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Acellular vaccines for preventing whooping cough in children (Review)

Zhang L, Prietsch SOM, Axelsson I, Halperin SA

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[Intervention Review]

Acellular vaccines for preventing whooping cough in children

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ABSTRACT

Background

Routine use of whole-cell pertussis (wP) vaccines was suspended in some countries in the 1970s and 1980s because of concerns about adverse effects. Following this action, there was a resurgence of whooping cough. Acellular pertussis (aP) vaccines, containing purified or recombinant *Bordetella pertussis* (*B. pertussis*) antigens, were developed in the hope that they would be as effective, but less reactogenic than the whole-cell vaccines. This is an update of a Cochrane review first published in 1999, and previously updated in 2012. In this update, we included no new studies.

Objectives

To assess the efficacy and safety of acellular pertussis vaccines in children and to compare them with the whole-cell vaccines.

Search methods

We searched CENTRAL (2013, Issue 12), MEDLINE (1950 to January week 2, 2014), EMBASE (1974 to January 2014), Biosis Previews (2009 to January 2014) and CINAHL (2009 to January 2014).

Selection criteria

We selected double-blind randomised efficacy and safety trials of aP vaccines in children up to six years old, with active follow-up of participants and laboratory verification of pertussis cases.

Data collection and analysis

Two review authors independently extracted data and assessed the risk of bias in the studies. Differences in trial design precluded a meta-analysis of the efficacy data. We pooled the safety data from individual trials using a random-effects meta-analysis model.

Main results

We included six efficacy trials with a total of 46,283 participants and 52 safety trials with a total of 136,541 participants. Most of the safety trials did not report the methods for random sequence generation, allocation concealment and blinding, which made it difficult to assess the risk of bias in the studies. The efficacy of multi-component (≥ three) vaccines varied from 84% to 85% in preventing typical whooping cough (characterised by 21 or more consecutive days of paroxysmal cough with confirmation of *B. pertussis* infection by culture, appropriate serology or contact with a household member who has culture-confirmed pertussis), and from 71% to 78% in preventing mild pertussis disease (characterised by seven or more consecutive days of cough with confirmation of *B. pertussis* infection by culture or appropriate serology). In contrast, the efficacy of one- and two-component vaccines varied from 59% to 78% against typical whooping cough and from 41% to 58% against mild pertussis disease. Multi-component acellular vaccines are more effective than low-efficacy

whole-cell vaccines, but may be less effective than the highest-efficacy whole-cell vaccines. Most systemic and local adverse events were significantly less common with aP vaccines than with wP vaccines for the primary series as well as for the booster dose.

Authors' conclusions

Multi-component (≥ three) aP vaccines are effective in preventing whooping cough in children. Multi-component aP vaccines have higher efficacy than low-efficacy wP vaccines, but they may be less efficacious than the highest-efficacy wP vaccines. Acellular vaccines have fewer adverse effects than whole-cell vaccines for the primary series as well as for booster doses.

PLAIN LANGUAGE SUMMARY

Acellular vaccines for preventing whooping cough (pertussis) in children

Review question
We aimed to answer the question of whether acellular pertussis vaccines are as effective as the whole-cell vaccines at protecting children against whooping cough (pertussis), but with fewer side effects.

Background
Whooping cough can be a serious respiratory infection in children and is caused by the bacterium *Bordetella pertussis* (*B. pertussis*). Vaccines made from killed whole *B. pertussis*, known as whole-cell pertussis vaccines, can cause severe neurologic disorders and minor side effects, such as anorexia, drowsiness, fever, irritability, prolonged crying, vomiting and pain/redness/swelling/hardening at the injection site. This led to a fall in immunisation rates, which resulted in an increase in the number of cases of whooping cough. Acellular pertussis vaccines (containing more purified antigens of *B. pertussis*) were developed in the hope that they would be as effective but safer than the whole-cell pertussis vaccines.

Search date
We searched for trials published up to January 2014.

Study characteristics
We included trials comparing the efficacy and safety of whole-cell and acellular pertussis vaccines in children up to six years old.

Key results
This updated review included six trials with 46,283 participants evaluating the efficacy and 52 trials with 136,541 participants assessing the safety of pertussis vaccines. Duration varied from 12 months to 27 months and from 3 days to 12 months for efficacy trials and safety trials, respectively. The efficacy of acellular vaccines with three or more components varied from 84% to 85% in preventing typical whooping cough (characterised by 21 or more consecutive days of severe coughing attacks with laboratory evidence of *B. pertussis* infection or contact with a household member who has culture-confirmed pertussis) and from 71% to 78% in preventing mild pertussis disease (characterised by seven or more consecutive days of cough with laboratory evidence of *B. pertussis* infection). In contrast, the efficacy vaccines with one and two components varied from 59% to 78% in protecting against typical whooping cough and from 41% to 58% against mild pertussis disease. Most systemic and local side effects were significantly less common with acellular vaccines than with whole-cell vaccines for the first doses and booster dose. We found that acellular pertussis vaccines with three or more components are more effective than low-efficacy whole-cell vaccines, but may be less effective than the highest-efficacy whole-cell vaccines. Acellular vaccines have fewer side effects than whole-cell vaccines.

Implications for practice
The implications of the findings of this review for clinical practice may be different in high-income and low-income countries. In high-income countries, death from whooping cough is rare and parental acceptance is a major determinant of immunisation uptake. In these circumstances, the improved side effect profile of acellular vaccines argues in favour of their use, even though they might sacrifice some degree of effectiveness compared to the best whole-cell vaccines. In low-income countries, where the risk of pertussis is higher and cases are more likely to be fatal, greater weight needs to be given to vaccine efficacy. If an acellular vaccine has been shown to be less effective than a high-efficacy whole-cell vaccine it is intended to replace, the safety advantage of the acellular vaccine may be offset by increased mortality and morbidity due to a significantly higher rate of pertussis. However, most of the whole-cell vaccines used in low-income countries have not been adequately studied for efficacy and, therefore, it is not known where on the wide spectrum of whole-cell vaccine efficacy an individual product lies.

Quality of evidence
All included trials were randomised and double-blind, that is, the participants had an equal chance of receiving either acellular or whole-cell vaccines and both researchers and participants were unaware of the treatment assignment. However, most of trials did not report details of these methodological techniques. This may cast some uncertainty on the quality of evidence in this review.

BACKGROUND

Description of the condition

Whooping cough, or pertussis, is a highly contagious disease caused predominantly by the fastidious Gram-negative coccobacillus, *Bordetella pertussis* (*B. pertussis*). The disease can occur at any age but is more severe in infants, with most deaths occurring in this age group (Singh 2006). The disease in this age group is also more easily diagnosed because they present with whooping cough, which is characterised by paroxysmal coughing followed by an audible inspiratory whoop and occasionally vomiting. Infants often have a cough and apnoeic episodes, which can be severe and may require admission to hospital. Although habitually a persistent, relatively benign respiratory illness, pertussis can result in serious consequences, such as pneumonia, seizures, encephalopathy and death, especially among infants (Galanis 2006). Immunised children, adolescents and adults may not exhibit whooping cough. They may be asymptomatic or present with a cough lasting several weeks.

The reported incidence of pertussis should be interpreted cautiously, because the case definitions and surveillance system performance vary markedly between countries. In low-income countries, case definition is mostly based on clinical confirmation due to limited access to laboratory facilities (Singh 2006). According to the World Health Organization (WHO) there are about 16 million pertussis cases annually worldwide among children, teenagers and adults, 95% of which are in low-income countries, and about 195,000 children die of the disease (WHO 2010). Before the introduction of the pertussis vaccine in the 1940s, there were approximately 200,000 cases reported annually in the United States. Immunisations reduced disease rates and there were only 1010 reported cases in 1976 (Bamberger 2008). The incidence decreased from 157 per 100,000 population in the early 1940s to less than 1 per 100,000 in 1973 (Cherry 2012). It has been generally believed that pertussis particularly affected children under six years of age, but recent trends show that in countries that have achieved good control of pertussis, there is a change in the epidemiology of pertussis in the older age group. Several factors have been proposed as possible causes for the increasing incidence of pertussis disease, including waning immunity with subsequent atypical disease manifestations (Singh 2006). There is a frequent misconception that protection provided by childhood immunisation is lifelong. However, the protection provided by vaccination tends to reduce over time. Evidence shows that the proportion of susceptible children with infections in countries with good vaccination coverage (70%) can be estimated at 10% by one year, 60% by five years and 100% by 15 years (Singh 2006).

Since the 1980s, there has been a substantial increase in the number of cases reported, especially in high-income countries. This has occurred in children and adolescents aged 6 to 10 years, after childhood immunisations were completed (Bamberger 2008; Singh 2006). In the USA, for example, there were 25,827 cases reported in 2004 and there has been a 19-fold increase of pertussis cases in adolescents (Bamberger 2008; CDC 2011). Affected adolescents and adults act as reservoirs of the disease to the vulnerable population of infants, for whom the disease can be life-threatening (Harnden 2009; WHO 2010).

Description of the intervention

After the isolation of *B. pertussis* in 1906, the possibility of vaccine development was considered. In 1933, Madsen reported some degree of protection in individuals who received a vaccine composed of suspended organisms in saline (Cherry 1996). Vaccines made from killed whole *B. pertussis* bacteria (whole-cell pertussis vaccines - wP) have been available since the 1940s. Today, wP vaccines are manufactured in many countries. Although their basic preparation procedures are similar, the vaccines frequently elicit markedly different immune responses to various *B. pertussis* antigens (Cherry 1996). The wP vaccines are based on regular cultures of selected *B. pertussis* strains that are killed, usually by being heating and treated with formalin. The methods used for the production vary between laboratories, therefore wP vaccines are relatively heterogeneous. Most wP vaccines are combined with diphtheria toxoid and tetanus toxoid. This combination has shown an efficacy of 80% and has been effective in reducing the incidence rates markedly in countries with good immunisation coverage (WHO 2010). The immune response to wP vaccines is directed against an array of antigens of whole bacterial cells. Significant differences in the immune responses to various antigens have been observed among the different wP vaccines. Unwanted components such as endotoxin cannot be eliminated during whole-cell vaccine production, therefore an acceptable level of potency is inevitably associated with a greater incidence of adverse effects.

Concerns about possible relations of wP vaccines with neurological disorders led to the development of acellular pertussis (aP) vaccines in the 1970s and they were widely tested and used in Japan during the 1980s (Sato 1984). aP vaccines consist of recombinant or isolated, purified antigens of *B. pertussis*. They include antigens extracted by various methods, as well as those produced by genetic recombinant technology. Five antigens have been identified as appropriate vaccine components: pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin and fimbriae type 2 and 3 (FIM 2 and 3) (Jefferson 2003; Singh 2006). One or more of these components may be included in various combinations to produce the vaccine. Vaccines differ from each other, with regard to the bacterial clone used for primary antigen production, methods of cleansing and detoxification, included adjuvants and the use of preservatives (WHO 2010). The exact contribution of the different aP antigens to protection is not well established.

Vaccination strategies vary by health policies in each country. Over the last several years, many potential immunisation strategies have been proposed to improve pertussis control. Immunogenicity data indicate that a primary series should consist of three doses and that booster doses are necessary at ages two and four to six years (Cherry 1996). Most immunisation schedules consist of five to six intramuscular injections given from the age two months to 16 years (CDC 2009; Rodríguez-Cobo 2008), but booster doses every 10 years throughout life have been suggested because protection provided by childhood immunisation is only partial and not lifelong (Forsyth 2004; Rodríguez-Cobo 2008).

In the 1990s, safety concerns prompted a switch from wP to aP vaccines in most high-income countries. However, wP vaccines remain the choice for the national childhood immunisation programmes in many low-income countries, as they are considerably less expensive and highly effective against pertussis (Singh 2006; WHO 2010). In children older than six years of age, only aP vaccines should be used for vaccination (WHO 2010).

How the intervention might work

The mechanism of vaccine-induced protection against *B. pertussis* is still not well understood. Induction of antibodies to the components of *B. pertussis* appears to be associated with protection by vaccines (Cherry 1998; Kerr 2000; Storsaeter 1998; Taranger 2000), and it is believed that anti-*B. pertussis* IgG antibodies may play a key role in preventing bacterial adherence (Mills 1999). However, no consensus has been reached regarding the protective antigens. A household study nested in the Swedish vaccine efficacy trial (Storsaeter 1998) (SmithKline Beecham DTaP 2 vaccine, Connaught DTaP 5 vaccine, Connaught DTwP vaccine, SBT DT vaccine) found a correlation between clinical protection and levels of anti-pertactin, anti-FIM2/3 and anti-PT antibodies in serum, listed in order of a decreasing degree of correlation. There was no correlation between anti-FHA antibodies and clinical protection. Similar results were found in the German vaccine efficacy trial (Cherry 1998) (Lederle/Takeda DTaP vaccine, Lederle wP vaccine).

Cell-mediated immunity has also been proposed as a possible protective mechanism of vaccines (Mills 1999; Plotkin 2008; Tran Minh 1998). Both human and animal studies demonstrate that aP and wP vaccines induce distinct T cell populations (Feunou 2010; Millis 1998; Mills 1999). Th1 responses are important for bacterial clearance following primary infection and in immunity induced with a wP vaccine, whereas Th2 cells play a more critical role in the protective mechanism of the aP vaccine (Mills 1999). It is believed that *B. pertussis*-specific T cells (probably IL-4 and IL-5 secreting Th0/Th2 cells) are required for the induction of humoral response, whereas Th1 cells function in limiting the course of infection through enhanced bacterial uptake and killing by phagocytic cells (Mills 1999).

Why it is important to do this review

This systematic review was initially conducted by Tinnion 1999 to assess the efficacy and safety of aP vaccines in children and to compare them with wP vaccines. The review has been regularly updated (Zhang 2009; Zhang 2012). This review can provide high-level evidence regarding the benefits and risks of vaccines against pertussis for health policy makers, as well as for paediatricians and parents.

OBJECTIVES

To assess the efficacy and safety of acellular pertussis vaccines in children and to compare them with the whole-cell vaccines.

The following four questions were answered by the review.

1. Do acellular vaccines protect against pertussis?
2. If so, do different vaccines confer different levels of protection?
3. Do acellular vaccines protect against pertussis to the same degree as the whole-cell vaccines, which they are intended to replace?
4. Do acellular vaccines cause fewer side effects than wP vaccines?

METHODS

Criteria for considering studies for this review

Types of studies

1. Double-blind randomised controlled trials (RCTs) of the efficacy of aP vaccines, with active follow-up of participants and laboratory verification of pertussis cases.
2. Double-blind RCTs of the safety of aP vaccines.

Active follow-up was required to minimise the potential for bias in the recording of pertussis cases. Passive follow-up (such as relying on parents to report cases spontaneously, or monitoring laboratory records of pertussis isolates) has been shown to lead to bias in case ascertainment. This occurs because disease in vaccinated individuals tends to be less severe than in unvaccinated ones and therefore less likely to come to the attention of a physician (Taranger 1997). Laboratory verification was required because case definitions of pertussis based on clinical criteria alone have been shown to lack specificity (Blackwelder 1991). There was no requirement for laboratory verification to be performed according to any particular method, because the most appropriate method will vary according to the composition of the vaccine under study.

We did not consider trials which only examined antibody response after immunisation in this review, as no particular antibody level has been found to correlate with the clinical efficacy of pertussis vaccines (Granoff 1997).

Types of participants

Children up to six years of age at time of study entry.

Types of interventions

We considered two types of interventions in the experimental (acellular vaccine) group.

1. aP vaccine: a vaccine containing purified, detoxified pertussis antigens. This includes antigens extracted from *B. pertussis* organisms by various purification methods, as well as those produced by genetic recombinant technology.
2. Diphtheria-tetanus-aP (DTaP) vaccine. An aP vaccine which also contains diphtheria and tetanus toxoids.

We included four types of control intervention.

1. wP vaccine: a vaccine containing killed, whole *B. pertussis* organisms. (An appropriate control where the acellular vaccine used in the experimental group contains only pertussis antigens).
2. Diphtheria-tetanus-wP vaccine (DTwP): a whole-cell pertussis vaccine, which also contains diphtheria and tetanus toxoids. (An appropriate control if these antigens are present in the acellular vaccine used in the experimental group).
3. Placebo: a preparation containing no antigens or organisms. (An appropriate control where the acellular vaccine used in the experimental group contains only pertussis antigens).
4. DT: diphtheria-tetanus (DT) toxoid vaccine. (An appropriate control if these antigens are present in the acellular vaccine used in the experimental group).

Types of outcome measures

Primary outcomes

The primary outcome measure was vaccine efficacy. Trials comparing acellular vaccines with a randomised placebo/DT group permitted the determination of absolute vaccine efficacy. This is the conventional parameter used to express effectiveness in vaccine trials and represents the percentage of potential disease cases prevented by the vaccine. Absolute vaccine efficacy is calculated as (1 - RR) x 100%, where risk ratio (RR) equals the risk of disease in the vaccine group divided by the risk of disease in the placebo/DT group. Trials with no placebo/DT control do not permit the estimation of absolute efficacy but do allow an assessment of the comparative efficacy of the various vaccines within each trial (expressed as the RR of disease in the acellular compared to the whole-cell group).

Estimates of pertussis vaccine efficacy may vary greatly according to the case definition used (Blackwelder 1991), and most studies report efficacy results for a range of case definitions. In this review, we examined two case definitions. The first, 'whooping cough', corresponds to the well-recognised clinical syndrome of pertussis, characterised by protracted, paroxysmal cough. The second, 'pertussis disease', includes milder cases that do not fit the classical picture but may be important in the spread of infection. The criteria for these two case definitions were as follows.

1. Whooping cough: 21 or more consecutive days of paroxysmal cough with confirmation of *B. pertussis* infection by culture, appropriate serology or contact with a household member who has culture-confirmed pertussis. This case definition is recommended by the WHO for use in pertussis vaccine trials (WHO 1991).
2. Pertussis disease: seven or more consecutive days of cough with confirmation of *B. pertussis* infection by culture or appropriate serology.

When studies did not report vaccine efficacy using these exact criteria, we reviewed efficacy for the case definitions that corresponded most closely to those above.

Where possible, we reviewed efficacy endpoints for the population who received all scheduled doses of the randomised vaccine ('per protocol' population) and for the population who received at least one dose of the randomised vaccine.

Secondary outcomes

The safety outcome measures were as follows.

1. Failure to complete all scheduled doses of the primary immunisation series because of adverse events.
2. Mortality due to any cause.
3. Mortality due to infection.
4. Encephalopathy.
5. Convulsions.
6. Hypotonic-hyporesponsive episodes.
7. Selected minor adverse events generally considered to be associated with wP vaccines: anorexia, drowsiness, fever, irritability/fretfulness, prolonged crying, vomiting, injection site pain/tenderness, injection site redness and injection site swelling/induration.

Search methods for identification of studies

Electronic searches

The initial search was carried out in March 1997 and updated in March 1998 (see Appendix 1 for details of the search terms). The search was updated again in April 2009. See Appendix 2 for details of search terms.

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 12), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (April 2009 to January week 2, 2014) and EMBASE (April 2009 to January 2014). We also searched Biosis Previews (2009 to January 2014) and CINAHL (2009 to January 2014) as we aimed to include a broader range of databases in order to identify potential studies.

We used the search strategy in Appendix 3 to search MEDLINE and CENTRAL. We combined the MEDLINE search 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 the search strategy to search EMBASE (Appendix 4), Biosis Previews (Appendix 5), and CINAHL (Appendix 6).

Searching other resources

We did not manually search the reference lists of retrieved papers for either initial or updated searches, and we made no systematic attempt to obtain unpublished articles. We did not limit the searches to English language reports because such limitation has been shown to be a potential source of bias (Egger 1997).

Data collection and analysis

Selection of studies

One of the original review authors identified and assessed trials in the first publication of this review (Tinnion 1999), to determine whether they satisfied the predefined inclusion criteria. The review author was not blinded to the trial authors or sources of the trial reports during study selection and data extraction.

Two review authors (LZ, SP) independently assessed the titles and abstracts of all studies identified by the searches to select new trials when updating this review. We obtained the full articles when they appeared to meet the inclusion criteria or there were insufficient data in the title and abstract to make a clear decision for their inclusion. We resolved any disagreement between the review authors about study inclusion by discussion.

Data extraction and management

We gave each study a unique identifier for use in RevMan 2012. When a single study was reported in several publications, we used the lead author of the publication containing the main efficacy or adverse event data in the identifier (for example, Decker 1995).

We extracted data into a database (MS Access 7.0) using pre-prepared electronic forms, which had been refined after testing on a sample of trials. We then sorted the data for entry into RevMan 2012. Two review authors (LZ, SP) independently extracted data from the new trials included for update using a standardised data extraction form. We resolved any disagreement by discussion.

A number of studies reported the percentage of vaccine recipients with each adverse event, but not the actual number. To permit entry into RevMan 2012, we calculated the number of participants experiencing each event from the reported percentage and the number vaccinated. This practice was required only for the common, minor adverse events. It may have introduced a small rounding error in some instances but would not have materially affected the odds ratio (OR) and overall conclusions for these common events.

We excluded the data from the review if adverse event data for a particular dose were available for less than 80% of those who had received the dose. This was done because excessive loss to follow-up could lead to a spurious reduction in the reported frequency of adverse events.

Study reports often graded adverse events according to severity. For the purposes of this review, we defined two (overlapping) severity categories. The primary category was the number of patients with any occurrence of the event under consideration. A secondary category was the number of patients with 'moderate to severe' grades of the event.

We applied the following rules during data extraction.

1. We defined primary series immunisation as the first series of up to three doses administered to children who had not previously been immunised against pertussis. We defined booster immunisation as doses administered at or after the age of 12 months to children who had completed a primary series.
2. When results for both pain and tenderness were reported, we used the result for pain. When results for both swelling and induration were reported, we used that for swelling.
3. We defined fever as a temperature of 38 °C or greater. When a study did not report a result using this cut-point, we entered the result for the cut-point closest to 38 °C but below 39 °C. We defined moderate to severe fever as a temperature at or above 39 °C. If a study did not report a result using this cut-point, we recorded the result for the next highest cut-point.
4. We defined moderate to severe redness and swelling/induration as reactions with a diameter of 2 cm or greater. When a study did not report a result using this cut-point, we recorded the result for the next highest cut-point.
5. We recorded data for deaths if the study report explicitly stated the number of deaths (or that there were no deaths), or if the absence of deaths could be confirmed by one or more of the following: (1) the number of withdrawals was stated and all were accounted for by causes other than death; (2) the report stated that there were no withdrawals, or that all participants completed the study; and (3) the report stated that there were no serious reactions and also defined death as a serious reaction. While the last requirement may seem superfluous, this was not the case, as one study stated that "there were no serious reactions to the vaccines" and then went on to report that there had been two convulsions and one death (Trollfors 1995).
6. We recorded data for encephalopathy, convulsions or hypotonic-hyporesponsive episodes if: (1) the report explicitly stated the number of these reactions (or that there were none); or (2) the report stated that there were no serious reactions and defined the event under consideration (encephalopathy, convulsions or hypotonic-hyporesponsive episodes) as a serious reaction.

Assessment of risk of bias in included studies

Two review authors (LZ, SP) independently assessed the risk of bias of each eligible RCT by using The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). The tool contains seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. We rated each domain as having 'low risk of bias', 'high risk of bias' or 'unclear risk of bias'.

Measures of treatment effect

We used risk ratio (RR) and 95% confidence interval (CI), rather than odds ratio (OR) and 95% CI, to estimate the risk of adverse events because the interpretation of the OR is more difficult, and it may produce inflated estimates of risk when the outcomes are frequent, as are minor adverse events.

Dealing with missing data

Selective reporting of outcomes in some included studies may result in missing data. We based the analysis on available data but the potential impact of missing data on the findings of the review is addressed in the Discussion section.

Assessment of heterogeneity

We assessed heterogeneity across studies using the Chi^2 test. We took a conservative approach, as the test for heterogeneity has low statistical power (Petitti 1994), whereby heterogeneity was assumed if the P value for the test was less than 0.10. We addressed the possible causes of heterogeneity across studies in the Discussion section.

Assessment of reporting biases

Reporting biases, especially publication bias, may be expected to occur in the majority of systematic reviews. Unfortunately there is no reliable method to detect publication bias. We examined the possibility of selective reporting of outcomes and its potential impact on the findings of the review is addressed in the Discussion section.

Data synthesis

Due to the small number of efficacy studies and differences between them in dose schedule, vaccine characteristics, case definitions and background pertussis incidence, we considered a meta-analysis of the efficacy data inappropriate. In any event, the adjusted absolute and relative vaccine efficacies in these studies were reported as percentages and RR, respectively. Data in this form cannot be entered into RevMan 2012.

We synthesised safety data using meta-analysis routines available in RevMan 2012. In the original review, the fixed-effect model was used for meta-analysis when the endpoints were homogeneous and the random-effects model was applied when there was significant heterogeneity across studies. However, this strategy is currently not recommended by The Cochrane Collaboration (Higgins 2011). In this updated review, we used only the Mantel-Haenszel (random-effects model) method for meta-analysis because it is more appropriate than a fixed-effect model and gives more conservative estimates with wider CIs when there is significant heterogeneity across studies. Otherwise, the two models generate similar results.

Subgroup analysis and investigation of heterogeneity

We analysed adverse events for the 'any' severity category. A few studies only contributed data in the 'moderate to severe' category for some reactions. We did not include these data in the analysis because we considered it inappropriate to combine them with the 'any' severity data.

We performed an analysis within the following Review Manager-defined hierarchy of comparisons, outcomes and subcategories.

1. Comparisons: the two comparisons were (1) safety - acellular versus whole-cell vaccines; and (2) safety - acellular vaccines versus placebo/DT.
2. Outcomes: each safety endpoint (as described in the Outcomes section of this review) constituted a separate outcome. We considered it inappropriate to combine data across event types (for example, 'children with any adverse event') because different studies examined different event subsets. Furthermore, data for different events were obtained from the same cohort of participants within the one study. Such data cannot be legitimately combined within Review Manager 5 (RevMan 2012), because the observations are not independent. Finally, the use of combined endpoints could lead to an increase in one type of adverse event (for example, convulsions) being offset and therefore hidden by a decrease in another type (for example, fever).
3. Subcategories: some events occurred only once in any individual, either by virtue of their nature (failure to complete the primary series and death), or because they consistently led to withdrawal from further vaccine doses (encephalopathy, convulsions and hypotonic-hyporesponsive episodes). We analysed these events in terms of the number of participants experiencing the event out of the total receiving at least one dose of the vaccine. We analysed deaths and encephalopathy only for the primary series because follow-up after single booster doses was generally too short to provide useful data for these potentially delayed events. We analysed convulsions and hypotonic-hyporesponsive episodes separately for the primary series and boosters to determine if risk varied across these subcategories.

Minor adverse events often occurred more than once in any individual (after successive doses of vaccine). Data for these events were almost always reported as the number of children experiencing the event after each dose of the vaccine. Events occurring in the same individual are not independent, therefore they could not then be combined across doses. We analysed such data, therefore, using separate subcategories for each dose of the primary series and two subcategories of booster dose (acellular boosters in children who had previously been vaccinated with whole-cell vaccines, and acellular boosters in children who had previously been vaccinated with acellular vaccines). We selected the booster subcategories on the basis of a preliminary reading of the literature, which suggested that when acellular vaccines are given after acellular priming, adverse events may be more common than when they are given after whole-cell priming.

We could not incorporate data in the meta-analysis for minor adverse events from studies that did not report results separately for each dose (for example, Greco 1996). We calculated a summary estimate of effect and 95% CI for each subcategory. We did not calculate an overall summary estimate for each type of adverse event for reasons given above.

Sensitivity analysis

We planned three sensitivity analyses, and conducted two. The first compared random- and fixed-effect analyses to determine whether the conclusions were sensitive to model selection.

The second pre-planned sensitivity analysis dropped any study which contributed more than 50% of the total weight to an endpoint. This was done in order to assess whether the summary estimate of effect was sensitive to the inclusion of individual, heavily weighted studies. The third pre-planned sensitivity analysis would have dropped any study with inadequate allocation concealment, but we did not identify such studies from those included in the meta-analyses.

RESULTS

Description of studies

Results of the search

During the initial search, the MEDLINE database yielded 13,509 citations; of these, 156 were reports of possibly eligible trials. The CENTRAL database yielded 129 citations and we identified 61 as potentially eligible trials. The updated search (March 1998) yielded 172 citations; of these, 57 were reports of possibly eligible trials. From an examination of the retrieved publications, we identified 52 eligible studies, of which we included 45 in the primary review and excluded the remaining seven studies for various reasons (see Characteristics of included studies and Characteristics of excluded studies tables).

The new comprehensive search in May 2008 yielded a total of 1197 citations (451 for MEDLINE, 403 for EMBASE and 343 for CENTRAL), plus an additional 31 search results when the searches were updated in April 2009. We identified 10 additional studies, of which we included seven and excluded three studies in the updated review (see Characteristics of included studies and Characteristics of excluded studies tables).

For the 2012 update, we identified 75 search results when the search was run in May 2011 and a further 29 search results when the search was updated in January 2012; although we did not identify any new eligible studies. For this new 2014 update, we identified 54 citations when the search was run in January 2014; again we did not identify any new eligible trials.

Included studies

Studies included in the review of efficacy

We included six eligible RCTs of acellular vaccine efficacy in the review (AHGSPV 1988; Greco 1996; Gustafsson 1996; PVSG 1998; Simondon 1997; Trollfors 1995), all of which were identified by the initial search. The trial of Afari 1996 compared two formulations of an acellular vaccine with a whole-cell vaccine but was ineligible because pertussis cases were not confirmed by any laboratory procedure. In any event, vaccine efficacy in this trial could not be calculated because no pertussis cases were reported in either the vaccine or control groups. Blennow 1988 reported the comparative efficacy of two acellular vaccines after randomised administration but did not employ active follow-up. In addition, it inappropriately

combined case data from three different vaccination schedules across two separate studies (Blennow 1988; Hedenskog 1987).

AHGSPV 1997 did not meet the active follow-up criterion specified in this review but was a very large and well publicised study which merits some consideration. It was conducted in Sweden and involved the randomised immunisation of 82,892 infants using a British whole-cell vaccine (Evans Medical, ex Wellcome), or one of three acellular vaccines: a two-component (SKB), a three-component (Chiron-Biocine) or a four-component (Connaught). Vaccines were given at three, five and 12 months to 72,698 infants and at two, four and six months to the remaining 10,194. Efficacy data were reported only for the three, five and 12-month schedule. Follow-up for the whole-cell, three- and four-component vaccines lasted for a mean of 22 months after the third dose. Part way through the trial, the two-component acellular vaccine was shown (in Gustafsson 1996) to have an unacceptably low efficacy, so the blind was broken for infants who had received this vaccine; they were offered boosting with a three-component vaccine, and efficacy data were only available for this group up to the time of the third dose.

Cases of whooping cough in AHGSPV 1997 were detected by surveillance of Swedish laboratories for reports of positive *B. pertussis* culture. Computer matching was performed on each report to determine if it originated from a study participant, and a nurse then contacted the family for clinical follow-up. Based on the incidence of whooping cough with the two- and five-component vaccines in Gustafsson 1996, this passive follow-up method appeared to miss about 90% of cases amongst the study participants. Despite this, the RR for culture-confirmed whooping cough (21 or more days of paroxysmal cough) in the five-component versus the two-component group was the same in both trials (0.25). This suggests that although the passive follow-up in AHGSPV 1997 had a low sensitivity, it was not associated with differential case ascertainment, at least for this case definition.

Studies included in the review of safety

Fifty-two included studies contributed safety data for one or more endpoints; of these we identified 45 in the initial search and seven in the updated search. The salient features of these trials, including details of the specific endpoints to which each trial contributed data, are summarised in the Characteristics of included studies table.

Excluded studies

We excluded 10 randomised trials from the review. The reasons for exclusion and study characteristics are summarised in the Characteristics of excluded studies table.

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.

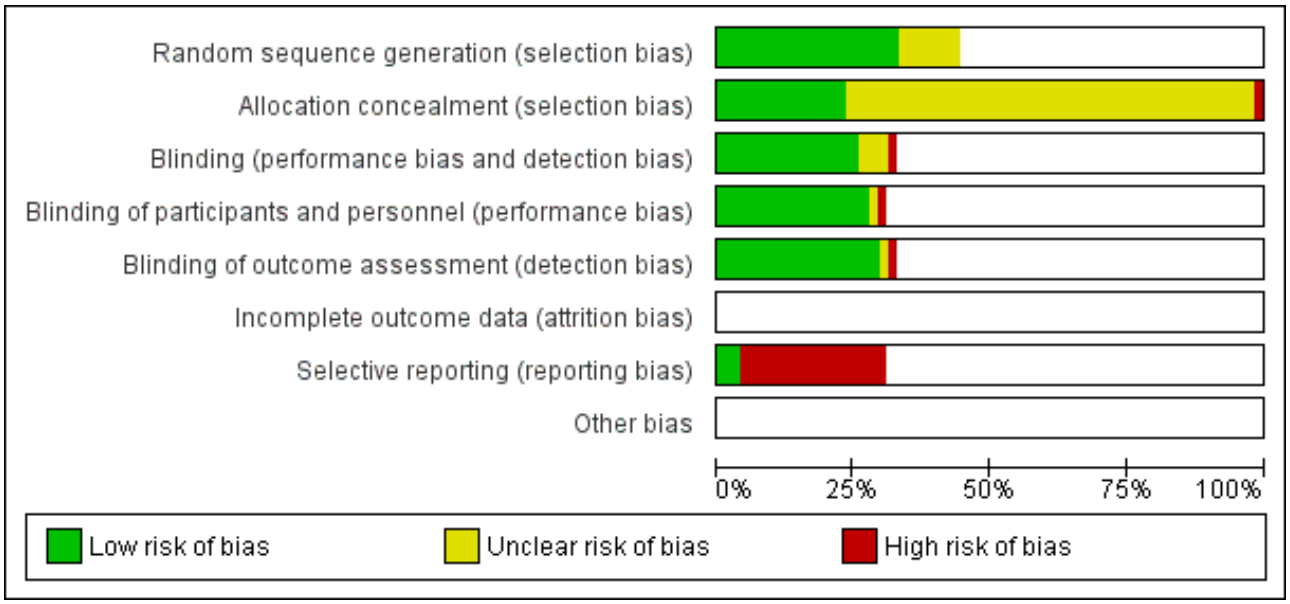


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

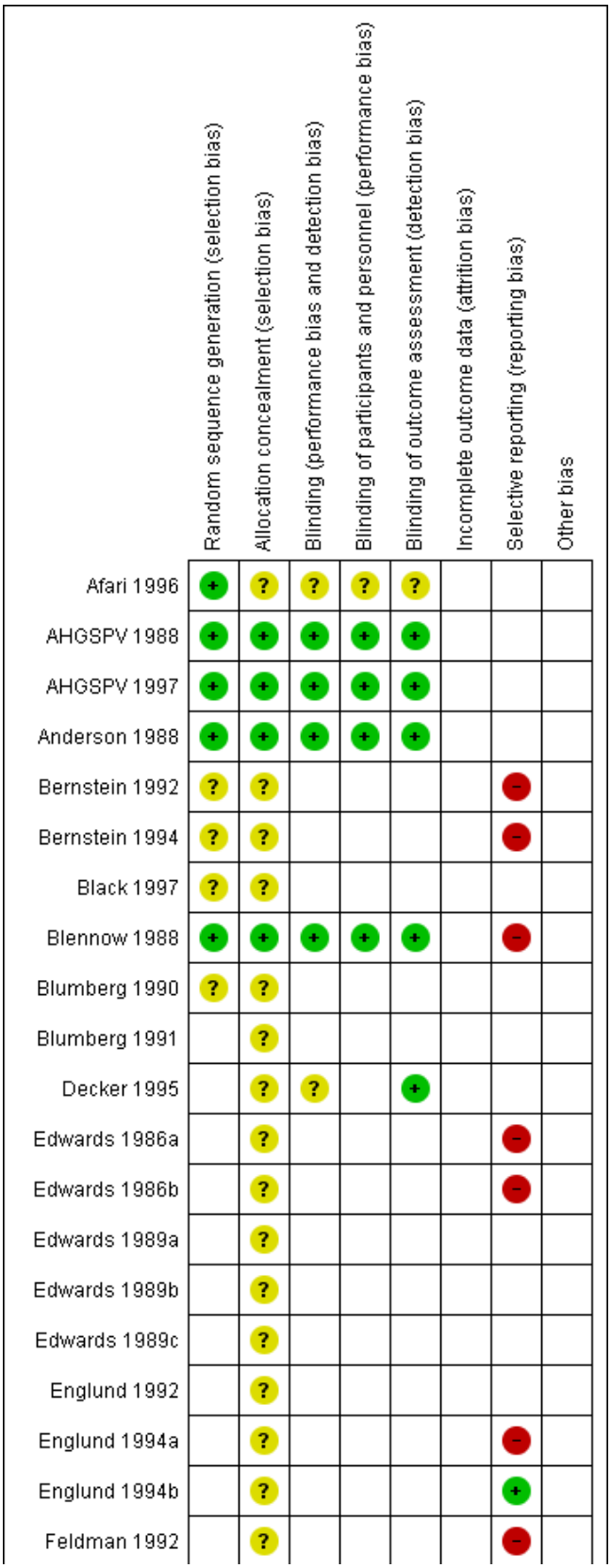


Figure 2. (Continued)

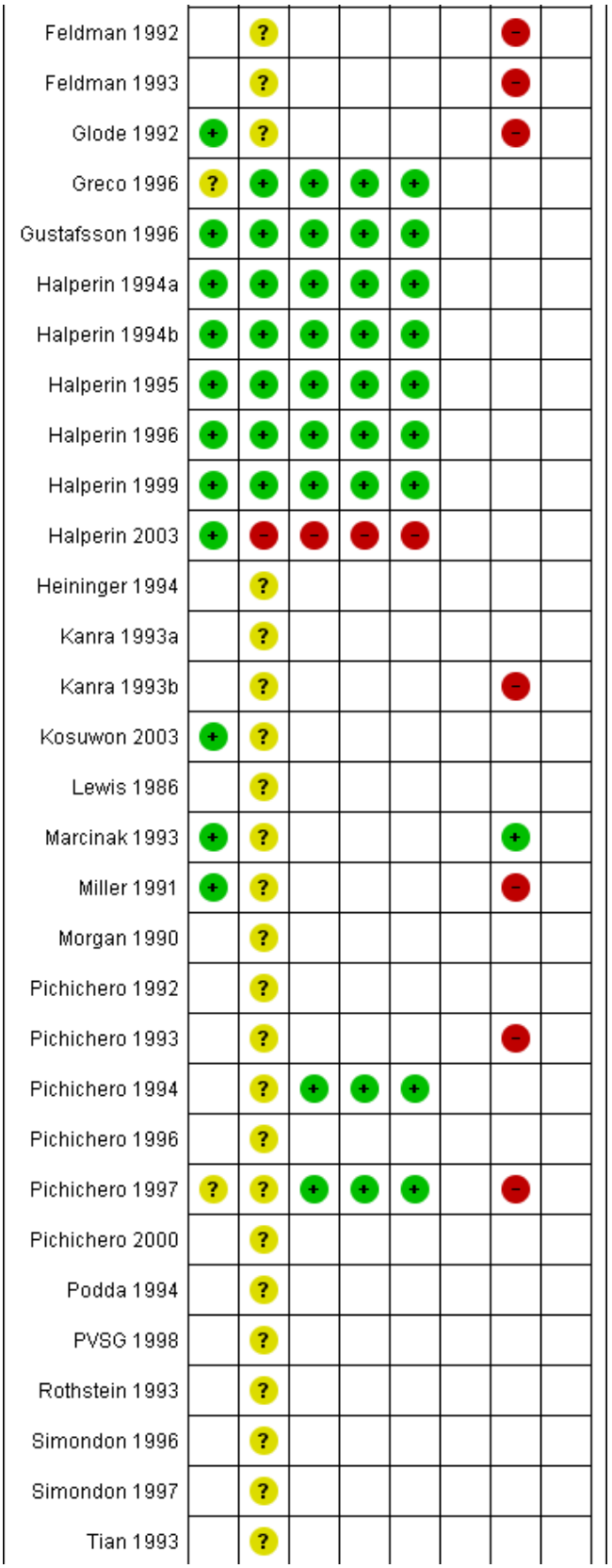
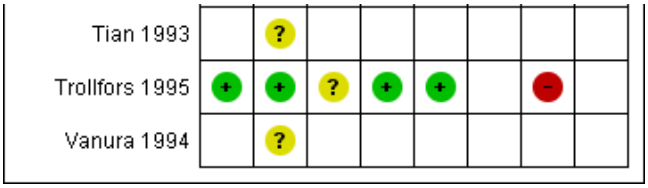


Figure 2. (Continued)



Allocation

Most of the safety trials did not describe the methods for random sequence generation and allocation concealment, which made it difficult to assess the risk of selection bias. However, selection bias may nevertheless have affected the assessment of adverse events at other than the first vaccine dose. This is because children were more likely to be withdrawn due to adverse events after whole-cell than after acellular vaccines. The incidence of adverse events in the whole-cell group after subsequent vaccine doses would be lower than if these children had remained in the study and this bias would tend to reduce the apparent difference in reactogenicity between the whole-cell and acellular vaccines. Selection bias may also have occurred in Pichichero 1996, a booster dose study performed as a follow-on to Pichichero 1993 and Pichichero 1994, in which parents of only 83% of the participants who had enrolled in the primary series studies elected to have their child continue into the booster study.

Blinding

To be eligible for inclusion, a claim of double-blinding had to be made in the study report. However, most of the safety trials did not provide details about the methods of blinding.

Bias in case ascertainment may have occurred in Gustafsson 1996 and possibly Greco 1996, due to partial unblinding of the whole-cell vaccine. It is uncertain in which direction such a bias may have operated. On the one hand, whole-cell vaccines are generally perceived to be effective, so one might expect any bias to favour of the whole-cell preparations. On the other hand, Europe has a history of withdrawal of wP vaccines due to inadequate efficacy, so observers in these European studies might have been biased against the whole-cell vaccines. In any event, the codified, active case ascertainment procedures used in the included studies would have minimised the potential for observer bias from any source. Moreover, observer bias alone would seem an unlikely explanation for the very low efficacy of the whole-cell vaccines in these two studies. Finally, unblinding of the whole-cell vaccine groups would not have affected the acellular versus placebo/DT comparisons.

