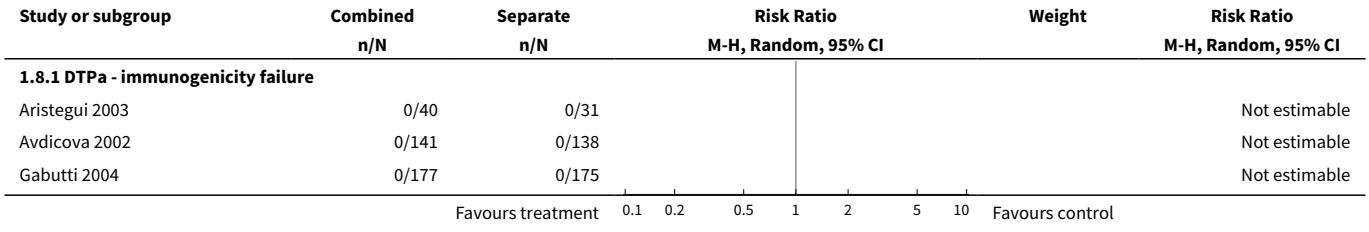
Analysis 1.6. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 6 Anti-BPT (Pertussis).

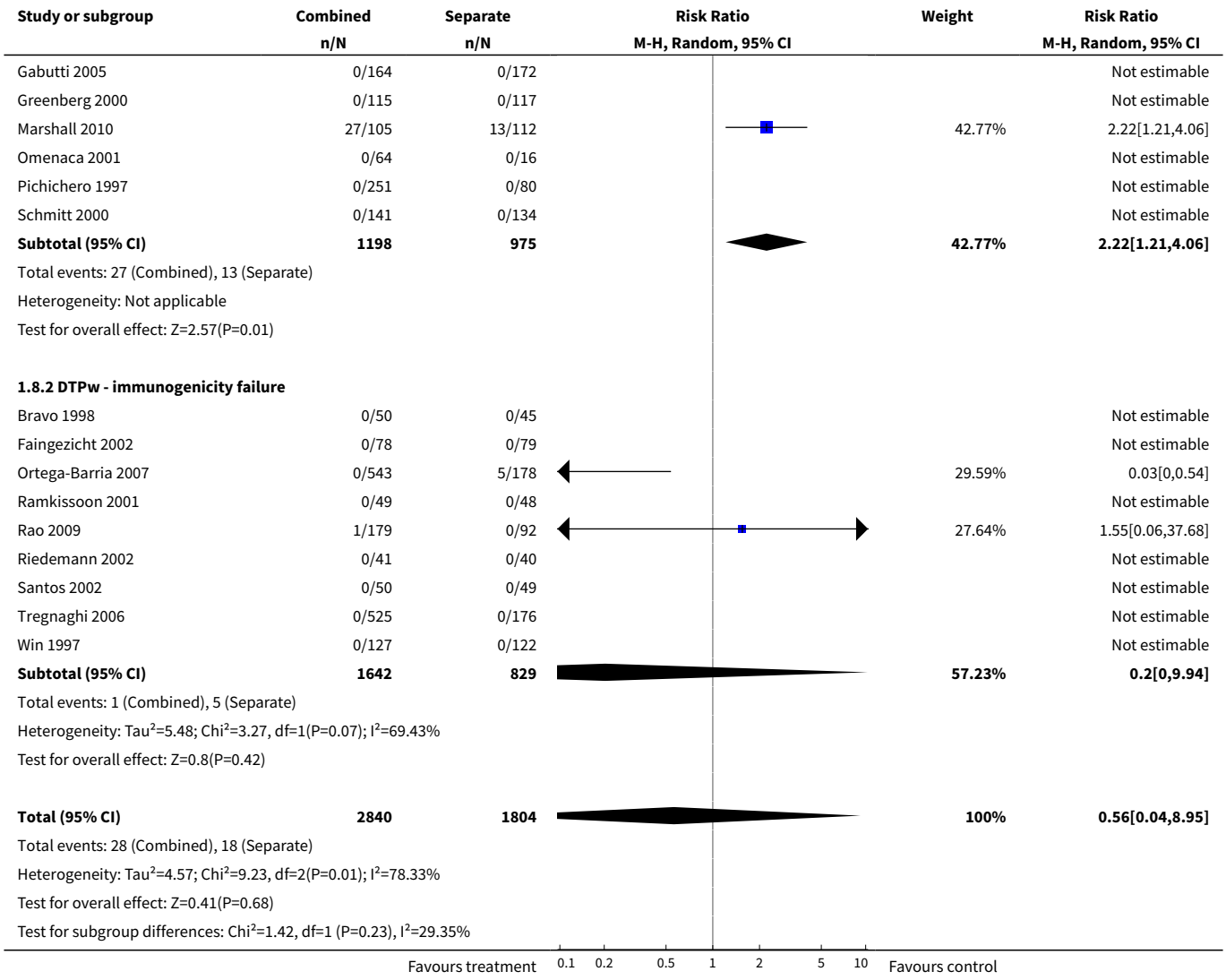


Analysis 1.7. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 7 Anti-D (Diphtheria).

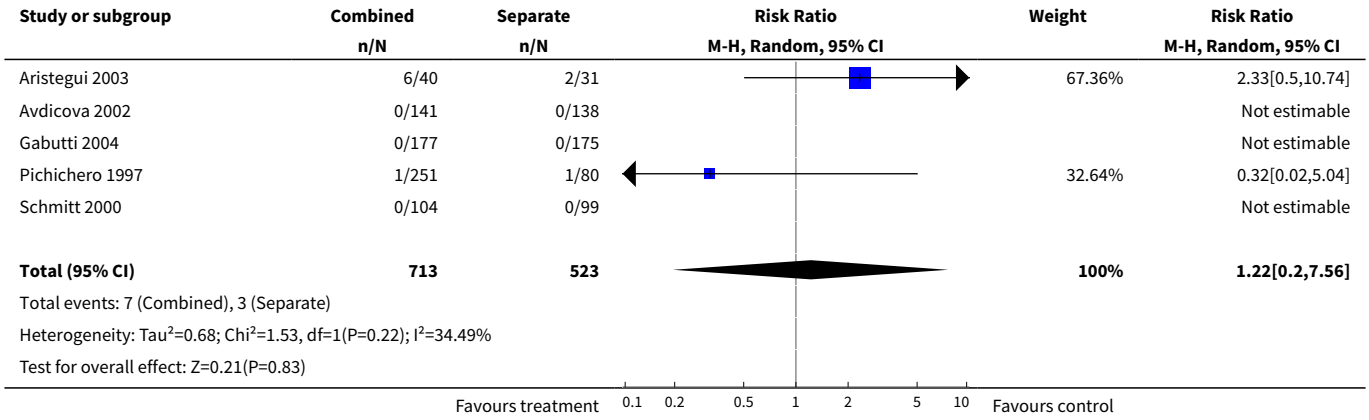


Analysis 1.8. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 8 Anti-T (Tetanus).





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 cut-off 1:8 IU/mL.



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 cut-off 1:8 IU/mL.

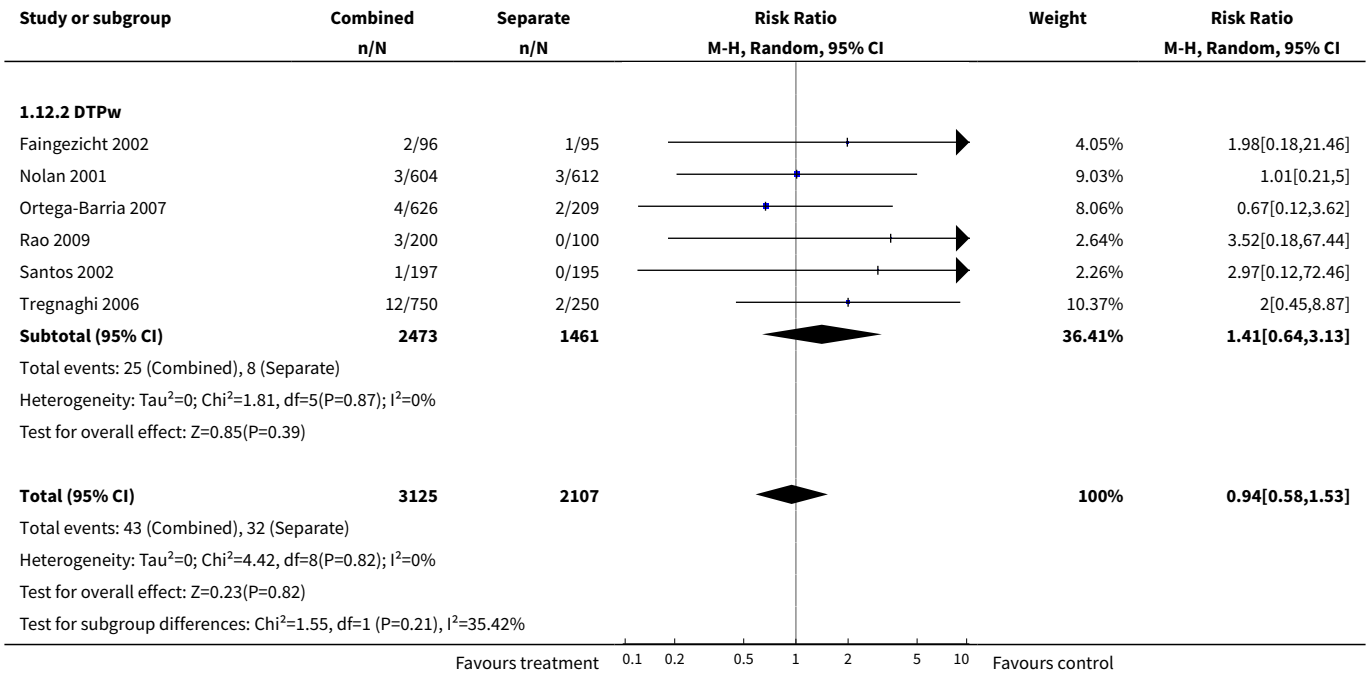
Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Aristegui 2003	9/40	4/31		89.7%	1.74[0.59,5.14]
Avdicova 2002	0/141	0/138			Not estimable
Gabutti 2004	0/177	0/175			Not estimable
Pichichero 1997	0/251	0/80			Not estimable
Schmitt 2000	1/98	0/97		10.3%	2.97[0.12,72.01]
Total (95% CI)	**707**	**521**		**100%**	**1.84[0.66,5.12]**
Total events: 10 (Combined), 4 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.76); I^2=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 cut-off 1:8 IU/mL.

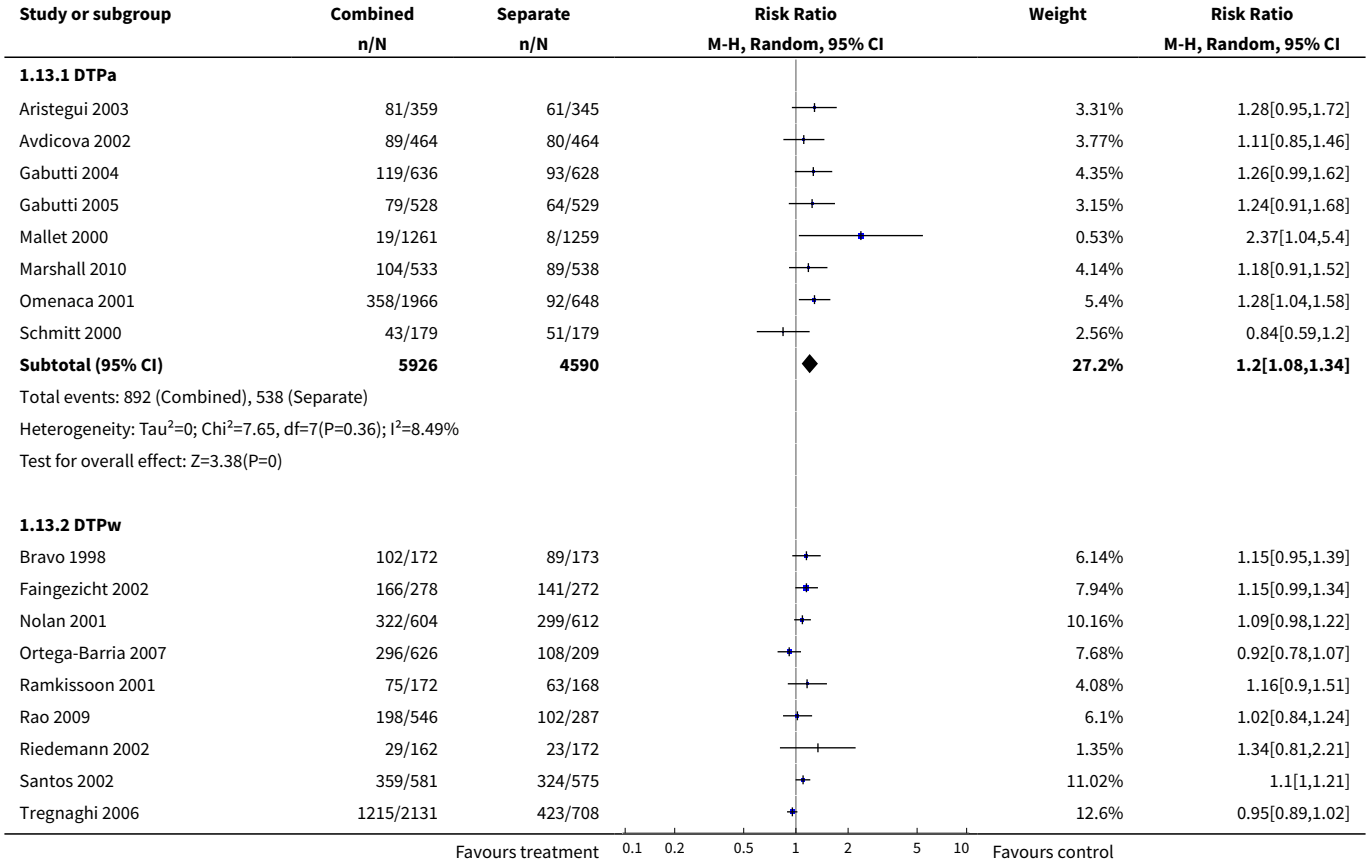
Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Aristegui 2003	8/40	3/31		86.86%	2.07[0.6,7.15]
Avdicova 2002	0/141	0/138			Not estimable
Gabutti 2004	0/177	0/175			Not estimable
Pichichero 1997	1/251	0/80		13.14%	0.96[0.04,23.44]
Schmitt 2000	0/102	0/98			Not estimable
Total (95% CI)	**711**	**522**		**100%**	**1.87[0.59,5.94]**
Total events: 9 (Combined), 3 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=1.06(P=0.29)					

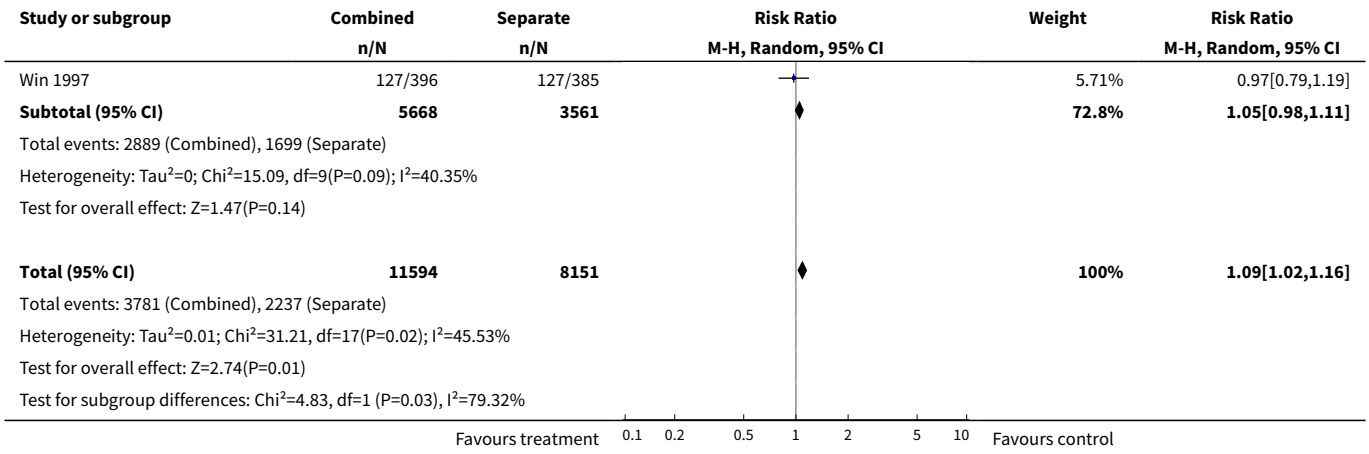
Analysis 1.12. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 12 Serious adverse events.

Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 DTPa					
Avdicova 2002	7/141	11/138		27.31%	0.62[0.25,1.56]
Gabutti 2004	10/177	10/175		31.77%	0.99[0.42,2.32]
Mallet 2000	1/334	3/333		4.51%	0.33[0.03,3.18]
Subtotal (95% CI)	**652**	**646**		**63.59%**	**0.75[0.41,1.37]**
Total events: 18 (Combined), 24 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=1.06, df=2(P=0.59); I^2=0%					
Test for overall effect: Z=0.94(P=0.35)					

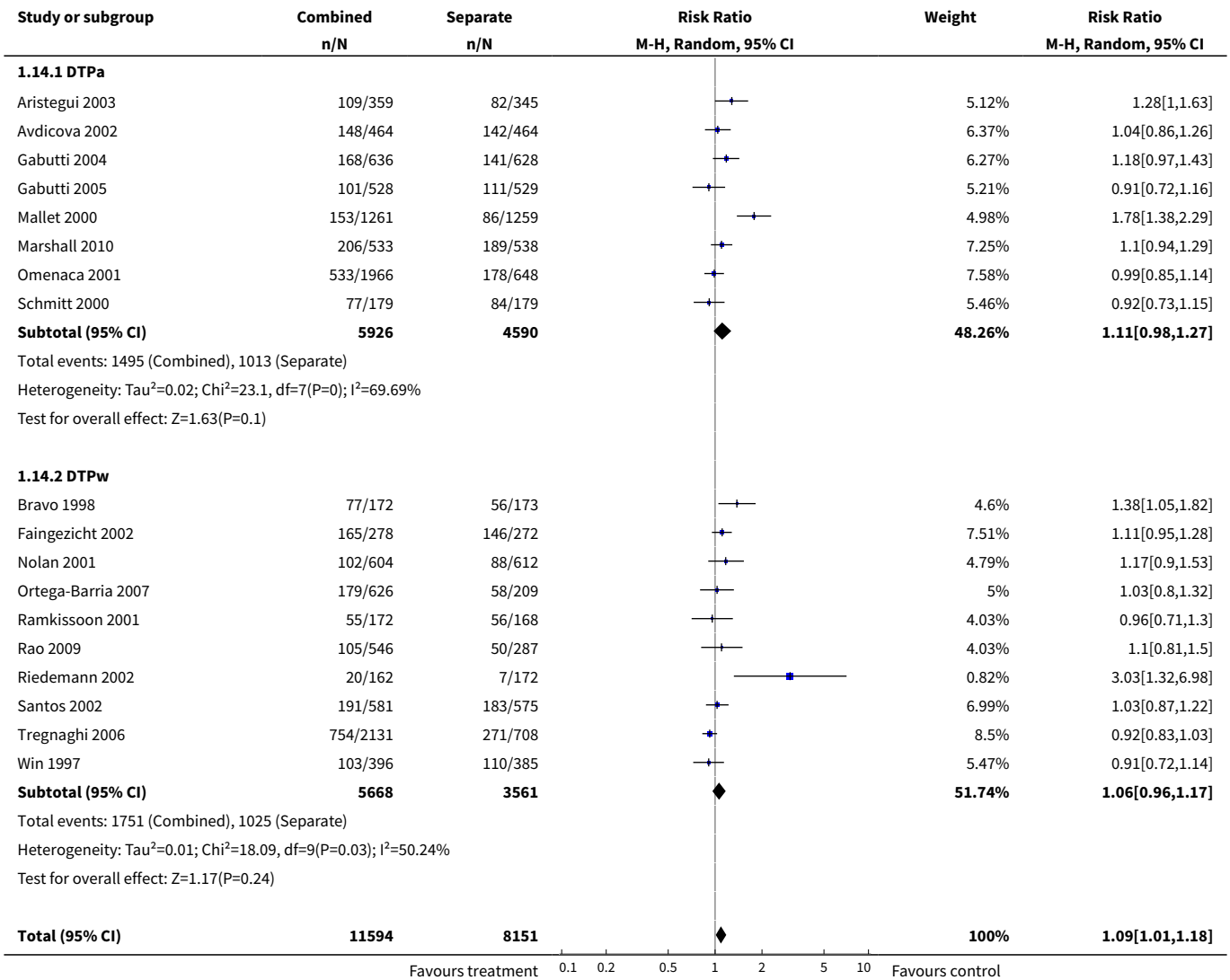


Analysis 1.13. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 13 Pain.





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



Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 3246 (Combined), 2038 (Separate)					
Heterogeneity: Tau²=0.02; Chi²=42.8, df=17(P=0); I²=60.28%					
Test for overall effect: Z=2.09(P=0.04)					
Test for subgroup differences: Chi²=0.32, df=1 (P=0.57), I²=0%					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

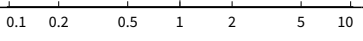
Analysis 1.15. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 15 Swelling.

Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 DTPa					
Aristegui 2003	81/359	57/345		3.55%	1.37[1.01,1.85]
Avdicova 2002	81/464	71/464		3.81%	1.14[0.85,1.53]
Gabutti 2004	142/636	106/628		5.52%	1.32[1.06,1.66]
Gabutti 2005	88/528	95/529		4.43%	0.93[0.71,1.21]
Mallet 2000	183/1261	174/1259		6.8%	1.05[0.87,1.27]
Marshall 2010	135/533	126/538		6.05%	1.08[0.88,1.34]
Omenaca 2001	374/1966	137/648		7.62%	0.9[0.76,1.07]
Schmitt 2000	66/179	71/179		4.44%	0.93[0.71,1.21]
Subtotal (95% CI)	**5926**	**4590**		**42.21%**	**1.06[0.95,1.18]**
Total events: 1150 (Combined), 837 (Separate)					
Heterogeneity: Tau²=0.01; Chi²=11.93, df=7(P=0.1); I²=41.31%					
Test for overall effect: Z=1.12(P=0.26)					
1.15.2 DTPw					
Bravo 1998	85/172	91/173		6.2%	0.94[0.76,1.16]
Faingezicht 2002	130/278	115/272		7.03%	1.11[0.92,1.33]
Nolan 2001	120/604	95/612		4.95%	1.28[1,1.63]
Ortega-Barria 2007	170/626	52/209		4.32%	1.09[0.83,1.43]
Ramkissoon 2001	78/172	66/168		4.81%	1.15[0.9,1.48]
Rao 2009	153/546	85/287		5.61%	0.95[0.76,1.18]
Riedemann 2002	16/162	12/172		0.77%	1.42[0.69,2.9]
Santos 2002	181/581	161/575		7.43%	1.11[0.93,1.33]
Tregnaghi 2006	702/2131	259/708		11.17%	0.9[0.8,1.01]
Win 1997	105/396	111/385		5.49%	0.92[0.73,1.15]
Subtotal (95% CI)	**5668**	**3561**		**57.79%**	**1.03[0.95,1.12]**
Total events: 1740 (Combined), 1047 (Separate)					
Heterogeneity: Tau²=0.01; Chi²=13.27, df=9(P=0.15); I²=32.2%					
Test for overall effect: Z=0.68(P=0.5)					
Total (95% CI)	**11594**	**8151**		**100%**	**1.04[0.98,1.11]**
Total events: 2890 (Combined), 1884 (Separate)					
Heterogeneity: Tau²=0.01; Chi²=25.87, df=17(P=0.08); I²=34.3%					
Test for overall effect: Z=1.29(P=0.2)					
Test for subgroup differences: Chi²=0.23, df=1 (P=0.63), I²=0%					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