Pertussis in immunised children tends to have a milder clinical course than in those who are not immunised. Such milder cases may be selectively excluded, leading to over-estimation of absolute vaccine efficacy (Fine 1997). Laboratory confirmation of cases did not eliminate this bias, because participants had to exhibit clinical symptoms (generally at least seven days of cough) before laboratory samples were collected. This problem should not occur in direct comparisons of acellular and whole-cell vaccines.

The partial unblinding in Gustafsson 1996, Halperin 2003 and possibly Greco 1996 might have biased the assessment of adverse events in favour of the acellular preparations. However, the only summary odds ratios (ORs) that were materially altered in the sensitivity analysis, which excluded these studies, were those for drowsiness and vomiting - endpoints which should be interpreted with caution due to other problems.

In all studies, detection bias could have arisen in the assessment of minor adverse event incidence because reactions to whole-cell vaccines tended to be more severe than those to acellular vaccines (more severe reactions would be more likely to be noticed by the parents). However, the requirement for parents to look for specific events and complete diaries or forms at regular intervals would have reduced the potential for such differential reporting.

Incomplete outcome data

Follow-up in all but one study was balanced across the vaccine groups and covered over 90% of available participants at each vaccine dose; the exception was Simondon 1996. The rates of withdrawal and loss to follow-up were high in this study, which was included for safety only. Eighty-one per cent of the acellular group and 87% of the whole-cell group contributed data after the first dose. Data for minor adverse events were available for less than 80% of vaccinated individuals after the second and third doses, and so we excluded these doses from the review, in accordance with the pre-defined data extraction rules. In addition, we conducted a sensitivity analysis in which this study was excluded entirely.

Active case ascertainment was a requirement for inclusion in the efficacy review. All but one of the studies included in the review of safety actively questioned parents at regular intervals regarding prospectively defined adverse events, using standardised forms or diaries; the exception was AHGSPV 1997. This large study, which enrolled over 80,000 infants, did not examine minor adverse events. Data for serious adverse events were collected from participating physicians and child health nurses, by weekly surveillance of admissions to hospitals within the study area (which covered much of Sweden) and by questioning parents at the time of each vaccine dose, and when the child was aged 18 months. It is possible that this type of follow-up may have led to under-reporting of serious adverse events. However, while reducing the power of the study to detect a significant difference, there is no reason to suspect that any such under-reporting would have been differential, or introduced a systematic bias. Nevertheless, we conducted sensitivity analyses, eliminating this study from the endpoints to which it contributed, to determine if the summary ORs were materially affected.

Selective reporting

Some studies reported results for only a subset of the adverse events for which data had been collected. Vomiting was the endpoint most affected, with up to 11 studies collecting data but failing to report it (Bernstein 1992; Bernstein 1994; Blennow 1988; Edwards 1986a; Edwards 1986b; Feldman 1992; Feldman 1993; Halperin 1996; Marcinak 1993; Pichichero 1993; Pichichero 1997). Six studies collected data on drowsiness and did not

report it (Edwards 1986a; Edwards 1986b; Kanra 1993a; Kanra 1993b; Pichichero 1993; Pichichero 1997), while data for anorexia were collected but not reported in three studies (Blennow 1988; Pichichero 1993; Trollfors 1995). Qualitative statements within some reports indicated that data for these events had been omitted because they had occurred with similar frequency in each vaccine group. In contrast, those studies which did include extractable data generally reported a significant difference. Accordingly, there is a possibility that inclusion of the missing data could significantly alter the pooled ORs for these endpoints.

Other potential sources of bias

1. Bias introduced by the methods of the review

a) Study selection and data extraction

The review author was not blinded to study authorship or journal of publication, allowing the potential for bias during study selection and data extraction. The use of predefined criteria for study inclusion and rules for data extraction helped to minimise this potential. While desirable, the need for review author blinding during study selection and data extraction is unproven. Berlin and co-workers have shown that rigorous blinding had neither a clinically nor statistically significant effect on the summary OR in a random sample of five meta-analyses (Berlin 1997).

b) Publication bias

It is well recognised that studies reporting statistically significant results are more likely to be published than those that do not (Mahid 2008). The review is potentially subject to bias arising from this source because the databases we searched for eligible trials only included published studies. While it would be desirable to identify unpublished studies and include these in the review, this was precluded by resource limitations. Although we may have missed small unpublished studies of vaccine safety in this manner, it seems unlikely that an efficacy or safety trial large enough to materially affect the conclusions of the review would have been suppressed from publication.

Publication bias also occurred within studies and took two forms. The first involved the selective reporting of events as previously mentioned. The second type of within-study publication bias was the tendency to collect adverse event data at several time points and then report the time point which showed the maximum difference between vaccines. This is not a problem as long as one remains aware that the summary results reflect the maximum observable difference between vaccines and not the difference at a specific time point.

2. Confounding in the included studies

a) Confounding due to the use of erythromycin for post-exposure prophylaxis of pertussis contacts

Erythromycin prophylaxis would not confound the assessment of vaccine safety. By reducing the number of pertussis cases observed in a study it could widen the CI for vaccine efficacy but as long as its use was not associated with one or other vaccine type, then it should not act as a confounder. Equivalent use would be expected in double-blind studies but there is some doubt that all the efficacy studies in this review were truly blinded in respect to the whole-cell vaccines. Gustafsson 1996 and possibly Greco 1996 used identifiable whole-cell vaccines and in all studies the rate of adverse reactions following whole-cell vaccines was appreciably higher than after the acellular vaccines or placebo/DT. These factors may have led to partial unblinding of the whole-cell vaccines during the efficacy follow-up period, which in turn may have allowed differential use of erythromycin prophylaxis.

Greco 1996 made no statement regarding erythromycin prophylaxis during the study. In Gustafsson 1996, prophylaxis was assumed to occur in accordance with Swedish guidelines, which recommend it only in infants under six months of age. Actual prophylaxis use was not documented in the trial, but if the assumption is valid then it should not have affected the main efficacy follow-up period (which started after the third vaccine dose, at the age of six months). In another Swedish study, AHGSPV 1988, the first vaccination was scheduled at a minimum age of five months in order to avoid potential problems due to use of prophylaxis during the efficacy follow-up period (which began at a minimum age of seven months). In any case, this study did not use a whole-cell vaccine, and blinding of the two acellular vaccines and placebo was confirmed by a questionnaire. In a third Swedish study, Trollfors 1995, prophylaxis use was low (six per cent) and equivalent in the two study groups. Simondon 1997 and PVSG 1998 included no information on this topic. The study vaccines were adequately blinded at administration, but partial unblinding may have occurred during the efficacy assessment due to a higher incidence of adverse events in the whole-cell arms. In theory this might have provided the opportunity for differential use of prophylaxis but the probability of such bias seems low.

Overall, erythromycin prophylaxis appears unlikely to have significantly confounded the estimation of vaccine efficacy.

b) Confounding due to the use of antipyretic/analgesic medication

The use of antipyretic/analgesic medication would be a potential confounding factor in the assessment of reactogenicity. Truly prophylactic use (i.e. use before a fever or pain appeared) should be non-differential in a blinded study, but by lowering the incidence of fever and pain in each treatment group, it would reduce the ability to detect a difference between vaccines. Antipyretic/analgesic medication might also be used in a 'reactive' fashion after a low fever or mild pain had occurred, in order to prevent a higher fever or more severe pain. One would expect this type of use to be differential (more common with the more reactogenic vaccines). The result would be to reduce the apparent difference between vaccines in the incidence of severe fever or pain. It would also reduce the apparent difference in the incidence of systemic events that may be associated with a high fever, such as convulsions, irritability, anorexia, vomiting, drowsiness and withdrawal from the study.

No study report specifically stated that prophylactic use of antipyretic/analgesic medications was permitted. A few stated that it was not permitted, or that it was discouraged, while most made no statement. Similarly, only a few studies documented 'reactive' use of antipyretic/analgesic medication. It is worth noting that where such use was recorded, parents were asked to give the drug only when the child's temperature had reached a point higher than that used for defining fever in the analysis of reactogenicity, or if the child was in obvious pain or distress. This would have served to minimise the effect on the assessment of fever and other minor adverse events.

Allowance for undocumented antipyretic/analgesic use would strengthen the conclusion that acellular vaccines are less reactogenic that the whole-cell vaccines, but weaken the finding of no significant difference between the acellular vaccines and placebo.

Effects of interventions

Primary outcome

Absolute vaccine efficacy - whooping cough

Four of the eligible efficacy trials included a randomised placebo/diphtheria-tetanus (DT) group and were able to determine the absolute efficacy of acellular vaccines against a case definition identical to, or closely approximating 'whooping cough', as specified in this review. These results are summarised below. 'All': efficacy (with 95% confidence interval (CI), where reported) in participants receiving all scheduled vaccine doses; "≥ 1 immunisation (immunis) dose": efficacy (with 95% CI, where reported) in participants receiving at least one dose of the randomised vaccine. See Characteristics of included studies table for information on the composition of each vaccine.

Study: Trollfors 1995
Dose schedule: 3, 5 and 12 months.
Vaccine: Amvax [1] - All: 71% (63 to 78); ≥ 1 immunisation dose: not reported.

Study: AHGSPV 1988
Dose schedule: 5 to 11, and 7 to 13 months.
Vaccine: JNIH7 [1] - All: 78% (57 to 88); ≥ 1 immunisation dose: not reported.
Vaccine: JNIH6 [2] - All: 78% (58 to 89), ≥ 1 immunisation dose: not reported.

Study: Greco 1996
Dose schedule: two, four and six months.
Vaccine: SKB [3] - All: 84% (76 to 89); ≥ 1 immunisation dose: 82% (73 to 87).
Vaccine: Chiron-Biocine [3] - All: 84% (76 to 90); ≥ 1 immunisation dose: 84% (76 to 89).
Vaccine: Connaught [W] - All: 36% (14 to 52); ≥ 1 immunisation dose: 34% (13 to 50).

Study: Gustafsson 1996
Dose schedule: two, four and six months.
Vaccine: SKB [2] - All: 59% (51 to 66); ≥ immunisation dose: 59% (51 to 66).
Vaccine: Connaught [5] - All: 85% (81 to 89); ≥ immunisation dose: 84% (80 to 88).
Vaccine: Connaught [W] - All: 48% (37 to 58); ≥ immunisation dose: 48% (37 to 57).

In the trial of PVSG 1998, comparison with a non-randomised controlled trial (RCT) DT control group gave an estimated absolute efficacy against whooping cough of 84% (95% CI 77% to 89%) for the whole-cell vaccine and 79% (95% CI 72% to 85%) for the acellular vaccine. In Simondon 1997, a substudy examined the incidence of whooping cough in vaccine recipients who came into household contact with confirmed pertussis cases. In this substudy, comparison with an unvaccinated control group gave an estimated absolute efficacy of 96% for the whole-cell vaccine and 85% for the acellular vaccine.

Relative vaccine efficacy - whooping cough

Four eligible studies determined the relative risk of whooping cough after administration of acellular vaccines compared to that after whole-cell vaccines. Results are summarised below. Risk ratios (RRs) are expressed in relation to the incidence in the whole-cell vaccine group. A RR < 1.0 favours the acellular vaccine.

Study: Greco 1996
Dose schedule: two, four and six months.
Whole-cell comparator: Connaught [W].
Vaccine: SKB [3] - All: 0.25 (0.17 to 0.36); ≥ 1 immunisation dose: 0.28 (0.20 to 0.39).
Vaccine: Chiron-Biocine [3P] - All: 0.25 (0.17 to 0.36); ≥ 1 immunisation dose: 0.25 (0.17 to 0.36).

Study: Gustafsson 1996
Dose schedule: two, four and six months.
Whole-cell comparator: Connaught [W].
Vaccine: SKB [2] - All: 0.83 (0.65 to 1.05); ≥ 1 immunisation dose: 0.83 (0.66 to 1.05).
Vaccine: Connaught [5] - All: 0.29 (0.21 to 0.40); ≥ 1 immunisation dose: 0.30 (0.22 to 0.42).

Study: PVSG 1998
Dose schedule: 2, 4 to 10, 6 to 12, and 15 to 18 months.
Whole-cell comparator: Lederle [W].
Vaccine: Lederle/Takeda [4] - All: 2.1 (upper 1-sided 95% CI = 3.3); ≥ 1 immunisation dose: not reported.

Study: Simondon 1997
Whole-cell comparator: Pasteur-Merieux [W].
Dose schedule: two, four and six months.
Pasteur-Merieux [2] - All: 2.42 (1.35 to 4.34); ≥ 1 immunisation dose: 2.06 (1.25 to 3.39).

As previously noted, AHGSPV 1997 did not meet the active follow-up criterion specified in this review, but the passive follow-up method used in that trial (although low in sensitivity) did not appear to be associated with differential case ascertainment for the 'whooping cough' case definition. Results from this study are summarised below:

Study: AHGSPV 1997
Dose schedule: 3, 5 and 12 months.
Whole-cell comparator: Evans Medical [W].
Vaccine: Chiron-Biocine [3] - All: 2.55 (1.50 to 4.33); ≥ 1 immunisation dose: 1.84 (1.36 to 2.51).
Vaccine: Connaught [5] - All: 1.40 (0.78 to 2.52); ≥ 1 immunisation dose: 1.25 (0.90 to 1.75).

Thus, the efficacy of the five-component vaccine against this case definition was not significantly different to that of the whole-cell vaccine, whereas that of the three-component vaccine was. While this suggests that the five-component vaccine may have an advantage over the three-component, it should be noted that the two acellular vaccines were not actually significantly different from each other (the 95% CIs overlapped). Furthermore, any conclusions from this study must be tempered by its reliance on passive follow-up.

Absolute vaccine efficacy - pertussis disease

Four trials determined absolute vaccine efficacy against pertussis disease, as defined in this review. These results are summarised below:

Study: Trollfors 1995
Dose schedule: 3, 5 and 12 months.
Vaccine: Amvax [1] - All: 54% (43 to 63); ≥ 1 immunisation dose: not reported.

Study: AHGSPV 1988
Dose schedule: 5 to 11, and 7 to 13 months.
Vaccine: JNIH7 [1] - All: 41% (12 to 60); ≥ 1 immunisation dose: not reported.
Vaccine: JNIH6 [2] - All: 58% (35 to 73); ≥ 1 immunisation dose: not reported.

Study: Greco 1996
Dose schedule: two, four and six months.
Vaccine: SKB [3] - All: 71% (61 to 78); ≥ 1 immunisation dose: not reported.
Vaccine: Chiron-Biocine [3] - All: 71% (61 to 79); ≥ 1 immunisation dose: not reported.
Vaccine: Connaught [W] - All: 23% (1 to 40); ≥ 1 immunisation dose: not reported.

Study: Gustafsson 1996
Dose schedule: two, four and six months.
Vaccine: SKB [2] - All: 44% (35 to 52); ≥ 1 immunisation dose: 44% (35 to 52).
Vaccine: Connaught [5] - All: 78% (73 to 83); ≥ 1 immunisation dose: 78% (73 to 83).
Vaccine: Connaught [W] - All: 42% (30 to 51); ≥ 1 immunisation dose: 41% (30 to 50).

In PVSG 1998, comparison with a non-RCT DT control group gave an estimated absolute efficacy against pertussis disease of 83% (95% CI 76% to 88%) for the whole-cell vaccine and 72% (95% CI 62% to 79%) for the acellular vaccine.

Relative vaccine efficacy - pertussis disease

One trial determined relative vaccine efficacy against pertussis disease, as defined in this review. The results of this trial are summarised below.

Study: Simondon 1997
Whole-cell comparator: Pasteur-Merieux (W).
Dose schedule: two, four and six months.
Pasteur-Merieux [2] - All: 1.54 (1.23 to 1.94); ≥ 1 immunisation dose: 1.43 (1.16 to 1.74).

Secondary outcomes

Comparison of acellular and whole-cell vaccines

Seven additional trials identified by the updated search (2009) provided available data only for minor adverse events. Updated meta-analysis including the data from these seven trials did not significantly alter the results of any endpoint (Appendix 7).

1. Failure to complete all scheduled doses of the primary immunisation series because of adverse events

The risk of failure to complete the primary series because of adverse events was significantly lower in acellular vaccine recipients compared to those immunised with whole-cell vaccines (11 trials with a total of 108,909 participants, RR 0.23, 95% CI 0.12 to 0.43, P value < 0.00001) (Analysis 1.1).

2. Mortality due to any cause

The risk of death due to any cause did not differ significantly between acellular and whole-cell recipients (nine trials with a total of 122,451 participants, RR 0.87, 95% CI 0.62 to 1.22, P value = 0.41) (Analysis 1.2).

3. Mortality due to infection

The risk of death due to infection did not differ significantly between acellular and whole-cell recipients (two trials with a total of 34,498 participants, RR 0.97, 95% CI 0.23 to 4.16, P value = 0.97) (Analysis 1.3).

4. Encephalopathy

No cases of encephalopathy after primary series immunisation were observed in 81,601 acellular and 32,161 whole-cell vaccine recipients (Analysis 1.4).

5. Convulsions

The risk of convulsion after primary series immunisation was significantly lower in acellular vaccine recipients compared to those immunised with whole-cell vaccines (nine trials with a total of 124,387 participants, RR 0.47, 95% CI 0.31 to 0.73, P value = 0.0007) (Analysis 1.5)

6. Hypotonic-hyporesponsive episodes

The risk of hypotonic-hyporesponsive episodes after primary series immunisation was significantly lower in acellular vaccine recipients compared to those immunised with whole-cell vaccines (six trials with a total of 121,573 participants, RR 0.26, 95% CI 0.08 to 0.81, P value = 0.02) (Analysis 1.6). No hypotonic-hyporesponsive episodes were recorded after any booster dose in the 2171 acellular and 316 whole-cell vaccine recipients for whom data were available (Appendix 8).

7. Minor adverse events

Minor adverse events (anorexia, drowsiness, fever, irritability/fretfulness, prolonged crying, vomiting, injection site pain/tenderness/redness/swelling) after most vaccine doses were significantly less common in acellular vaccine recipients than in those immunised with whole-cell vaccines (Analysis 1.7 to Analysis 1.15).

We conducted two pre-planned sensitivity analyses. The first compared random-effects and fixed-effect analyses to determine whether the conclusions were sensitive to model selection. This led to changes from a non-significant difference (a random-effects model) to a significant difference in favour of acellular vaccines for two endpoints: vomiting (the third primary dose and booster after acellular priming), and drowsiness (the first primary dose). The second repeated the random-effects analysis after removing, from each endpoint, any study allocated more than 50% of the total weight in the original analysis. This led to changes from

a significant difference in favour of acellular vaccines to a non-significant difference for vomiting after the first and second primary series doses.

We performed an unplanned sensitivity analysis excluding AHGSPV 1997. This was the largest study in the review and differed from the others in that follow-up was not fully active. Removal of this study did not change the significance or otherwise of any endpoints.

We performed a second unplanned sensitivity analysis excluding three studies with possible inadequate blinding (Greco 1996; Gustafsson 1996; Halperin 2003). This resulted in the summary OR for drowsiness changing from non-significant to significant (in favour of acellular vaccines), while that for vomiting after the first and second primary series doses changed from significant to non-significant.

No analysis of any endpoint resulted in a RR that significantly favoured whole-cell vaccines.

We also examined the incidence of minor adverse events in cohorts of children after successive doses of acellular and whole-cell vaccines. The incidence of anorexia and vomiting fell with successive doses of the primary series for both acellular and whole-cell vaccines. The incidence of irritability and injection site pain/tenderness remained relatively constant, whereas the incidence of fever, local redness and swelling/induration increased markedly over the primary series of acellular vaccines (Appendix 9).

The incidence of minor adverse reactions in children boosted with acellular vaccines after whole-cell priming was lower than if whole-cell vaccines were used for every dose. However, an unexpected rise in the incidence of fever, irritability, local pain, redness and swelling was seen among children primed and boosted with acellular vaccines compared with those boosted with acellular vaccines after whole-cell priming (Appendix 10).

Comparison of acellular vaccines and placebo/DT

The number of studies and participants in this comparison was considerably less than in the comparison of acellular with whole-cell vaccines, with a maximum of four studies contributing data to any endpoint. No booster data were available (Appendix 11; Appendix 12).

1. Failure to complete all scheduled doses of the primary immunisation series because of adverse events

There was no statistically significant difference between acellular and placebo/DT recipients in terms of the risk of failure to complete the primary series because of adverse events (four trials with a total of 25,901 participants, RR 0.70, 95% CI 0.38 to 1.29, P value = 0.25) (Analysis 2.1).

2. Mortality due to any cause

The risk of death due to any cause did not differ significantly between acellular and placebo/DT recipients (four trials with a total of 25,901 participants, RR 1.08, 95% CI 0.26 to 4.42, P value = 0.91) (Analysis 2.2).

3. Mortality due to infection

The risk of death due to infection did not differ significantly between acellular and placebo/DT recipients (four trials with a total of 25,901 participants, RR 1.21, 95% CI 0.19 to 7.80, P value = 0.84) (Analysis 2.3).

4. Encephalopathy

No cases of encephalopathy after primary series immunisation were observed in 14,521 acellular and 4129 placebo/DT recipients (Analysis 2.4).

5. Convulsions

There was no statistically significant difference between acellular and placebo/DT recipients in terms of the risk of convulsion after primary series immunisation (four trials with a total of 25,901 participants, RR 0.44, 95% CI 0.12 to 1.69, P value = 0.23) (Analysis 2.5)

6. Hypotonic-hyporesponsive episodes

The risk of hypotonic-hyporesponsive episodes after primary series immunisation did not differ significantly between acellular and placebo/DT recipients (four trials with a total of 25,901 participants, RR 0.29, 95% CI 0.02 to 5.13, P value = 0.40) (Analysis 2.6).

7. Minor adverse events

There was no statistically significant difference between acellular and placebo/DT in terms of the risk of minor adverse events (anorexia, drowsiness, fever, irritability/fretfulness, prolonged crying, vomiting, injection site pain/tenderness, injection site redness and injection site swelling/induration) after most vaccine doses (Analysis 2.7 to Analysis 2.15).

Most endpoints in this comparison were homogeneous. For these, the fixed-effect analysis differed from the random-effects analysis in only three cases: the RRs for convulsions in the primary series and swelling/induration after the first two primary doses were significantly in favour of placebo/DT in the fixed-effect analysis but non-significant in the random-effects analysis.

We conducted a second planned sensitivity analysis in which the random-effects analysis was repeated after removing from each endpoint any study which had been assigned more than 50% of the total weight. A number of endpoints contained data from only a single study and were thus not evaluable after that study had been excluded. In addition, the RR for swelling/induration after the second dose became significant and after the third dose became non-significant.

No analysis of any endpoint resulted in a RR which significantly favoured acellular vaccines over placebo/DT.

DISCUSSION

Summary of main results

Efficacy

Due to a small number of efficacy trials and significant heterogeneity across studies regarding immunisation schedules, case definitions, follow-up duration and background pertussis rates, it was not applicable to conduct a meta-analysis in this review to estimate the pooled efficacy of acellular pertussis vaccines against whooping cough. However, some considerations could be made on the basis of the data from six included trials.

Firstly, comparisons across studies suggest that multi-component (≥ three) acellular vaccines have a higher efficacy than one- and two-component vaccines against both typical whooping cough (characterised by 21 or more consecutive days of paroxysmal cough with confirmation of *B. pertussis* infection by culture, appropriate serology or contact with a household member who has culture-confirmed pertussis) and mild pertussis disease (characterised by seven or more consecutive days of cough with confirmation of *B. pertussis* infection by culture or appropriate serology) (WHO 1991). The efficacy of multi-component vaccines varied from 84% to 85% in preventing typical whooping cough and from 71% to 78% in preventing mild pertussis disease (Greco 1996; Gustafsson 1996). In contrast, the efficacy of one- and two-component vaccines varied from 59% to 78% against typical whooping cough and from 41% to 58% against mild pertussis disease (AHGSPV 1988; Trollfors 1995). The superiority of five-component vaccines over two-component vaccines in preventing typical whooping cough has been confirmed by direct comparison of such vaccines in the trials of Gustafsson 1996 and AHGSPV 1997. However, the data are insufficient to determine whether there is a clinically significant difference between three- and five-component vaccines. Comparisons across trials do not confirm such a difference. A small and statistically non-significant difference was observed in the trial of AHGSPV 1997, but incomplete case ascertainment would have reduced the statistical power of the study.

Secondly, not all whole-cell vaccines are efficacious, as has traditionally been thought, as evidenced by the low efficacy of the Connaught whole-cell vaccine used in the trials of Greco 1996 (efficacy: 36%; 95% confidence interval (CI) 14% to 52%) and Gustafsson 1996 (efficacy: 48%; 95% CI 37% 58%). This makes it more difficult to interpret the results of direct efficacy comparisons between acellular vaccines and whole-cell vaccines across studies. The multi-component (≥ 3) acellular vaccines are more effective than low-efficacy whole-cell vaccines, but may be less effective than the highest-efficacy whole-cell vaccines in preventing whooping cough (AHGSPV 1997; Greco 1996; Gustafsson 1996; PVSG 1998; Simondon 1997).

Thirdly, randomised controlled trials (RCTs) generally measure vaccine efficacy but not the effectiveness of a large-scale vaccination programme. Compliance with immunisation is likely to be higher in these studies than would be expected in actual practice and 'real world' effectiveness would probably be correspondingly lower. Having said this, it is encouraging that where data were available for the population who did not complete all scheduled doses, efficacy was only marginally lower than in those who had received all vaccine doses. Moreover, the effectiveness of national vaccination programmes with acellular pertussis (aP) vaccines in preventing whooping cough in children has been shown in Japan, the United States and Canada, where such vaccines have been routinely used among infants and young children (Bettinger 2007; Bisgard 2005; Kuno-Sakai 2004; Watanabe 2005). In contrast, recent research from Queensland, Australia (Sheridan 2012) and Oregon, United States (Liko 2013) suggests that children primed with acellular rather than whole-cell pertussis vaccine are at a higher risk of subsequent pertussis. The authors raised the hypothesis that the recent pertussis epidemic in many high-income countries might be related to the shift from whole-cell pertussis (wP) to aP vaccines. However, further nationwide studies are needed to test this hypothesis.

Safety

The comparison of acellular vaccines with whole-cell vaccines displays that the former have a better safety profile. The superiority of acellular vaccines over whole-cell vaccines is evident for all selected minor reactions during the primary and booster doses. The incidence of primary series non-completion due to adverse events is significantly lower for acellular vaccines than for whole-cell vaccines. Acellular vaccines are also less likely to cause febrile convulsions and hypotonic-hyporesponsive episodes during the primary series. A benefit has not been seen in respect to febrile convulsions after booster doses, hypotonic-hyporesponsive episodes after booster doses or encephalopathy during the primary series, but the former was very uncommon, while the latter two were non-existent with either type of vaccine. The risk of death due to any cause, and death due to infection, were similar between acellular and whole-cell vaccine recipients.

The comparison of acellular vaccines with placebo/DT also reveals a good safety profile of such vaccines. There is no significant difference between acellular vaccines and placebo/DT in the incidence of severe or minor adverse events, with the exception of injection site swelling, which was significantly more common among recipients of acellular vaccines than placebo/DT after the third dose during the primary series. However, given the uncommon occurrence of severe adverse reactions, the statistical power of this meta-analysis may be not enough to detect small but clinically relevant differences between acellular vaccines and placebo/DT. In this sense, continuing surveillance for rare severe adverse reactions of aP vaccines may be warranted.

Two points about minor adverse events of acellular vaccines deserve special comment. Firstly, a significant increase in incidence (number of events per 1000 recipients) from the first dose to the third dose during the primary series has been observed for some minor adverse reactions, such as fever (from 60 to 162), local redness (from 96 to 162) and swelling (from 117 to 275). In spite of this increase, the incidence of these minor adverse events among recipients of acellular vaccines is still lower than that among recipients of whole-cell vaccines. Secondly, the incidence of adverse reactions in children boosted with acellular vaccines after whole-cell priming is lower than if whole-cell vaccines are used for every dose. Comparison across studies displays a rise in the incidence of some minor adverse reactions (fever, irritability, local pain, redness and swelling) among children primed and boosted with acellular vaccines compared with those boosted with acellular vaccines after whole-cell priming. The rate of reported injection site reactions continues to increase after the fifth consecutive dose of aP vaccine at four to six years of age. Although redness and swelling increase to rates similar to those associated with five consecutive doses of whole-cell vaccine, injection site tenderness after five does of acellular vaccine is significantly lower than after five doses of whole-cell vaccine, and the vaccine is preferred by parents of these preschool-aged children. These increases in injection site reactions may have limited clinical implications as the current evidence suggests an acceptable safety profile of acellular vaccines for booster doses among preschool children and adolescents who had been primed with acellular vaccines (Jacquet 2006; Pichichero 2005; Pichichero 2006).

Overall completeness and applicability of evidence

This review provides evidence to answer the questions posed in the Objectives section.

1. Do acellular vaccines protect against pertussis?

All aP vaccines reported in the efficacy trials protect against pertussis. Acellular vaccines with three or more components (multi-component vaccines) are effective against both classical whooping cough and mild pertussis disease.

2. Do different types of acellular vaccine confer different levels of protection?

Currently available evidence suggests that multi-component vaccines confer better protection against both classical whooping cough and mild pertussis infection than vaccines containing only one or two components. However, the clinical implication of any possible superiority of multi-component vaccines over mono- and bivalent vaccines in the efficacy demonstrated by RCTs should be considered with caution. The effectiveness of vaccination programmes on a national scale for controlling infectious disease depends not only on the efficacy of the vaccine, but also other factors such as the vaccination schedule and adherence, and transportation and storage of the vaccine. Moreover, indirect effects in producing herd immunity in the population may also contribute to the effectiveness of large-scale vaccination in controlling infectious diseases (Carlsson 2009; Stephens 2008). Therefore, successful control of pertussis infections by two-component vaccines in Japan and in other countries (Carlsson 2009; Hviid 2004; Kuno-Sakai 2004) does not necessarily exclude the potential additional benefits of large-scale vaccination with multi-component vaccines.

3. Do acellular vaccines protect against pertussis to the same degree as the whole-cell vaccines which they are intended to replace?

The answer here remains unclear because the effectiveness of whole-cell vaccines varies and there are limited efficacy and effectiveness data with different whole-cell vaccines. Studies to date indicate that multi-component acellular vaccines are more effective than low-efficacy whole-cell vaccines but may be less effective than the highest-efficacy whole-cell vaccines.

4. Do acellular vaccines cause fewer side effects than whole-cell vaccines?

Acellular vaccines cause fewer side effects than whole-cell vaccines during the primary immunisation series, when used as a booster in toddlers and four-to-six-year-olds who have previously received whole-cell vaccines, and when used in toddlers after acellular priming.

Quality of the evidence

As previously mentioned, meta-analysis was not applicable in this review to estimate the pooled efficacy. However, three large, double-blind RCTs from Italy, Sweden and Germany (Greco 1996; Gustafsson 1996; PVSG 1998) provide high-level evidence about effectiveness of multi-component aP vaccines against whooping cough.

Regarding the safety profile, meta-analysis of 52 studies provides robust evidence about the superiority of aP vaccines over whole-cell vaccines. However, the heterogeneity of results across studies deserves special consideration.

Heterogeneity in the meta-analysis of safety endpoints

Many of the safety endpoints in the comparison of acellular with whole-cell vaccines displayed significant heterogeneity. This heterogeneity did not invalidate the finding of significant differences for various endpoints because the point estimates for the individual studies were almost always in favour of the acellular vaccines. In other words, the individual study results were quantitatively but not qualitatively different.

Possible explanations for the heterogeneity, which was sometimes substantial, include the following.

1. Differences between studies in the definition or recording of adverse events. For example, the threshold for fever differed slightly amongst studies, albeit within the confines of the definition specified in the review. Prolonged crying was defined as longer then one hour in some studies and longer than three hours in others. In some studies the mildest recorded category of redness or swelling was 'any', whereas in others it was a diameter of one centimetre. Some studies reported the incidence of events within a certain time period of each dose, whereas others reported the incidence at a specific time point.
2. The use of different immunisation schedules. Most studies used a two-, four- and six-month schedule for the primary series but others used a three-, five- and 12-month schedule. AHGSPV 1988 used a 5 to 11-month, and 7 to 14-month schedule. The difference in reactogenicity between acellular and whole-cell vaccines has been shown to be less with the earlier dose schedule, primarily because the reactogenicity of whole-cell vaccines increases with the age of administration (for example, in Miller 1997).
3. Differences in the reactogenicity of separate acellular vaccines. This is a possibility, although a number of head-to-head studies of acellular vaccines have not shown any consistent differences (for example, AHGSPV 1988; AHGSPV 1997; Decker 1995; Englund 1994a; Greco 1996; Pichichero 1997).
4. Differences in the reactogenicity of the whole-cell vaccines used as controls.
5. Differences in the duration over which adverse events were recorded.
6. Differences in the susceptibility of different patient populations (for example, different racial groups) to adverse events after pertussis immunisation.
7. Given the large number of endpoints examined in the review and the conservative critical value for determining heterogeneity, approximately 10% of the endpoints would be expected to fail the test of homogeneity by chance alone.

A special comment is warranted about drowsiness after the first and second doses of the primary series. The statistical test displays an extreme heterogeneity for this endpoint and it strongly suggests inconsistent findings across studies. By visual inspection of the forest plot, we identified that Gustafsson 1996 was responsible for this extreme heterogeneity. In contrast with other studies, Gustafsson 1996 demonstrated the results in favour of whole-cell vaccines. This is only one safety endpoint where the superiority

of whole-cell vaccines over acellular vaccines was reported. Partial unblinding of the whole-cell vaccine arm occurred in this trial but the expected effect of unblinding would be to bias the assessment of adverse events in favour of the acellular preparations. We have no plausible explanations for this finding.

Potential biases in the review process

The potential sources and impact of bias and confounding have been addressed in the Risk of bias in included studies section. In addition to the potential bias and confounding, the following limitations of the review should also be noted.

1. The review examines the safety of acellular vaccines as a group and does not attempt to determine whether different vaccines have different safety profiles.
2. The absence of statistically significant differences between acellular vaccines and placebo/DT in respect to severe adverse events may be due to a lack of statistical power in the meta-analysis, rather than a true lack of difference.
3. The review is based entirely on public domain information and did not use any confidential vaccine manufacturer data that might contribute to the decisions of regulatory agencies.

Agreements and disagreements with other studies or reviews

We searched CENTRAL, MEDLINE and EMBASE for systematic reviews of pertussis vaccines and identified 11 papers. Two could be compared to our review (Casey 2005; Jefferson 2003). Like us, Jefferson 2003 searched the literature without any publication year restriction, whereas Casey 2005 limited their search to efficacy studies from 1990 onwards. Unlike us, both reviews included observational studies. Jefferson 2003 and our review both included 52 studies; most but not all studies were common to Jefferson 2003 and our review.

Efficacy

All efficacy studies of acceptable quality were published between 1988 and 1997.

Casey 2005 retrieved eight efficacy trials; six of them were also included in our efficacy review. Of the remaining two, one was a case-controlled study (Liese 1997) and the other a cohort study (Schmitt 1996).

Jefferson 2003 included Afari 1996 and Decker 1995, which we excluded due to the absence of laboratory-confirmed pertussis cases. (Decker 1995 also lacked efficacy data). However, we included these studies in the safety review.

In contrast to Jefferson 2003, we did not study the absolute efficacy of whole-cell vaccines and we did not perform meta-analyses of efficacy studies due to significant heterogeneity.

Several studies of acellular vaccines with three to five components showed that the efficacy of the acellular vaccines was superior or equal to the whole-cell comparator. Jefferson 2003 claims that AHGSPV 1997 "is the source of the widely-held view that acellular vaccines are less effective than high-efficacy whole-cell vaccines". However, both Jefferson 2003 and our review included several studies with acellular vaccines inferior to whole-cell vaccines, including a study of a four-component acellular vaccine (PVSG 1998).

Safety

Jefferson 2003 included a systematic review of studies assessing the safety of DTP vaccines. We excluded some of these studies because of lack of sufficient data. However, the results of the reviews were largely similar.

Booster doses

Casey 2005 found that booster doses of all DTaP vaccines in 1% to 2% of individuals caused large, local injection reactions, in most cases probably IgE-mediated. These reactions cause no permanent harm, and the authors of Casey 2005 argue that everybody should have access to a booster dose every 10 years throughout life.

Despite different designs, there are no significant disagreements between our review and the above mentioned two systematic reviews regarding efficacy and safety of aP vaccines.

Observational studies have also demonstrated the effectiveness of aP vaccines. Gustafsson 2006 (Swedish birth cohorts) showed that immunisation with aP vaccines at three, five and 12 months of age resulted in a reduction in the incidence of laboratory-confirmed pertussis from 113 to 150 per 100,000 during 1992/1995, to 11 to 16 per 100,000 during 2001/2004. Bisgard 2005 (case-control study of 1072 children in the United States) found that any combination of ≥ three DTwP/DTaP vaccine doses was highly protective against pertussis. As compared with 0 doses, the unadjusted vaccine effectiveness was 83.6%, 95.6% and 97.7% for one or two, three and ≥ four vaccine doses, respectively. In contrast with the findings of our review, this study showed that four-component DTaP vaccine was less effective than two-component DTaP vaccine, however, the potential biases related to study design might cast serious doubt on the validity of comparison between different vaccines.

AUTHORS' CONCLUSIONS

Implications for practice

Multi-component acellular vaccines are effective against both typical whooping cough and mild pertussis disease, with a good safety profile. However, the implications of this finding for clinical practice may be different in high-income and low-income countries. In high-income countries, death from whooping cough is rare and parental acceptance is a major determinant of immunisation uptake. In these circumstances, the improved side effect profile of acellular vaccines argues in favour of their use, even though they might sacrifice some degree of effectiveness compared to the best whole-cell vaccines. The available efficacy data favours the multi-component acellular vaccines over the one- and two-component vaccines in this regard.

In low-income countries, where the risk of pertussis is higher and cases are more likely to be fatal, greater weight needs to be given to vaccine efficacy. If an acellular vaccine has been shown to be less effective than a high-efficacy whole-cell vaccine it is intended to replace, the reactogenicity advantage of the acellular vaccine may be offset by increased mortality and morbidity due to a higher breakthrough rate of pertussis. However, most of the whole-cell vaccines used in low-income countries have not been studied for efficacy or effectiveness and, therefore, it is not known where on the

wide spectrum of whole-cell vaccine efficacy an individual product lies. The more consistent manufacturing of the acellular vaccines may lead to more consistent efficacy of these products. However, the higher cost of acellular vaccines at this time would seem likely to affect their usefulness in low-income countries.

Implications for research

There are several gaps in our current knowledge of acellular pertussis vaccines. One of the more notable is that the optimal composition of these vaccines has yet to be defined. All vaccines in this review included some form of inactivated pertussis toxin, while those with more than one component all included filamentous haemagglutinin. Although the available multi-component vaccines are more effective than those with one or two components, it has not yet been determined what the optimal composition is for the acellular vaccines.

More data are needed on the optimal timing of booster doses, school-entry acellular boosting in children who have received acellular vaccines for all previous doses, the effectiveness of acellular vaccines in adults and what is the proper interval for subsequent doses of acellular pertussis vaccine in adulthood.

Ethical barriers to the inclusion of a placebo group, combined with the evidence that whole-cell vaccines are not uniformly effective, will create problems for future efficacy studies. Such studies will need to include a self selected, non-immunised and potentially biased control group, in order to provide an estimate of absolute vaccine efficacy. Further analyses of the data from existing placebo-controlled studies, with the aim of determining characteristics of participants and their environment which affect vaccine efficacy, will permit future studies to improve these estimates of absolute efficacy by adjusting for such factors.