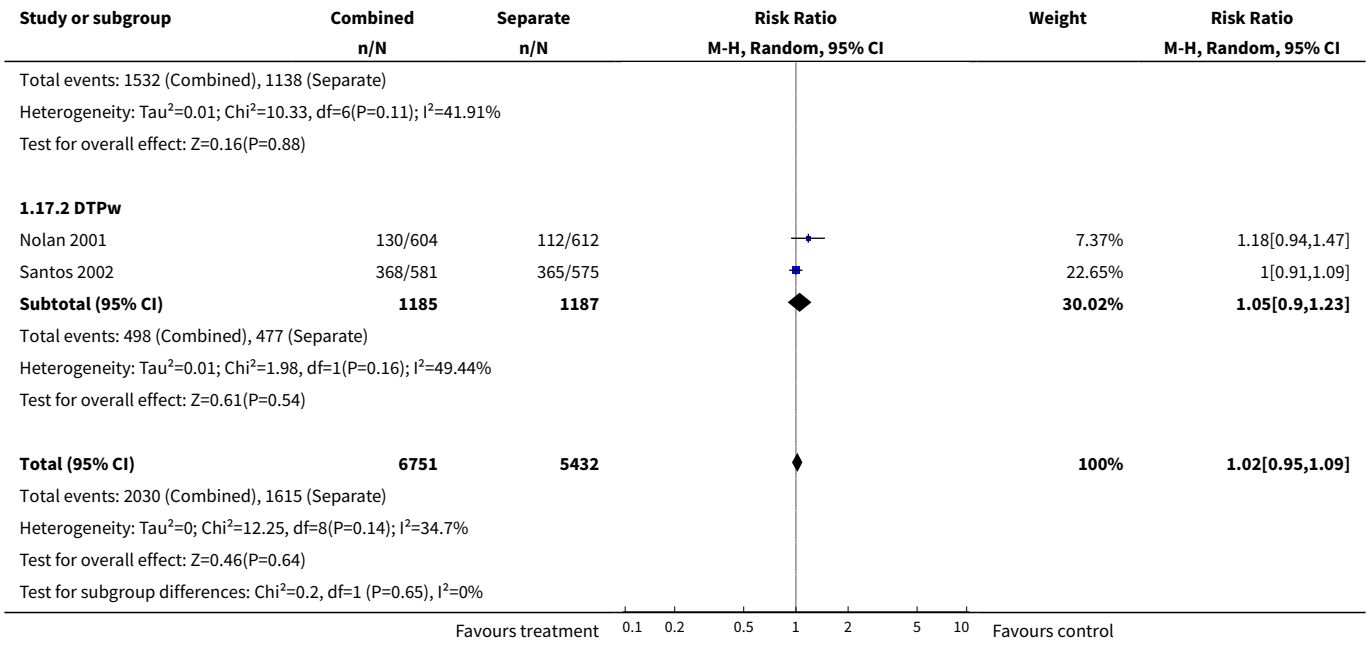
Analysis 1.16. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 16 Fever.

Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 DTPa					
Avdicova 2002	51/464	42/464		2.52%	1.21[0.82,1.79]
Gabutti 2004	186/635	147/628		8.53%	1.25[1.04,1.51]
Gabutti 2005	59/528	71/529		3.49%	0.83[0.6,1.15]
Mallet 2000	185/1261	183/1259		8.35%	1.01[0.84,1.22]
Marshall 2010	77/533	60/538		3.65%	1.3[0.94,1.78]
Omenaca 2001	301/1966	87/648		6.57%	1.14[0.91,1.42]
Schmitt 2000	32/179	31/179		1.92%	1.03[0.66,1.62]
Subtotal (95% CI)	**5566**	**4245**		**35.02%**	**1.11[1,1.24]**
Total events: 891 (Combined), 621 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=6.89, df=6(P=0.33); I^2=12.9%					
Test for overall effect: Z=1.98(P=0.05)					
1.16.2 DTPw					
Nolan 2001	161/604	154/612		8.26%	1.06[0.88,1.28]
Ortega-Barria 2007	322/626	104/209		10.81%	1.03[0.88,1.21]
Rao 2009	31/546	19/287		1.29%	0.86[0.49,1.49]
Riedemann 2002	52/162	68/172		4.21%	0.81[0.61,1.09]
Santos 2002	290/581	307/575		15.69%	0.93[0.84,1.05]
Tregnaghi 2006	484/2131	175/708		11.31%	0.92[0.79,1.07]
Win 1997	219/396	201/385		13.4%	1.06[0.93,1.21]
Subtotal (95% CI)	**5046**	**2948**		**64.98%**	**0.98[0.92,1.04]**
Total events: 1559 (Combined), 1028 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=5.71, df=6(P=0.46); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					
Total (95% CI)	**10612**	**7193**		**100%**	**1.02[0.96,1.09]**
Total events: 2450 (Combined), 1649 (Separate)					
Heterogeneity: Tau^2=0; Chi^2=17.6, df=13(P=0.17); I^2=26.16%					
Test for overall effect: Z=0.68(P=0.5)					
Test for subgroup differences: Chi^2=4.22, df=1 (P=0.04), I^2=76.32%					