Finally, the lack of a laboratory correlate of efficacy means that the testing of new acellular pertussis vaccines currently requires prolonged and expensive clinical trials. Research into determining such a laboratory correlate should be a priority.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Afari 1996

Methods	Site: Ghana Design: parallel-group RCT
Participants	Included: age 6 weeks Excluded: neurological disorder; serious disease; birth weight < 2 kg
Interventions	Primary series (aP versus wP) 1. DTaP: Biken[2] liquid 2. DTaP: Biken[2] freeze dried 3. DTwP: Connaught[W] Number randomised: 266 aP, 137 wP Dose schedule: 3 doses (6, 10, 14 weeks) Concurrent vaccine: not stated

Afari 1996 *(Continued)*

Outcomes	1. Efficacy: excluded (no laboratory confirmation of pertussis cases) 2. Primary series non-completion (due to adverse events): no data 3. Deaths: until 12 months after 3rd dose (16 months after 1st dose) 4. Encephalopathy: no data 5. Convulsions: within 7 days of any dose 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: drowsiness, fever, prolonged crying, vomiting within 7 days of each dose
Notes	Local adverse events excluded (results only for all local adverse event types combined). No statement on antipyretic/analgesic use. In this review, results are combined for the 2 aP vaccine formulations

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computer program (EPI Info)
Allocation concealment (selection bias)	Unclear risk	On-site computer assignment but file locking not reported. Vaccines visually distinguishable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Parents and nurses collecting efficacy and adverse event data were blinded but blinding details not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Parents and nurses collecting efficacy and adverse event data were blinded but blinding details not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Parents and nurses collecting efficacy and adverse event data were blinded but blinding details not stated

AHGSPV 1988

Methods	Site: Sweden Design: DB parallel-group RCT Active case ascertainment (monthly telephone). Case incidence adjusted for follow-up duration by actuarial method. Parents recorded adverse events in diary
Participants	Included: age 5 to 11 months Excluded: suspected progressive neurological disease; failure to thrive; renal failure; cardiac failure; prior pertussis or pertussis immunisation
Interventions	Primary series (aP versus placebo) 1. aP: JNIH7[1] 2. aP: JNIH6[2] 3. Placebo Number randomised: 2837 aP, 954 placebo Dose schedule: 2 doses (entry + 8 to 12 weeks later)

AHGSPV 1988 *(Continued)*

	Concurrent vaccines: DT and IPV (not within 1 week before or 2 weeks after aP or wP)
Outcomes	1. Efficacy: 3801 infants randomised in a 3:3:2 ratio - 1428 to JNIH7, 1419 to JNIH6, 954 to placebo. Of these, 1403, 1385 and 923 were assessed for efficacy in the 3 groups, respectively. Assessment commenced 30 days after the second dose and lasted for 17 to 19 months. Efficacy data were not available for the intention-to-treat population. Several case definitions, those closest to the definitions selected for review were: whooping cough = 21 days paroxysmal cough with whoops "after adjustment for non-pertussis disease" (i.e. exclusion of cases that could not be verified by culture, serology or contact with culture-proven case). Pertussis disease = cough for 7 days or more or household exposure to pertussis, with confirmation by appropriate serology 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 15 to 17 months after 2nd dose (17 to 19 months after 1st dose) 4. Encephalopathy: no data 5. Convulsions: within 14 days of any dose 6. Hypotonic-hyporesponsive episodes: within 14 days of any dose 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, vomiting, pain/tenderness, redness, swelling/induration within 1 day of each dose
Notes	Macrolide prophylaxis not used (not recommended in Sweden for age > 6 months and efficacy follow-up in this study started at minimum age of 7 months). Reactive antipyretic/analgesic use allowed. Blinding of study nurses confirmed by questionnaire

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally generated random sequence
Allocation concealment (selection bias)	Low risk	Vaccines in identical, coded vials
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

AHGSPV 1997

Methods	Site: Sweden Design: DB parallel-group RCT Passive case ascertainment (based on laboratory reports of pertussis and questionnaire of parents at 18-month visit). Case incidence adjusted for follow-up duration by Cox proportional hazard regression. Follow-up of serious adverse events by active weekly surveillance in study area hospitals, reports from participating physicians and child health nurses, plus questioning of parents at each trial dose and when the child was 18 months old

AHGSPV 1997 *(Continued)*

Participants	Included: age 2 months Excluded: progressive neurological disease; uncontrolled epilepsy; infantile spasm; failure to thrive; renal failure; cardiac failure; immunosuppression; prior pertussis
Interventions	Primary series (aP versus wP) 1. DTaP: SKB[2] 2. DTaP: Chiron-Biocine[3] 3. DTaP: Connaught[5] 4. DTwP: Connaught[W] Number randomised: 62172 aP, 2072 wP Dose schedules: 3 doses (3, 5, 10 months - 88% of vaccinees; 2, 4, 6 months - 12% of vaccinees) Concurrent vaccines: HiB and IPV
Outcomes	1. Efficacy: excluded (case ascertainment not active) 2. Primary series non-completion (due to adverse events): included 3. Deaths: until mean of 22 months after 3rd dose 4. Encephalopathy: within 2 days of any dose 5. Convulsions: within 2 days of any dose 6. Hypotonic-hyporesponsive episodes: within 3 days of any dose 7. Minor adverse events: not studied
Notes	There was good evidence that the passive case ascertainment led to significant under-reporting of cases. It is possible (not discussed in study report) that under-reporting of serious adverse events may have occurred but there are no grounds to suspect that under-reporting would affect the acellular and whole-cell groups differently Deaths recorded for this study are due to any cause and include at least 1 due to injury (vaccine group not specified) No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally generated random sequence
Allocation concealment (selection bias)	Low risk	Vaccines in identical, coded vials
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

Anderson 1988

Methods	Site: USA Design: DB parallel-group RCT
Participants	Included: age 2 months; healthy Excluded: not stated
Interventions	Primary series (aP versus wP) 1. DTaP: Wyeth/Takeda[4] 2. DTwP: Wyeth[W] Number randomised: 19 aP, 20 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied. 2. Primary series non-completion (due to adverse events): included 3. Deaths: no data 4. Encephalopathy: within 14 days of any dose 5. Convulsions: within 14 days of any dose 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, irritability, prolonged crying, pain/tenderness, redness, swelling/induration within 2 days of each dose
Notes	Reactive analgesic/antipyretic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Vaccines in coded vials
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

Bernstein 1992

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms

Bernstein 1992 *(Continued)*

Participants	Included: age 4 to 6 years; healthy; completed DTwP primary series and 15- to 24-month booster Excluded: personal or family history of developmental delay or neurological disorder; previous aP or DTaP; previous contraindicating reaction to DTwP
Interventions	Booster (wP.wP.aP versus wP.wP.wP) 1. DTaP: Connaught/Biken[2] 2. DTwP: Connaught[W] Number randomised: 240 aP, 76 wP Dose schedule: 1 dose (4 to 6 years) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: within 14 days of dose 6. Hypotonic-hyporesponsive episodes: within 14 days of dose 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	Prophylactic antipyretic/analgesic use not allowed. Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation at study site, but details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment details not reported
Selective reporting (reporting bias)	High risk	Data for vomiting collected but not reported

Bernstein 1994

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Age: 15 to 20 months; healthy; completed DTwP primary series Excluded: personal or family history of developmental delay or neurological disorder; previous DTaP; previous contraindicating reaction to DTwP
Interventions	BOOSTER (wP.aP versus wP.wP) 1. DTaP: SKB[3] 2. DTwP: Lederle[W] Number randomised: 110 aP, 22 wP Dose schedule: 1 dose (15 to 20 months)

Bernstein 1994 *(Continued)*

	Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied. 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not reported
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for vomiting collected but not reported (stated to be "infrequent" and "not significantly different")

Black 1997

Methods	Site: USA Design: parallel-group RCT
Participants	Included: age 2 months Excluded: not stated
Interventions	Primary series (aP versus wP) 1. DTaP: Chiron/Biocine[3] 2. DTwP: Connaught[W] Number randomised: 2000 aP, 498 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccines: HiB (separate injection site) and OPV
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): no data 3. Deaths: data incomplete (SIDS only) 4. Encephalopathy: no data 5. Convulsions: within 2 days of any dose 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, irritability, pain/tenderness, redness, swelling/induration within 2 days of each dose
Notes	Booster dose of Chiron/Biocine[3] or Lederle/Takeda[4] at age 15 to 18 months. Data for this dose are not included as there was no DTwP or placebo control

Black 1997 *(Continued)*

	SIDS was recorded in 4/2000 (0.2%) DTaP and 1/498 (0.2%) DTwP recipients in the first year of life. Death due to other causes was not studied Late onset fever (> 3 days after dose) occurred in both groups, with peak percentage slightly higher in DTaP group (approximately 5% versus 4.5% in DTwP group) but the overall percentage with fever over the 14-day follow-up was lower in the DTaP group No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not reported
Allocation concealment (selection bias)	Unclear risk	Details not reported

Blennow 1988

Methods	Site: Sweden Design: parallel-group RCT
Participants	Included: age 6 months Excluded: contraindication to DTP vaccine as per ref Anon 1977
Interventions	Primary series (aP versus wP - see notes) 1. aP: JNIH6[2] 2. wP: Wellcome[W] 3. Placebo - see notes Number randomised: 121 aP, 119 P, 79 wP Dose schedule: 3 doses (6, 7, 8 months) Concurrent vaccine: DT and polio vaccines not given within 2 weeks of dose
Outcomes	1. Efficacy: excluded (no data on number of cases in DTwP group) 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 1 month after 3rd dose (5 months after 1st dose) 4. Encephalopathy: until at least 1 week after 3rd dose (4 months after 1st dose) 5. Convulsions: until at least 1 week after 3rd dose (4 months after 1st dose) 6. Hypotonic-hyporesponsive episodes: until at least 1 week after 3rd dose (4 months after 1st dose) 7. Minor adverse events: drowsiness, fever, irritability, redness, swelling/induration within 1 day of dose
Notes	The whole-cell series was given as 3 doses of whole-cell vaccine. The acellular series was given as 3 doses of acellular vaccine, or 2 doses of acellular vaccine plus 1 dose of placebo (replacing the 1st, 2nd or 3rd dose of acellular vaccine). In this review, data for series non-completion, deaths and serious adverse events relate to all acellular-containing vaccine regimens. The acellular primary series non-completion (due to adverse events) data include 1 infant who withdrew after receiving placebo at the 1st dose. Data for minor adverse events at each dose are recorded only for those patients who actually received the acellular vaccine at that dose Data for anorexia and vomiting collected but not reported No statement on antipyretic/analgesic use

Risk of bias

Blennow 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence key concealed from study personnel and parents
Allocation concealment (selection bias)	Low risk	Vaccines indistinguishable
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Data for anorexia and vomiting collected but not reported

Blumberg 1990

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 17 to 24 months; healthy; completed DTwP primary series Excluded: not stated
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Lederle/Takeda[4] 2. DTwP: Lederle[W] Number randomised: 38 aP, 37 wP Dose schedule: 1 dose (17 to 24 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, vomiting, pain/tenderness, redness, swelling/induration within 2 days of dose
Notes	Reactive antipyretic/analgesic use allowed
Risk of bias	

Blumberg 1990 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not reported
Allocation concealment (selection bias)	Unclear risk	Details not reported

Blumberg 1991

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 2 months; healthy Excluded: not stated
Interventions	Primary series (aP versus wP) 1. DTaP: Lederle/Takeda[4] 2. DTwP: Lederle/Takeda[W] Number randomised: 245 aP, 252 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 12 months after 3rd dose (16 months after 1st dose) 4. Encephalopathy: no data 5. Convulsions: within 3 days of any dose 6. Hypotonic-hyporesponsive episodes: within 3 days of any dose 7. Minor adverse events: drowsiness, fever, irritability, prolonged crying, vomiting, pain/tenderness, redness, swelling/induration within 3 days of each dose
Notes	1 death in DTwP arm due to accident (strangulation by pacifier cord) 4th dose of DTaP given at 18 months to all children. 4th dose not included in review because no DTwP control group for that dose. Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Decker 1995

Methods	Site: USA Phased parallel-group RCT (2 to 3 vaccines per phase)

Decker 1995 *(Continued)*

	Parents recorded adverse events on forms
Participants	Included: age 6 to 12 weeks; healthy Excluded: born < 36 weeks gestation; immune system disease; major congenital malformation; serious chronic disease; developmental delay; neurological disease; convulsions; other contraindications to DTP vaccine as per ref CID 1991a
Interventions	Primary series (aP versus wP) 1. DTaP: Biocine[1] 2. DTaP: SSVI[1] 3. DTaP: Connaught/Biken[2] 4. DTaP: Michigan[2] 5. DTaP: Pasteur-Merieux[2] 6. DTaP: SKB[2] 7. DTaP: Biocine[3] 8. DTaP: Lederle[3] 9. DTaP: SKB[3P] 10. DTaP: Connaught[4] 11. DTaP: Porton[4] 12. DTaP: Lederle/Takeda[4] 13. DTaP: Connaught[5] 14. DTwP: Lederle[W] Number randomised: 1827 aP, 373 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: HiB
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 1 month after 3rd dose (5 months after 1st dose) 4. Encephalopathy: until 1 month after 3rd dose 5. Convulsions: until 1 month after 3rd dose 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, pain/tenderness, redness, swelling/induration within 3 days of each dose
Notes	In this review, safety results are combined for all acellular vaccines. Irritability and pain were reported only for the moderate/severe category At an additional retrospective medical record review 1 year after dose 3 (not all subjects studied), convulsions were documented in 1.1% DTaP recipients compared to 0.7% DTwP Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Vaccine vials labelled with letter codes instead of type/manufacturer details but unable to ascertain from study report whether vaccinators remained unaware of what each code represented
Blinding of outcome assessment (detection bias)	Low risk	Vaccinators took no further part in the study and did not participate in follow-up data collection, so outcome assessment was double-blind

Decker 1995 *(Continued)*
All outcomes

Edwards 1986a

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: age 18 to 24 months; completed DTwP primary series Excluded: not stated
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Wyeth/Takeda[4] 2. DTwP: Wyeth[W] Number randomised: 20 aP, 20 wP Dose schedule: 1 dose (18 to 24 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: within 1 month of dose 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, irritability, pain/tenderness, redness, swelling/induration within 1 day of dose
Notes	No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for drowsiness and vomiting collected but not reported (stated to be "rare"). Data for irritability, pain, redness and induration only reported for moderate/severe category

Edwards 1986b

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: age 4 to 6 years; completed DTwP primary series and 15- to 24-month booster Excluded: not stated

Edwards 1986b *(Continued)*

Interventions	Booster (wP.wP.aP versus wP.wP.wP) 1. DTaP: Wyeth/Takeda[4] 2. DTwP: Wyeth[W] Number randomised: 20 aP, 20 wP Dose schedule: 1 dose (4 to 6 years) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: within 1 month of dose 5. Convulsions: within 1 month of dose 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, irritability, pain/tenderness, redness, swelling/induration within 1 day of dose
Notes	No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for drowsiness and vomiting collected but not reported (stated to be "rare''). Data for irritability, pain, redness and induration only reported for moderate/severe category

Edwards 1989a

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: infants Excluded: previous DTP vaccination
Interventions	Primary series (aP versus wP) 1. DTaP: Merieux[2] 2. DTwP: Connaught[W] Number randomised: 23 aP, 27 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: until at least 2 weeks after 3rd dose (4 months after 1st dose) 4. Encephalopathy: until at least 2 weeks after 3rd dose (4 months after 1st dose) 5. Convulsions: until at least 2 weeks after 3rd dose (4 months after 1st dose)

Edwards 1989a *(Continued)*

	6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, fever, irritability, pain/tenderness within 3 days of dose; redness, swelling/induration within 1 day of dose
Notes	Follow-up for deaths probably longer than until 2 weeks after dose 3 but not clearly stated to be so No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Edwards 1989b

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: age 18 to 24 months; completed DTwP primary series Excluded: not stated
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Merieux[2] 2. DTwP: Connaught[W] Number randomised: 19 aP, 21 wP Dose schedule: 1 dose (18 to 24 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: until at least 2 weeks after dose 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, fever, irritability, pain/tenderness within 3 days of dose; redness, swelling/induration within 1 day of dose
Notes	No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Edwards 1989c

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: age 4 to 6 years; completed DTwP primary series and 18- to 24-month booster Excluded: not stated
Interventions	Booster (wP.wP.aP versus wP.wP.wP) 1. DTaP: Merieux[2] 2. DTwP: Connaught[W] Number randomised: 20 aP, 20 wP Dose schedule: 1 dose (4 to 6 years) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: until at least 2 weeks after dose 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, fever, irritability, pain/tenderness within 3 days of dose; redness, swelling/induration within 1 day of dose
Notes	No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Englund 1992

Methods	Site: Houston, USA Design: parallel-group RCT Parents were interviewed by telephone. Parents recorded adverse events in diary for 14 days after immunisations
Participants	Included: ages 16 to 20 months, who had received primary immunisation with DTwP Excluded: not stated
Interventions	Booster (aP versus wP) 1. DTaP: local laboratory [5] 2. DTwP: Connaught [W] Number randomised: 28 aP, 13 wP Dose schedule: 1 dose (16 to 20 months) Concurrent vaccines: none

Englund 1992 *(Continued)*

Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability/fretfulness, prolong crying, vomiting, pain/tenderness, redness, swelling/induration
Notes	Prolonged crying was studied as increased crying. Use of analgesic/antipyretic was allowed during the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Englund 1994a

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: age 16 to 21 months; healthy; completed DTwP primary series Excluded: known immune deficiency; receipt of blood products in past month; contraindication to DTwP as specified in ref CID 1991a; physician did not recommend DTwP
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Massachusetts[1] 2. DTaP: Biocine[1] 3. DTaP: Connaught/Biken[2] 4. DTaP: Lederle[3] 5. DTaP: Biocine[3] 6. DTaP: SKB[3] 7. DTaP: Porton[4] 8. DTaP: Wyeth/Takeda[4] 9. DTaP: Connaught[5] 10. DTwP: Connaught[W] 11. DTwP: Massachusetts[W] 12. DTwP: Lederle[W] Number studied: 102 aP, 29 wP Dose schedule: 1 dose (16 to 21 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: until post-vaccination phlebotomy (timing not specified)

Englund 1994a *(Continued)*

	6. Hypotonic-hyporesponsive episodes: until post-vaccination phlebotomy (timing not specified) 7. Minor adverse events: fever, pain/tenderness, redness, swelling/induration within 2 days of dose
Notes	The number of 16- to 24-month old children randomised to aP or wP was not stated. A total of 258 children aged 16 to 24 months or 4 to 6 years were randomised in Englund 1994a and Englund 1994b combined: 192 to aP and 66 to wP. 240 of these contributed safety data Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for irritability collected but not reported

Englund 1994b

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: age 4 to 6 years; healthy; completed DTwP primary series and 15- to 24-month booster Excluded: known immune deficiency; receipt of blood products in past month; contraindication to DTwP as specified in ref CID 1991a; physician did not recommend DTwP
Interventions	Booster (wP.wP.aP versus wP.wP.wP) 1. DTaP: Massachusetts[1] 2. DTaP: Biocine[1] 3. DTaP: Connaught/Biken[2] 4. DTaP: Lederle[3] 5. DTaP: Biocine[3] 6. DTaP: SKB[3] 7. DTaP: Porton[4] 8. DTaP: Wyeth/Takeda[4] 9. DTwP: Connaught[W] 10. DwTP: Massachusetts[W] 11. DTwP: Lederle[W] Number studied: 80 aP, 29 wP Dose schedule: 1 dose (16 to 21 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: until post-vaccination phlebotomy (timing not specified) 6. Hypotonic-hyporesponsive episodes: until post-vaccination phlebotomy (timing not specified) 7. Minor adverse events: fever, pain/tenderness, redness, swelling/induration within 2 days of dose

Englund 1994b *(Continued)*

Notes	Number of 4 to 6-year old children randomised to aP or wP not stated. A total of 258 children aged 16 to 24 months or 4 to 6 years were randomised in Englund 1994a and Englund 1994b combined: 192 to aP and 66 to wP. 240 of these contributed safety data. Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	Low risk	Data for irritability collected but not reported

Feldman 1992

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 15 to 24 months; healthy; completed DTwP primary series Excluded: immune dysfunction; major congenital malformation; serious chronic disorder; developmental delay; receipt of immunoglobulin within past 3 months
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Connaught/Biken[2] 2. DTwP: Connaught[W] Number randomised: 84 aP, 78 wP Dose schedule: 1 dose (15 to 24 months) Concurrent vaccine: OPV; HiB 4 weeks after study vaccine
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: within 3 days of dose 6. Hypotonic-hyporesponsive episodes: within 3 days of dose 7. Minor adverse events: anorexia, drowsiness, fever, irritability, pain/tenderness, redness, swelling/induration within 1 day of dose; prolonged crying within 3 days of dose
Notes	Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for vomiting collected but not reported

Feldman 1993

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 2 months; healthy Excluded: born < 36 weeks gestation; immune disorder; major congenital malformation; serious chronic disease; ongoing immunoglobulin therapy; pertussis infection; personal or family history of neurological disorder or developmental delay
Interventions	Primary series (aP versus wP) 1. DTaP: Connaught/Biken[2] 2. DTwP: Connaught[W] Number randomised: 109 aP, 36 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: OPV
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded - see notes 3. Deaths: until at least 14 days after 3rd dose (4 months after 1st dose) 4. Encephalopathy: until age 12 months (10 months after 1st dose) 5. Convulsions: within 14 days of any dose 6. Hypotonic-hyporesponsive episodes: within 14 days of any dose 7. Minor adverse events: excluded (separate data for each dose not available)
Notes	1 infant did not complete the primary series due to an adverse event (high pitched cry) but the report does not state whether this infant received aP or wP. Deaths were not specifically reported but all infants either completed the study up to the final dose or withdrew due to reasons other than death Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for vomiting collected but not reported

Glode 1992

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 17 to 24 months; healthy; full-term; completed DTwP primary series Excluded: acute or chronic illness; history of diphtheria, tetanus or pertussis; known contraindication to DTP
Interventions	Booster (wP.aP versus wP.wP)

Glode 1992 *(Continued)*

	1. DTaP: Lederle/Takeda[4] (lot 1) 2. DTaP: Lederle/Takeda[4] (lot 2) 3. DTaP: Lederle/Takeda[4] (lot 3) 4. DTwP: Lederle[W] Number randomised: 345 aP, 52 wP Dose schedule: 1 dose (17 to 24 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: within 10 days of dose 6. Hypotonic-hyporesponsive episodes: within 10 days of dose 7. Minor adverse events: drowsiness, fever, irritability, vomiting, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	Results for DTaP lots combined Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On-site randomisation
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for prolonged crying collected but not reported

Greco 1996

Methods	Site: Italy Design: DB parallel-group RCT Passive and active case ascertainment (parent report and monthly telephone). Case incidence adjusted for follow-up duration by use of incidence density. Parents recorded adverse events in diary
Participants	Included: age 6 to 12 weeks; weight > 3rd percentile Excluded: history of seizures or central nervous system disease; known/suspected immunological deficit; major congenital abnormality; failure to thrive; renal failure; prior pertussis or pertussis vaccination
Interventions	Primary series (aP versus wP versus DT) 1. DTaP: SKB[3] 2. DTaP: Biocine[3] 3. DTwP: Connaught[W] 4. DT Number randomised: 9368 aP, 4678 wP, 1555 DT Dose schedule: 3 doses (6 to 12, 13 to 20, and 21 to 28 weeks)

Greco 1996 *(Continued)*

	Concurrent vaccine: OPV and hepatitis B vaccine with doses 1 and 2. Booster dose of DT to all subjects at 12 months of age
Outcomes	1. Efficacy: 15,601 infants randomised and received at least 1 dose of vaccine: 4696 SKB, 4672 Biocine, 4678 DTwP and 1555 DT (randomisation ratio 3:3:3:1). Main efficacy assessment was in children who had received all 3 doses of study vaccine, commenced 30 days after 3rd dose and lasted 17 months. It included 4481 SKB, 4452 Biocine, 4358 DTwP and 1470 DT subjects. Efficacy data were also available for the intent-to-treat population. Several case definitions used. Those closest to the definitions selected for review were: whooping cough = 21 days or more of paroxysmal cough with confirmation by culture or appropriate serology. Pertussis disease = 7 days or more of paroxysmal cough with confirmation by culture or appropriate serology 2. Primary series non-completion (due to adverse events): included 3. Deaths: within 60 days of any dose (6 months after 1st dose) 4. Encephalopathy: within 60 days of any dose (6 months after 1st dose) 5. Convulsions: within 60 days of any dose (6 months after 1st dose) 6. Hypotonic-hyporesponsive episodes: within 2 days of each dose 7. Minor adverse events: excluded (separate data for each dose not available)
Notes	No statement on macrolide prophylaxis. Possible partial unblinding of DTwP (not discussed in article but study used same DTwP as Gustafsson96) No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not reported
Allocation concealment (selection bias)	Low risk	Vaccines in identical, coded vials
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

Gustafsson 1996

Methods	Site: Sweden Design: DB parallel-group RCT Passive and active case ascertainment (parent report and telephone every 6 to 8 weeks). Case incidence adjusted for follow-up duration by use of Cox proportional hazards regression. Parents recorded adverse events in diary
Participants	Included: age 2 to 3 months

Gustafsson 1996 *(Continued)*

	Excluded: progressive neurological disease; failure to thrive; renal failure; cardiac failure; uncontrolled epilepsy; infantile spasms; immunosuppression; prior pertussis or pertussis vaccination
Interventions	Primary series (aP versus wP versus DT) 1. DTaP: SKB[2] 2. DTaP: Connaught[5] 3. DTwP: Connaught[W] 4. DT Number randomised: 5153 aP, 2102 wP, 2574 DT Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: inactivated polio vaccine and HiB at least 2 weeks after study vaccine
Outcomes	1. Efficacy: 9829 infants randomised and received at least 1 dose of vaccine: 2566 SKB, 2587 Connaught DTaP, 2102 DTwP and 2574 DT. Due to delayed availability of the DTwP, children were randomised only to DTaP and DT vaccines during the first 2 months of the trial. Main efficacy assessment was in children who had received all 3 doses of study vaccine, commenced 30 days after the 3rd dose and lasted for 21 months. It included 2538 SKB, 2551 Connaught DTaP, 2001 DTwP and 2538 DT subjects. Efficacy data were also available for the intention-to-treat population. Comparisons between DTaP and DT vaccines utilised data from all children randomised to those vaccines over the whole trial period. Comparisons involving the whole-cell vaccine utilised data only from children who were enrolled after the date the whole-cell vaccine became available. Several case definitions used. Those closest to the definitions selected for review were: whooping cough = 21 days or more of paroxysmal cough with confirmation by culture, appropriate serology or documented household contact with a culture-confirmed case. Pertussis disease = more than 7 days of cough with confirmation as above 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 2 years after 3rd dose (28 months after 1st dose) 4. Encephalopathy: within 60 days of any dose (6 months after 1st dose) 5. Convulsions: within 60 days of any dose (6 months after 1st dose) 6. Hypotonic-hyporesponsive episodes: within 60 days of any dose (6 months after 1st dose) 7. Minor adverse events: fever, prolonged crying, redness, swelling/induration, pain/tenderness within 1 day of dose
Notes	Macrolide prophylaxis not used (not recommended in Sweden for age > 6 months and main efficacy follow-up in this study started at age 6 months) DTwP unavailable for first 2 months of study. Only DTaP and DT randomised during that period. Questionnaire of study nurses showed partial post-allocation unblinding of DTwP (harder to re-suspend and more likely to be followed by adverse events). Pre-allocation concealment was determined to be adequate (see text for reasons) Redness reported only for moderate/severe category Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally generated randomisation in blocks of 12 or 16
Allocation concealment (selection bias)	Low risk	Vaccines in identical vials. At each study site, vaccines administered in numbered order
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind

Gustafsson 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk
Blinding of outcome assessment (detection bias) All outcomes	Low risk

Halperin 1994a

Methods	Site: Canada Design: DB parallel-group RCT Adverse events recorded by structured telephone interview of parents
Participants	Included: age 2 months; healthy Excluded: children with contraindications to pertussis vaccine as specified in ref NACI 1989
Interventions	Primary series (aP versus wP) 1. DTaP: Connaught[5] 2. DTaP: Connaught[5] 3. DTaP: Connaught[W] Number randomised: 67 aP, 33 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: HiB
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 1 month after 3rd dose (5 months after 1st dose) 4. Encephalopathy: no data 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, vomiting, pain/tenderness, redness, swelling/induration within 2 days of each dose
Notes	The 2 acellular vaccines had differing amounts of PT and FH. In this review, results for the 2 acellular vaccine formulations are combined Antipyretic/analgesic prophylaxis was discouraged but not prohibited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list kept in a locked file
Allocation concealment (selection bias)	Low risk	Vaccines in identical, coded vials
Blinding (performance bias and detection bias)	Low risk	Double-blind

Halperin 1994a *(Continued)*

All outcomes	
Blinding of participants and personnel (performance bias) All outcomes	Low risk
Blinding of outcome assessment (detection bias) All outcomes	Low risk

Halperin 1994b

Methods	Site: Canada Design: DB parallel-group RCT Adverse events recorded by structured telephone interview of parents
Participants	Included: age 17 to 19 months; healthy Excluded: children with contraindications to pertussis vaccine as specified in ref NACI 1989
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Connaught[5] 2. DTaP: Connaught[5] 3. DTwP: Connaught[W] Number randomised: 61 aP, 30 wP Dose schedule: 1 dose (17 to 19 months) Concurrent vaccine: Hib
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, vomiting, pain/tenderness, redness, swelling/induration within 2 days of dose
Notes	The 2 acellular vaccines had differing amounts of PT, FH, Prn and Fim2,3. In this review, results for the 2 acellular vaccine formulations are combined Antipyretic/analgesic prophylaxis was discouraged but not prohibited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list kept in a locked file
Allocation concealment (selection bias)	Low risk	Vaccines in identical, coded vials
Blinding (performance bias and detection bias)	Low risk	Double-blind

Halperin 1994b *(Continued)*

All outcomes	
Blinding of participants and personnel (performance bias) All outcomes	Low risk
Blinding of outcome assessment (detection bias) All outcomes	Low risk

Halperin 1995

Methods	Site: Canada Design: DB parallel-group RCT. Subjects had been randomised and received primary series in Halperin 1994a Adverse events recorded by structured telephone interview of parents
Participants	Included: age 17 to 19 months; healthy; primary series DTaP or DTwP given in Halperin 1994a Excluded: children with contraindications to pertussis vaccine as specified in ref NACI 1989
Interventions	Booster (aP.aP versus wP.wP) 1. DTaP: Connaught[5] 2. DTaP: Connaught[5] 3. DTwP: Connaught[W] Number studied: 56 aP, 30 wP Dose schedule: 1 dose (17 to 19 months) Concurrent vaccine: Hib
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: within 2 days of dose 6. Hypotonic-hyporesponsive episodes: within 2 days of dose 7. Minor adverse events: anorexia, fever, irritability, vomiting, pain/tenderness, redness, swelling/induration within 2 days of dose
Notes	The 2 acellular vaccines had differing amounts of PT and FH. In this review, results for the 2 acellular vaccine formulations are combined. DTaP or DTwP primary series was given in Halperin 1994a. Randomisation took place in that study, parents and investigators remained blinded and children received the same vaccine in Halperin 1995 as they had received in Halperin 1994a Antipyretic/analgesic prophylaxis was discouraged but not prohibited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list kept in a locked file

Halperin 1995 *(Continued)*

Allocation concealment (selection bias)	Low risk	Vaccines in identical, coded vials
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

Halperin 1996

Methods	Site: Canada Design: DB parallel-group RCT Adverse events recorded by structured telephone interview of parents
Participants	Included: age 2 to 3 months; healthy Excluded: children with contraindications to pertussis vaccine
Interventions	Primary series + booster (aP.aP versus wP.wP) 1. DTaP: Connaught[5] 2. DTwP: Connaught[W] Number randomised: 324 aP, 108 wP 4 doses (2, 4, 6, 17 to 19 months) Concurrent vaccine: Hib
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: included up to 3rd dose (4 months after 1st dose). Excessive loss to follow-up after that dose 4. Encephalopathy: no data 5. Convulsions: until 1 to 2 months after 3rd dose 6. Hypotonic-hyporesponsive episodes: until 1 to 2 months after 3rd dose 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, pain/tenderness, redness, swelling/induration within 2 days of each dose
Notes	Antipyretic/analgesic prophylaxis was discouraged but not prohibited

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list kept in a locked file
Allocation concealment (selection bias)	Low risk	Vaccines in identical, coded vials

Halperin 1996 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

Halperin 1999

Methods	Site: Canada Design: DB parallel-group RCT Adverse events recorded by structured telephone interview of parents
Participants	Included: age 4 to 6 years; healthy; primary series DTaP or DTwP given in Halperin 1994 or Halperin 1996 Excluded: children with contraindications to pertussis vaccine as specified in ref NACI 1989
Interventions	Booster (aP versus wP) 1. 5 doses DTaP-IPV: Connaught[5] 2. 4 doses DTwP-IPV + 1 dose DTaP-IPV: Connaught[5] 3. 4 doses DTaP-IPV+ 1 dose DTwP: Connaught[W] 4. 5 doses DTwP-IPV: Connaught[W] Number studied: 178 aP, 178 wP Dose schedule: 1 dose (4 to 6 years) Concurrent vaccine: IPV
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: excluded (booster) 6. Hypotonic-hyporesponsive episodes: excluded (booster) 7. Minor adverse events: anorexia, drowsiness, fever, irritability, vomiting, pain/tenderness, redness, swelling/induration
Notes	Antipyretic/analgesic prophylaxis was discouraged but not prohibited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list kept in a locked file
Allocation concealment (selection bias)	Low risk	Vaccines in identical, coded vials

Halperin 1999 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

Halperin 2003

Methods	Site: Canada Design: parallel-group RCT Computer-generated randomisation list kept in a locked file. Study personnel collecting telephone reactogenicity data were blinded as to which vaccine the subject had received
Participants	Included: age 4 to 6 years; healthy Excluded: children with contraindications to pertussis vaccine
Interventions	Booster (aP versus wP) 1. 4 doses DTaP-Hib+DTaP-IPV: Pasteur [5] 2. 4 doses DTwP-Hib+DTaP-IPV: Pasteur [5] 3. 4 doses DTwP+DTwP-IPV: Pasteur [W] Number randomised: 408 aP, 97 wP 1 dose (4 to 6 years) Concurrent vaccines: Hib; IPV
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, pain/tenderness, redness, swelling/induration within 2 days of each dose
Notes	Only participants who had received 4 previous doses of DTwP were blinded to which vaccine they received for the fifth dose, because of different vaccine container formats. Antipyretic/analgesic prophylaxis was discouraged but not prohibited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list kept in a locked file

Halperin 2003 *(Continued)*

Allocation concealment (selection bias)	High risk	Different vaccine container formats
Blinding (performance bias and detection bias) All outcomes	High risk	Study personnel collecting telephone reactogenicity data were blinded as to which vaccine the subject had received. Only participants who had received 4 previous doses of DTwP were blinded to which vaccine they received for the fifth dose
Blinding of participants and personnel (performance bias) All outcomes	High risk	Only participants who had received 4 previous doses of DTwP were blinded to which vaccine they received for the fifth dose
Blinding of outcome assessment (detection bias) All outcomes	High risk	Only participants who had received 4 previous doses of DTwP were blinded to which vaccine they received for the fifth dose

Heininger 1994

Methods	Site: Germany Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 2 to 4 months; healthy Excluded: not stated
Interventions	Primary series (aP versus wP) 1. DTaP: Lederle/Takeda[4] 2. DTwP: Lederle[W] Number randomised: 75 aP, 74 wP Dose schedule: 3 doses (2 to 4 months, then 2 doses at 6-week intervals) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): no data 3. Deaths: no data 4. Encephalopathy: no data 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, redness, swelling/induration within 2 days of each dose
Notes	Excluded for adverse events after 2nd and 3rd doses (number vaccinated/studied at these doses was uncertain due to inconsistencies in tabulated data). Redness and induration were reported only for the moderate/severe category No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement

Heininger 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details not reported

Kanra 1993a

Methods	Site: Turkey Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 15 to 20 months; completed DTwP primary series Excluded: history of pertussis or progressive neurological disease; chronic drug therapy
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: SKB[3] 2. DTwP: Behringwerke[W] Number randomised: 55 aP, 55 wP Dose schedule: 1 dose (15 to 20 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	Data for drowsiness, irritability (restlessness), "unusual" crying and "gastrointestinal symptoms" collected but not reported. Report states "no serious events" but serious events not defined No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Kanra 1993b

Methods	Site: Turkey Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 4 to 6 years; completed DTwP primary series and 15- to 24-month booster Excluded: history of pertussis or progressive neurological disease; chronic drug therapy
Interventions	Booster (wP.wP.aP versus wP.wP.wP) 1. DTaP: SKB[3]

Kanra 1993b *(Continued)*

	2. DTwP: Behringwerke[W] Number studied: 53 aP, 52 wP Dose schedule: 1 dose (4 to 6 years) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	Total 108 randomised, data for 105 No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for drowsiness, irritability (restlessness), "unusual" crying and "gastrointestinal symptoms" collected but not reported

Kosuwon 2003

Methods	Site: Thailand Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 4 to 6 years old; healthy, who had received 4 doses of DTwP at 2, 4, 6 and 18 months Excluded: history of diphtheria or tetanus at any time, confirmed pertussis in the previous 5 years, if received vaccines not foreseen in the protocol within 30 days prior to study start or after receiving a study vaccine, history of allergic disease or reactions by any component of the vaccine or previously recorded following previous DTP, history of any serious adverse reactions following previous DTP vaccination, history of administration of immunosuppressive agents, immunoglobulin or blood products within the previous 3 months or during the trial, major congenital defects, neurological including seizure disorders and acute febrile illness
Interventions	Booster (aP versus wP) 1. DTaP: GSK [3] 2. DTwP: GSK [W] Number studied: 165 aP, 165 wP Dose schedule: 1 dose (4 to 6 years) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster)

Kosuwon 2003 *(Continued)*

5. Convulsions: no data
6. Hypotonic-hyporesponsive episodes: no data
7. Minor adverse events: anorexia, drowsiness, fever, irritability, pain/tenderness, redness, swelling/induration

Notes	All symptoms (solicited or unsolicited) were classified by the investigators as not related, unlikely, suspected or probably related. But not a clear temporal definition of this criterion (before or after data collection)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Details not reported

Lewis 1986

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 18 to 24 months; healthy; completed DTwP primary series Excluded: contraindication to DTwP as specified in ref CID 1982 or in the Wyeth [W] pack insert
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Wyeth/Takeda[4] 2. DTwP: Wyeth[W] Number randomised: 40 aP, 20 wP Dose schedule: 1 dose (18 to 24 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, vomiting, pain/tenderness, redness, swelling/induration within 2 days of dose
Notes	Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Marcinak 1993

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 15 to 20 months; completed DTwP primary series Excluded: routine contraindications to DTP vaccine; immunodeficiency; immunosuppressive therapy; major congenital malformation; serious chronic disease; personal or immediate family history of developmental delay or neurological disorder; antibiotic therapy within 7 days before enrolment
Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Connaught/Biken[2] 2. DTwP: Connaught[W] Number randomised: 164 aP, 82 wP Dose schedule: 1 dose (15 to 20 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, pain/tenderness, redness, swelling/induration at 1 day after dose
Notes	Study report states that only adverse events for which there was a significant difference between vaccines were reported. Not clear whether adverse event types were omitted or just certain time points for individual adverse events Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation but no statement regarding file locking
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	Low risk	Vomiting is the only target adverse event without data. Redness reported only for moderate/severe category

Miller 1991

Methods	Site: UK Design: parallel-group RCT Parents and study nurses recorded adverse events on forms

Miller 1991 *(Continued)*

Participants	Included: infants attending clinics for 1st dose DTP (due at age 3 months) Excluded: history of neurological disorder, serious chronic disease or confirmed pertussis; immediate family history of idiopathic epilepsy
Interventions	Primary series (aP versus wP) 1. DTaP: CAMR[4] 2. DTwP: Wellcome[W] Number randomised: 94 aP, 94 wP Dose schedule: 3 doses (3, 5, 8 to 10 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 3rd dose (5 to 7 months after 1st dose) 4. Encephalopathy: no data 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever within 1 day of each dose
Notes	Minor adverse event data for fever only. Anorexia, drowsiness, irritability, prolonged crying and vomiting combined as "any systemic symptom" No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data for redness, swelling collected but not reported (stated not to differ in frequency)

Morgan 1990

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 4 to 6 years; healthy; completed DTwP primary series and 15- to 24-month booster Excluded: not stated
Interventions	Booster (wP.wP.aP versus wP.wP.wP) 1. DTaP: Lederle/Takeda[4] 2. DTwP: Lederle[W] Number randomised: 41 aP, 42 wP Dose schedule: 1 dose (4 to 6 years)

Morgan 1990 *(Continued)*

	Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, vomiting, pain/tenderness, redness, swelling/induration within 2 days of dose
Notes	No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Pichichero 1992

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on questionnaires and measured their child's rectal temperature
Participants	Included: infants due to receive 1st dose DTP (mean age = 2 months), 2nd dose (mean age = 4 months) and 3rd dose (mean age = 6 months) Excluded: contraindication to DTP vaccine as specified in ref CID 1988
Interventions	Primary series (aP versus wP) 1. DTaP: Biken/Connaught [2] 2. DTwP: Connaught [W] Number randomised: • 1 dose: 218 aP versus 72 wP • 2 dose: 207 aP versus 62 wP • 3 dose: 204 aP versus 57 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): no data 3. Deaths: no data 4. Encephalopathy: no data 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolong crying, vomiting, pain/tenderness, redness, swelling/induration, within 2 days of each dose

Pichichero 1992 *(Continued)*

Notes	The pattern of crying is not clear, considered unusual, or high-pitched cries. 7 children left the study for severe reactions not described and 2 experienced hypotonic/hyporesponsive episodes following the second vaccination. Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Pichichero 1993

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: infants due to receive 1st dose DTP (mean age = 2 months) Excluded: contraindication to DTP vaccine as specified in ref CID 1988
Interventions	Primary series (aP versus wP) 1. DTaP: SKB[2] 2. DTwP: Lederle[W] Number randomised: 88 aP, 22 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 3rd dose (4 months after 1st dose) 4. Encephalopathy: no data 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, irritability, pain/tenderness, redness, swelling/induration within 2 days of each dose
Notes	The choice of reported adverse event types was not limited to those showing a significant difference between vaccines but was based on the preliminary results of Decker 1995 (reported in Pichichero 1995), which identified the chosen adverse events as sufficient to differentiate between DTP vaccines in regard to reactogenicity. Irritability and pain were reported only for the moderate/severe category. Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Selective reporting (reporting bias)	High risk	Data on anorexia, drowsiness and vomiting were collected but not reported

Pichichero 1994

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: age 2 months (6 to 12 weeks); healthy Excluded: contraindication to DTP vaccine as specified in ref CID 1988
Interventions	Primary series (aP versus wP) 1. DTaP: SKB[3] 2. DTwP: Lederle[W] Number randomised: 62 aP, 18 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): no data 3. Deaths: no data 4. Encephalopathy: no data 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, irritability, pain/tenderness, redness, swelling/induration, within 2 days of each dose
Notes	Redness and pain were reported only for the moderate/severe category Antipyretic/analgesic use discouraged but allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Parents and investigators are unaware of the type of vaccination
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	

Pichichero 1996

Methods	Site: USA

Pichichero 1996 *(Continued)*

	Design: parallel-group RCT. Subjects had been randomised and received primary series in Pichichero 1993 and Pichichero 1994 (latter excluded due to discrepancies in reported data). 158 out of 190 (83%) parents elected to remain blinded and allow child to participate in booster study Parents recorded adverse events on forms
Participants	Included: age 15 to 20 months; primary series DTaP or DTwP given in Pichichero 1993 or Pichichero 1994 Excluded: not stated
Interventions	Booster (aP.aP versus wP.wP) 1. DTaP: SKB[2] 2. DTaP: SKB[3P] 3. DTwP: Lederle[W] Number studied: 124 aP, 34 wP Dose schedule: 1 dose (15 to 20 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, irritability, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	Possible bias due to parental self selection of 83% subset who continued in the study. Number of subjects studied for redness and pain in the DTwP group is unclear due to discrepancies in the data table. Irritability and pain were reported only for the moderate/severe category Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Pichichero 1997

Methods	Site: USA Design: parallel-group RCT. Subjects had been randomised and received primary series in Decker 1995. 1374 of 2264 (61%) parents elected to remain blinded and allow child to participate in booster study Parents recorded adverse events on forms
Participants	Included: completed DTaP or DTwP primary series in Decker 1995 Excluded: see Decker 1995; contraindications to DTP vaccine as per ref CID 1994
Interventions	Booster (aP.aP versus wP.aP versus wP.wP) Children who had received DTaP primary series received the same DTaP as a booster, except for those who had received Lederle[3P] (no longer available) who were boosted with Lederle/Takeda[4F2]. Chil-

Pichichero 1997 *(Continued)*

	dren who had received DTwP primary series were re-randomised to receive 1 of the 12 DTaP vaccines or DTwP 1. DTaP: Biocine[1] 2. DTaP: SSVI[1] 3. DTaP: Connaught/Biken[2] 4. DTaP: Michigan[2] 5. DTaP: Pasteur-Merieux[2] 6. DTaP: SKB[2] 7. DTaP: Biocine[3P] 8. DTaP: SKB[3P] 9. DTaP: Connaught[4] 10. DTaP: Porton[4] 11. DTaP: Lederle/Takeda[4] 12. DTaP: Connaught[5] 13. DTwP: Lederle[W] Number studied: 1079 aP.aP, 187 wP.aP, 16 wP.wP Dose schedule: 1 dose (15 to 20 months) Concurrent vaccine: OPV
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: within 3 days of dose (possibly 2 weeks) 6. Hypotonic-hyporesponsive episodes: within 3 days of dose (possibly 2 weeks) 7. Minor adverse events: fever, irritability, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	Most failures to proceed from primary series to booster study were due to prior receipt of booster dose or reluctance regarding venipuncture. Possible selection bias exists due to loss of 39% of subjects after primary series, although authors state that DTwP primary series recipients with severe reactions were not less likely to proceed to the booster study. Safety results are combined for all acellular vaccines. Data for drowsiness and vomiting were collected but not reported (stated to be not significantly different between groups) Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not reported
Allocation concealment (selection bias)	Unclear risk	Vaccine vials labelled with letter codes instead of type/manufacturer details but unable to ascertain from study report whether vaccinators remained unaware of what each code represented
Blinding (performance bias and detection bias) All outcomes	Low risk	Vaccinators took no further part in the study and did not participate in follow-up data collection, so outcome assessment was double-blind
Blinding of participants and personnel (performance bias)	Low risk	

Pichichero 1997 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Data for drowsiness and vomiting were collected but not reported (stated to be not significantly different between groups)

Pichichero 2000

Methods	Site: USA Design: parallel-group RCT. Subjects had been randomised and received primary series in Decker 1995 and Pichichero 1997. Details of allocation concealment in Decker 1995 and Pichichero 1997. Parents recorded adverse events on forms. Parents elected to remain blinded and allow child to participate in booster study
Participants	Included: age 4 to 6 years of age who had completed earlier National Institute of Allergy and Infectious Diseases (NIAID) multicentre acellular pertussis vaccine trials in Decker 1995, Pichichero 1997 Excluded: subjects with contraindications or precautions to immunisations as specified in the Report of the Committee on Infectious Diseases of the American Academy of Pediatrics
Interventions	Booster (same aPaPaP, mixed aPaPaP, wPaPaP versus wPwPwP) 1. DTaP: Connaught/Biken[2] 2. DTaP: Connaught[2] 3. DTaP: Chiron [3] 4. DTaP: SKB[3] 5. DTaP: Connaught[4] 6. DTaP: Lederle [4] 7. DTwP: Lederle [W] Number of studies: 316 aP, 10 wP Dose schedule: 1 dose (4 to 6 years) Concurrent vaccine: OPV
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, irritability, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	Possible bias due to parental self selection of 83% subset who continued in the study Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement

Pichichero 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details not reported

Podda 1994

Methods	Site: Italy Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 2 months; healthy Excluded: not stated
Interventions	Primary series (aP versus wP) 1. DTaP: Biocine[3] 2. DTwP: Biocine[W] Number randomised: 240 aP, 240 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: until 3rd dose (4 months after 1st dose) 4. Encephalopathy: until 7 days after 3rd dose 5. Convulsions: until 7 days after 3rd dose 6. Hypotonic-hyporesponsive episodes: until 7 days after 3rd dose 7. Minor adverse events: anorexia, drowsiness, fever, irritability, vomiting, pain/tenderness, redness, swelling/induration within 2 days of each dose
Notes	No statement on antipyretic/analgesic use

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Details not reported

PVSG 1998

Methods	Site: Germany Design: parallel-group RCT Active case ascertainment (bi-weekly telephone). Case incidence adjusted for follow-up duration by use of incidence density. Parents recorded adverse events in diary
Participants	Included: age 2 to 4 months; healthy Excluded: known or suspected neurological disorder, immunological dysfunction or immunosuppressive therapy; birth weight < 2 kg; significant congenital abnormality or chronic illness; history of convul-

PVSG 1998 *(Continued)*

	sions; hereditary disease in the family with an increased risk of neurological manifestations after vaccination (for example, tuberous sclerosis); immunoglobulins in previous 4 weeks
Interventions	Primary series + booster (aP.aP versus wP.wP) 1. DTaP: Lederle/Takeda[4] 2. DTwP: Lederle[W] A third non-randomised group received DT (n = 1739) Number randomised: 4273 aP, 4259 wP Dose schedule: 4 doses (dose 1: 2 to 4 months; dose 2: at least 6 weeks after dose 1; dose 3: at least 6 weeks after dose 2 but before 1st birthday; dose 4: at least 6 months after dose 3, at 15 to 18 months of age). DT vaccinees received doses at times corresponding to doses 1, 2 and 4 of the randomised schedule Concurrent vaccines: not stated
Outcomes	1. Efficacy: the main efficacy assessment was conducted in children who had received all 3 doses of study vaccine and commenced 2 weeks after the third dose (or at age 7 months in DT recipients). Follow-up duration not reported but must have been at least 12 months, based on reported study dates. The number of participants in the efficacy analysis was not stated and data were not available for the intention-to-treat population at the time of this review. Several case definitions; that closest to a definition selected for review was: whooping cough = 21 days or more of cough with paroxysms, whoops or post-tussive vomiting, confirmed by culture, serology or contact with a culture-proven case). Results for other case definitions were not reported at the time of this review 2. Primary series non-completion (due to adverse events): no data 3. Deaths: until at least 6 months after 3rd dose (12 months after 1st dose) 4. Encephalopathy: until at least 6 months after 3rd dose (12 months after 1st dose) 5. Convulsions: within 3 days of each dose 6. Hypotonic-hyporesponsive episodes: until at least 6 months after 3rd dose (12 months after 1st dose) 7. Minor adverse events: anorexia, drowsiness, fever, irritability, prolonged crying, redness, swelling/induration within 3 days of each dose
Notes	Macrolide prophylaxis was not documented During the total period of the study (until at least 6 months after 3rd dose) convulsions occurred in 46 (1.1%) DTaP, 56 (1.3%) DTwP and 19 (1.1%) DT recipients Redness and induration were reported only for the moderate/severe category No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Rothstein 1993

Methods	Site: USA Design: parallel-group RCT Parents recorded adverse events on forms
Participants	Included: age 15 to 16 months; healthy; completed DTwP primary series Excluded: past pertussis, mumps, measles or rubella; previous DTaP; contraindication to DTP, OPV or MMR vaccine

Rothstein 1993 *(Continued)*

Interventions	Booster (wP.aP versus wP.wP) 1. DTaP: Lederle/Takeda[4] 2. DTwP: Lederle[W] Number randomised: 48 aP, 49 wP Dose schedule: 1 dose (age 15 to 16 months) Concurrent vaccine: OPV and MMR vaccine
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): excluded (booster) 3. Deaths: excluded (booster) 4. Encephalopathy: excluded (booster) 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, drowsiness, fever, irritability, pain/tenderness, redness, swelling/induration within 3 days of dose
Notes	No "severe" or contraindicating adverse events but these not defined in the study report. DTaP or DTwP administered at same time as OPV and MMR (but MMR at a different injection site) Reactive antipyretic/analgesic use allowed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Simondon 1996

Methods	Site: Senegal Design: parallel-group RCT Study physicians visited homes, recorded adverse events and measured temperature at 2 to 3 days after each dose. Parents interviewed regarding deaths
Participants	Included: age 2 months Excluded: not stated
Interventions	Primary series (aP versus wP) 1. DTaP: Pasteur-Merieux[2] 2. DTwP: Pasteur-Merieux[W] Number randomised: 141 aP, 145 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: Bacille Calmette-Guérin (BCG) (2 months); IPV (2, 4, 6 months), measles and yellow fever (6 months)
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): no data 3. Deaths: within 2 months of any dose (until 5 months after 1st dose) 4. Encephalopathy: no data 5. Convulsions: no data

Simondon 1996 *(Continued)*

6. Hypotonic-hyporesponsive episodes: no data
7. Minor adverse events: anorexia, drowsiness, irritability, vomiting within 2 to 3 days of first dose; fever, pain/tenderness, redness, swelling/induration at 2 to 3 days after first dose

Notes	Study conducted in Senegal in an area with high background infant mortality. High loss to follow-up (see text). Data included for 1st dose only. Second and third doses excluded because follow-up for those doses was less than 80% in both vaccine groups. Irritability and pain were reported only for the moderate/severe category No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Simondon 1997

Methods	Site: Senegal Design: parallel-group RCT Active case ascertainment (weekly visit by field workers). Case incidence adjusted for follow-up duration by use of incidence density. Field workers recorded adverse events during 2 weekly visits after each dose
Participants	Included: age 2 months Excluded: serious congenital defect; serious chronic illness manifested as failure to thrive or cardiac failure; history of seizure or neurological disorder; history of pertussis
Interventions	Primary series (aP versus wP) 1. DTaP: Pasteur-Merieux[2] 2. DTaP: Pasteur-Merieux[W] Number studied (efficacy): 1847 aP, 1772 wP Number studied (safety): 2396 aP, 2379 wP Dose schedule: 3 doses (2, 4, 6 months) Concurrent vaccine: BCG (2 months); IPV (2, 4, 6 months)
Outcomes	1. Efficacy: children randomised in a 1:1 ratio but the number of children receiving each vaccine was not stated. A total of 3619 were studied for efficacy (1847 DTaP and 1772 DTwP). The main efficacy assessment was conducted in children who had received all 3 doses of study vaccine, commenced 28 days after the third dose and lasted for a mean of 22 months. Efficacy data were not available for the intention-to-treat population. Several case definitions used. That closest to 1 of the definitions selected for review was: whooping cough = 21 days or more of paroxysmal cough with confirmation by culture or appropriate serology. Results were not reported for other case definitions at the time of review 2. Primary series non-completion (due to adverse events): no data 3. Deaths: within 2 months of any trial dose (until 5 months after 1st dose) 4. Encephalopathy: no data 5. Convulsions: within 2 days of any dose 6. Hypotonic-hyporesponsive episodes: within 2 days of any dose 7. Minor adverse events: not recorded systematically due to trial conditions. Available results were reported combined across 3 doses

Simondon 1997 *(Continued)*

Notes	Number randomised not stated. A total of 4821 were studied for safety. No statement on macrolide prophylaxis Study conducted in Senegal in an area with high background infant mortality. Deaths recorded are due to any cause and may include some due to injury. No breakdown by vaccine group of the number of deaths due to infection A household contact substudy compared pertussis attack rates with non-randomised unvaccinated controls No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Tian 1993

Methods	Site: China Design: parallel-group RCT Adverse event recording method not stated
Participants	Included: age 3 to 6 months Excluded: not stated
Interventions	Primary series (aP versus wP versus P) 1. aP: Canton[2] 2. wP: Wuhan[W] 3. Placebo Number studied: 105 aP, 101 wP, 100 P Dose schedule: 3 doses at 4-week intervals Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): no data 3. Deaths: no data 4. Encephalopathy: no data 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: fever, swelling/induration at 2 days after each dose
Notes	Number randomised not stated Data for redness and tenderness excluded (combined as 1 outcome in study report) No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Trollfors 1995

Methods	Site: Sweden Design: DB parallel-group RCT Passive and active case ascertainment (parent report and monthly telephone). Case incidence adjusted for follow-up duration by use of incidence density. Parents recorded adverse events in diary
Participants	Included: full-term, healthy infants Excluded: none stated
Interventions	Primary series (aP versus DT) 1. DTaP: Amvax[1] 2. DT Number randomised: 1724 aP, 1726 DT Dose schedule: 3 doses (3, 5, 12 months) Concurrent vaccine: nil
Outcomes	1. Efficacy (median 17.5 months follow-up after 3rd dose). Several case definitions used. Those closest to the definitions selected for review were: whooping cough = 21 days or more of paroxysmal cough with confirmation by culture, appropriate serology or household contact with a culture-confirmed case; pertussis disease = cough for 7 days or more with confirmation as above 2. Primary series non-completion (due to adverse events): included 3. Deaths: until (median) 17.5 months after 3rd dose 4. Encephalopathy: no data 5. Convulsions: within 7 days of any dose 6. Hypotonic-hyporesponsive episodes: within 7 days of any dose 7. Minor adverse events: excluded. Data were reported only as percentages, rounded to nearest percent (e.g. 6%). With approximately 1700 participants in each group, numeric values could not be calculated with sufficient confidence for inclusion in the review
Notes	Macrolide prophylaxis not used (not recommended in Sweden for age > 6 months and main efficacy follow-up in this study started at age 10 months) Target adverse events assessed in the trial included anorexia, irritability, fever, redness and induration. Data for anorexia and irritability were collected but not reported (stated to be equally frequent with both vaccines). Data for other events are not included in the review because the number of children experiencing the event could not be determined with sufficient confidence (fever) and because data were reported only for the moderate/severe category (redness and induration) No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Vaccines indistinguishable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind

Trollfors 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Data for anorexia and irritability were collected but not reported (stated to be equally frequent with both vaccines)

Vanura 1994

Methods	Site: Austria and Switzerland Design: parallel-group RCT Parents recorded adverse events in diary
Participants	Included: age 10 to 16 weeks; healthy Excluded: not stated
Interventions	Primary series (aP versus wP) 1. DTaP: SKB[2] 2. DTaP: SKB[2] 3. DTwP: Behringwerke[W] Number studied: 200 aP, 101 wP Dose schedule: 3 doses (3, 4, 5 months) Concurrent vaccine: not stated
Outcomes	1. Efficacy: not studied 2. Primary series non-completion (due to adverse events): included 3. Deaths: no data 4. Encephalopathy: no data 5. Convulsions: no data 6. Hypotonic-hyporesponsive episodes: no data 7. Minor adverse events: anorexia, fever, irritability, pain/tenderness, redness, swelling/induration within 2 days of each dose
Notes	The 2 acellular vaccine formulations contained differing amounts of PT. In this review, data for the 2 acellular vaccine formulations are combined Total 308 enrolled but cannot determine number randomised to each vaccine. Denominator for primary series non-completion is the number with adverse event data at the first dose (200 DTaP, 101 DTwP) No statement on antipyretic/analgesic use

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Details not reported

Interventions

Primary series: primary series pertussis immunisation performed in the study.
Booster: pertussis booster immunisation performed in the study.
The pertussis immunisation history of study participants (including doses received in the study under consideration) is indicated in the form (X.Y.Z). The first element (X) indicates the type of pertussis vaccine received in the primary series (aP = acellular, wP = whole-cell, P = placebo, DT = diphtheria-tetanus toxoids). The second element (Y) indicates the vaccine type received at the 15- to 24-month booster and the third element (Z) indicates the vaccine type received at the 4- to 6-year booster. For example: aP = acellular primary series; wP.wP.aP = acellular 4- to 6-year booster after whole-cell primary series and whole-cell 18- to 24-month booster.
The vaccines used in each study are further identified by type, manufacturer and number, and type of pertussis components, as follows:
Vaccine types:
aP: acellular pertussis vaccine
DTaP: diphtheria-tetanus-acellular pertussis vaccine
wP: whole-cell pertussis vaccine
DTwP: diphtheria-tetanus-whole-cell pertussis vaccine
DT: diptheria-tetanus (toxoids) vaccine
DTP: diptheria-tetanus (toxoids) pertussis vaccine
P: placebo
Manufacturer abbreviations:
CAMR: Centre for Applied Microbiology and Research
Canton: Canton Department of Health
JNIH: Japanese National Institute of Health
Massachusetts: Massachusetts Public Health Laboratory
Michigan: Michigan Department of Health
Porton: Porton Products (later Speywood Pharmaceuticals)
SKB: SmithKline Beecham
SSVI: Swedish Serum and Vaccine Institute
Wuhan: Wuhan Department of Health
Pertussis components (in square brackets after manufacturer: [1] = PT (inactivated pertussis toxin); [2] = PT+FH (filamentous haemagglutinin); [3] = PT+FH+Prn (pertactin); [4] = PT+FH+Fim2&3 (fimbrial antigen serotypes 2 and 3) or PT+FH+Prn+Fim2 or PT+FH+Prn +Fim (serotype unspecified); [5] = PT+FH+Prn+Fim2&3; [W] = killed whole *Bordetella pertussis* organisms.

Outcomes

Non-completion of the primary series due to adverse events, defined as withdrawal from the study due to an adverse event or events before completion of all scheduled doses of the primary series.
Deaths, encephalopathy, convulsions, hypotonic-hyporesponsive episodes (HT-HR): these events generally led to withdrawal from the study and were reported and analysed across all doses in a study.
Minor adverse events: fever, irritability, drowsiness, anorexia, vomiting, redness, pain/tenderness and swelling/induration. These events usually did not lead to withdrawal and data were reported and analysed separately for each dose within a study. Data for these events were not combined across doses (see 'Methods' section of the review for reasons).

Other abbreviations

BCG: Bacille Calmette-Guérin
DB: double-blind (claim made in study report)
Hib: *Haemophilus influenzae* type B vaccine
IPV: inactivated polio vaccine
MMR: measles-mumps-rubella vaccine
OPV: oral polio vaccine
RCT: randomised controlled trial
SIDS: sudden infant death syndrome

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

Study	Reason for exclusion
Annunziato 1994	Booster Efficacy: not studied Primary series non-completion: booster Deaths: booster, no data Encephalopathy: booster, no data Convulsions: no data Hypotonic-hyporesponsive episodes: no data Minor AEs: data expressed as percentages in graph form only. Could not be converted to numeric values with sufficient accuracy

Study	Reason for exclusion
Bernstein 1993	Booster Efficacy: not studied Primary series non-completion: booster Deaths: booster, no data Encephalopathy: booster, no data Convulsions: no data Hypotonic-hyporesponsive episodes: no data Minor AEs: data expressed as percentages in graph form only. Could not be converted to numeric values with sufficient accuracy
Bernstein 1995	Primary series Efficacy: not studied Primary series non-completion: cannot determine number studied for each vaccine Deaths: cannot determine number studied for each vaccine Encephalopathy: cannot determine number studied for each vaccine Convulsions: cannot determine number studied for each vaccine Hypotonic-hyporesponsive episodes: cannot determine number studied for each vaccine Minor AEs: data combined across 3 doses. Cannot determine number receiving each vaccine or experiencing AEs at each dose
Hori 1994	Primary series Efficacy: not studied Primary series non-completion: no data Deaths: no data Encephalopathy: no data Convulsions: no data Hypotonic-hyporesponsive episodes: no data Minor AEs: unable to extract data separately for each event
Hori 1995	Booster Efficacy: not studied Safety: not reported (immunogenicity only)
Just 1991	Primary series Report of 2 studies comparing acellular versus whole-cell primary series immunisation (1 study in Turkey, 1 in Switzerland); Swiss study possibly reported in Vanura 1994 Efficacy: not studied Primary series non-completion: no data Deaths: 1 death (pneumonia) in acellular arm in Turkey but cannot determine number receiving each vaccine Encephalopathy: cannot determine number studied for each vaccine Convulsions: cannot determine number studied for each vaccine Hypotonic-hyporesponsive episodes: cannot determine number studied for each vaccine Minor AEs: unable to determine number studied for each vaccine (Turkey). Swiss results were combined across doses or across different reaction types
Miller 1997	Primary series Efficacy: not studied Primary series non-completion: no data Deaths: no data Encephalopathy: no data Convulsions: no data Hypotonic-hyporesponsive episodes: no data Minor AEs: data combined across 3 doses. Unable to extract data separately for each dose This report examines 2-4-6 and 3-5-10 month immunisation schedules. It includes some data previously reported in Miller 1991
Murphy 1983	Primary series

Study	Reason for exclusion
	Efficacy: not studied Primary series non-completion: no data Deaths: cannot determine number studied for each vaccine Encephalopathy: cannot determine number studied for each vaccine Convulsions: cannot determine number studied for each vaccine Hypotonic-hyporesponsive episodes: cannot determine number studied for each vaccine Minor AEs: cannot determine number studied for each vaccine
Pichichero 1987	Booster Efficacy: not studied Primary series non-completion: booster Deaths: follow-up of only 65% of participants Encephalopathy: follow-up of only 65% of participants Convulsions: follow-up of only 65% of participants Hypotonic-hyporesponsive episodes: follow-up of only 65% of participants Minor AEs: follow-up of only 65% of participants
Shek 2003	Primary series Efficacy: not studied Primary series non-completion: no data Deaths: no data Encephalopathy: no data Convulsions: no data Hypotonic-hyporesponsive episodes: no data Minor AEs: data combined across 3 doses

AEs: adverse events

DATA AND ANALYSES

Comparison 1. Safety: acellular versus whole-cell pertussis vaccines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary series non-completion due to adverse events	14	108909	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.12, 0.43]
2 Death (all causes)	16	122451	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.62, 1.22]
2.1 Primary series	16	122451	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.62, 1.22]
3 Death (infection)	13	34498	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.23, 4.16]
3.1 Primary series	13	34498	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.23, 4.16]
4 Encephalopathy	9	113762	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Primary series	9	113762	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Convulsions	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Primary series	15	124387	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.31, 0.73]
5.2 Booster	11	2647	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.02, 11.20]
6 Hypotonic hyporesponsive episodes	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Primary series	11	121573	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.08, 0.81]
6.2 Booster	7	2487	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Anorexia	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Primary series: Dose 1	11	19632	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.32, 0.57]
7.2 Primary series: Dose 2	8	18501	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.33, 0.60]
7.3 Primary series: Dose 3	9	18646	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.43, 0.60]
7.4 aP booster (previous wP) versus wP booster (previous wP)	14	1939	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.30, 0.54]
7.5 aP booster (previous aP) versus wP booster (previous wP)	4	8447	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.31, 0.58]
8 Drowsiness	25		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Primary series: Dose 1	12	20490	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.45, 0.68]
8.2 Primary series: Dose 2	9	19308	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.60]
8.3 Primary series: Dose 3	10	19430	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.40, 0.77]
8.4 aP booster (previous wP) versus wP booster (previous wP)	13	2254	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.41, 0.56]

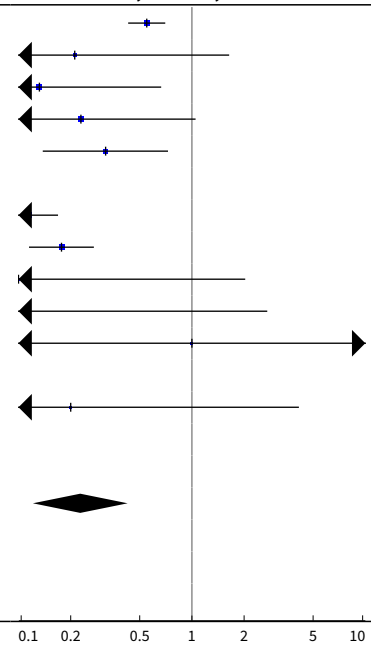
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.5 aP booster (previous aP) versus wP booster (previous wP)	3	8367	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.44, 0.54]
9 Fever	46		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Primary series: Dose 1	19	23267	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.13, 0.20]
9.2 Primary series: Dose 2	17	22001	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.26, 0.37]
9.3 Primary series: Dose 3	17	21731	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.30, 0.38]
9.4 aP booster (previous wP) versus wP booster (previous wP)	24	3381	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.26, 0.43]
9.5 aP booster (previous aP) versus wP booster (previous wP)	8	9879	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.22, 0.55]
10 Irritability/fretfulness	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Primary series: Dose 1	15	20707	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.42, 0.56]
10.2 Primary series: Dose 2	12	19429	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.41, 0.56]
10.3 Primary series: Dose 3	13	19511	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.47, 0.59]
10.4 aP booster (previous wP) versus wP booster (previous wP)	17	2596	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.28, 0.47]
10.5 aP booster (previous aP) versus wP booster (previous wP)	6	9856	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.44, 0.51]
11 Prolonged crying	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Primary series: Dose 1	8	17184	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.11, 0.19]
11.2 Primary series: Dose 2	6	16347	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.24, 0.35]
11.3 Primary series: Dose 3	7	16545	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.24, 0.46]
11.4 aP booster (previous wP) versus wP booster (previous wP)	6	996	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.10, 0.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.5 aP booster (previous aP) versus wP booster (previous wP)	2	7943	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.02, 3.12]
12 Vomiting	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Primary series: Dose 1	8	11450	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.66, 0.88]
12.2 Primary series: Dose 2	7	10985	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.45, 0.86]
12.3 Primary series: Dose 3	7	10813	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.04]
12.4 aP booster (previous wP) versus wP booster (previous wP)	6	744	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.22, 1.11]
12.5 aP booster (previous aP) versus wP booster (previous wP)	1	86	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.10, 11.34]
13 Pain/tenderness	35		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Primary series: Dose 1	13	14180	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.16, 0.25]
13.2 Primary series: Dose 2	11	13186	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.15, 0.22]
13.3 Primary series: Dose 3	12	13333	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.17, 0.24]
13.4 aP booster (previous wP) versus wP booster (previous wP)	21	3051	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.36, 0.53]
13.5 aP booster (previous aP) versus wP booster (previous wP)	5	2263	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.32, 0.58]
14 Redness	35		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Primary series: Dose 1	13	7153	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.23, 0.39]
14.2 Primary series: Dose 2	12	6427	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.29, 0.51]
14.3 Primary series: Dose 3	13	6632	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.41, 0.54]
14.4 aP booster (previous wP) versus wP booster (previous wP)	21	3055	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.44, 0.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.5 aP booster (previous aP) versus wP booster (previous wP)	5	2263	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.52, 0.80]
15 Swelling/induration	39		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Primary series: Dose 1	15	14612	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.19, 0.31]
15.2 Primary series: Dose 2	14	13779	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.28, 0.45]
15.3 Primary series: Dose 3	15	13916	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.29, 0.54]
15.4 aP booster (previous wP) versus wP booster (previous wP)	22	3301	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.46, 0.57]
15.5 aP booster (previous aP) versus wP booster (previous wP)	6	2421	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.58, 0.80]

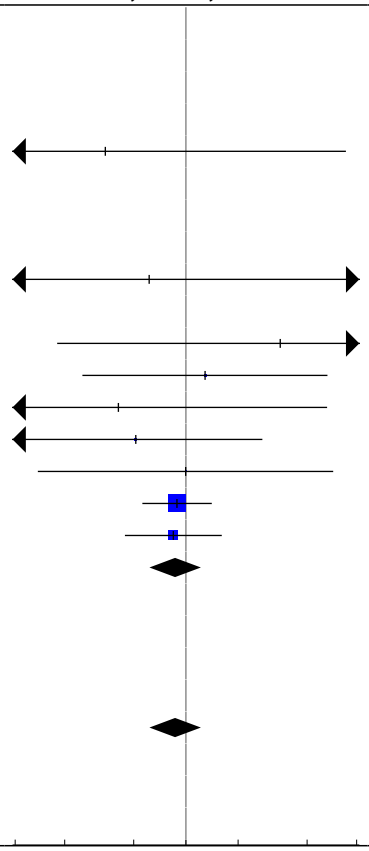
Analysis 1.1. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 1 Primary series non-completion due to adverse events.

Study or subgroup	Acellular vaccine n/N	Whole-cell vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
AHGSPV 1997	168/62172	102/20720		17.03%	0.55[0.43,0.7]
Anderson 1988	1/19	5/20		6.12%	0.21[0.03,1.64]
Blennow 1988	2/240	5/79		8.1%	0.13[0.03,0.67]
Blumberg 1991	2/245	9/252		8.65%	0.23[0.05,1.05]
Decker 1995	14/1827	9/373		13.41%	0.32[0.14,0.73]
Edwards 1989a	0/23	0/27			Not estimable
Greco 1996	31/9368	135/4678		16.39%	0.11[0.08,0.17]
Gustafsson 1996	29/5153	67/2102		16.15%	0.18[0.11,0.27]
Halperin 1994a	0/67	2/33		3.5%	0.1[0,2.03]
Halperin 1996	0/324	1/108		3.18%	0.11[0,2.72]
Miller 1991	1/94	1/94		4.02%	1[0.06,15.75]
Pichichero 1993	0/88	0/22			Not estimable
Podda 1994	0/240	2/240		3.46%	0.2[0.01,4.14]
Vanura 1994	0/200	0/101			Not estimable
Total (95% CI)	**80060**	**28849**		**100%**	**0.23[0.12,0.43]**
Total events: 248 (Acellular vaccine), 338 (Whole-cell vaccine)					
Heterogeneity: Tau^2=0.59; Chi^2=56.23, df=10(P<0.0001); I^2=82.22%					
Test for overall effect: Z=4.62(P<0.0001)					



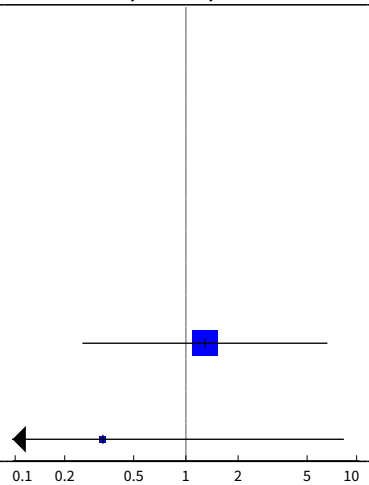
Analysis 1.2. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 2 Death (all causes).

Study or subgroup	Acellular vaccine n/N	Whole-cell-vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Primary series					
Anderson 1988	0/19	0/20			Not estimable
Blennow 1988	0/240	0/79			Not estimable
Edwards 1989a	0/23	0/27			Not estimable
Blumberg 1991	0/245	1/252		1.14%	0.34[0.01,8.37]
Feldman 1993	0/109	0/36			Not estimable
Podda 1994	0/240	0/240			Not estimable
Halperin 1994a	0/67	0/33			Not estimable
Decker 1995	1/1827	0/373		1.14%	0.61[0.03,15.04]
Halperin 1996	0/324	0/108			Not estimable
Greco 1996	3/9368	0/4678		1.32%	3.5[0.18,67.66]
Afari 1996	5/266	2/137		4.39%	1.29[0.25,6.55]
Gustafsson 1996	1/5153	1/2102		1.51%	0.41[0.03,6.52]
Simondon 1996	2/141	4/145		4.11%	0.51[0.1,2.76]
PVSG 1998	2/4273	2/4259		3.03%	1[0.14,7.07]
Simondon 1997	34/2396	38/2379		55.12%	0.89[0.56,1.41]
AHGSPV 1997	33/62172	13/20720		28.24%	0.85[0.45,1.61]
Subtotal (95% CI)	**86863**	**35588**		**100%**	**0.87[0.62,1.22]**
Total events: 81 (Acellular vaccine), 61 (Whole-cell-vaccine)					
Heterogeneity: Tau^2=0; Chi^2=2.14, df=8(P=0.98); I^2=0%					
Test for overall effect: Z=0.83(P=0.41)					
Total (95% CI)	**86863**	**35588**		**100%**	**0.87[0.62,1.22]**
Total events: 81 (Acellular vaccine), 61 (Whole-cell-vaccine)					
Heterogeneity: Tau^2=0; Chi^2=2.14, df=8(P=0.98); I^2=0%					
Test for overall effect: Z=0.83(P=0.41)					

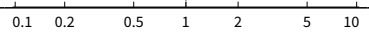


Analysis 1.3. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 3 Death (infection).

Study or subgroup	Acellular vaccine n/N	Whole-cell-vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Primary series					
Anderson 1988	0/19	0/20			Not estimable
Blennow 1988	0/240	0/79			Not estimable
Edwards 1989a	0/23	0/27			Not estimable
Blumberg 1991	0/245	0/252			Not estimable
Feldman 1993	0/109	0/36			Not estimable
Halperin 1994a	0/67	0/33			Not estimable
Podda 1994	0/240	0/240			Not estimable
Decker 1995	0/1827	0/373			Not estimable
Greco 1996	0/9368	0/4678			Not estimable
Afari 1996	5/266	2/137		79.47%	1.29[0.25,6.55]
Halperin 1996	0/324	0/108			Not estimable
Gustafsson 1996	0/5153	0/2102			Not estimable
PVSG 1998	0/4273	1/4259		20.53%	0.33[0.01,8.15]

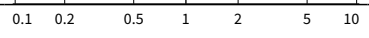


Study or subgroup	Acellular vaccine n/N	Whole-cell-vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**22154**	**12344**		**100%**	**0.97[0.23,4.16]**
Total events: 5 (Acellular vaccine), 3 (Whole-cell-vaccine)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=0.03(P=0.97)					
Total (95% CI)	**22154**	**12344**		**100%**	**0.97[0.23,4.16]**
Total events: 5 (Acellular vaccine), 3 (Whole-cell-vaccine)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=0.03(P=0.97)					



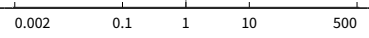
Analysis 1.4. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 4 Encephalopathy.

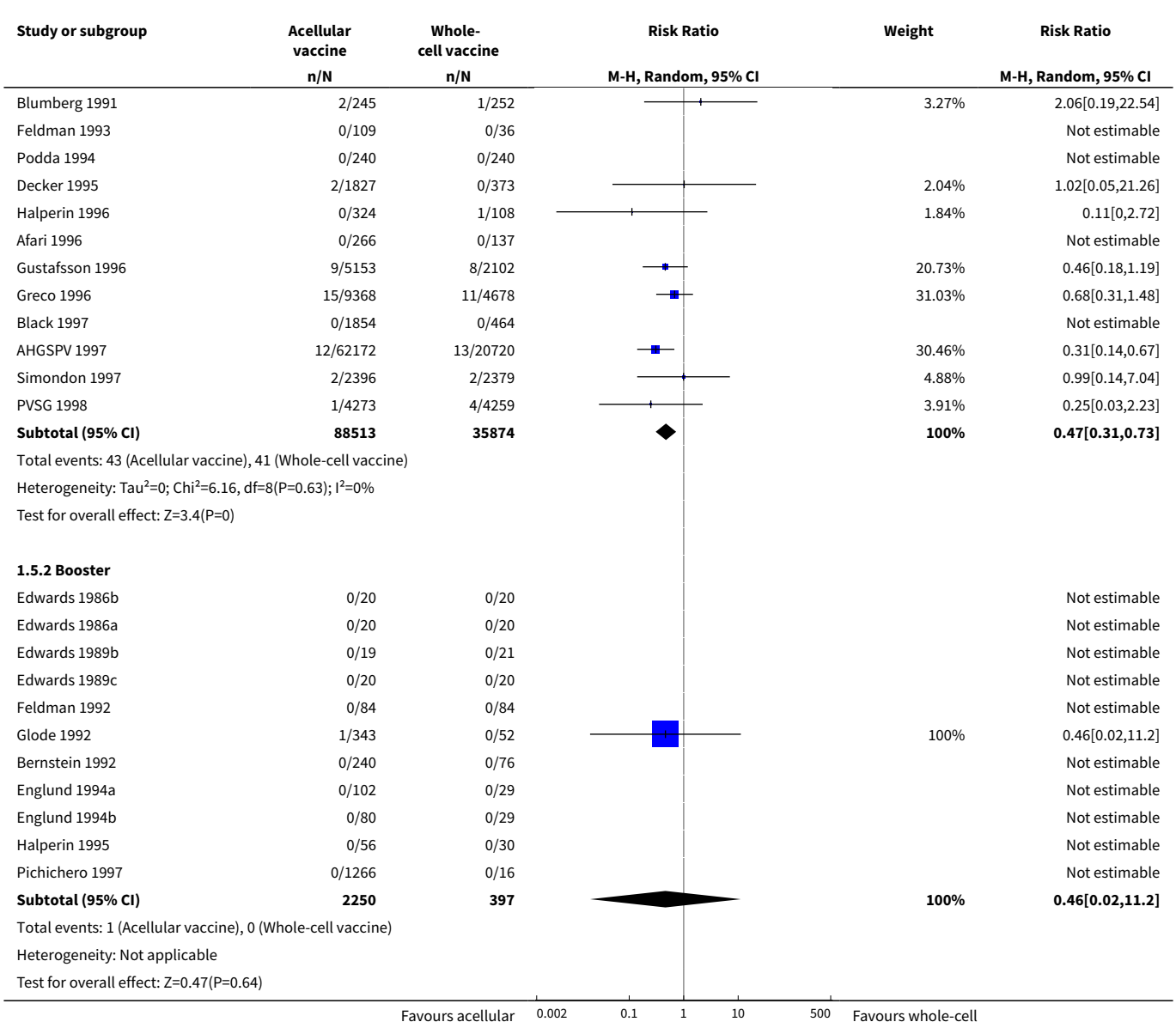
Study or subgroup	Acellular vaccine n/N	Whole-cell vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Primary series					
Blennow 1988	0/240	0/79			Not estimable
Anderson 1988	0/19	0/20			Not estimable
Edwards 1989a	0/27	0/27			Not estimable
Feldman 1993	0/109	0/36			Not estimable
Podda 1994	0/240	0/240			Not estimable
Greco 1996	0/9368	0/4678			Not estimable
Gustafsson 1996	0/5153	0/2102			Not estimable
PVSG 1998	0/4273	0/4259			Not estimable
AHGSPV 1997	0/62172	0/20720			Not estimable
Subtotal (95% CI)	**81601**	**32161**			**Not estimable**
Total events: 0 (Acellular vaccine), 0 (Whole-cell vaccine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**81601**	**32161**			**Not estimable**
Total events: 0 (Acellular vaccine), 0 (Whole-cell vaccine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



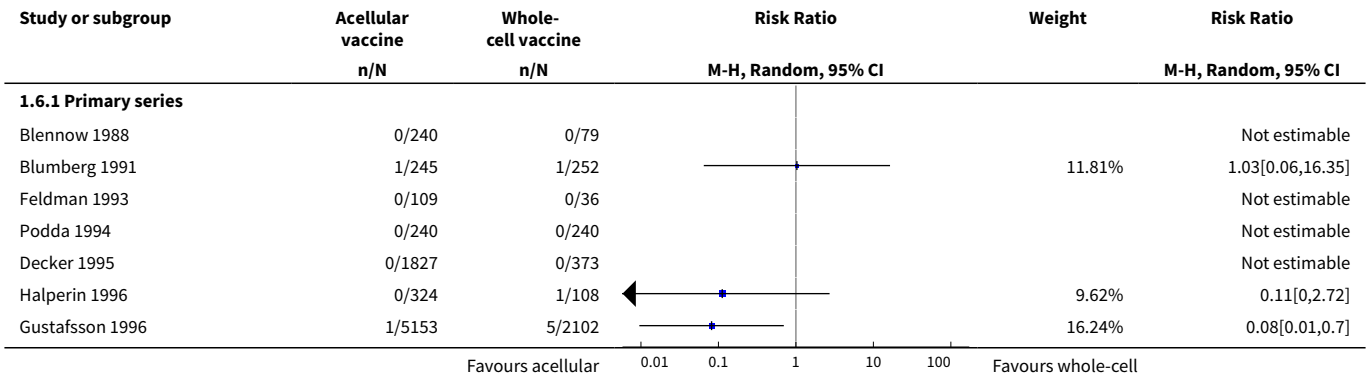
Analysis 1.5. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 5 Convulsions.