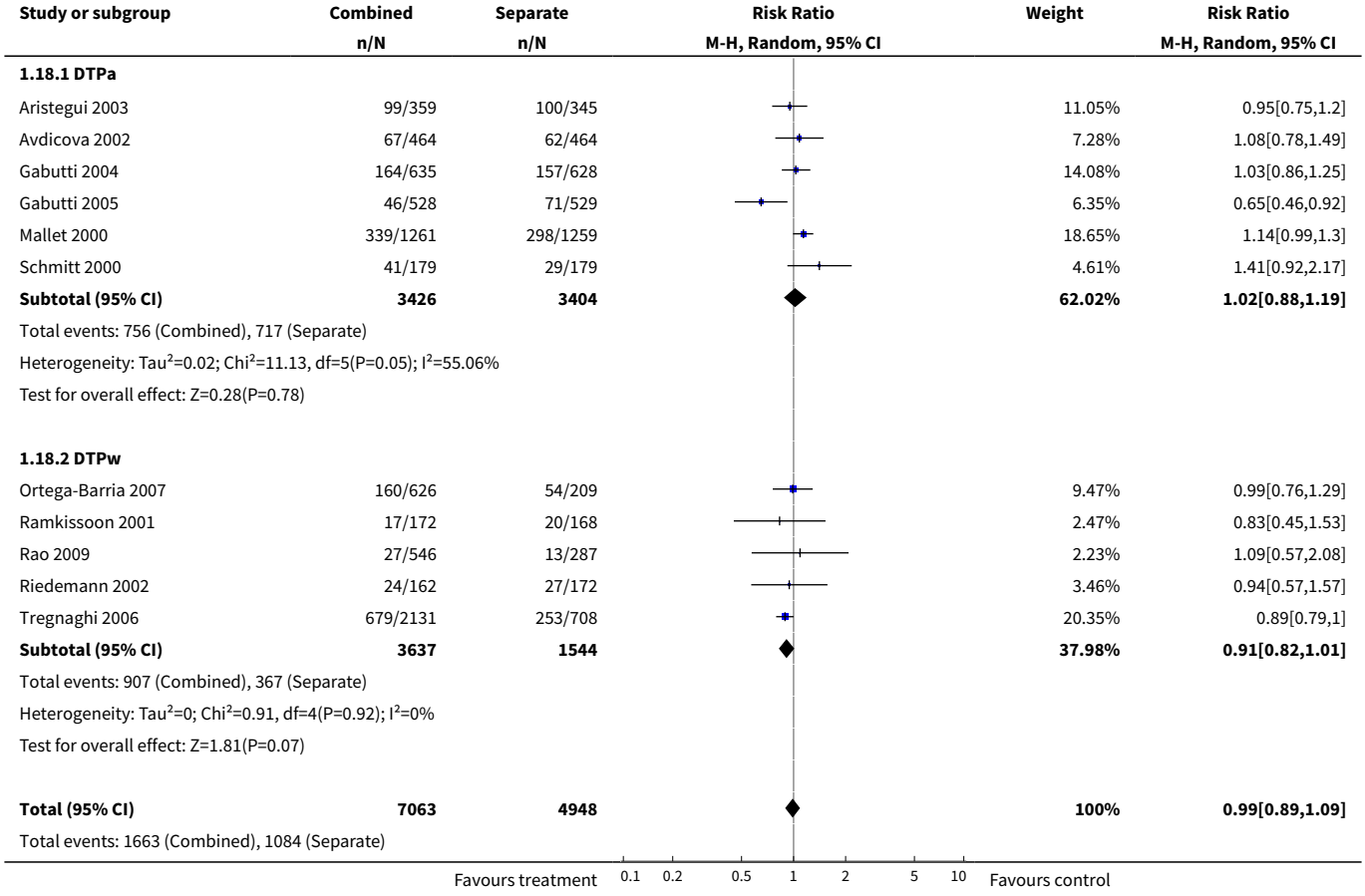


Analysis 1.17. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 17 Fussiness or restlessness.

Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 DTPa					
Avdicova 2002	81/464	65/464		4.61%	1.25[0.92,1.68]
Gabutti 2004	189/635	198/628		11.64%	0.94[0.8,1.11]
Gabutti 2005	49/528	67/529		3.54%	0.73[0.52,1.04]
Mallet 2000	339/1261	298/1259		15.13%	1.14[0.99,1.3]
Marshall 2010	277/533	294/538		18.36%	0.95[0.85,1.06]
Omenaca 2001	563/1966	187/648		14.5%	0.99[0.86,1.14]
Schmitt 2000	34/179	29/179		2.21%	1.17[0.75,1.84]
Subtotal (95% CI)	**5566**	**4245**		**69.98%**	**1.01[0.92,1.11]**



Analysis 1.18. 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
Heterogeneity: Tau²=0.01; Chi²=16.34, df=10(P=0.09); I²=38.82%					
Test for overall effect: Z=0.23(P=0.81)					
Test for subgroup differences: Chi²=1.56, df=1 (P=0.21), I²=35.94%					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

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

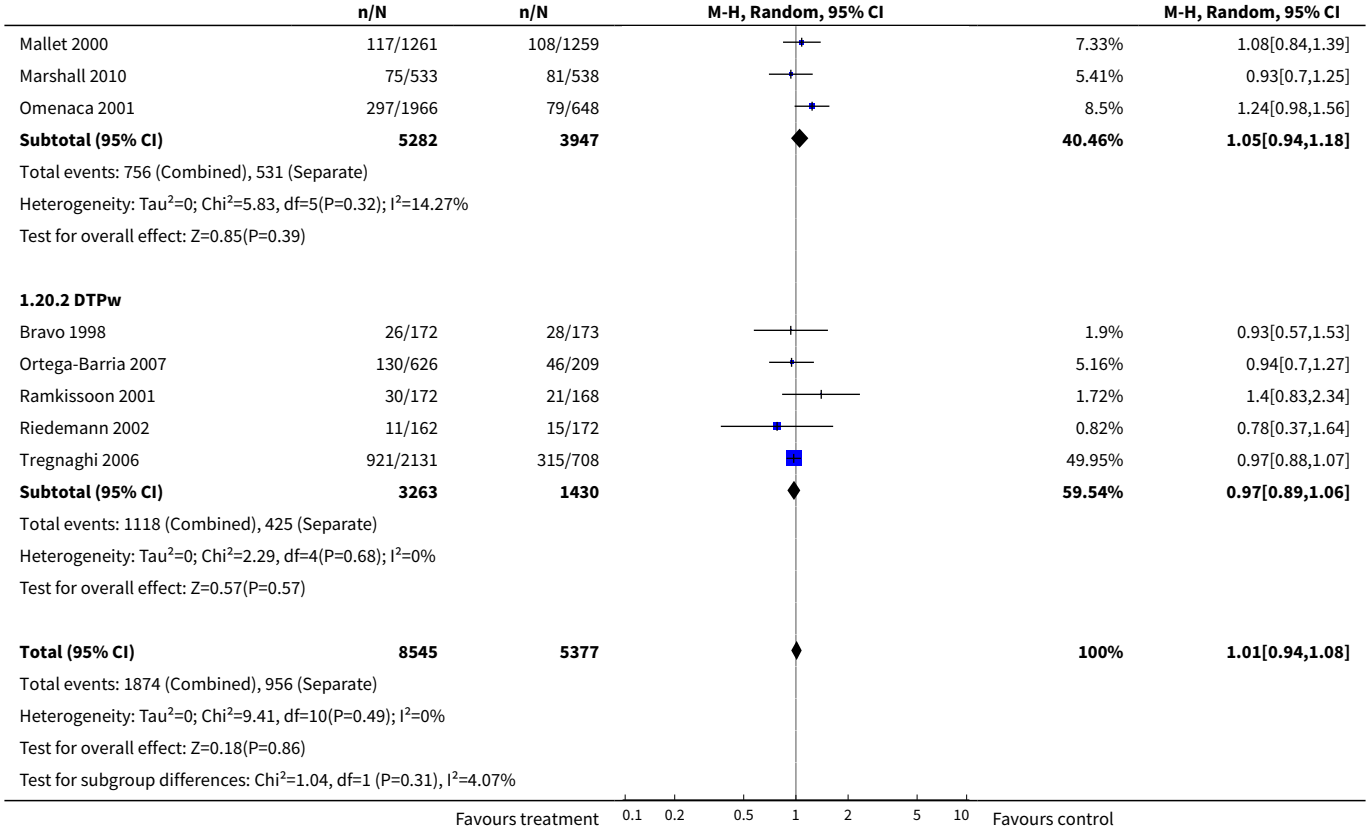
Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 DTPa					
Aristegui 2003	143/359	113/345		9.2%	1.22[1,1.48]
Gabutti 2005	112/528	129/529		7.5%	0.87[0.7,1.09]
Subtotal (95% CI)	**887**	**874**		**16.7%**	**1.03[0.74,1.44]**
Total events: 255 (Combined), 242 (Separate)					
Heterogeneity: Tau²=0.05; Chi²=4.91, df=1(P=0.03); I²=79.64%					
Test for overall effect: Z=0.19(P=0.85)					
1.19.2 DTPw					
Faingezicht 2002	153/278	142/272		13.51%	1.05[0.9,1.23]
Ortega-Barria 2007	304/626	103/209		13.02%	0.99[0.84,1.16]
Ramkissoon 2001	47/172	52/168		3.62%	0.88[0.63,1.23]
Rao 2009	113/546	57/287		4.83%	1.04[0.78,1.39]
Riedemann 2002	49/162	63/172		4.24%	0.83[0.61,1.12]
Tregnaghi 2006	1185/2131	417/708		33.88%	0.94[0.88,1.01]
Win 1997	136/396	148/385		10.19%	0.89[0.74,1.08]
Subtotal (95% CI)	**4311**	**2201**		**83.3%**	**0.95[0.9,1.01]**
Total events: 1987 (Combined), 982 (Separate)					
Heterogeneity: Tau²=0; Chi²=3.74, df=6(P=0.71); I²=0%					
Test for overall effect: Z=1.65(P=0.1)					
Total (95% CI)	**5198**	**3075**		**100%**	**0.97[0.91,1.04]**
Total events: 2242 (Combined), 1224 (Separate)					
Heterogeneity: Tau²=0; Chi²=9.97, df=8(P=0.27); I²=19.8%					
Test for overall effect: Z=0.87(P=0.39)					
Test for subgroup differences: Chi²=0.21, df=1 (P=0.65), I²=0%					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