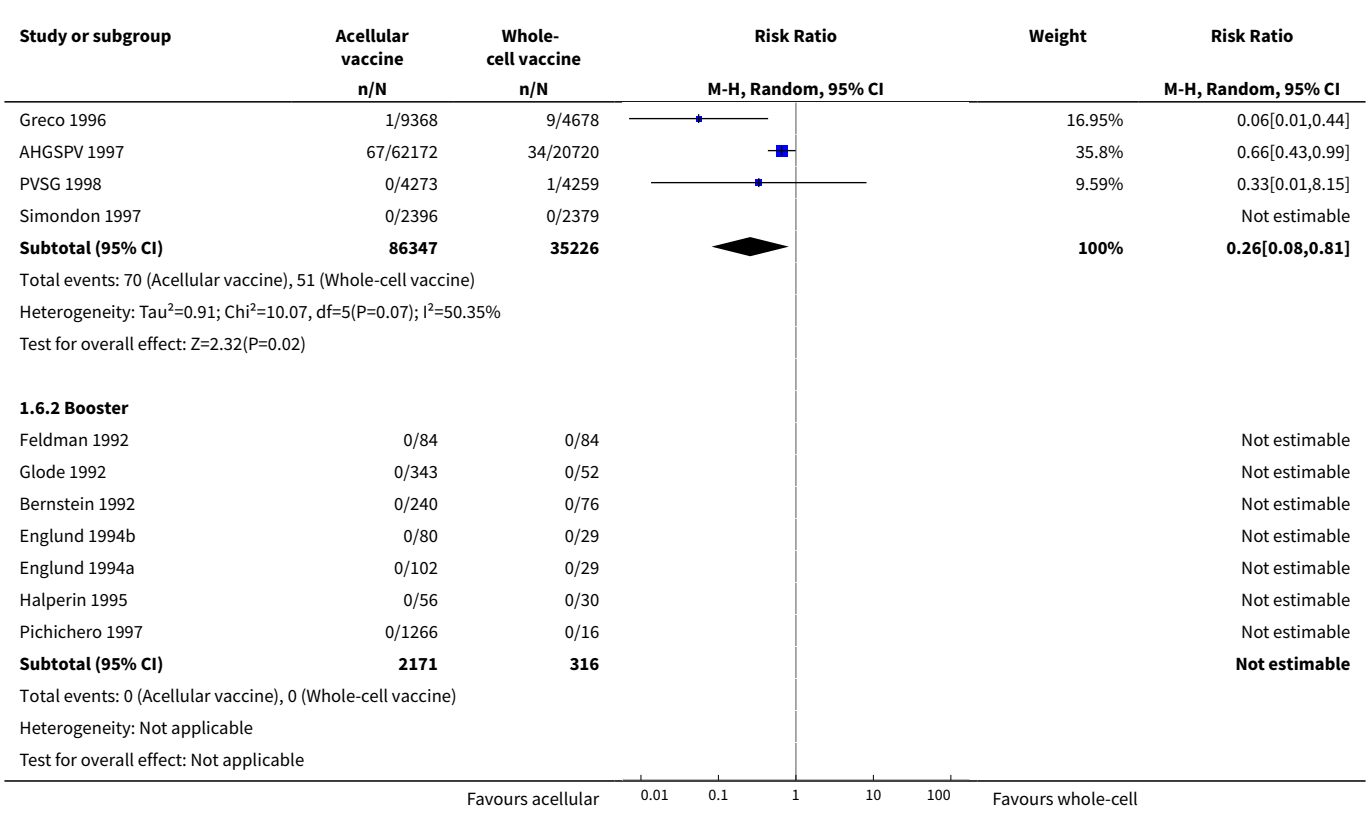
Study or subgroup	Acellular vaccine n/N	Whole-cell vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Primary series					
Blennow 1988	0/240	1/79		1.84%	0.11[0,2.69]
Anderson 1988	0/19	0/20			Not estimable
Edwards 1989a	0/27	0/27			Not estimable



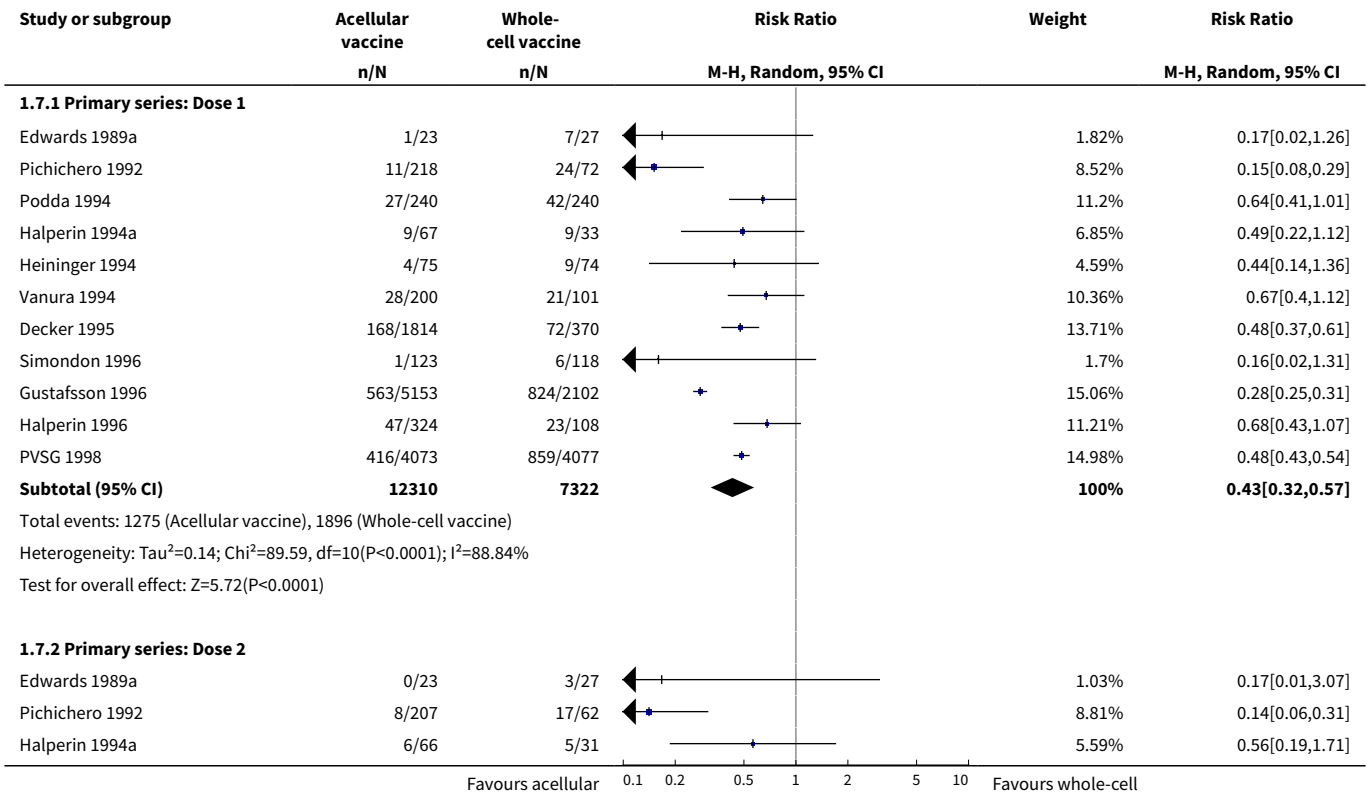


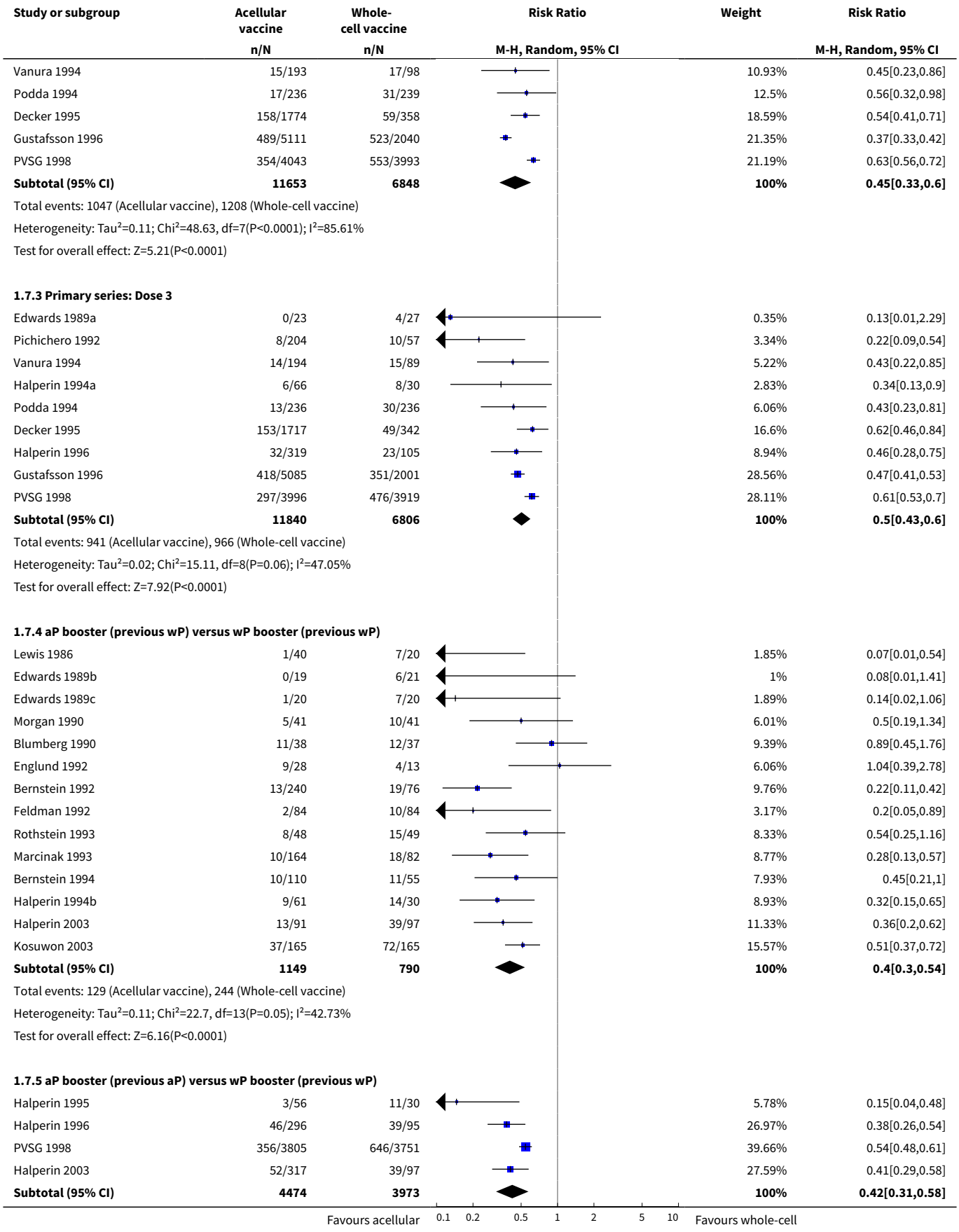
Analysis 1.6. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 6 Hypotonic hyporesponsive episodes.



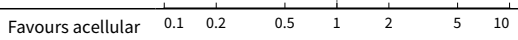


Analysis 1.7. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 7 Anorexia.



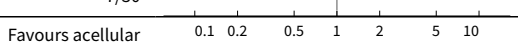


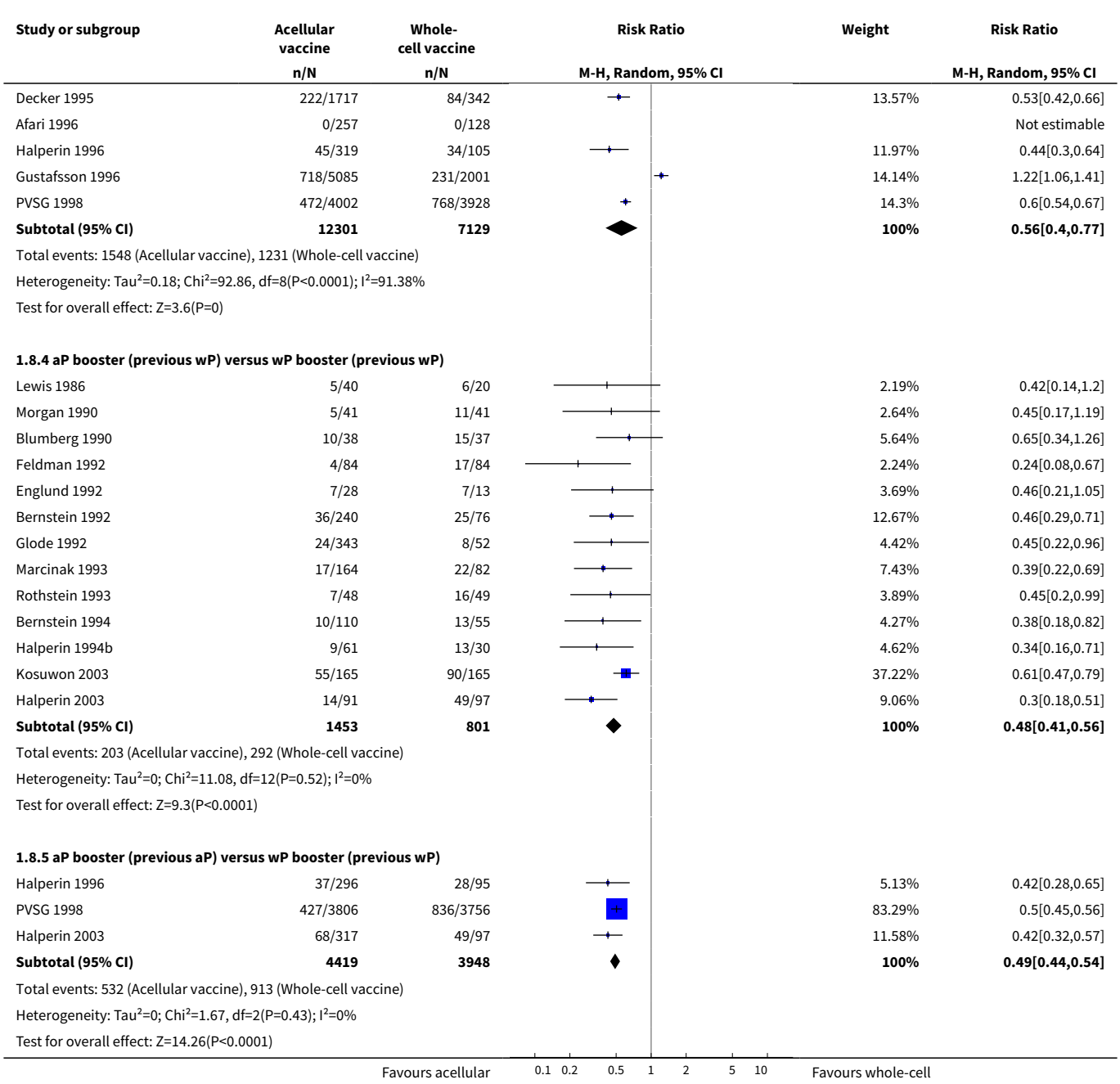
Study or subgroup	Acellular vaccine n/N	Whole-cell vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 457 (Acellular vaccine), 735 (Whole-cell vaccine)					
Heterogeneity: Tau²=0.06; Chi²=9.52, df=3(P=0.02); I²=68.49%					
Test for overall effect: Z=5.46(P<0.0001)					



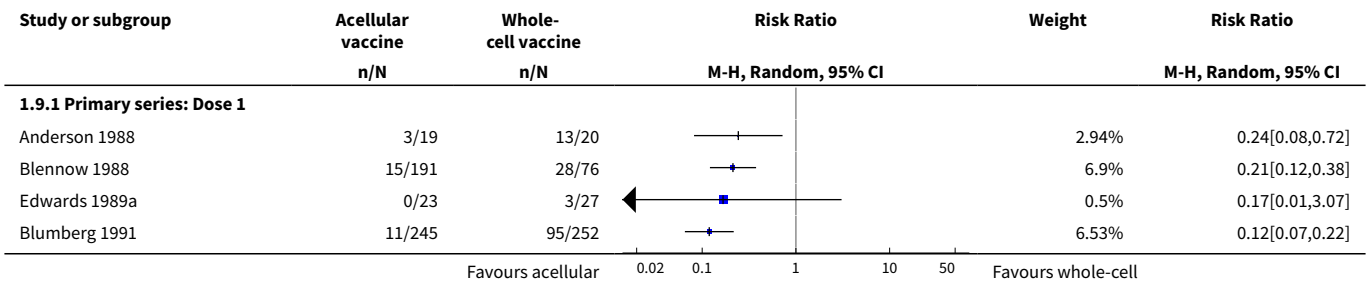
Analysis 1.8. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 8 Drowsiness.

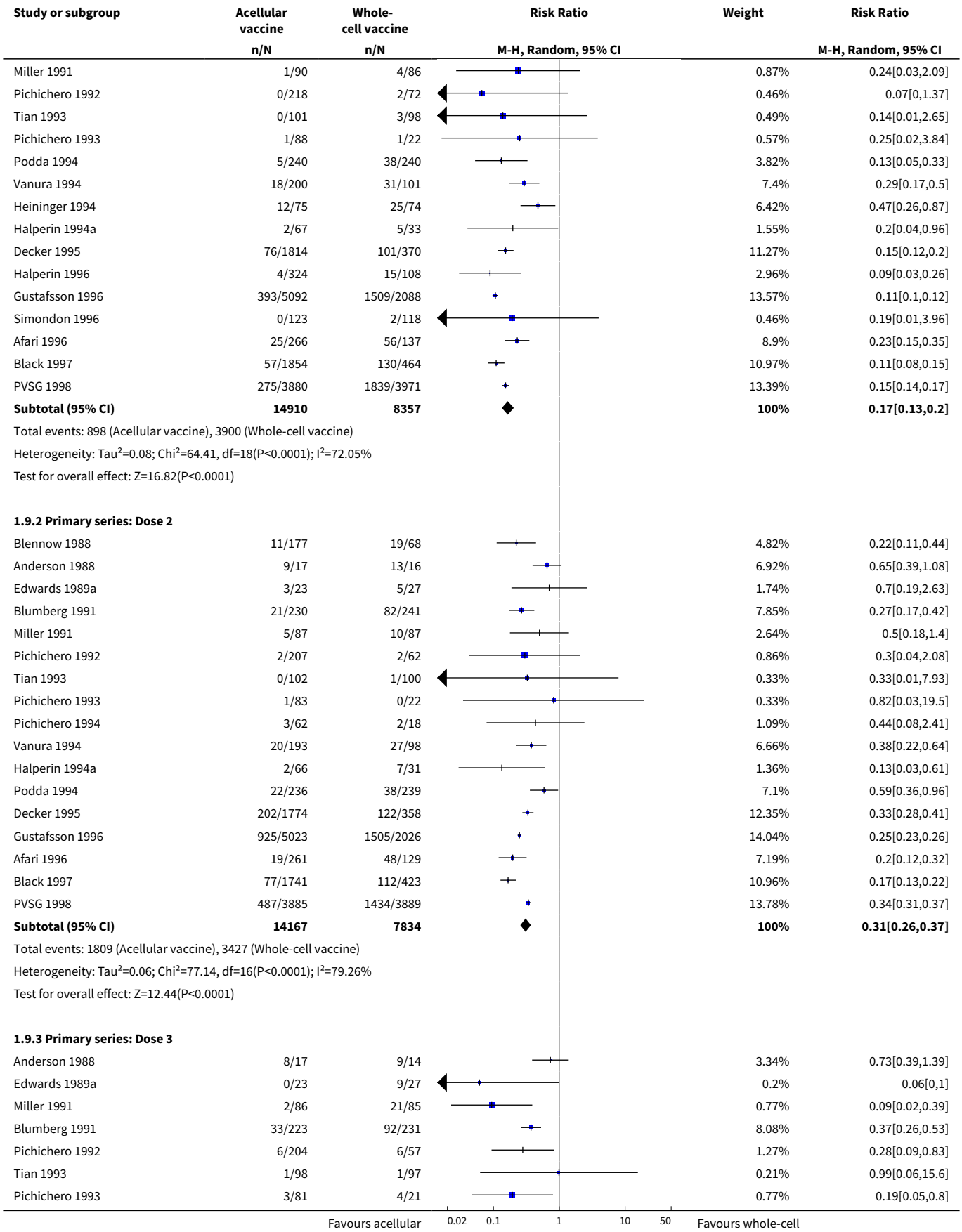
Study or subgroup	Acellular vaccine n/N	Whole-cell vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Primary series: Dose 1					
Blennow 1988	34/200	26/78		7.94%	0.51[0.33,0.79]
Blumberg 1991	43/245	78/252		9.33%	0.57[0.41,0.79]
Pichichero 1992	87/218	51/72		10.62%	0.56[0.45,0.7]
Halperin 1994a	34/67	19/33		8.72%	0.88[0.61,1.28]
Podda 1994	37/240	57/240		8.76%	0.65[0.45,0.94]
Heininger 1994	12/75	26/74		6.1%	0.46[0.25,0.83]
Decker 1995	543/1814	161/370		11.43%	0.69[0.6,0.79]
Halperin 1996	137/324	56/108		10.6%	0.82[0.65,1.02]
Afari 1996	3/266	1/137		0.83%	1.55[0.16,14.71]
Gustafsson 1996	26/5153	107/2102		8.1%	0.1[0.06,0.15]
Simondon 1996	14/123	19/118		5.73%	0.71[0.37,1.34]
PVSG 1998	952/4088	1636/4093		11.84%	0.58[0.54,0.62]
Subtotal (95% CI)	**12813**	**7677**		**100%**	**0.55[0.45,0.68]**
Total events: 1922 (Acellular vaccine), 2237 (Whole-cell vaccine)					
Heterogeneity: Tau²=0.1; Chi²=89.39, df=11(P<0.0001); I²=87.69%					
Test for overall effect: Z=5.49(P<0.0001)					
1.8.2 Primary series: Dose 2					
Blennow 1988	20/191	22/75		10.4%	0.36[0.21,0.61]
Blumberg 1991	29/230	48/241		12.45%	0.63[0.41,0.97]
Pichichero 1992	37/207	32/62		13.29%	0.35[0.24,0.51]
Podda 1994	19/236	30/239		10.36%	0.64[0.37,1.11]
Halperin 1994a	15/66	13/31		9.4%	0.54[0.3,1]
Decker 1995	313/1774	111/358		16.61%	0.57[0.47,0.68]
Afari 1996	0/261	0/129			Not estimable
Gustafsson 1996	15/5111	47/2040		9.84%	0.13[0.07,0.23]
PVSG 1998	659/4058	1006/3999		17.67%	0.65[0.59,0.7]
Subtotal (95% CI)	**12134**	**7174**		**100%**	**0.46[0.35,0.6]**
Total events: 1107 (Acellular vaccine), 1309 (Whole-cell vaccine)					
Heterogeneity: Tau²=0.11; Chi²=42.23, df=7(P<0.0001); I²=83.43%					
Test for overall effect: Z=5.69(P<0.0001)					
1.8.3 Primary series: Dose 3					
Blennow 1988	16/192	16/71		9.19%	0.37[0.2,0.7]
Blumberg 1991	22/223	52/231		11.12%	0.44[0.28,0.7]
Pichichero 1992	35/204	19/57		10.98%	0.51[0.32,0.83]
Podda 1994	9/236	20/236		7.9%	0.45[0.21,0.97]
Halperin 1994a	9/66	7/30		6.83%	0.58[0.24,1.42]



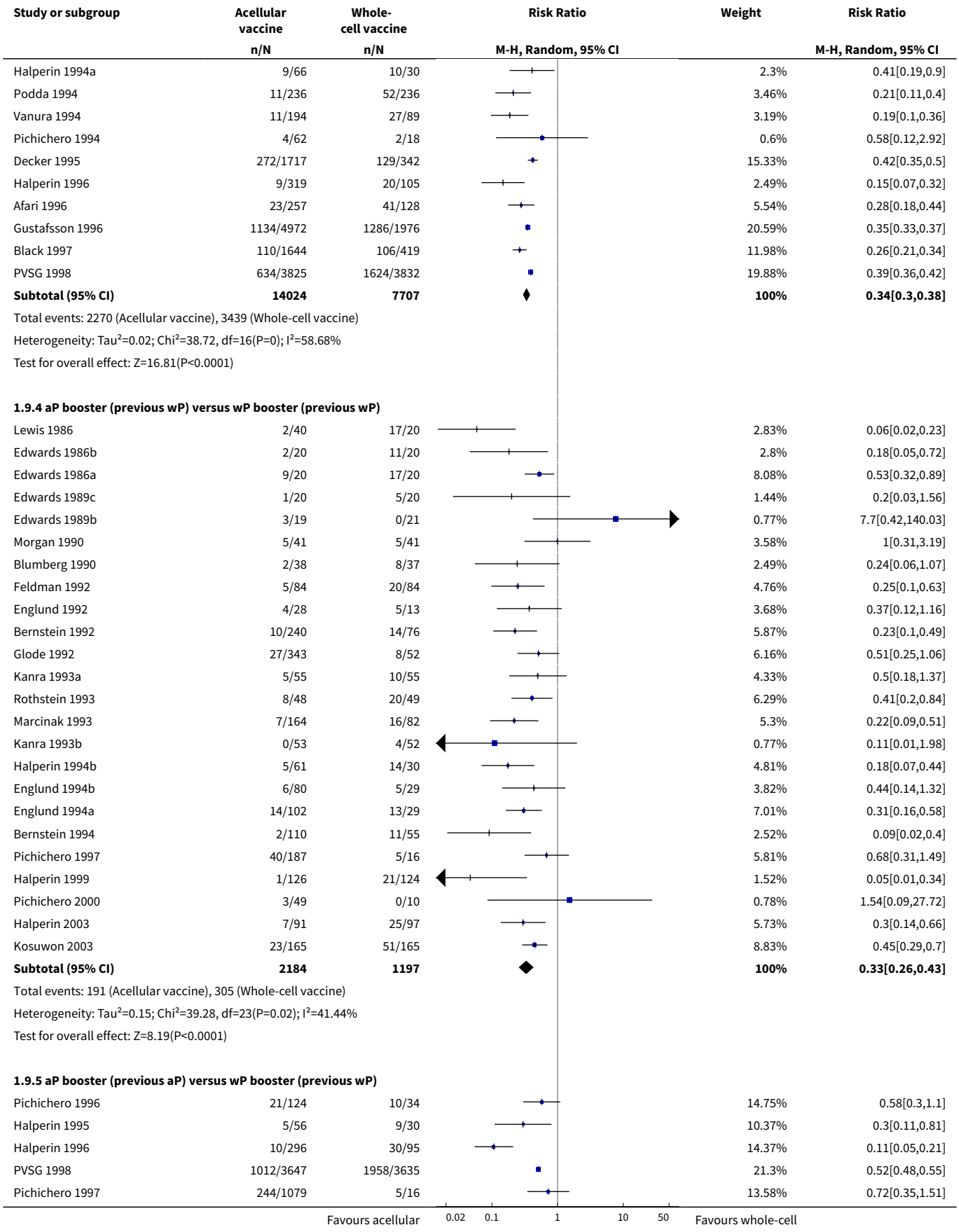


Analysis 1.9. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 9 Fever.

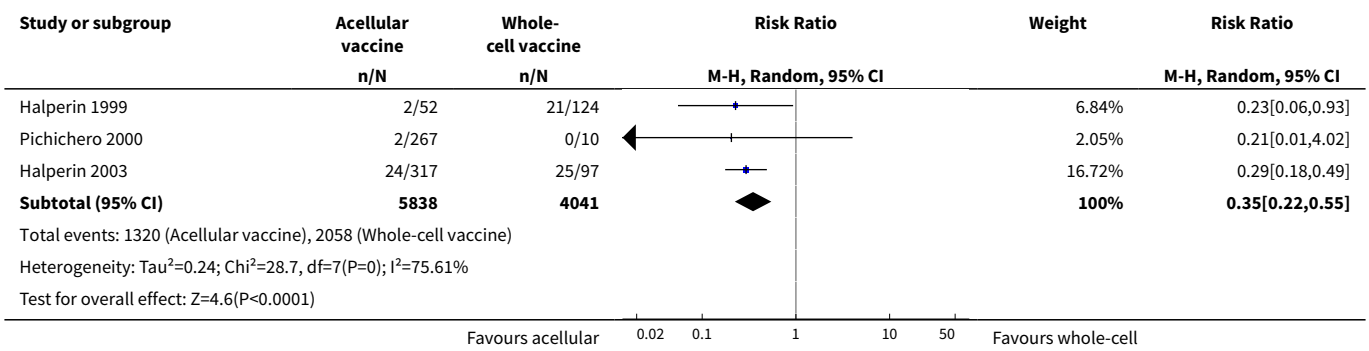




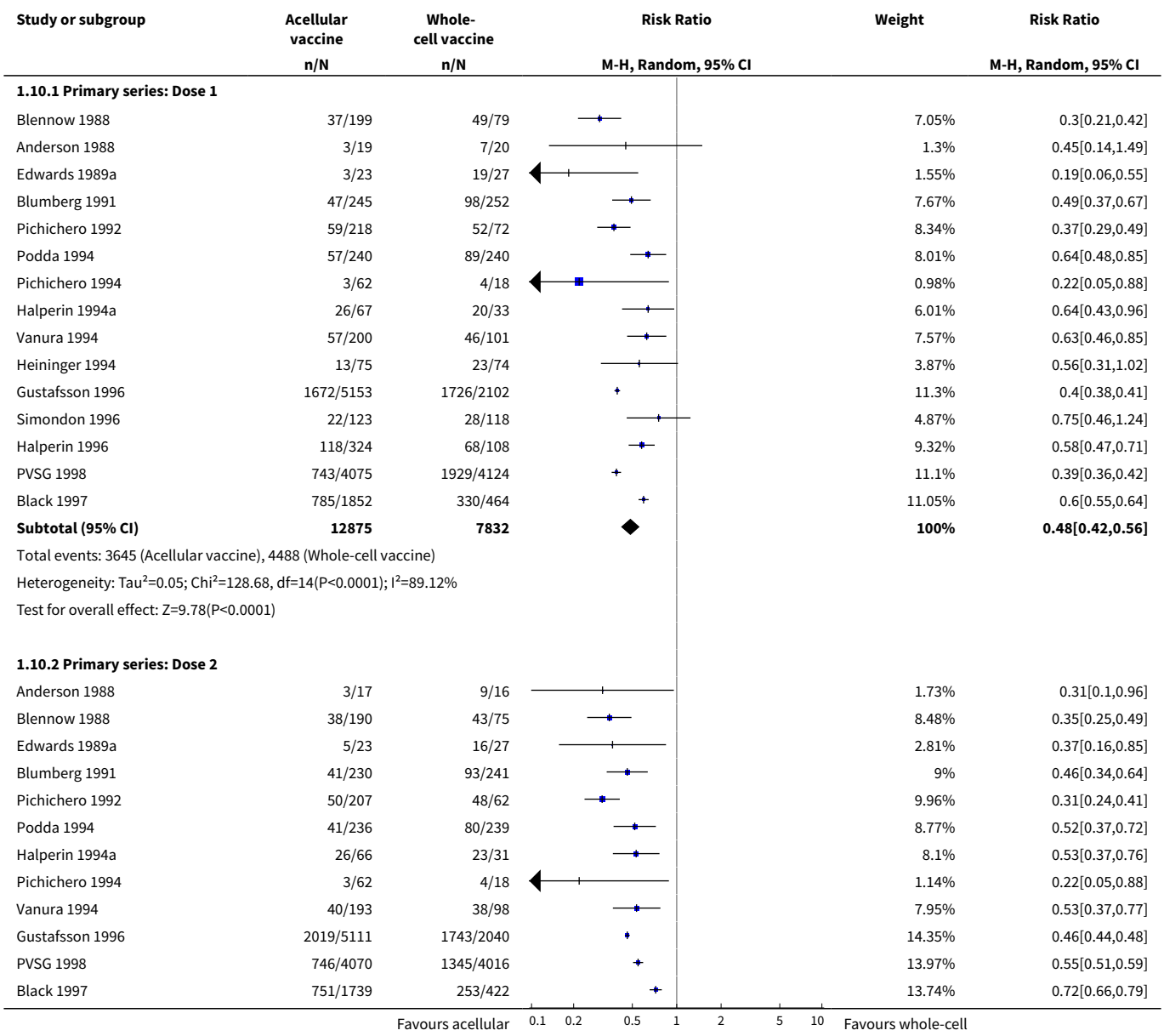
Study or subgroup	Acellular vaccine n/N	Whole-cell vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Miller 1991	1/90	4/86		0.87%	0.24[0.03,2.09]
Pichichero 1992	0/218	2/72		0.46%	0.07[0,1.37]
Tian 1993	0/101	3/98		0.49%	0.14[0.01,2.65]
Pichichero 1993	1/88	1/22		0.57%	0.25[0.02,3.84]
Podda 1994	5/240	38/240		3.82%	0.13[0.05,0.33]
Vanura 1994	18/200	31/101		7.4%	0.29[0.17,0.5]
Heininger 1994	12/75	25/74		6.42%	0.47[0.26,0.87]
Halperin 1994a	2/67	5/33		1.55%	0.2[0.04,0.96]
Decker 1995	76/1814	101/370		11.27%	0.15[0.12,0.2]
Halperin 1996	4/324	15/108		2.96%	0.09[0.03,0.26]
Gustafsson 1996	393/5092	1509/2088		13.57%	0.11[0.1,0.12]
Simondon 1996	0/123	2/118		0.46%	0.19[0.01,3.96]
Afari 1996	25/266	56/137		8.9%	0.23[0.15,0.35]
Black 1997	57/1854	130/464		10.97%	0.11[0.08,0.15]
PVSG 1998	275/3880	1839/3971		13.39%	0.15[0.14,0.17]
Subtotal (95% CI)	**14910**	**8357**		**100%**	**0.17[0.13,0.2]**
Total events: 898 (Acellular vaccine), 3900 (Whole-cell vaccine)					
Heterogeneity: Tau^2=0.08; Chi^2=64.41, df=18(P<0.0001); I^2=72.05%					
Test for overall effect: Z=16.82(P<0.0001)					
1.9.2 Primary series: Dose 2					
Blennow 1988	11/177	19/68		4.82%	0.22[0.11,0.44]
Anderson 1988	9/17	13/16		6.92%	0.65[0.39,1.08]
Edwards 1989a	3/23	5/27		1.74%	0.7[0.19,2.63]
Blumberg 1991	21/230	82/241		7.85%	0.27[0.17,0.42]
Miller 1991	5/87	10/87		2.64%	0.5[0.18,1.4]
Pichichero 1992	2/207	2/62		0.86%	0.3[0.04,2.08]
Tian 1993	0/102	1/100		0.33%	0.33[0.01,7.93]
Pichichero 1993	1/83	0/22		0.33%	0.82[0.03,19.5]
Pichichero 1994	3/62	2/18		1.09%	0.44[0.08,2.41]
Vanura 1994	20/193	27/98		6.66%	0.38[0.22,0.64]
Halperin 1994a	2/66	7/31		1.36%	0.13[0.03,0.61]
Podda 1994	22/236	38/239		7.1%	0.59[0.36,0.96]
Decker 1995	202/1774	122/358		12.35%	0.33[0.28,0.41]
Gustafsson 1996	925/5023	1505/2026		14.04%	0.25[0.23,0.26]
Afari 1996	19/261	48/129		7.19%	0.2[0.12,0.32]
Black 1997	77/1741	112/423		10.96%	0.17[0.13,0.22]
PVSG 1998	487/3885	1434/3889		13.78%	0.34[0.31,0.37]
Subtotal (95% CI)	**14167**	**7834**		**100%**	**0.31[0.26,0.37]**
Total events: 1809 (Acellular vaccine), 3427 (Whole-cell vaccine)					
Heterogeneity: Tau^2=0.06; Chi^2=77.14, df=16(P<0.0001); I^2=79.26%					
Test for overall effect: Z=12.44(P<0.0001)					
1.9.3 Primary series: Dose 3					
Anderson 1988	8/17	9/14		3.34%	0.73[0.39,1.39]
Edwards 1989a	0/23	9/27		0.2%	0.06[0,1]
Miller 1991	2/86	21/85		0.77%	0.09[0.02,0.39]
Blumberg 1991	33/223	92/231		8.08%	0.37[0.26,0.53]
Pichichero 1992	6/204	6/57		1.27%	0.28[0.09,0.83]
Tian 1993	1/98	1/97		0.21%	0.99[0.06,15.6]
Pichichero 1993	3/81	4/21		0.77%	0.19[0.05,0.8]

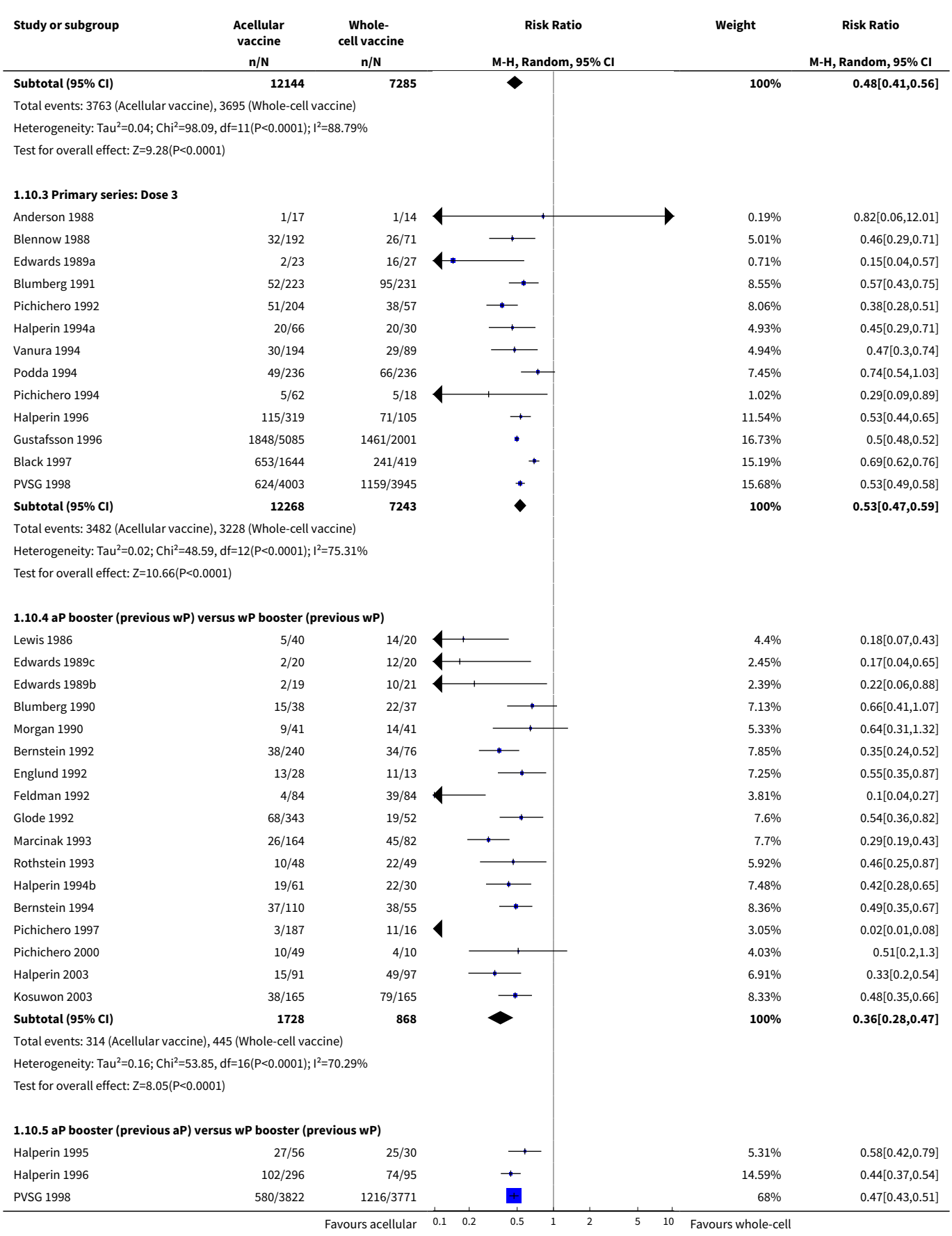


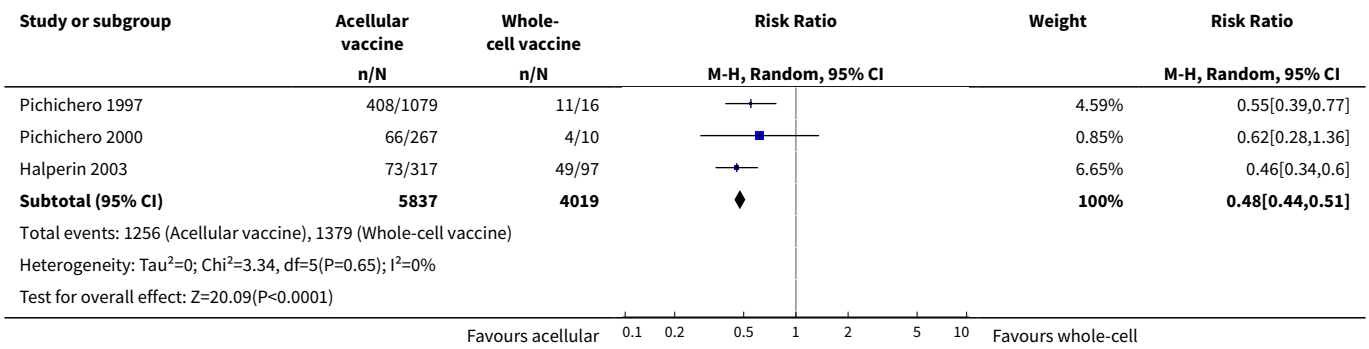
Study or subgroup	Acellular vaccine n/N	Whole-cell vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Halperin 1994a	9/66	10/30		2.3%	0.41[0.19,0.9]
Podda 1994	11/236	52/236		3.46%	0.21[0.11,0.4]
Vanura 1994	11/194	27/89		3.19%	0.19[0.1,0.36]
Pichichero 1994	4/62	2/18		0.6%	0.58[0.12,2.92]
Decker 1995	272/1717	129/342		15.33%	0.42[0.35,0.5]
Halperin 1996	9/319	20/105		2.49%	0.15[0.07,0.32]
Afari 1996	23/257	41/128		5.54%	0.28[0.18,0.44]
Gustafsson 1996	1134/4972	1286/1976		20.59%	0.35[0.33,0.37]
Black 1997	110/1644	106/419		11.98%	0.26[0.21,0.34]
PVSG 1998	634/3825	1624/3832		19.88%	0.39[0.36,0.42]
Subtotal (95% CI)	**14024**	**7707**		**100%**	**0.34[0.3,0.38]**
Total events: 2270 (Acellular vaccine), 3439 (Whole-cell vaccine)					
Heterogeneity: Tau^2=0.02; Chi^2=38.72, df=16(P=0); I^2=58.68%					
Test for overall effect: Z=16.81(P<0.0001)					
1.9.4 aP booster (previous wP) versus wP booster (previous wP)					
Lewis 1986	2/40	17/20		2.83%	0.06[0.02,0.23]
Edwards 1986b	2/20	11/20		2.8%	0.18[0.05,0.72]
Edwards 1986a	9/20	17/20		8.08%	0.53[0.32,0.89]
Edwards 1989c	1/20	5/20		1.44%	0.2[0.03,1.56]
Edwards 1989b	3/19	0/21		0.77%	7.7[0.42,140.03]
Morgan 1990	5/41	5/41		3.58%	1[0.31,3.19]
Blumberg 1990	2/38	8/37		2.49%	0.24[0.06,1.07]
Feldman 1992	5/84	20/84		4.76%	0.25[0.1,0.63]
Englund 1992	4/28	5/13		3.68%	0.37[0.12,1.16]
Bernstein 1992	10/240	14/76		5.87%	0.23[0.1,0.49]
Glode 1992	27/343	8/52		6.16%	0.51[0.25,1.06]
Kanra 1993a	5/55	10/55		4.33%	0.5[0.18,1.37]
Rothstein 1993	8/48	20/49		6.29%	0.41[0.2,0.84]
Marcinak 1993	7/164	16/82		5.3%	0.22[0.09,0.51]
Kanra 1993b	0/53	4/52		0.77%	0.11[0.01,1.98]
Halperin 1994b	5/61	14/30		4.81%	0.18[0.07,0.44]
Englund 1994b	6/80	5/29		3.82%	0.44[0.14,1.32]
Englund 1994a	14/102	13/29		7.01%	0.31[0.16,0.58]
Bernstein 1994	2/110	11/55		2.52%	0.09[0.02,0.4]
Pichichero 1997	40/187	5/16		5.81%	0.68[0.31,1.49]
Halperin 1999	1/126	21/124		1.52%	0.05[0.01,0.34]
Pichichero 2000	3/49	0/10		0.78%	1.54[0.09,27.72]
Halperin 2003	7/91	25/97		5.73%	0.3[0.14,0.66]
Kosuwon 2003	23/165	51/165		8.83%	0.45[0.29,0.7]
Subtotal (95% CI)	**2184**	**1197**		**100%**	**0.33[0.26,0.43]**
Total events: 191 (Acellular vaccine), 305 (Whole-cell vaccine)					
Heterogeneity: Tau^2=0.15; Chi^2=39.28, df=23(P=0.02); I^2=41.44%					
Test for overall effect: Z=8.19(P<0.0001)					
1.9.5 aP booster (previous aP) versus wP booster (previous wP)					
Pichichero 1996	21/124	10/34		14.75%	0.58[0.3,1.1]
Halperin 1995	5/56	9/30		10.37%	0.3[0.11,0.81]
Halperin 1996	10/296	30/95		14.37%	0.11[0.05,0.21]
PVSG 1998	1012/3647	1958/3635		21.3%	0.52[0.48,0.55]
Pichichero 1997	244/1079	5/16		13.58%	0.72[0.35,1.51]



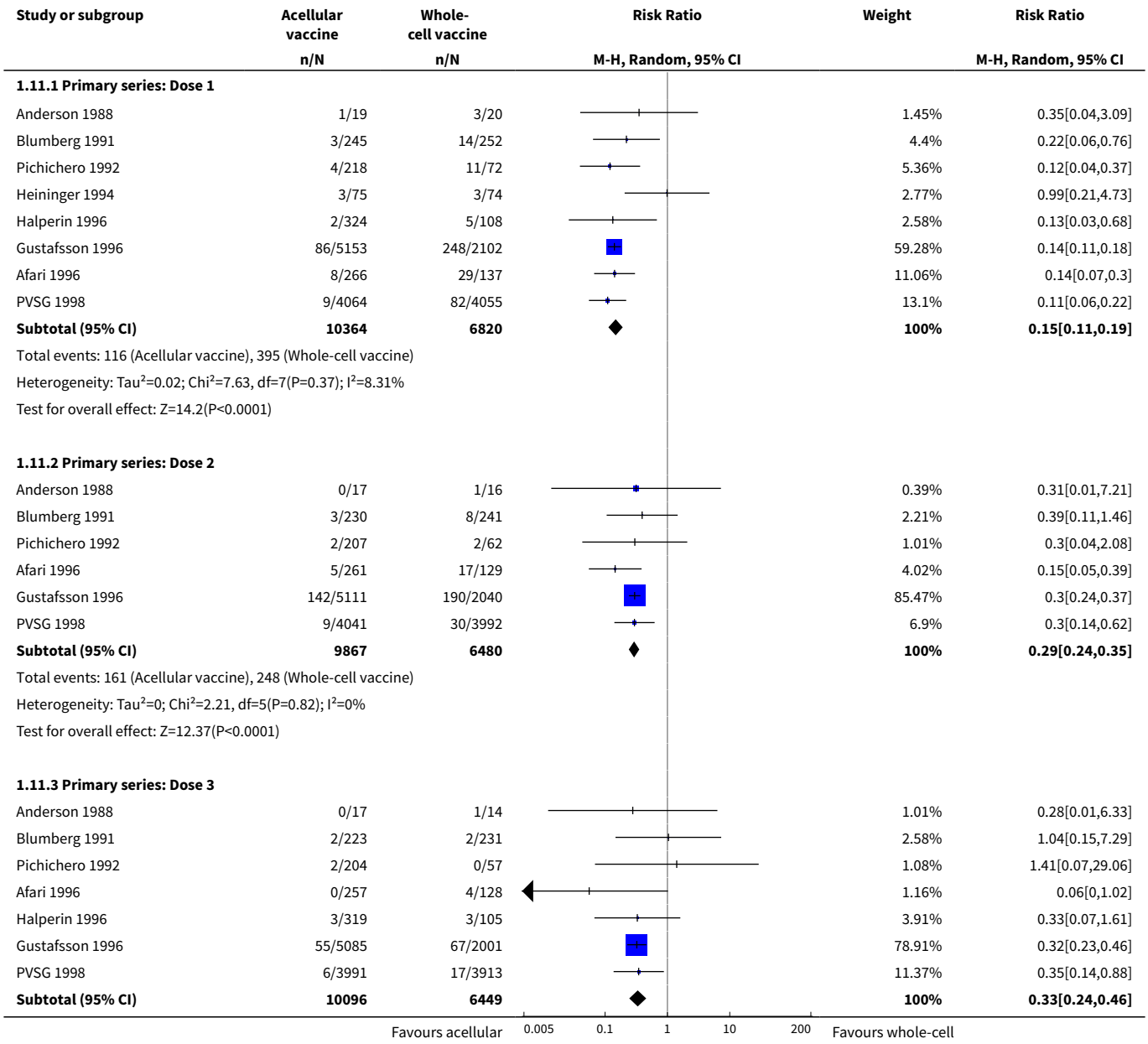
Analysis 1.10. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 10 Irritability/fretfulness.

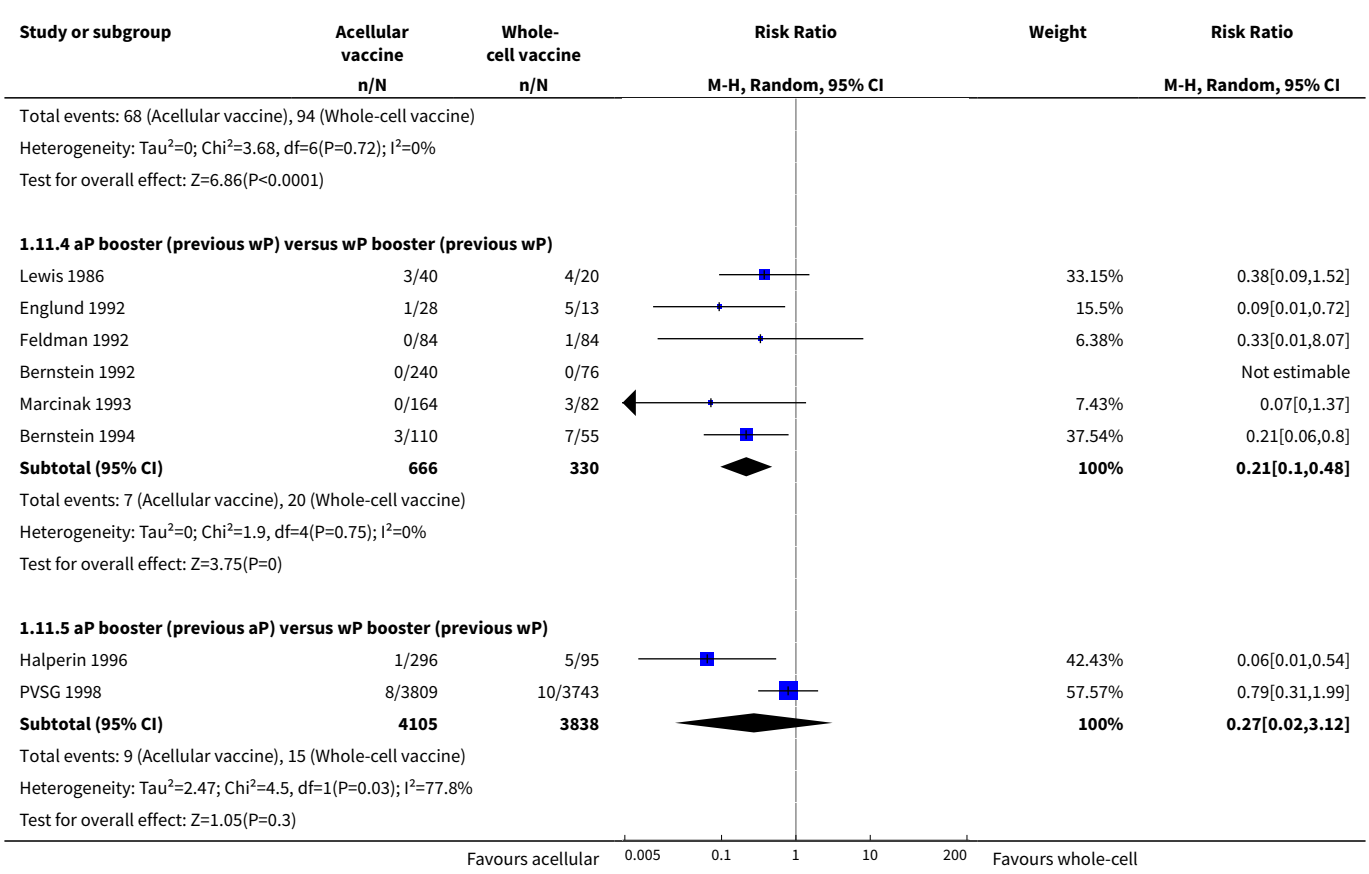




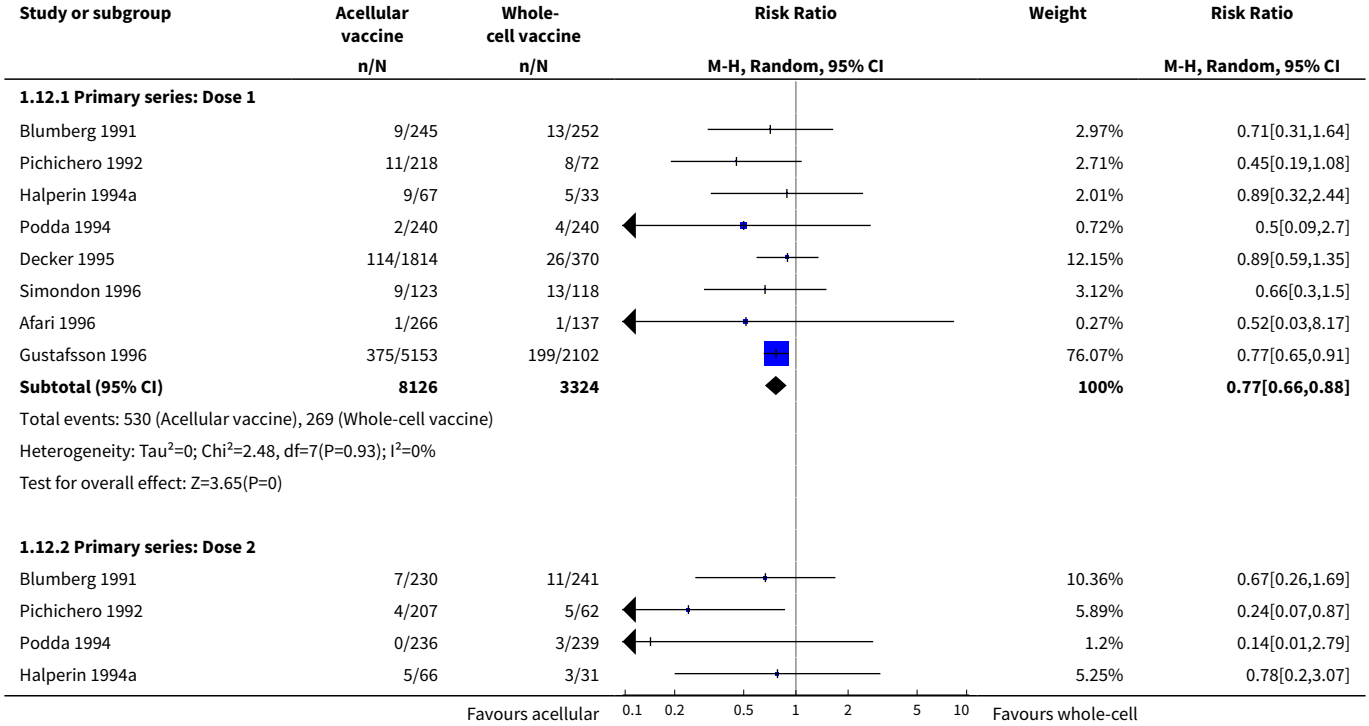


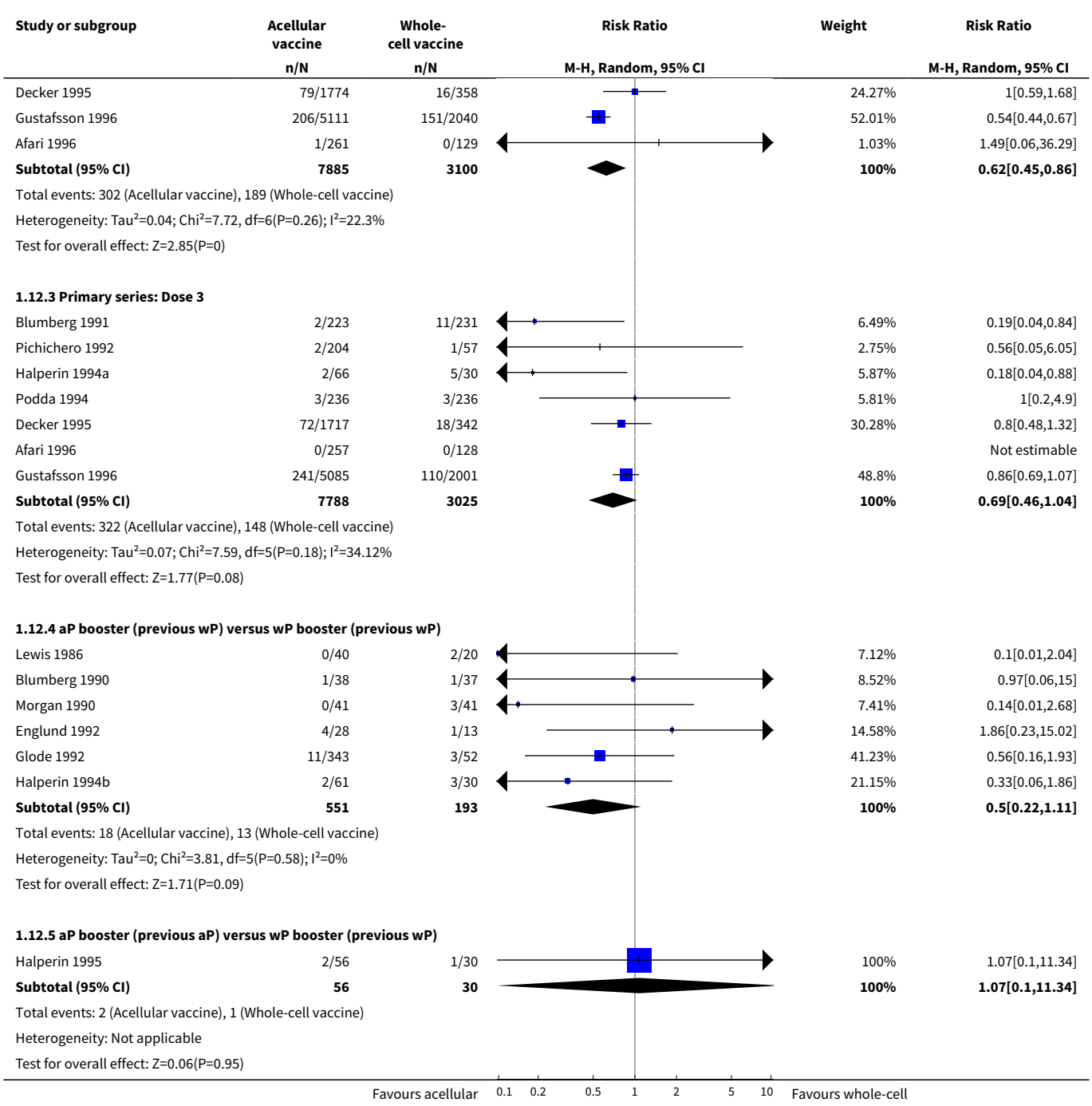
Analysis 1.11. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 11 Prolonged crying.



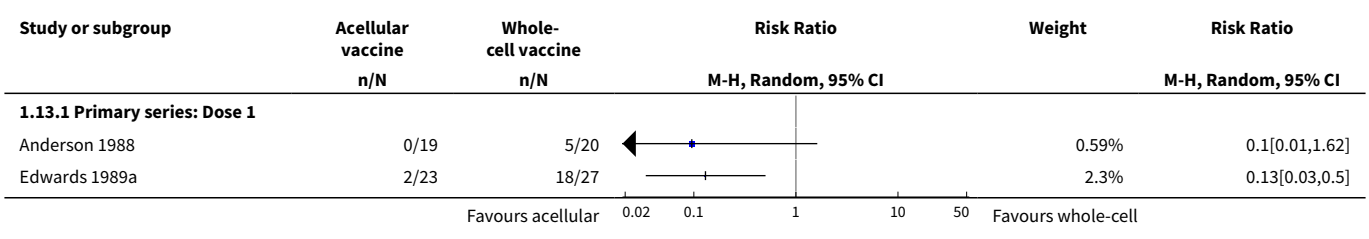


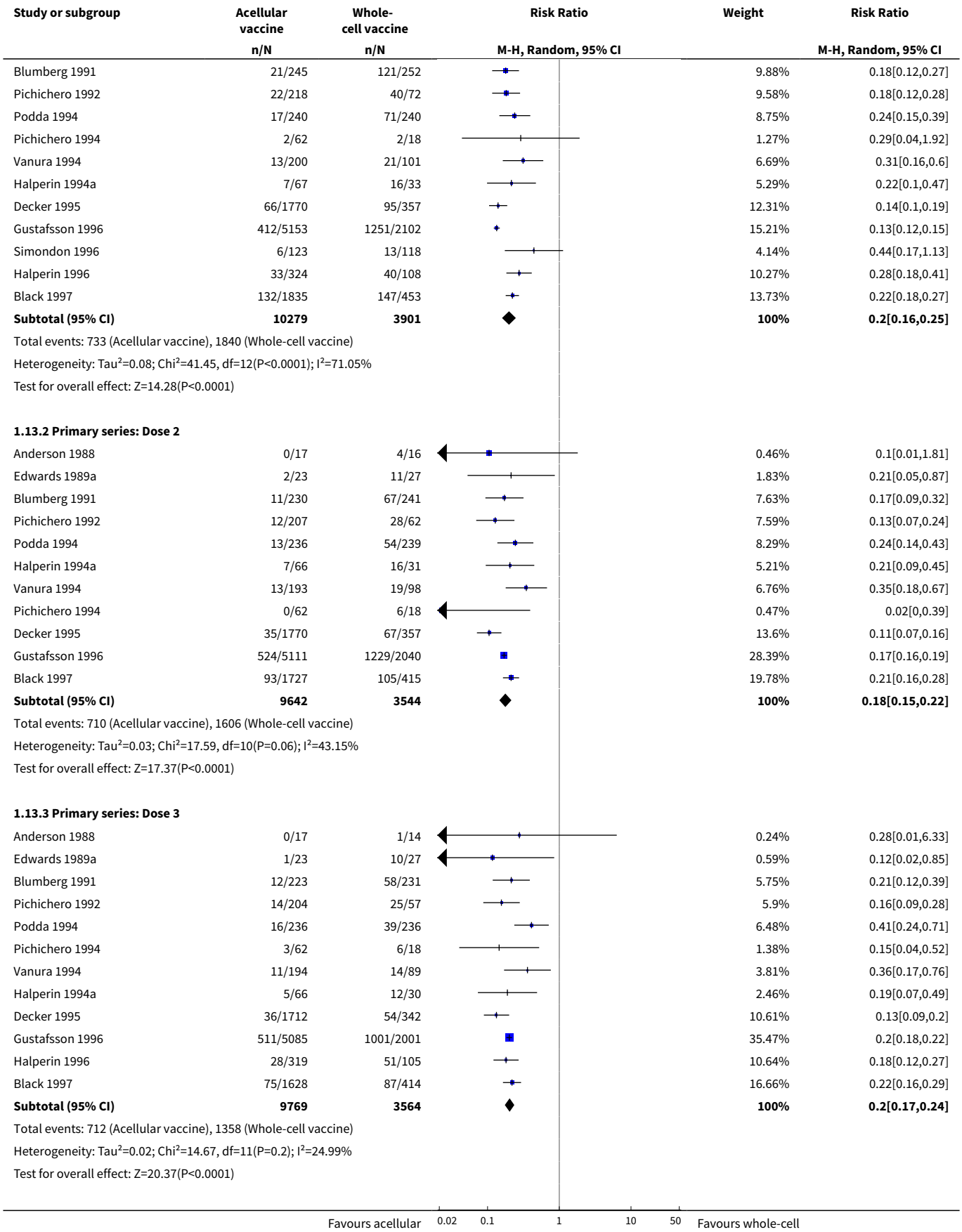
Analysis 1.12. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 12 Vomiting.

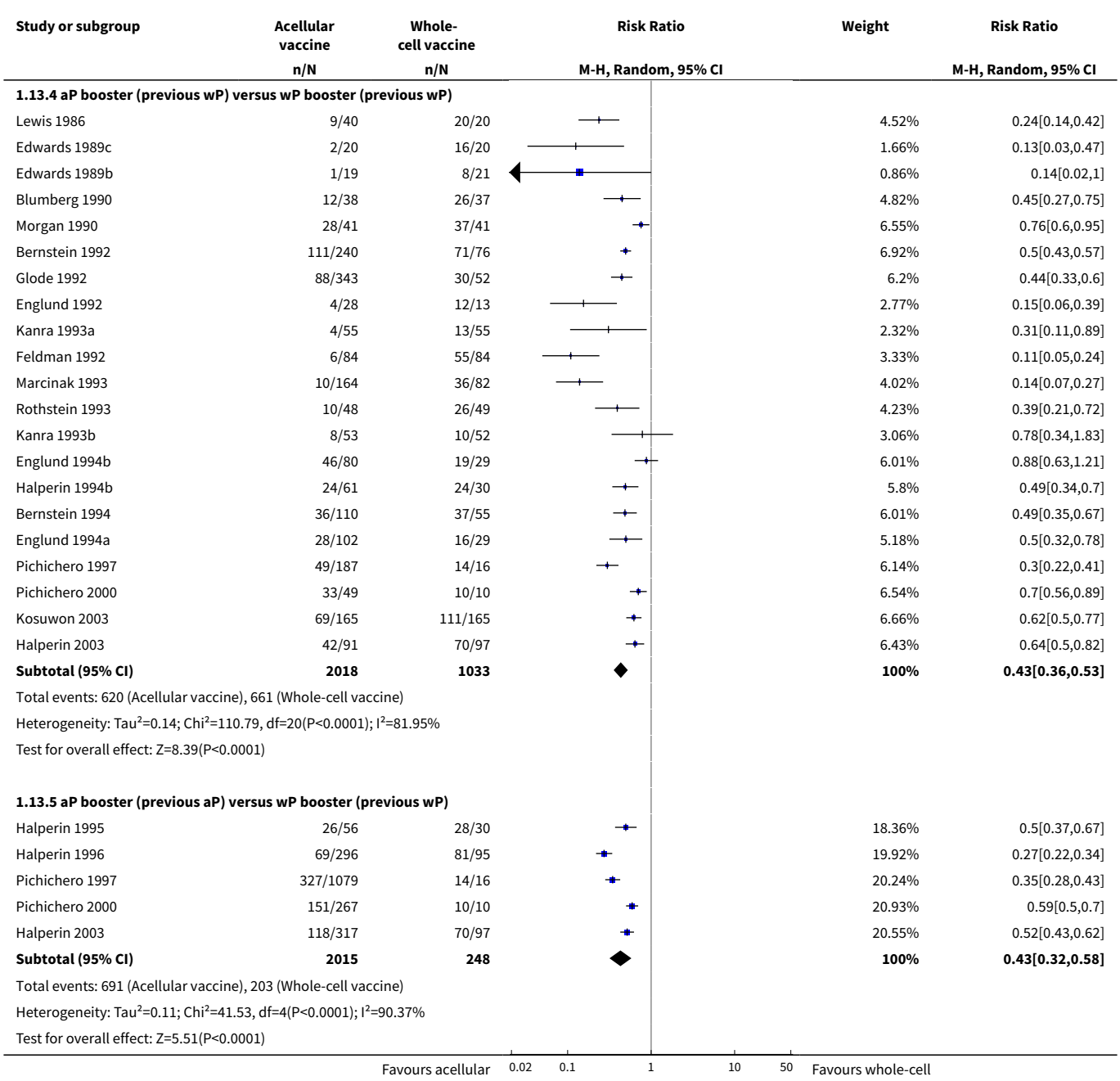




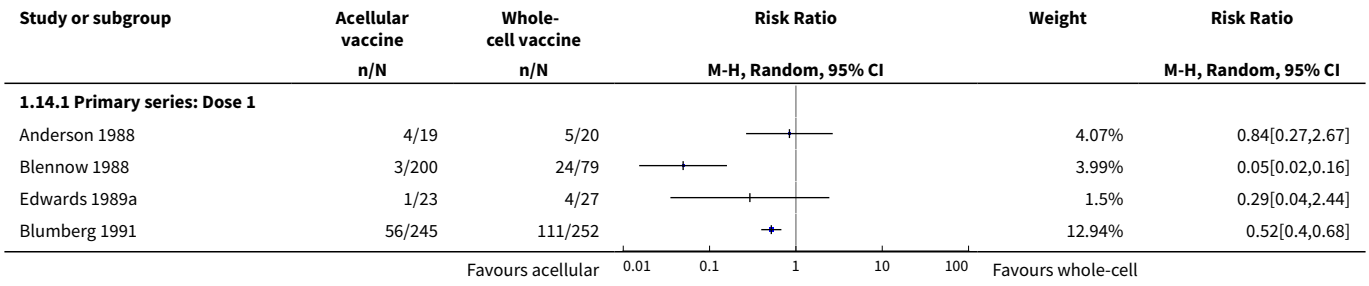
Analysis 1.13. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 13 Pain/tenderness.

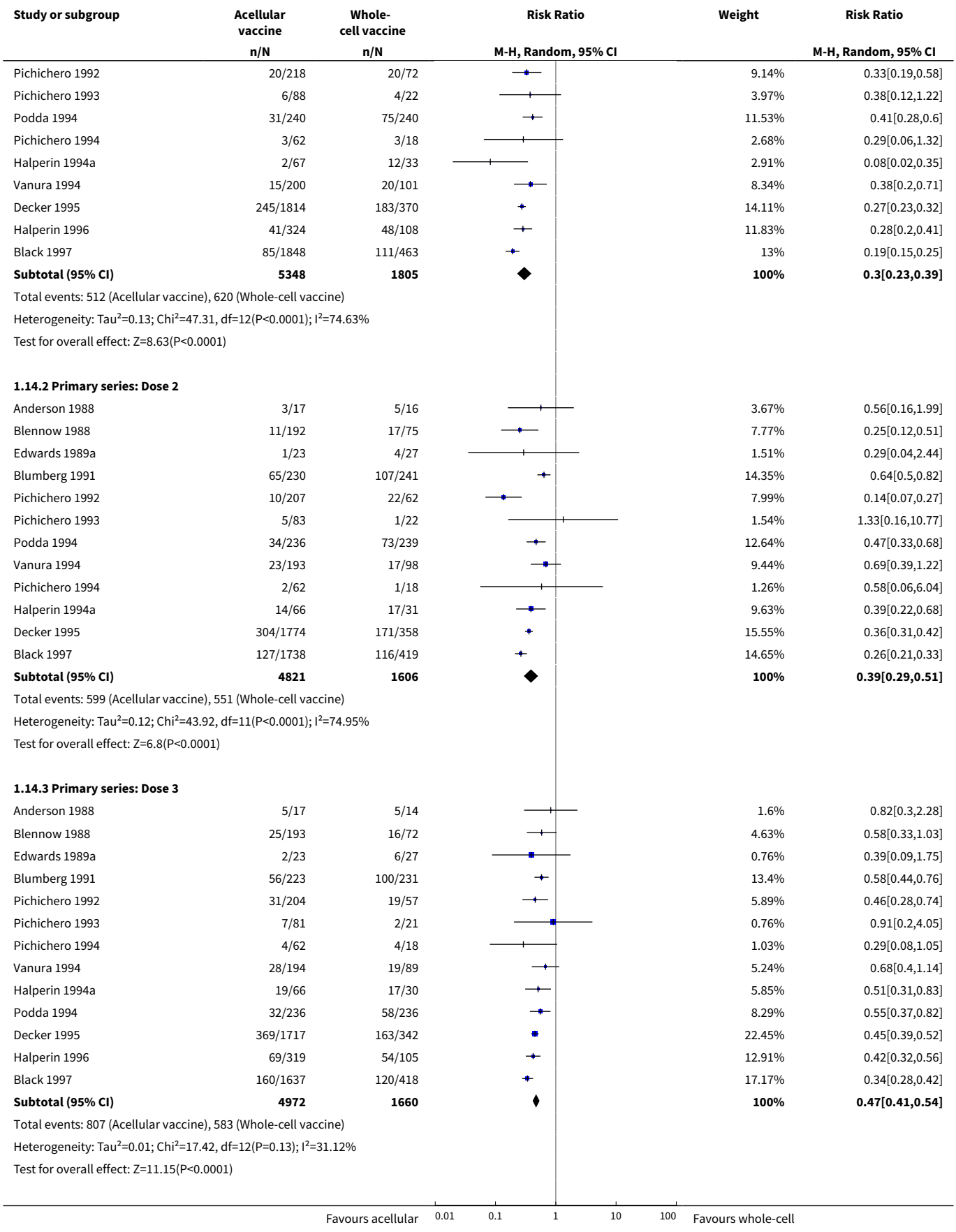


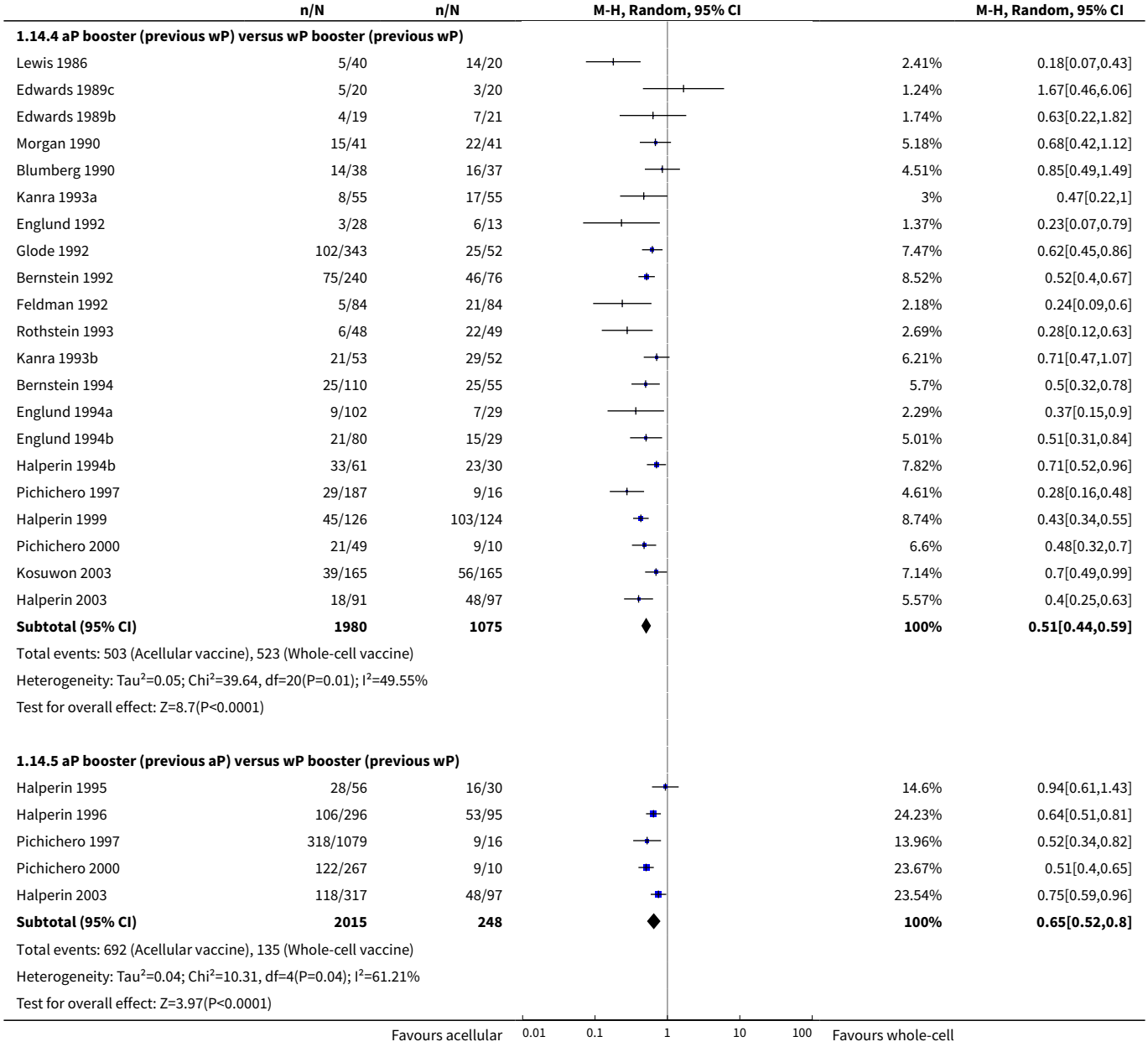




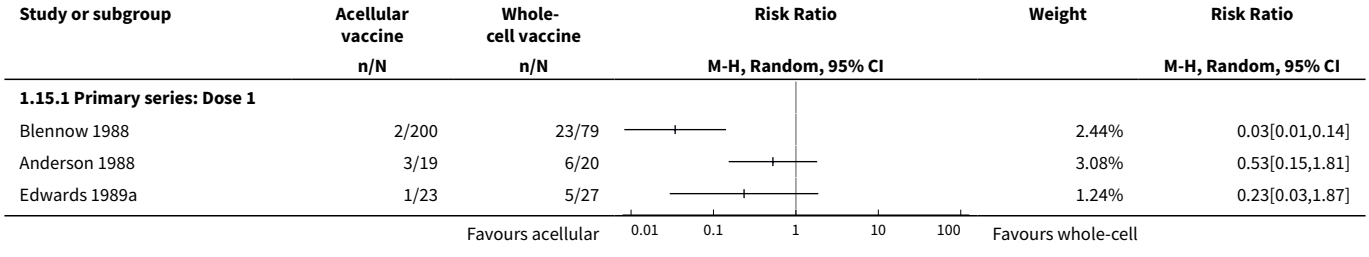
Analysis 1.14. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 14 Redness.

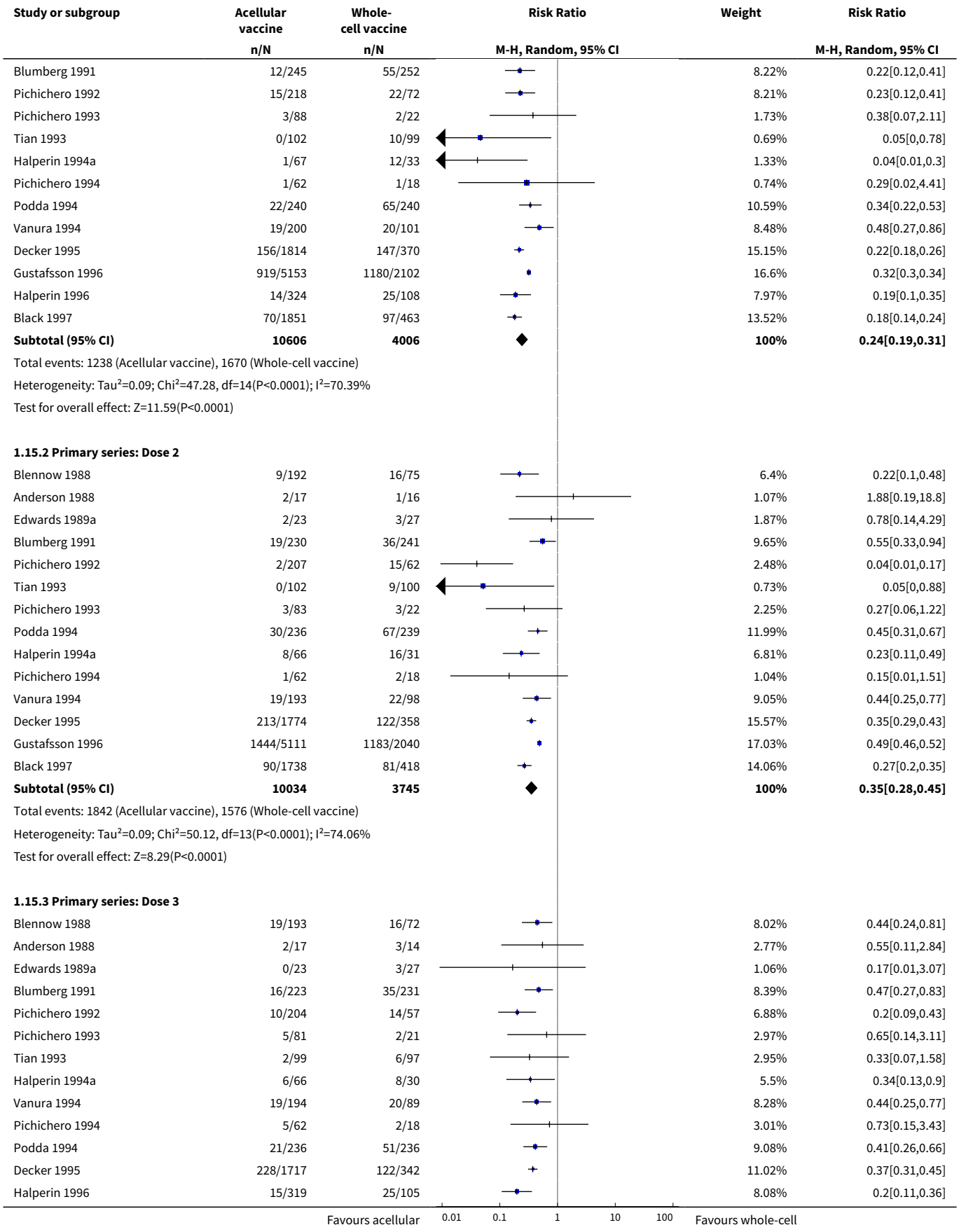




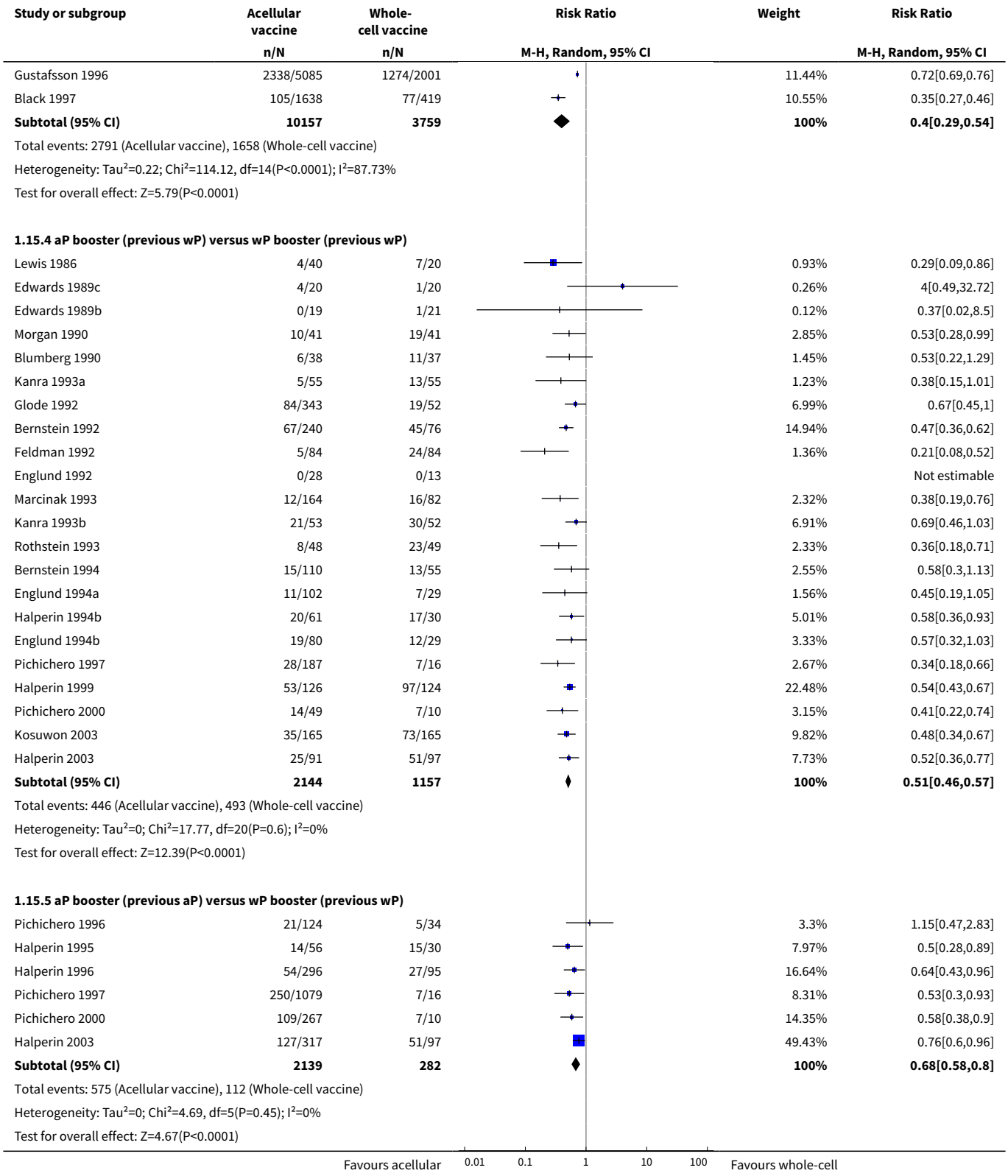


Analysis 1.15. Comparison 1 Safety: acellular versus whole-cell pertussis vaccines, Outcome 15 Swelling/induration.