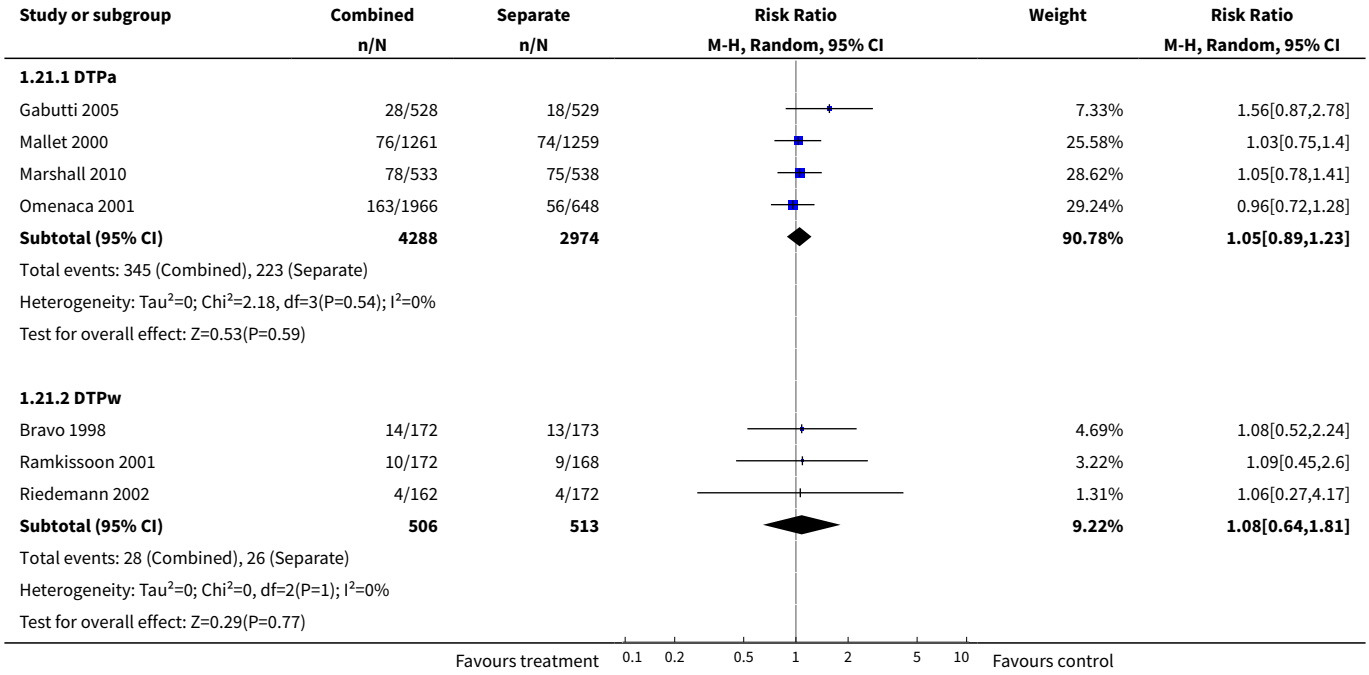
Analysis 1.20. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 20 Poor appetite.

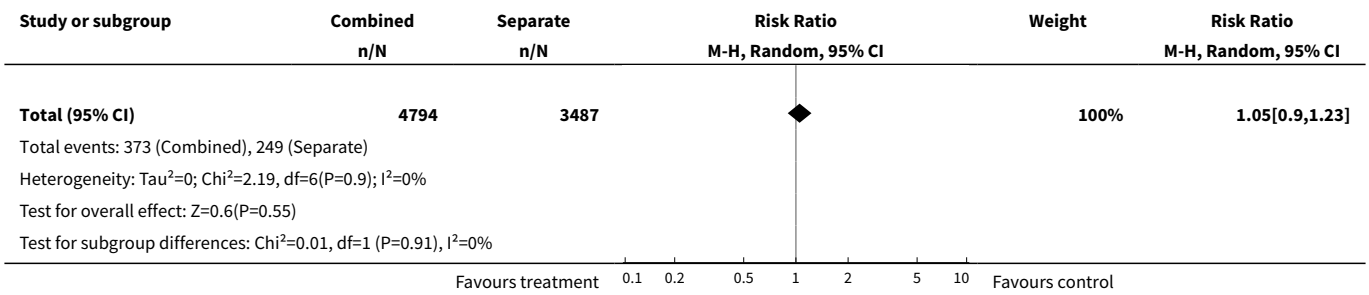
Study or subgroup	Combined n/N	Separate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 DTPa					
Aristegui 2003	91/359	74/345		6.31%	1.18[0.9,1.55]
Gabutti 2004	115/635	115/628		8.35%	0.99[0.78,1.25]
Gabutti 2005	61/528	74/529		4.55%	0.83[0.6,1.13]

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

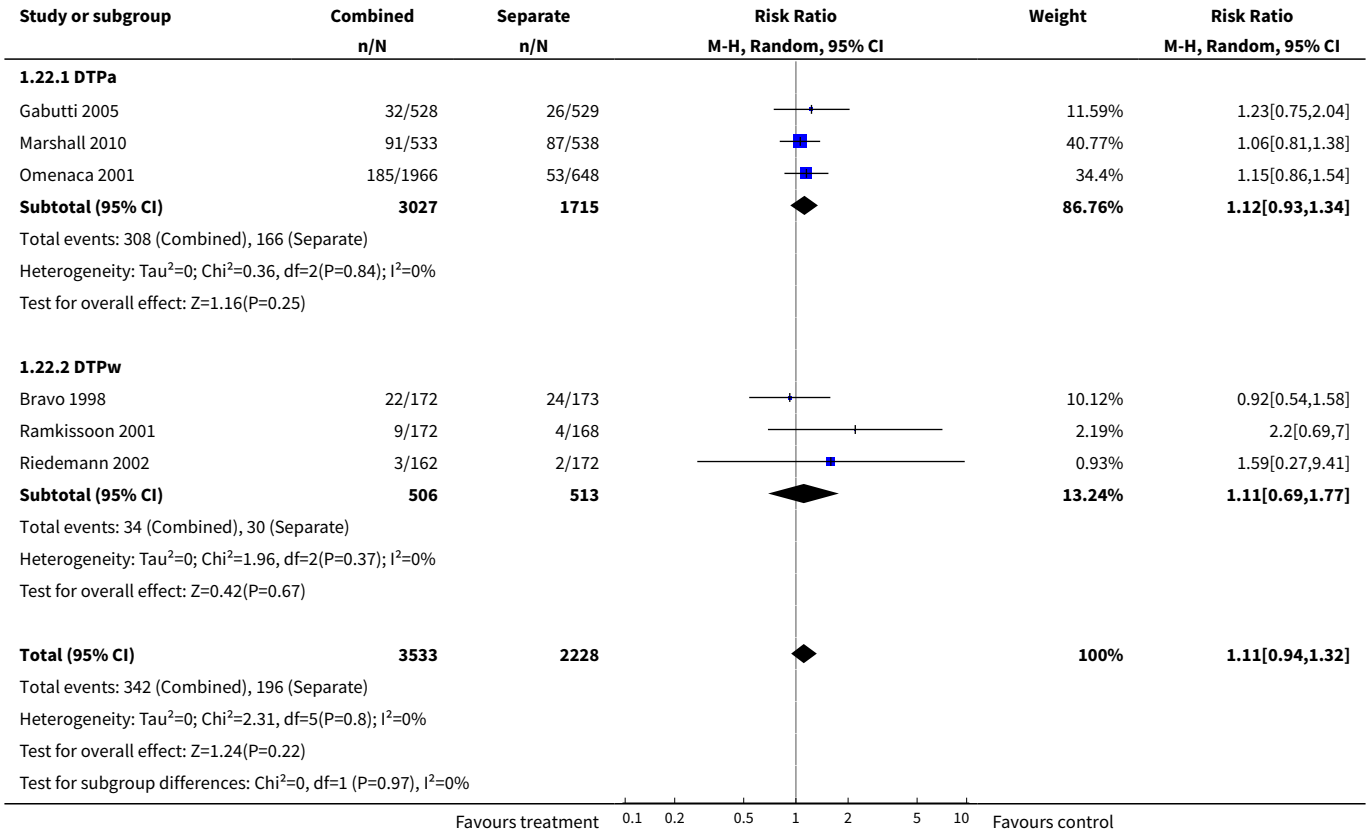


Analysis 1.21. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 21 Vomiting.