Study or subgroup	Acellular vaccine n/N	Whole-cell vaccine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Blumberg 1991	12/245	55/252		8.22%	0.22[0.12,0.41]
Pichichero 1992	15/218	22/72		8.21%	0.23[0.12,0.41]
Pichichero 1993	3/88	2/22		1.73%	0.38[0.07,2.11]
Tian 1993	0/102	10/99		0.69%	0.05[0,0.78]
Halperin 1994a	1/67	12/33		1.33%	0.04[0.01,0.3]
Pichichero 1994	1/62	1/18		0.74%	0.29[0.02,4.41]
Podda 1994	22/240	65/240		10.59%	0.34[0.22,0.53]
Vanura 1994	19/200	20/101		8.48%	0.48[0.27,0.86]
Decker 1995	156/1814	147/370		15.15%	0.22[0.18,0.26]
Gustafsson 1996	919/5153	1180/2102		16.6%	0.32[0.3,0.34]
Halperin 1996	14/324	25/108		7.97%	0.19[0.1,0.35]
Black 1997	70/1851	97/463		13.52%	0.18[0.14,0.24]
Subtotal (95% CI)	**10606**	**4006**		**100%**	**0.24[0.19,0.31]**
Total events: 1238 (Acellular vaccine), 1670 (Whole-cell vaccine)					
Heterogeneity: Tau^2=0.09; Chi^2=47.28, df=14(P<0.0001); I^2=70.39%					
Test for overall effect: Z=11.59(P<0.0001)					
1.15.2 Primary series: Dose 2					
Blennow 1988	9/192	16/75		6.4%	0.22[0.1,0.48]
Anderson 1988	2/17	1/16		1.07%	1.88[0.19,18.8]
Edwards 1989a	2/23	3/27		1.87%	0.78[0.14,4.29]
Blumberg 1991	19/230	36/241		9.65%	0.55[0.33,0.94]
Pichichero 1992	2/207	15/62		2.48%	0.04[0.01,0.17]
Tian 1993	0/102	9/100		0.73%	0.05[0,0.88]
Pichichero 1993	3/83	3/22		2.25%	0.27[0.06,1.22]
Podda 1994	30/236	67/239		11.99%	0.45[0.31,0.67]
Halperin 1994a	8/66	16/31		6.81%	0.23[0.11,0.49]
Pichichero 1994	1/62	2/18		1.04%	0.15[0.01,1.51]
Vanura 1994	19/193	22/98		9.05%	0.44[0.25,0.77]
Decker 1995	213/1774	122/358		15.57%	0.35[0.29,0.43]
Gustafsson 1996	1444/5111	1183/2040		17.03%	0.49[0.46,0.52]
Black 1997	90/1738	81/418		14.06%	0.27[0.2,0.35]
Subtotal (95% CI)	**10034**	**3745**		**100%**	**0.35[0.28,0.45]**
Total events: 1842 (Acellular vaccine), 1576 (Whole-cell vaccine)					
Heterogeneity: Tau^2=0.09; Chi^2=50.12, df=13(P<0.0001); I^2=74.06%					
Test for overall effect: Z=8.29(P<0.0001)					
1.15.3 Primary series: Dose 3					
Blennow 1988	19/193	16/72		8.02%	0.44[0.24,0.81]
Anderson 1988	2/17	3/14		2.77%	0.55[0.11,2.84]
Edwards 1989a	0/23	3/27		1.06%	0.17[0.01,3.07]
Blumberg 1991	16/223	35/231		8.39%	0.47[0.27,0.83]
Pichichero 1992	10/204	14/57		6.88%	0.2[0.09,0.43]
Pichichero 1993	5/81	2/21		2.97%	0.65[0.14,3.11]
Tian 1993	2/99	6/97		2.95%	0.33[0.07,1.58]
Halperin 1994a	6/66	8/30		5.5%	0.34[0.13,0.9]
Vanura 1994	19/194	20/89		8.28%	0.44[0.25,0.77]
Pichichero 1994	5/62	2/18		3.01%	0.73[0.15,3.43]
Podda 1994	21/236	51/236		9.08%	0.41[0.26,0.66]
Decker 1995	228/1717	122/342		11.02%	0.37[0.31,0.45]
Halperin 1996	15/319	25/105		8.08%	0.2[0.11,0.36]

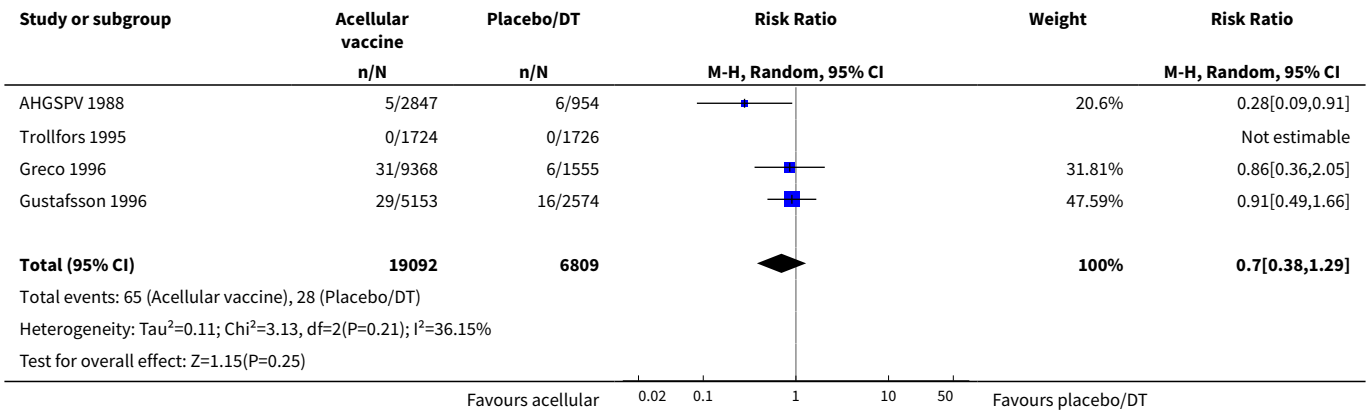


Comparison 2. Safety: acellular vaccines versus placebo/DT

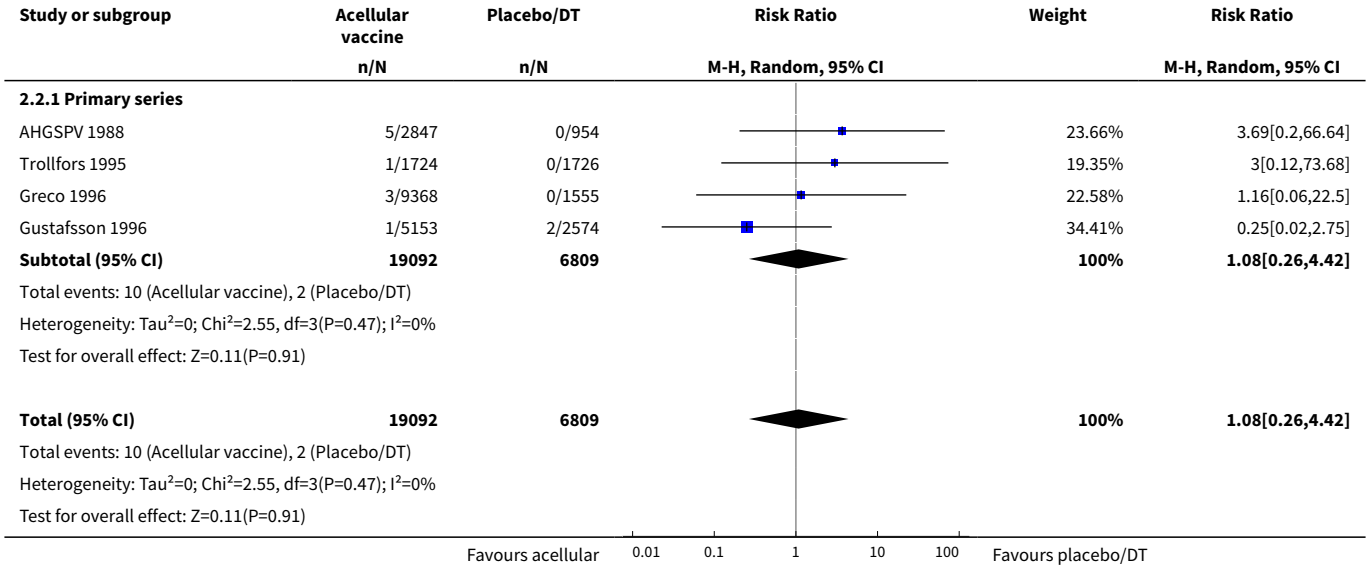
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary series non-completion due to adverse events	4	25901	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.38, 1.29]
2 Death (all causes)	4	25901	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.26, 4.42]
2.1 Primary series	4	25901	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.26, 4.42]
3 Death (infection)	4	25902	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.19, 7.80]
3.1 Primary series	4	25902	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.19, 7.80]
4 Encephalopathy	2	18650	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.1 Primary series	2	18650	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Convulsions	4	25901	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.12, 1.69]
5.1 Primary series	4	25901	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.12, 1.69]
6 Hypotonic hyporesponsive episodes	4	25901	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.02, 5.13]
6.1 Primary series	4	25901	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.02, 5.13]
7 Anorexia	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Primary series: Dose 1	2	11526	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.93, 1.20]
7.2 Primary series: Dose 2	2	11386	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.66, 1.46]
7.3 Primary series: Dose 3	1	7623	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.91, 1.26]
8 Drowsiness	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Primary series: Dose 1	2	10954	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.96, 1.11]
8.2 Primary series: Dose 2	2	10620	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.09]
8.3 Primary series: Dose 3	1	7623	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.15]
9 Fever	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Primary series: Dose 1	3	11255	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.73, 1.90]
9.2 Primary series: Dose 2	3	10853	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.11]
9.3 Primary series: Dose 3	2	7654	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.13]
10 Irritability/fretfulness	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Primary series: Dose 1	2	11526	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Primary series: Dose 2	2	11386	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.03]
10.3 Primary series: Dose 3	1	7623	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.02]
11 Prolonged crying	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Primary series: Dose 1	2	11525	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.71, 2.34]
11.2 Primary series: Dose 2	2	11386	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.83, 1.40]
11.3 Primary series: Dose 3	1	7623	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.66, 1.68]
12 Vomiting	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Primary series: Dose 1	2	11526	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.94, 1.30]
12.2 Primary series: Dose 2	2	11386	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.07]
12.3 Primary series: Dose 3	1	7623	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.75, 1.13]
13 Pain/tenderness	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Primary series: Dose 1	2	11451	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.78, 1.32]
13.2 Primary series: Dose 2	2	11202	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.81, 1.51]
13.3 Primary series: Dose 3	1	7623	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.16]
14 Swelling/induration	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Primary series: Dose 1	3	11652	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.62, 2.68]
14.2 Primary series: Dose 2	3	11401	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.54, 8.01]
14.3 Primary series: Dose 3	2	7816	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.07, 1.20]
15 Redness	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Primary series: Dose 1	1	3724	Risk Ratio (M-H, Random, 95% CI)	3.03 [0.38, 23.85]
15.2 Primary series: Dose 2	1	3535	Risk Ratio (M-H, Random, 95% CI)	8.76 [3.89, 19.72]
15.3 Primary series: Dose 3	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

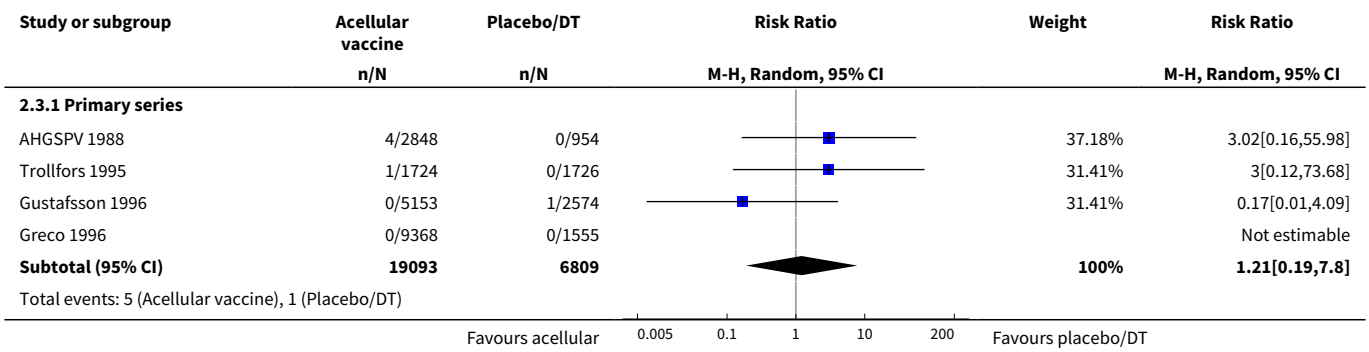
Analysis 2.1. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 1 Primary series non-completion due to adverse events.

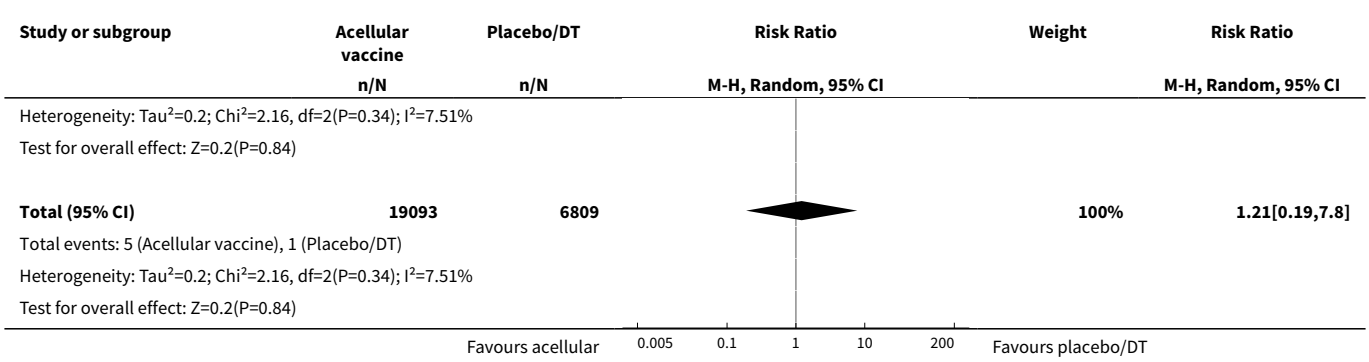


Analysis 2.2. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 2 Death (all causes).

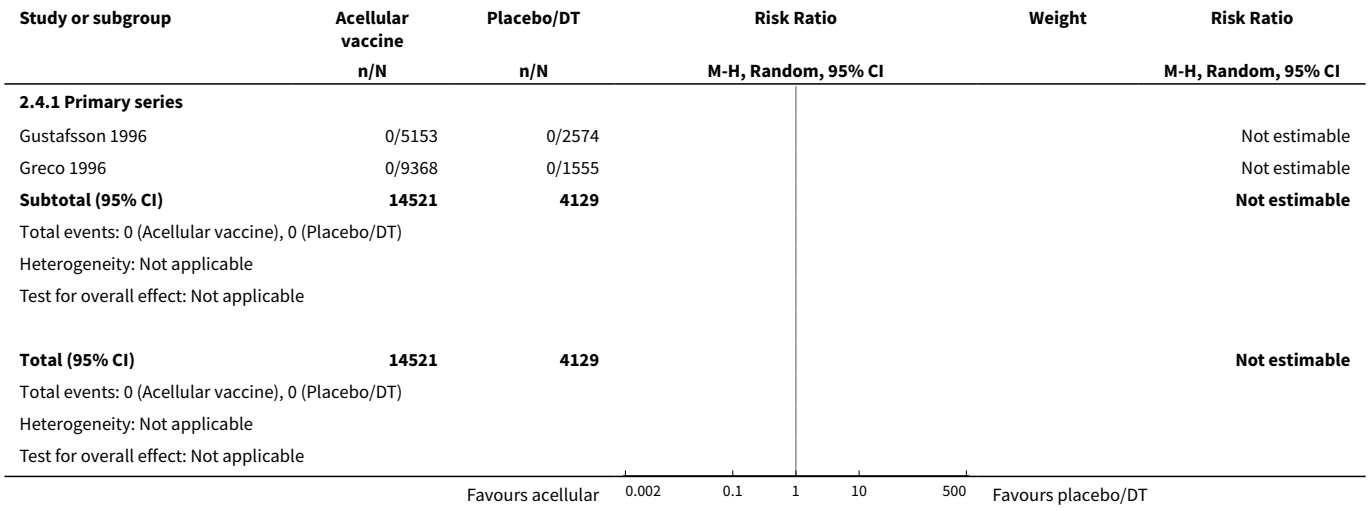


Analysis 2.3. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 3 Death (infection).

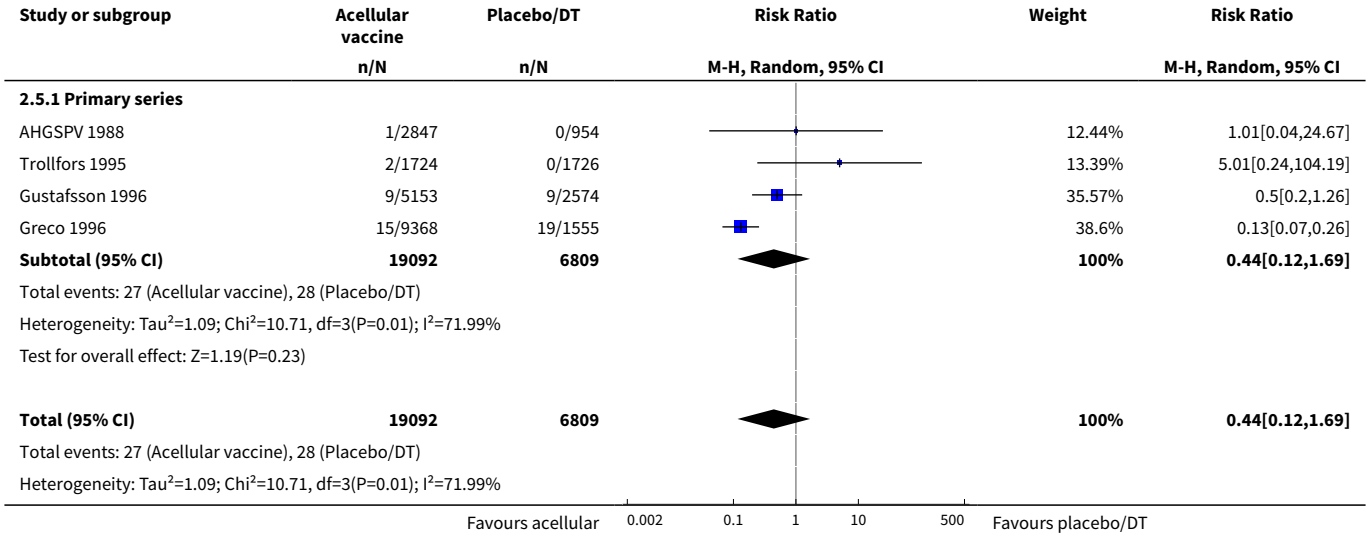


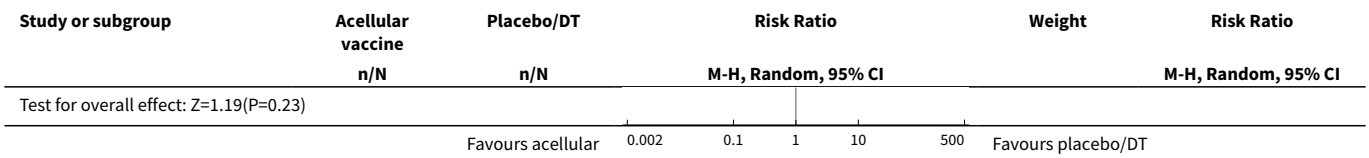


Analysis 2.4. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 4 Encephalopathy.

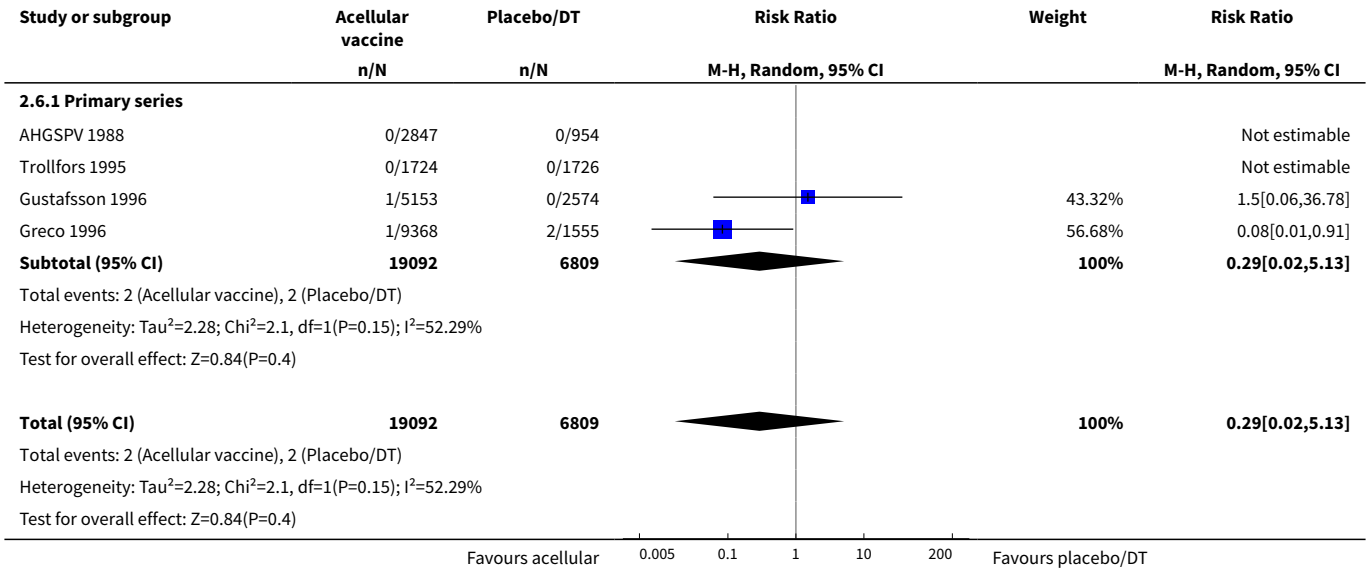


Analysis 2.5. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 5 Convulsions.

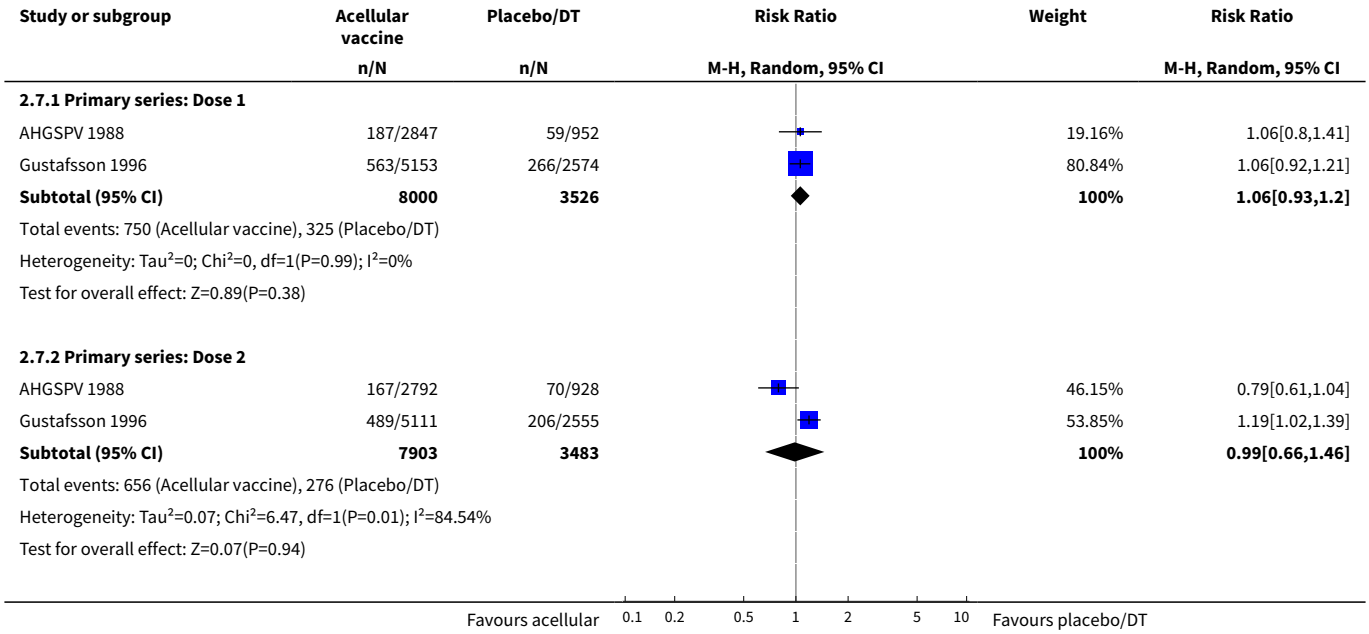


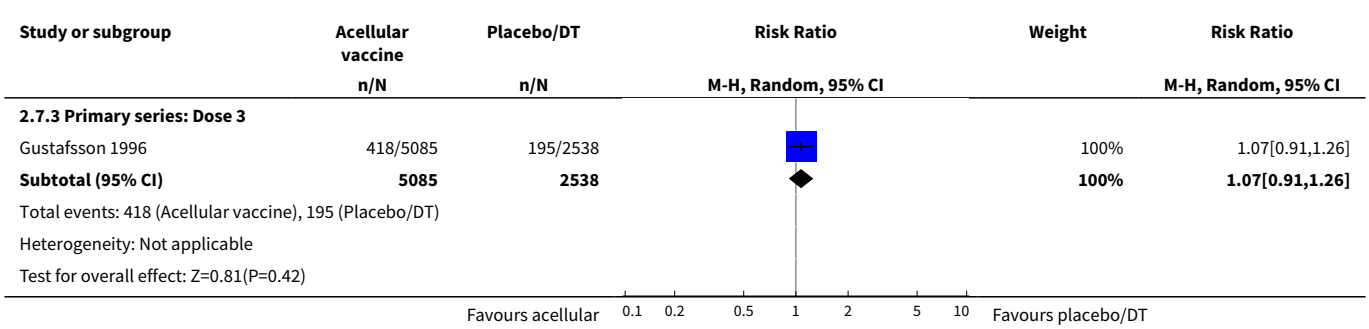


Analysis 2.6. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 6 Hypotonic hyporesponsive episodes.

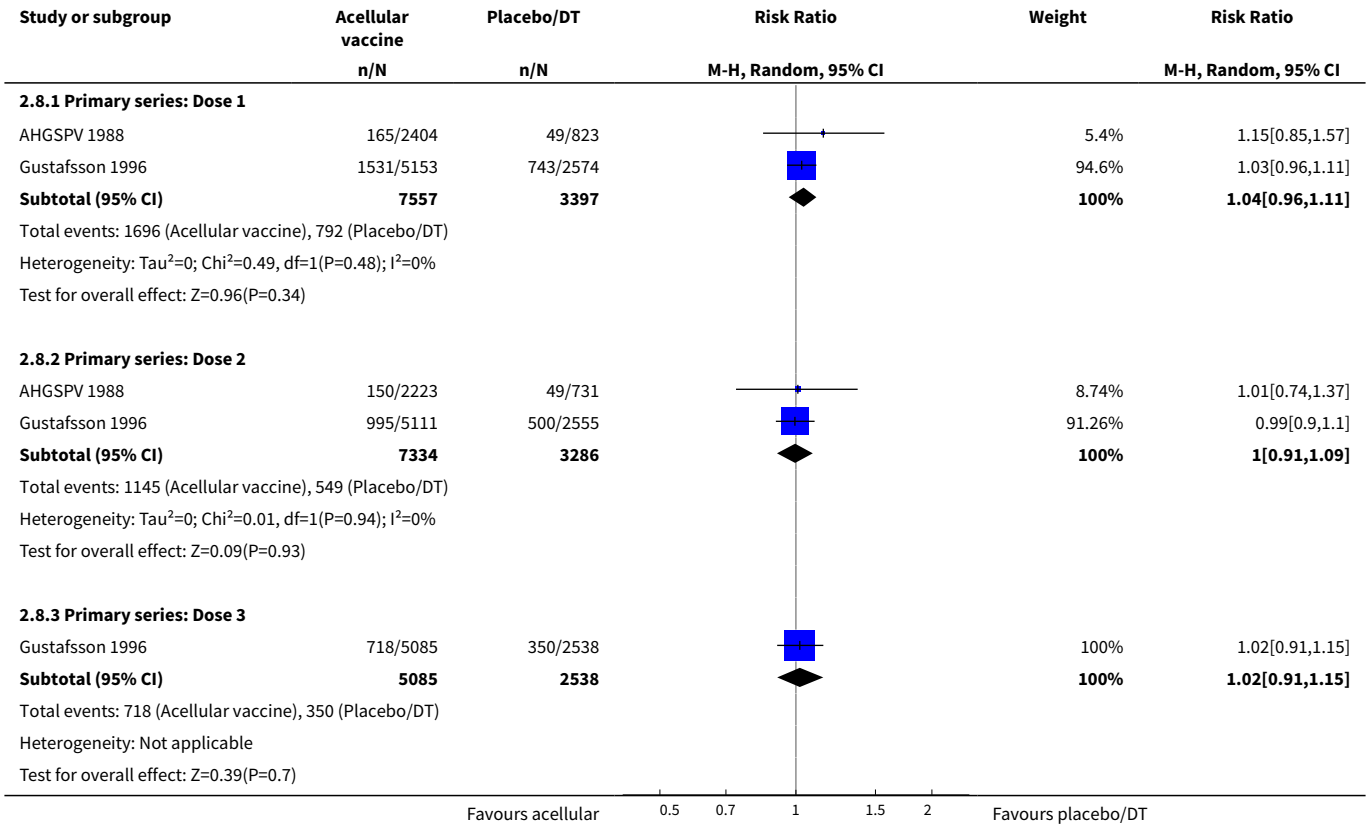


Analysis 2.7. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 7 Anorexia.

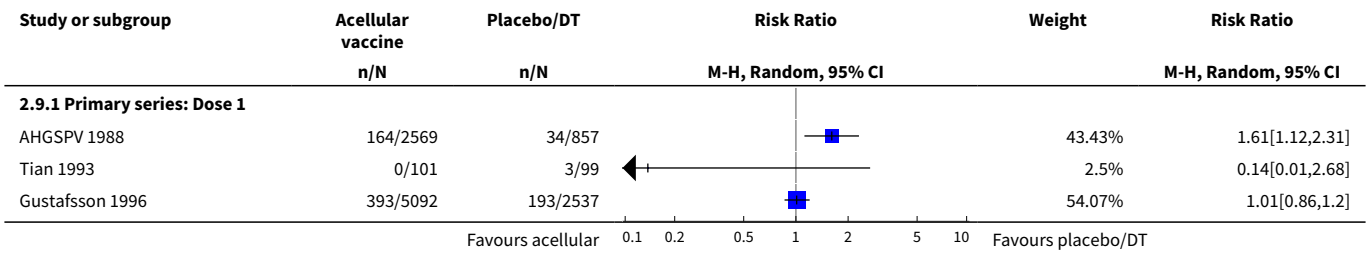


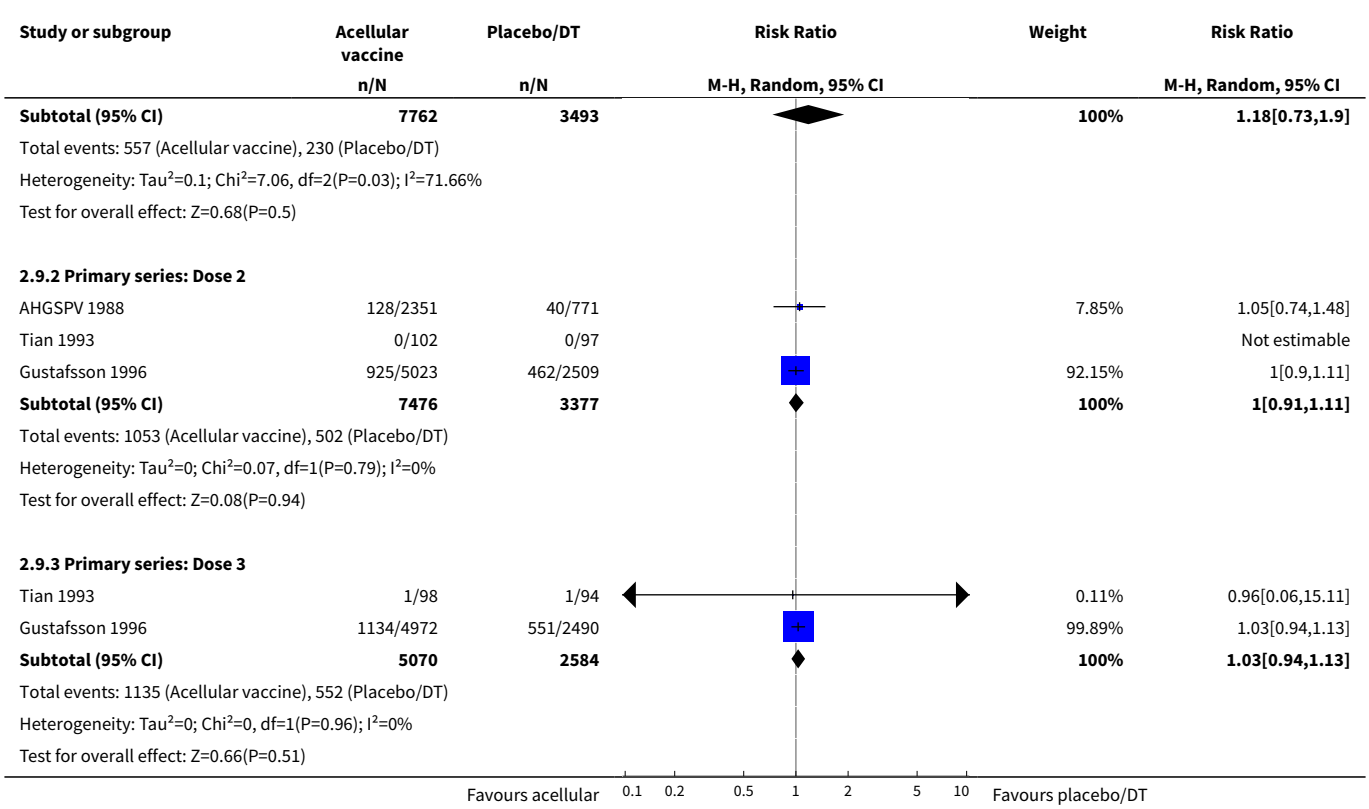


Analysis 2.8. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 8 Drowsiness.

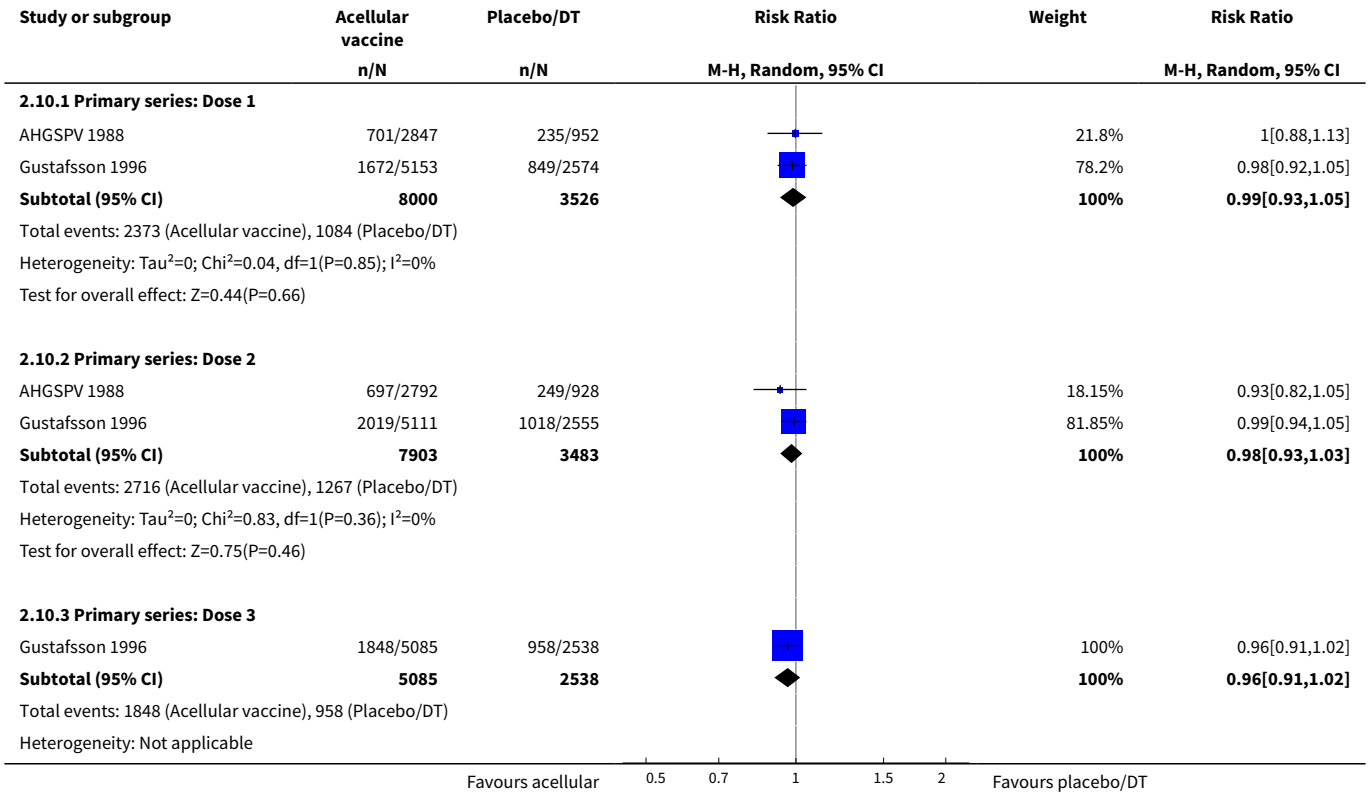


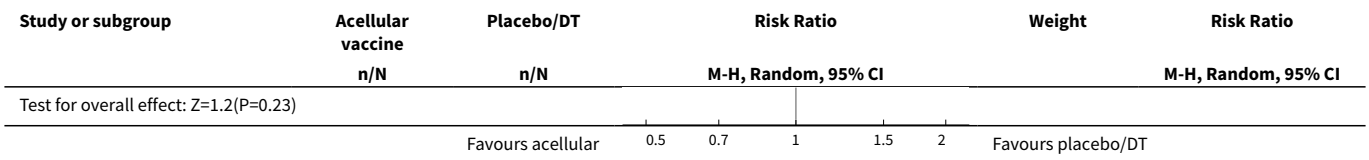
Analysis 2.9. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 9 Fever.



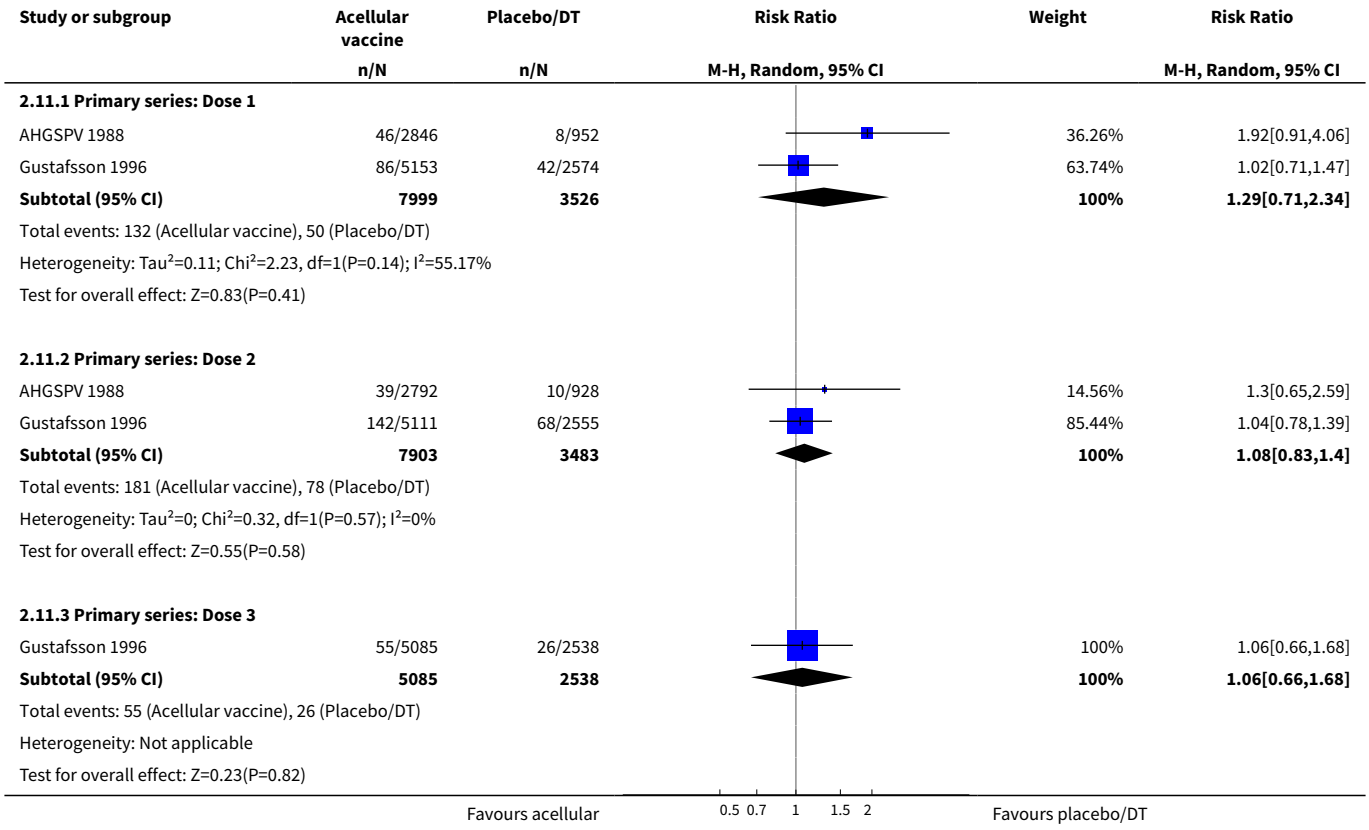


Analysis 2.10. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 10 Irritability/fretfulness.