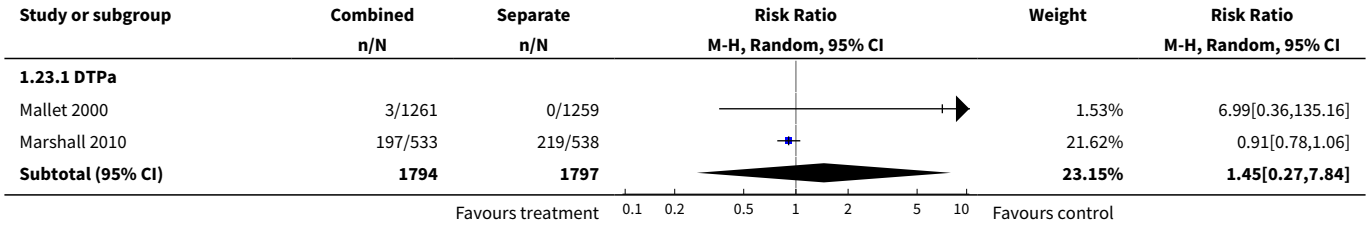


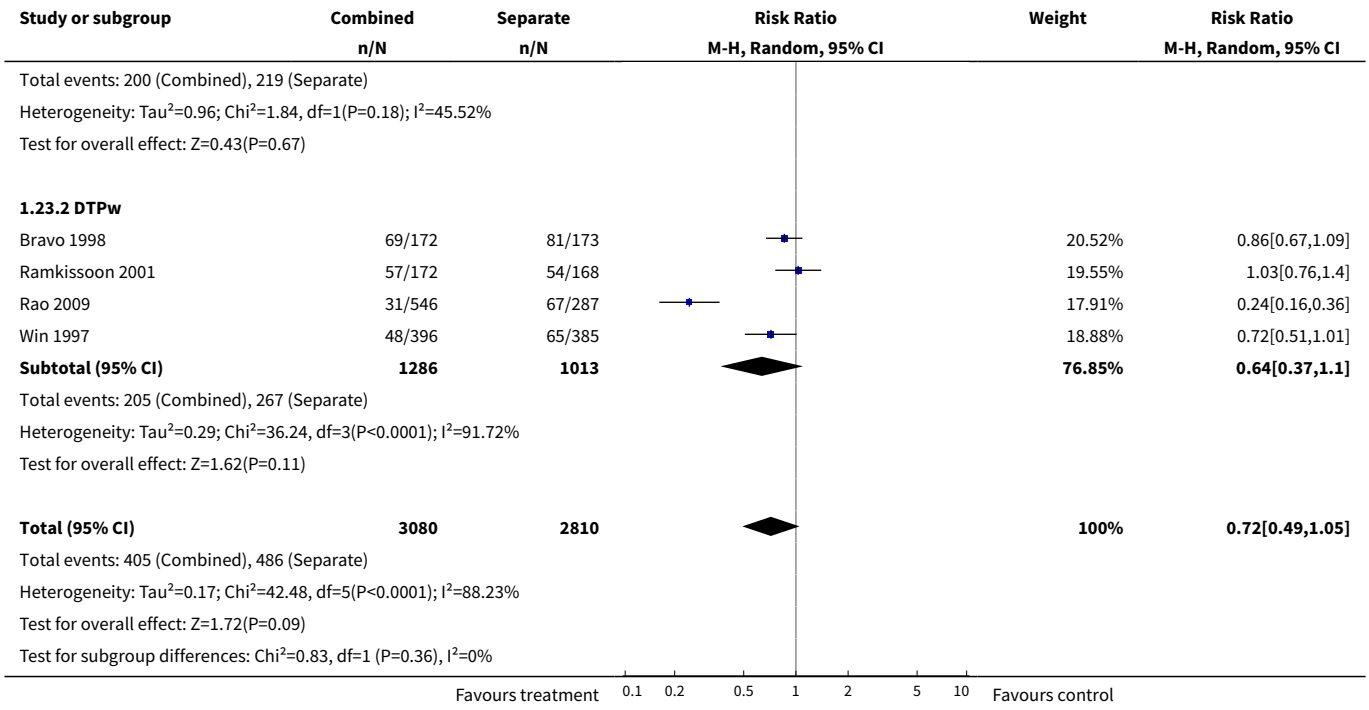


Analysis 1.22. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 22 Diarrhoea.

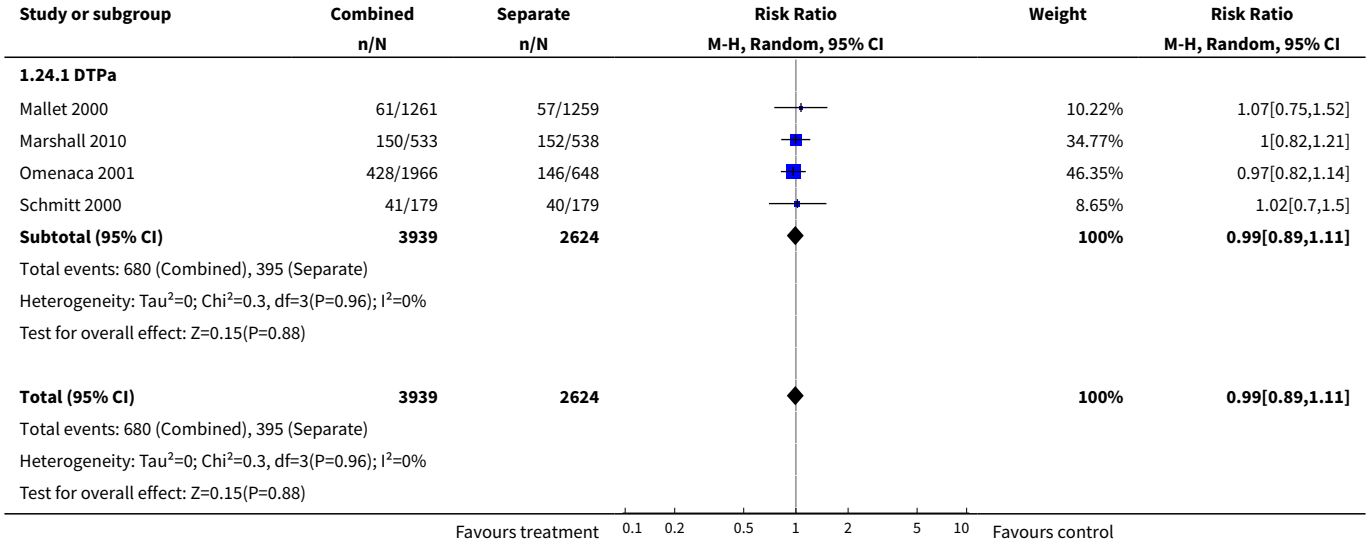


Analysis 1.23. Comparison 1 DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines, Outcome 23 Unusual crying.





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



ADDITIONAL TABLES

Table 1. Serious adverse events (DTPw): details

Combined group	Separate group	Not given

Table 1. Serious adverse events (DTPw): details *(Continued)*

A few hours after the first vaccine dose, 1 child experienced seizures, which resolved spontaneously 2 weeks after the first vaccine dose, another child was diagnosed with acute bronchiolitis and subsequently died due to respiratory distress (Faingezicht 2002)	1 acute bronchiolitis case, due to respiratory syncytials virus infection, occurred 3 days after the first vaccination. The child recovered after treatment and hospitalisation (Faingezicht 2002)	5 participants were hospitalised or experienced a serious adverse event, including 1 participant who died as a secondary result of sudden infant death syndrome 52 days after the first dose vaccine (Greenberg 2000)
3 events: one hypotonic-hyporesponsiveness, 2 seizures (Nolan 2001)	3 events of seizures (Nolan 2001)	
In 1 case 4 booster doses were followed by unsolicited grade '3' symptoms (pharyngitis and severe asthma) (Santos 2002)		
12 serious adverse events were reported by 10 participants (Tregnaghi 2006)	2 serious adverse events after the primary vaccination course were reported by 2 participants (Tregnaghi 2006)	
4 serious adverse events occurred in subjects receiving DTPw-HBV/HIB 2.5 vaccine. 2 hypotonic-hyporesponsive episodes (HHE) in HIB-078 and 2 cases of convulsions in HIB-079. All 4 participants recovered (Ortega-Barria 2007)	2 events occurred following the administration of Tritanrix™-Hep B and Hiberix™ vaccines in HIB-078. 1 case of HHE and one case of viral meningoencephalitis (Ortega-Barria 2007).	
2 siblings (twins) presented with symptoms of fever and decreased feeding 17 days after the second dose of vaccine (Shan 5) with one of them progressing to seizures. A diagnosis of septicaemia with meningitis was made. Another infant presented 10 days after the first dose of Shan 5 with symptoms of fever, irritability and breathlessness, a condition which upon investigation was diagnosed as bronchiolitis (Rao 2009)		

DTPw-HBV/HIB: diphtheria, tetanus, whole cell pertussis/hepatitis B virus/*H. influenzae* type B
HHE: hypotonic-hyporesponsive episode

Table 2. Serious adverse events (DTPa): details

Combined group	Separate group	Not given
7 SAEs were hospitalisations due to vaccination-related common childhood infections (Avdicova 2002). 10 SAEs including one drop-out following a serious adverse event and another following a non-serious adverse event (Gabutti 2004). 1 case of large, local reactions after the sec-	11 SAEs were hospitalisations due to vaccination-related common childhood infections (1 erythematous rash) (Avdicova 2002). 10 SAEs including one drop-out following a serious adverse event (Gabutti 2004). 3 infants presented symptoms that were considered as a contradiction for further vaccination:inconsolable crying i.e. more than three hours after first dose (n = 1), second dose (n = 1) and third dose (n = 1) (Mallet 2000)	2 episodes of "inconsolable crying" were reported within the context of multiple severe local reactions without further sequelae (Mallet 2000). 4 serious adverse events were reported (Aristegui 2003). 8 serious adverse events occurred (Schmitt 2000)

Table 2. Serious adverse events (DTPa): details *(Continued)*

ond and third injections (Mallet 2000)		
	1 SAE was assessed as probably related to vaccination, a hypotonic hyporesponsive episode (Marshall 2010)	26 SAEs were reported during the study. All were considered unrelated to vaccination by the investigators (Marshall 2010)

n: Number of participants
SAEs: Serious Adverse Events

APPENDICES

Appendix 1. CENTRAL and MEDLINE search strategy

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

Appendix 2. EMBASE.COM search strategy

#19. #15 AND #18 156 16 Mar 2011
#18. #16 OR #17 837,345 16 Mar 2011
#17. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti AND [embase]/lim 793,290 16 Mar 2011
#16. 'randomised controlled trial'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de AND [embase]/lim 238,781 16 Mar 2011
#15. #5 AND #10 AND #14 576 16 Mar 2011
#14. #11 OR #12 OR #13 61,025 16 Mar 2011
#13. 'hepatitis b':ab,ti OR hbv:ab,ti AND [embase]/lim 48,241 16 Mar 2011
#12. 'hepatitis b'/de AND [embase]/lim 37,360 16 Mar 2011
#11. 'hepatitis b vaccine'/de AND [embase]/lim 11,421 16 Mar 2011
#10. #6 OR #7 OR #8 OR #9 18,750 16 Mar 2011
#9. haemophilus:ab,ti OR hemophilus:ab,ti OR hib:ab,ti AND [embase]/lim 17,035 16 Mar 2011
#8. 'haemophilus'/de AND [embase]/lim 1,545 16 Mar 2011
#7. 'haemophilus influenzae type b'/de AND [embase]/lim 3,371 16 Mar 2011
#6. 'haemophilus vaccine'/de AND [embase]/lim 242 16 Mar 2011
#5. #1 OR #2 OR #3 OR #4 6,261 16 Mar 2011
#4. dtp:ab,ti OR dtap:ab,ti AND [embase]/lim 1,255 16 Mar 2011
#3. diphtheria:ab,ti AND tetanus:ab,ti AND pertussis:ab,ti AND [embase]/lim 1,961 16 Mar 2011
#2. 'diphtheria pertussis tetanus haemophilus influenzae type b hepatitis b vaccine'/de OR 'diphtheria pertussis tetanus haemophilus influenzae type b vaccine'/de OR 'diphtheria
pertussis poliomyelitis tetanus vaccine'/de OR 'diphtheria pertussis poliomyelitis tetanus haemophilus influenzae type b hepatitis b vaccine'/de AND [embase]/lim 916 16 Mar 2011

#1. 'diphtheria pertussis tetanus vaccine'/de AND [embase]/lim 4,736 16 Mar 2011

WHAT'S NEW

Date	Event	Description
11 November 2011	New citation required but conclusions have not changed	The conclusions remain unchanged, although results differed slightly from the last publication of this review
11 November 2011	New search has been performed	Searches conducted. We included two new trials (Marshall 2010; Rao 2009) and excluded six new trials (Diaz-Mitoma 2011; Gentile 2011; Halperin 2009; Kilpi 2009; Madhi 2011; Tregnaghi 2011). The two studies added to this update slightly changed the results. In anti-T (tetanus) immunological responses, the combined vaccine achieved lower responses than the separate vaccines. This result changed from the last publication where in anti-hepatitis B immunological responses, the combined vaccine achieved lower responses than the separately administered vaccines

HISTORY

Protocol first published: Issue 4, 2005
Review first published: Issue 3, 2009

Date	Event	Description
6 October 2010	Amended	Contact details updated.
9 September 2010	Amended	Contact details updated.
5 August 2010	Amended	Contact details updated.
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 and updating the review.
Abigail Fraser (AF): assisted with writing the protocol.
Sarah Hellmann (SH): has assisted with writing the protocol, analysing and updating the review.
Goldberg Elad (GE): was responsible for the reference searches, article retrieval, study inclusion and exclusion, data extraction and analysis and interpretation of results of the review and update.
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 and update.

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 (Pa) and whole cell pertussis (Pw) was added after the protocol was written.

INDEX TERMS

Medical Subject Headings (MeSH)

Diphtheria [immunology] [*prevention & control]; Diphtheria-Tetanus-Pertussis Vaccine [*administration & dosage] [immunology]; Haemophilus Infections [immunology] [*prevention & control]; Haemophilus Vaccines [*administration & dosage] [immunology]; Hepatitis B [immunology] [*prevention & control]; Hepatitis B Vaccines [*administration & dosage] [immunology]; Tetanus [immunology] [*prevention & control]; Vaccines, Combined [administration & dosage] [immunology]; Whooping Cough [immunology] [*prevention & control]

MeSH check words

Child, Preschool; Female; Humans; Infant; Infant, Newborn