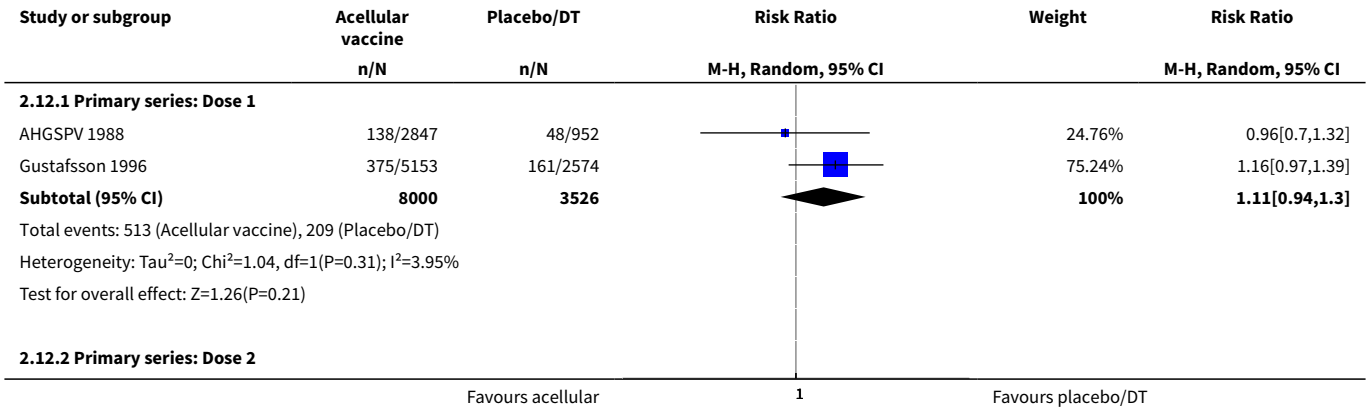


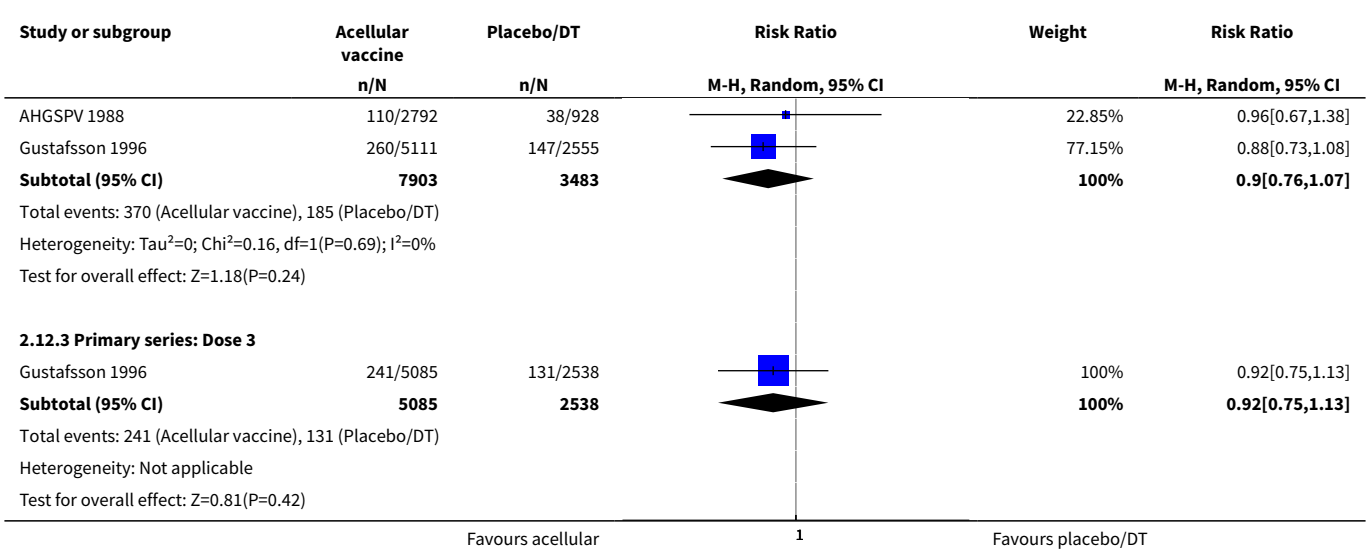


Analysis 2.11. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 11 Prolonged crying.

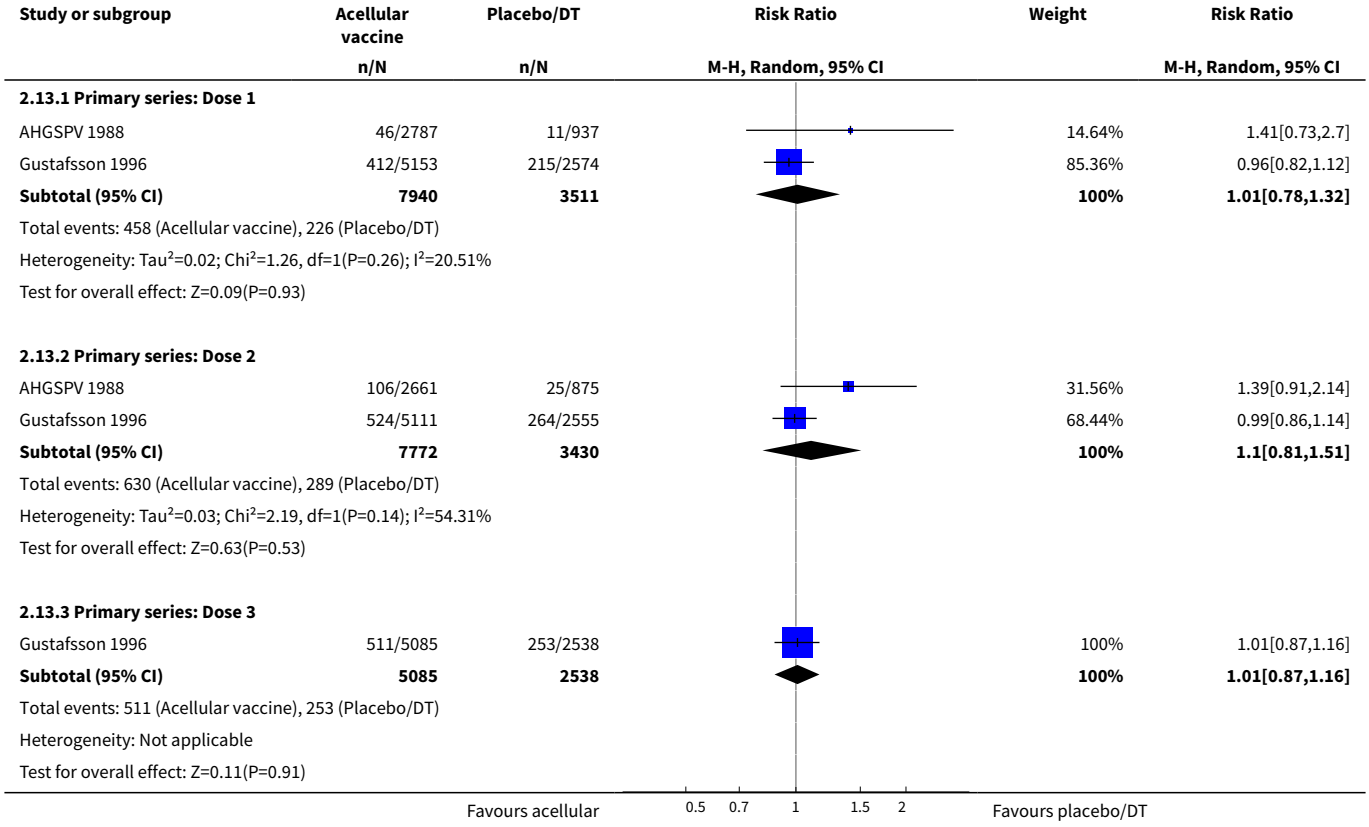


Analysis 2.12. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 12 Vomiting.

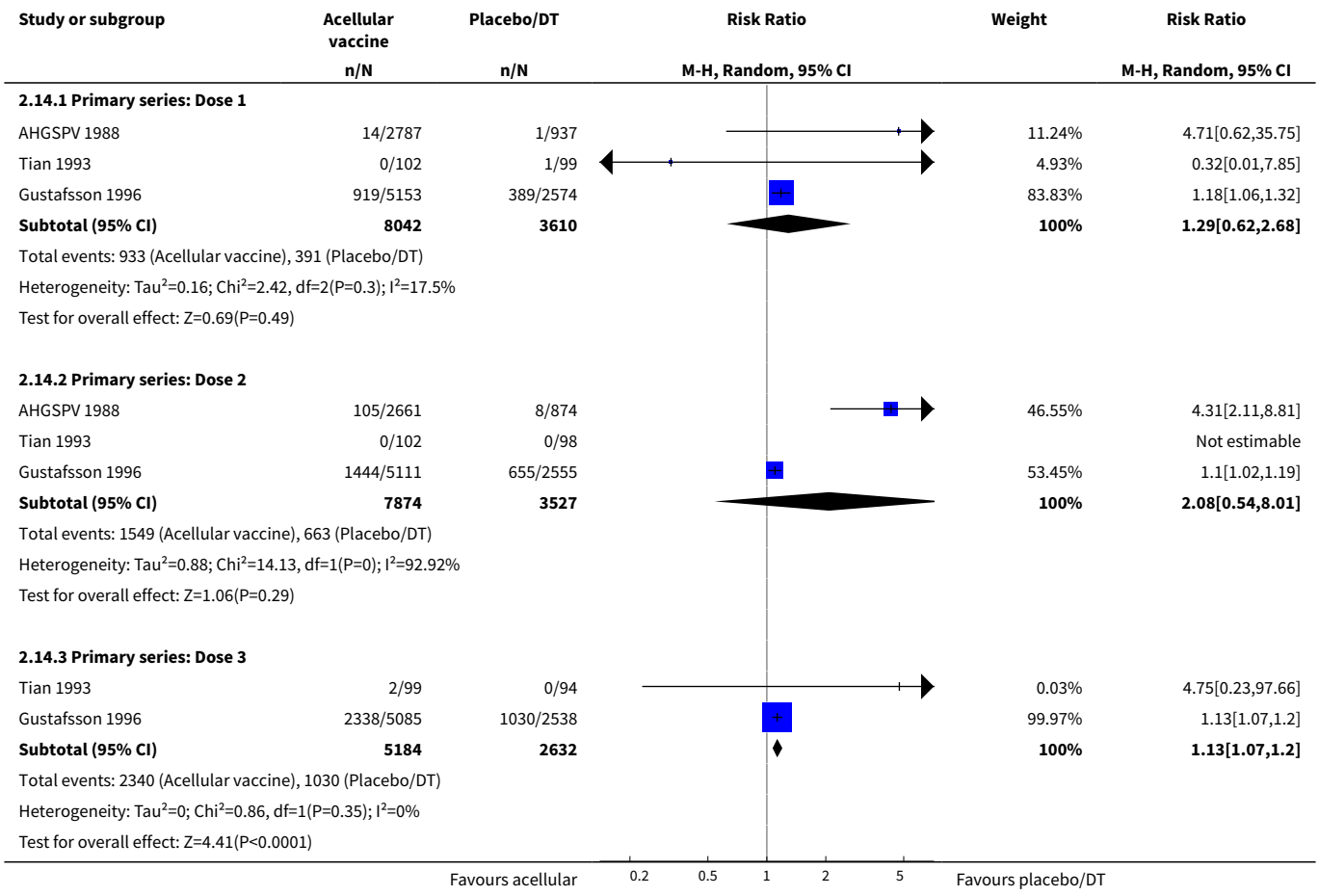




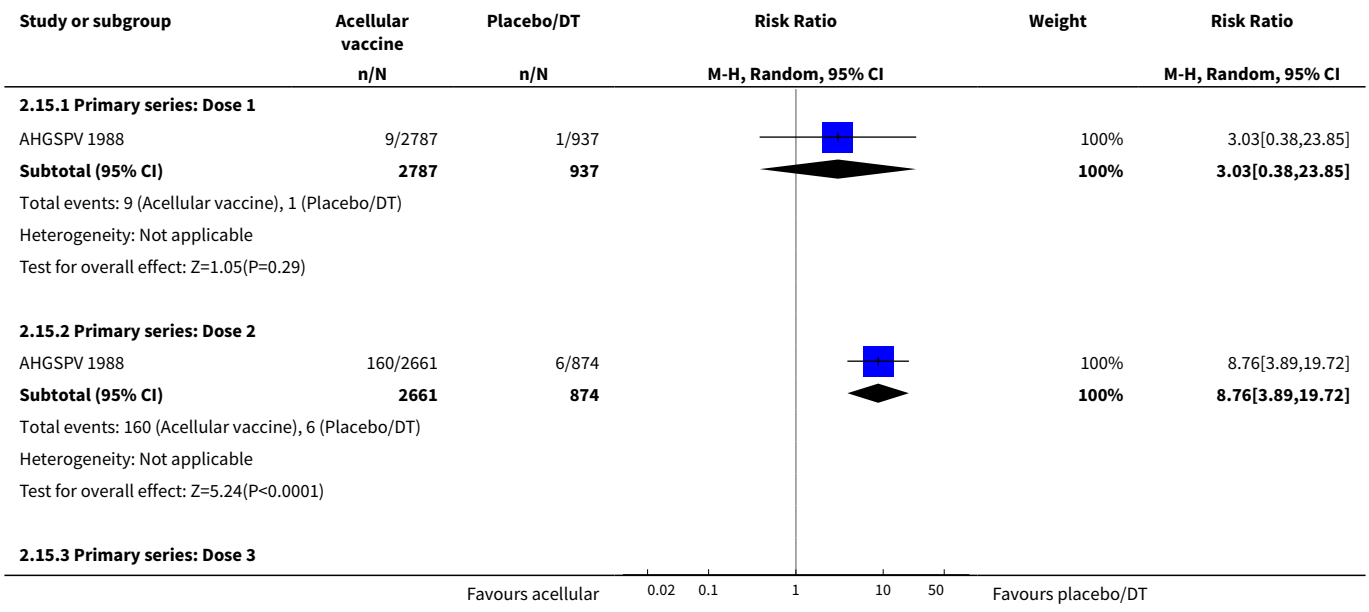
Analysis 2.13. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 13 Pain/tenderness.

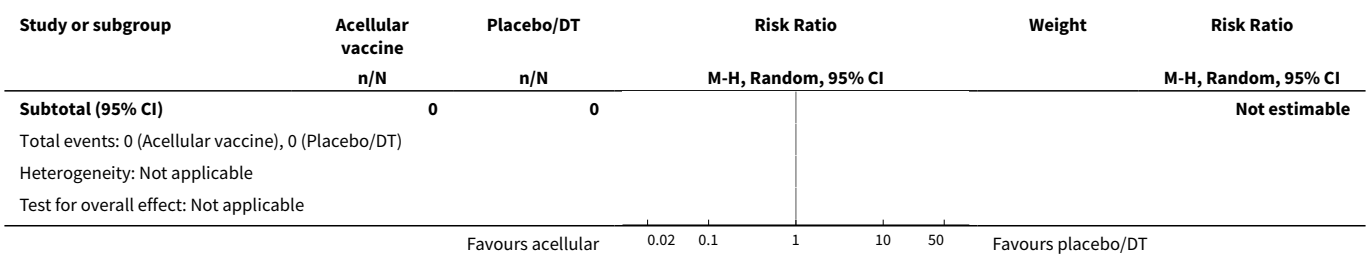


Analysis 2.14. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 14 Swelling/induration.



Analysis 2.15. Comparison 2 Safety: acellular vaccines versus placebo/DT, Outcome 15 Redness.





APPENDICES

Appendix 1. Initial search 1997 and 1998

The initial search was carried out in March 1997 and updated in March 1998, covering the period up to and including January 1998. The databases used were MEDLINE (Medline SilverPlatter CD-ROM) and the Cochrane Central Register of Controlled Trials (CENTRAL). We searched CENTRAL using the term 'pertus* OR whoop*'. We searched MEDLINE using the following strategy:

1. explode PERTUSSIS-VACCINE / all subheadings
2. explode BORDETELLA-PERTUSSIS / all subheadings
3. explode WHOOPING-COUGH / all subheadings
4. PERTUS*
5. WHOOP*
6. #1 or #2 or #3 or #4 or #5

The files downloaded from MEDLINE SilverPlatter were screened for randomised controlled trials using the RCT FILTER.

Appendix 2. April 2009 updated search strategies

In the 2009 updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to April week 2 2009) and EMBASE.com (1974 to April 2009).

We used the following search strategy to search MEDLINE and CENTRAL. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision- maximising version (2008 revision); Ovid format (Lefebvre 2011). We modified the search strategy to search Embase.com (see below).

MEDLINE (Ovid)

1 exp Pertussis Vaccine/
2 pertussis vaccin*.tw.
3 Whooping Cough/
4 whoop*.tw.
5 Bordetella pertussis/
6 pertuss*.tw.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Vaccines, Acellular/
9 (acellular adj5 vaccin*).tw.
10 8 or 9
11 7 and 10

EMBASE.com

1. 'pertussis vaccine'/de
2. 'diphtheria pertussis tetanus vaccine'/de
3. 'diphtheria pertussis poliomyelitis tetanus vaccine'/de
4. 'diphtheria pertussis tetanus haemophilus influenzae type b hepatitis b vaccine'/de
5. 'diphtheria pertussis tetanus haemophilus influenzae type b vaccine'/de
6. 'bordetella pertussis'/de
7. 'pertussis'/de
8. 'dpt vaccine':ti,ab

9. pertuss*:ti,ab
10. whoop*:ti,ab
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. 'acellular vaccine'/de
13. (acellular:ti,ab AND vaccin*:ti,ab)
14. #12 OR #13
15. #11 AND #14
16. 'randomized controlled trial'/de
17. 'controlled clinical trial'/de
18. 'single blind procedure'/de
19. 'double blind procedure'/de
20. 'phase 3 clinical trial'/de
21. random*:ti,ab
22. placebo*:ti,ab
23. 'clinical trial':it
24. 'randomized controlled trial':it
25. (singl*:ti,ab OR doubl*:ti,ab OR trebl*:ti,ab OR tripl*:ti,ab) AND (mask*:ti,ab OR blind*:ti,ab)
26. 'controlled clinical trial':ti,ab
27. 'controlled clinical trials':ti,ab
28. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
29. ('nonhuman'/exp OR 'animal'/exp) NOT 'human'/exp
30. #28 NOT #29
31. #15 AND #30

Appendix 3. MEDLINE search strategy

1 exp Pertussis Vaccine/
2 pertussis vaccin*.tw.
3 Whooping Cough/
4 whoop*.tw.
5 Bordetella pertussis/
6 pertuss*.tw.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Vaccines, Acellular/
9 (acellular adj5 vaccin*).tw.
10 8 or 9
11 7 and 10

Appendix 4. EMBASE search strategy

#14. #10 AND #13 269 17 May 2011
#13. #11 OR #12 861,917 17 May 2011
#12. 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 OR ((singl* OR doubl*) NEAR/1
blind*):ab,ti AND [embase]/lim 822,212 17 May 2011
#11. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim 241,991 17 May 2011
#10. #6 AND #9 1,393 17 May 2011
#9. #7 OR #8 1,451 17 May 2011
#8. (acellular NEAR/5 vaccin*):ab,ti AND [embase]/lim 1,321 17 May 2011
#7. 'acellular vaccine'/de AND [embase]/lim 271 17 May 2011
#6. #1 OR #2 OR #3 OR #4 OR #5 25,318 17 May 2011
#5. pertuss*:ab,ti OR whoop*:ab,ti AND [embase]/lim 19,626 17 May 2011
#4. 'bordetella pertussis'/de AND [embase]/lim 4,046 17 May 2011
#3. 'pertussis'/de AND [embase]/lim 5,903 17 May 2011
#2. 'diphtheria pertussis tetanus vaccine'/de OR 'diphtheria pertussis tetanus hepatitis b vaccine'/de OR 'diphtheria pertussis tetanus haemophilus influenzae type b vaccine'/de OR
'diphtheria pertussis tetanus haemophilus influenzae type b hepatitis b vaccine'/de OR 'diphtheria pertussis poliomyelitis tetanus vaccine'/de OR 'diphtheria pertussis poliomyelitis tetanus hepatitis b vaccine'/de OR 'diphtheria pertussis poliomyelitis tetanus haemophilus influenzae type b hepatitis b vaccine'/de AND [embase]/lim 5,402 17 May 2011
#1. 'pertussis vaccine'/de AND [embase]/lim 4,338 17 May 2011

Appendix 5. Biosis Previews (Thomson ISI)

Topic=(pertuss* or whoop* or bordetella*) AND Topic=(acellular vaccin*)

Refined by: Topic=(random* or placebo* or clinical trial* or singl* blind* or doubl* blind*)

Appendix 6. CINAHL (Ebsco)

S18 S7 and S16
S17 S7 and S16
S16 S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15
S15 (MH "Quantitative Studies")
S14 (MH "Placebos")
S13 TI placebo* or AB placebo*
S12 TI random* or AB random*
S11 TI (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*) or AB (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl*
mask* or doubl* mask* or tripl* mask* or trebl* mask*)
S10 TI clinic* trial* or AB clinic* trial*
S9 PT clinical trial
S8 (MH "Clinical Trials+")
S7 S5 and S6 Search modes
S6 TI acellular N5 vaccin* or AB acellular N5 vaccin*
S5 S1 or S2 or S3 or S4
S4 TI (whoop* or pertuss*) or AB (whoop* or pertuss*)
S3 (MH "Bordetella Pertussis")
S2 (MH "Whooping Cough")
S1 (MH "Pertussis Vaccine+")

Appendix 7. Comparison of results between the first published (primary) review and the updated reviews

Minor adverse events: acellular vaccines versus whole-cell vaccines

Outcomes	Number of trials		Sample size (n)		Effect size - RR (95% CI)	
	Primary	Update	Primary	Update	Primary	Update
Anorexia	10	11				
Primary dose 1	7	8	13,942	19,632	0.47 (0.35 to 0.64)	0.43 (0.32 to 0.57)
Primary dose 2	8	9	18,232	18,501	0.50 (0.37 to 0.67)	0.45 (0.33 to 0.60)
Primary dose 3	11	14	18,385	18,646	0.52 (0.45 to 0.61)	0.50 (0.43 to 0.60)
aP booster (pre wP)	3	4	1380	1939	0.35 (0.24 to 0.51)	0.40 (0.30 to 0.54)
aP booster (pre aP)			8033	8447	0.41 (0.26 to 0.64)	0.42 (0.31 to 0.58)
Drowsiness						
Primary dose 1	11	12	20,200	20,490	0.74 (0.50 to 1.09)	0.72 (0.50 to 1.03)
Primary dose 2	7	8	19,039	19,308	0.67 (0.43 to 1.03)	0.61 (0.41 to 0.93)
Primary dose 3	8	9	19,169	19,430	0.56 (0.40 to 0.79)	0.56 (0.40 to 0.77)
aP booster (pre wP)	10	14	1695	2254	0.43 (0.34 to 0.53)	0.48 (0.41 to 0.56)
aP booster (pre aP)	2	3	7953	8367	0.50 (0.45 to 0.55)	0.49 (0.44 to 0.54)

(Continued)

Fever						
Primary dose 1	18	19	22,977	23,267	0.17 (0.13 to 0.21)	0.17 (0.13 to 0.20)
Primary dose 2	15	17	21,652	22,001	0.31(0.25 to 0.37)	0.31 (0.26 to 0.37)
Primary dose 3	15	17	21,390	21,731	0.34 (0.29 to 0.38)	0.34 (0.30 to 0.38)
aP booster (pre wP)	19	25	2513	3381	0.33 (0.24 to 0.45)	0.33 (0.26 to 0.43)
aP booster (pre aP)	5	8	9012	9879	0.38 (0.21 to 0.68)	0.35 (0.22 to 0.55)
Irritability/fretfulness						
Primary dose 1	13	15	20,337	20,707	0.50 (0.43 to 0.58)	0.48 (0.42 to 0.56)
Primary dose 2	10	12	19,080	19,429	0.51 (0.43 to 0.60)	0.48 (0.41 to 0.56)
Primary dose 3	11	13	19,170	19,511	0.55 (0.49 to 0.62)	0.53 (0.47 to 0.59)
aP booster (pre wP)	13	16	1978	2596	0.32 (0.23 to 0.45)	0.36 (0.28 to 0.47)
aP booster (pre aP)	4	6	9165	9856	0.48 (0.44 to 0.51)	0.48 (0.44 to 0.51)
Prolonged crying						
Primary dose 1	7	8	16,849	17,184	0.14 (0.12 to 0.18)	0.15 (0.11 to 0.19)
Primary dose 2	5	6	16,078	16,347	0.29 (0.24 to 0.35)	0.29 (0.24 to 0.35)
Primary dose 3	6	7	16,248	16,545	0.32 (0.24 to 0.44)	0.33 (0.24 to 0.46)
aP booster (pre wP)	4	7	955	996	0.23 (0.10 to 0.55)	0.21 (0.10 to 0.48)
aP booster (pre aP)	2	2	7943	7943	0.48 (0.22 to 1.02)	0.27 (0.02 to 3.12)
Vomiting						
Primary dose 1	7	8	11,160	11,450	0.78 (0.67 to 0.90)	0.77 (0.66 to 0.88)
Primary dose 2	6	7	10,716	10,985	0.71 (0.60 to 0.85)	0.62 (0.45 to 0.86)
Primary dose 3	5	6	10,552	10,813	0.80 (0.66 to 0.97)	0.69 (0.46 to 1.04)
aP booster (pre wP)	5	6	703	744	0.35 (0.15 to 0.82)	0.50 (0.22 to 1.11)
aP booster (pre aP)	1	1	86	86	1.07 (0.10 to 11.34)	1.07 (0.10 to 11.34)
Pain/tenderness						
Primary dose 1	10	13	11,683	14,180	0.21 (0.16 to 0.28)	0.20 (0.16 to 0.25)
Primary dose 2	8	11	10,710	13,186	0.19 (0.16 to 0.22)	0.18 (0.15 to 0.22)
Primary dose 3	9	12	10,938	13,333	0.21 (0.19 to 0.25)	0.20 (0.17 to 0.24)
aP booster (pre wP)	16	21	2433	3051	0.40 (0.31 to 0.51)	0.43 (0.36 to 0.53)
aP booster (pre aP)	3	5	1572	2263	0.36 (0.26 to 0.49)	0.43 (0.32 to 0.58)
Redness						
Primary dose 1	11	13	6783	7253	0.30 (0.22 to 0.40)	0.30 (0.23 to 0.39)

(Continued)

Primary dose 2	10	12	6078	6427	0.42 (0.32 to 0.55)	0.39 (0.29 to 0.51)
Primary dose 3	11	13	6291	6632	0.48 (0.41 to 0.56)	0.47 (0.41 to 0.54)
aP booster (pre wP)	16	22	2187	3055	0.52 (0.43 to 0.63)	0.51 (0.44 to 0.59)
aP booster (pre aP)	3	5	1572	2263	0.67 (0.51 to 0.89)	0.65 (0.52 to 0.80)
Swelling/induration						
Primary dose 1	13	15	14,242	14,612	0.24 (0.19 to 0.31)	0.24 (0.19 to 0.31)
Primary dose 2	12	14	13,430	13,779	0.38 (0.30 to 0.47)	0.35 (0.28 to 0.45)
Primary dose 3	13	15	13,575	13,916	0.41 (0.30 to 0.57)	0.40 (0.29 to 0.54)
aP booster (pre wP)	17	22	2433	3301	0.51 (0.44 to 0.59)	0.51 (0.46 to 0.57)
aP booster (pre aP)	4	6	1730	2421	0.61 (0.47 to 0.80)	0.68 (0.58 to 0.80)

CI: confidence interval
RR: risk ratio

Appendix 8. Incidence of severe adverse events: acellular vaccines versus whole-cell vaccines

Outcomes	Number of trials	Acellular vaccines		Whole-cell vaccines		RR 95% CI
		n/N*	Incidence #	n/N	Incidence	
Primary series non-completion due to adverse events	11	248/80,060	3.09	338/28,849	11.72	0.23 (0.12 to 0.43)
Death (infection)						
Primary series	13	5/22,154	0.23	3/12,344	0.24	0.97 (0.23 to 4.16)
Death (all causes)						
Primary series	16	81/86,863	0.93	61/35,588	1.71	0.87 (0.62 to 1.22)
Encephalopathy						
Primary series	9	0/81,601	0.0	0/32,161	0.0	-
Convulsions						
Primary series	15	43/88,513	0.49	41/35,874	1.14	0.47 (0.31 to 0.73)
Booster	11	1/2250	0.44	0/397	0.0	0.46 (0.02 to 11.2)
Hypotonic hyporesponsive episodes						
Primary series	11	70/86,347	0.81	51/35,226	1.45	0.26 (0.08 to 0.81)
	7	0/2171	0.0	0/316	0.0	

(Continued) Booster	-

*n/N: number of events/number of recipients
Incidence: number of events per 1000 recipients
CI: confidence interval
RR: risk ratio

Appendix 9. Incidence of minor adverse events over the primary series: acellular vaccines versus whole-cell vaccines

Outcomes	Dose 1		Dose 2		Dose 3	
	Acellular	Whole-cell	Acellular	Whole-cell	Acellular	Whole-cell
	n/N*	n/N	n/N	n/N	n/N	n/N
	Incidence#	Incidence	Incidence	Incidence	Incidence	Incidence
	Number of trials		Number of trials		Number of trials	
Anorexia	1275/12,310	1896/7322	1047/11,653	1208/6848	941/11,840	966/6806
	103.57	258.95	89.85	176.40	79.48	141.93
	11		8		9	
Drowsiness	3427/12,813	2435/7677	2087/12,134	1500/7174	1548/12,301	1231/7129
	267.46	317.18	171.99	209.09	125.84	172.67
	11		9		10	
Fever	898/14,910	3900/8357	1809/14,167	3427/7834	2270/14,024	3439/7707
	60.23	466.67	127.69	437.45	161.87	446.22
	19		17		17	
Irritability/fretfulness	3645/12,875	4488/7832	3763/12,144	3695/7285	3482/12,268	3228/7243
	283.11	573.03	309.86	507.21	283.83	445.67
	15		12		13	
Prolonged crying	116/10,364	395/6820	161/9867	248/6480	68/10,096	94/6449
	11.19	57.92	16.32	38.27	6.74	14.58
	8		6		7	
Vomiting	530/8126	269/3324	356/7885	189/3100	322/7788	148/3025
	65.22	80.93	45.15	60.97	41.35	48.93
	8		7		7	
Pain/tenderness	733/10,279	1840/3901	710/9642	1606/3544	712/9769	1358/3564
	71.31	471.67	73.64	453.16	72.88	381.03

(Continued)

	13		11		12	
Redness	512/5348	620/1805	599/4821	551/1606	807/4972	583/1660
	95.74	343.49	124.25	343.09	162.31	351.20
	13		12		13	
Swelling/induration	1238/10,606	1670/4006	1842/10,034	1576/3745	2791/10,157	1658/3759
	116.73	416.87	183.58	420.83	274.79	441.07
	15		14		15	

*n/N: number of events/number of recipients
Incidence: number of events per 1000 recipients

Appendix 10. Incidence of minor adverse events in boosters: acellular vaccines versus whole-cell vaccines

Outcomes	**aP booster (previous wP) versus wP booster (previous wP)**		**aP booster (previous aP) versus wP booster (previous wP)**	
	Acellular	**Whole-cell**	**Acellular**	**Whole-cell**
	n/N*	**n/N**	**n/N**	**n/N**
	Incidence#	**Incidence**	**Incidence**	**Incidence**
	Number of trials		**Number of trials**	
Anorexia	129/1149	244/790	457/4474	735/3973
	112.27	308.86	102.15	184.99
	14		4	
Drowsiness	203/1453	292/801	532/4419	913/3948
	139.71	364.54	120.39	231.26
	13		3	
Fever	191/2184	305/1197	1320/5838	2058/4041
	87.45	254.80	226.10	509.28
	24		8	
Irritability/fretfulness	314/1728	445/868	1256/5837	1379/4019
	181.71	512.67	215.18	343.12
	17		6	
Prolonged crying	7/666	20/330	9/4105	15/3838
	10.51	60.61	2.19	3.91

(Continued)

	6		2	
Vomiting	18/551	13/193	2/56	1/30
	32.67	67.36	35.71	33.33
	6		1	
Pain/tenderness	620/2018	661/1033	691/2015	203/248
	307.23	639.88	342.93	818.55
	21		5	
Redness	503/1980	523/1075	692/2015	135/248
	254.04	486.51	343.42	544.35
	21		5	
Swelling/induration	446/2144	493/1157	575/2139	112/282
	208.02	426.10	268.82	397.16
	22		6	

*n/N: number of events/number of recipients
Incidence: number of events per 1000 recipients

Appendix 11. Incidence of severe adverse events: acellular vaccines versus placebo/DT

Outcomes	Number of trials	Acellular vaccine		Placebo/DT		RR 95% CI
		n/N*	Incidence#	n/N	Incidence	
Primary series non-completion due to adverse events	4	65/19,092	3.40	28/6809	4.11	0.70 (0.38 to 1.29)
Death (infection)						
Primary series	4	5/19,093	0.26	1/6809	0.15	1.21 (0.19 to 7.80)
Death (all causes)						
Primary series	4	10/19,092	0.52	2/6809	0.29	1.08 (0.26 to 4.42)
Encephalopathy						
Primary series	2	0/14,521	0.0	0/4129	0.0	-
Convulsions						
Primary series	4	27/19,092	1.41	28/6809	4.11	0.44 (0.12 to 1.69)

(Continued)

Hypotonic hyporesponsive episodes Primary series	4	2/19,092	0.10	2/6809	0.29	0.29 (0.02 to 5.13)

*n/N: number of events/number of recipients
Incidence: number of events per 1000 recipients
CI: confidence interval
RR: risk ratio

Appendix 12. Incidence of minor adverse events over the primary series: acellular vaccines versus placebo/DT

Outcomes	Dose 1		Dose 2		Dose 3	
	Acellular	Placebo/DT	Acellular	Placebo/DT	Acellular	Placebo/DT
	n/N*	n/N	n/N	n/N	n/N	n/N
	Incidence#	Incidence	Incidence	Incidence	Incidence	Incidence
	Number of trials		Number of trials		Number of trials	
Anorexia	750/8000	325/3526	656/7903	276/3483	418/5085	195/2538
	93.75	92.17	83.00	79.24	82.20	76.83
	2		2		1	
Drowsiness	1696/7557	792/3397	1145/7334	549/3286	718/5085	350/2538
	224.43	233.15	156.12	167.07	141.20	137.90
	2		2		1	
Fever	557/7762	230/3493	1053/7476	502/3377	1135/5070	552/2584
	71.76	65.85	140.85	148.65	223.87	213.63
	3		3		2	
Irritability/fretfulness	2373/8000	1084/3526	2716/7903	1267/3483	1848/5085	958/2538
	296.63	307.43	343.67	368.53	363.42	377.46
	2		2		1	
Prolonged crying	132/7999	50/3526	181/7903	78/3483	55/5085	26/2538
	16.50	14.18	22.90	22.39	10.82	10.24
	2		2		1	
Vomiting	513/8000	209/3526	370/7903	185/3483	241/5085	131/2538
	64.13	59.27	46.82	53.12	47.39	51.62
	2		2		1	

(Continued)

Pain/tenderness	458/7940 57.68 2	226/3511 64.37	630/7772 81.06 2	289/3430 84.26	511/5085 100.49 1	253/2538 99.68
Redness	9/2787 3.23 1	1/937 1.07	160/2661 60.13 1	6/874 6.86	-	-
Swelling/induration	933/8042 116.02 3	391/3610 108.31	1549/7874 196.72 3	663/3527 187.98	2340/5184 451.39 2	1030/2632 391.34

*n/N: number of events/number of recipients
Incidence: number of events per 1000 recipients

F E E D B A C K

Response to Zhang et al: Acellular vaccines for preventing whooping cough in children. Cochrane Database of Systematic Reviews 2011, Issue 1, 25 January 2011

Summary

A meta-analysis initially done by Jefferson et al (1) of acellular (acP) vaccine efficacy and safety in children was revisited by Zhang et al in the Cochrane Library (2). Zhang correctly did not perform a formal meta-analysis, stating that it was not appropriate due to the small number of efficacy trials and the significant heterogeneity across these trials with respect to immunization schedules, case definitions, follow-up duration, products used, and background pertussis rates. The inappropriateness of applying a meta-analysis methodology to these studies was previously highlighted by Desauziers et al (3) and Simondon (4) following Jefferson et al's previous publication (1).

The review by Zhang et al concludes that "of the currently available acellular vaccines, multi-component vaccines confer better protection, against both classical whooping cough and mild pertussis infection, than vaccines containing only one or two components." Although it is intuitively attractive to adopt a "more components is better" position on acP vaccines, this strong conclusion on differential efficacy of acellular vaccines is not objectively supported by the reviewed trials nor by the data these trials generated. Nor is this conclusion supported by previously published commentaries or by the positions expressed by professional pediatric and national immunization policy bodies.

Zhang et al included in their review six controlled trials that were designed well enough to ensure high internal validity and one trial without active surveillance of cases. All of these trials were performed between 1988 and 1997. Only three of these trials were efficacy trials that directly compared different acellular vaccines in a double-blind, randomized design, with an active follow-up, and laboratory confirmation of cases. The majority of currently licensed pertussis vaccines have not been compared in head-to-head efficacy trials. Most critically there are no clinical trials that directly compare the efficacy of licensed 2-acP vaccines with that of licensed 3-acP or 5-acP vaccines. In fact, the only study in which a 2-acP vaccine was less efficacious than multi-component acellular vaccines involved an experimental 2-acP vaccine that was never licensed/registered, precisely because of its limited efficacy. Since other 2-acP vaccines did demonstrate sufficient efficacy to be licensed, the more appropriate interpretation of the experimental 2-acP vaccine data is that it is not the number of acP components but rather some other feature or combination of features (e.g. the source of the antigens, their relative concentrations, the processes for their purification and detoxification, or the nature and concentration of the adjuvants) of each individual vaccine that determine efficacy. The biasing potential of including data from the unlicensed, experimental 2-acP vaccine is not clearly discussed in Zhang et al's review.

The Zhang et al publication highlights the continuing debate over the relative merits of data from randomized controlled trials (RCTs) versus data from observational studies in evidence-based reviews. Our belief is that, in the real world of vaccination policy decision making, these two different data sets are entirely complementary. Well-designed RCTs offer higher internal validity, while equally well-designed observational studies provide higher external validity and a better reflection of the real world. For example, a well-designed case-control study performed in Germany by Liese et al (5) reported that a licensed 2-acP vaccine was 93% effective in prevention of 21 or more days of paroxysmal cough that was laboratory-confirmed as pertussis. This study was excluded from the review because it was not a RCT. The exclusion of this study and the associated potential for bias should also have been discussed by Zhang et al.

Other published effectiveness data clearly support the effectiveness of both 1- and 2-acP vaccines as well as other multi-component acP vaccines. These data, with their high external validity, have been reported not only from Japan, the United States and Canada (6-10) but also from France, Austria, Finland, Denmark, Sweden and Germany (11-16), and underscore the effectiveness of national vaccination programs in preventing whooping cough in children, regardless of the number of acP components in the licensed vaccines used.

Observational studies might overestimate vaccine effectiveness, if persons included as cases in the studies had more severe pertussis than persons not included, or if the vaccination status would influence the likelihood of the diagnosis of pertussis in a coughing person. Nonetheless, none of these studies identified a lower effectiveness of 2-acP licensed vaccines in pre-school children compared to “multi-component vaccines or whole cell vaccines” (9, 15). These results contradict the conclusions of Zhang et al and as a result they should have been discussed.

The studies included in the review did not use the same follow-up duration but these differences are not addressed even though they contribute to the heterogeneity of the data. The impact of duration of follow-up on efficacy estimates has been well illustrated. In one study (17), a highly effective whole cell vaccine and a 2-acP vaccine demonstrated equivalent efficacies until 18 months of age with a relative risk: 1.16 (95%CI 0.77-1.72). Only after 18 months of age was the whole cell vaccine shown to retain higher efficacy (relative risk: 1.76 [95%CI 1.33-2.33]) than the acellular vaccine in the absence of a booster dose in the two groups.

The inappropriateness of relating acP vaccine efficacy to the number of pertussis components has been addressed by both American and European regulatory authorities (18, 19) and by international expert panels charged with comparing results between studies (20-22). These groups have concluded that the available data support the practical policy guidance that all licensed acellular vaccines are highly effective.

In summary, the overall body of available data supports a conclusion that all licensed acP vaccines, regardless of the number of pertussis components, have proven highly effective. Despite the intrinsic attractiveness of such a conclusion, these data do not support the Zhang et al conclusion that 1- and 2-acP vaccines are less effective than those with more acellular components. The dangers of this conclusion coming from such respected authors include confusion in the vaccination community and the inappropriate preference for one group of vaccines over another. This in turn might lead to negative impacts on vaccine supply and immunization rates.

[1] *Sanofi Pasteur, Lyon France*

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Reply

We thank Philippe P. J. André and David R. Johnson from Sanofi Pasteur (Lyon, France) for their interests and comments on our review. Their main concern is one of the review's conclusions "Of the currently available acellular vaccines, multi-component vaccines confer better protection against both classical whooping cough and mild pertussis infection than vaccines containing only one or two components". We recognise that this conclusion is based on indirect evidence since the majority of currently licensed pertussis vaccines have not been compared in head to head efficacy trials as André and Johnson pointed out.

André and Johnson's comments are likely to provoke an old and ongoing debate on the comparative efficacy of acellular pertussis vaccines with different antigen components which is ironic since Sanofi Pasteur markets both two and five component acellular pertussis vaccines. This question has been well addressed by Patrick Olin in 1997 (1). In this commentary, Olin stated that "Contrary to the position taken in most commentaries, analysis of the results of the four placebo-controlled trials of two one-component, two two-component, two three-component and one five-component vaccine unequivocally demonstrate the multi-component vaccines to have better protective efficacy against both mild and typical pertussis than one- and two-component vaccines". The results from another recent systematic review with 49 randomised controlled trials (RCTs) and 3 cohort studies are also consistent with the findings of our review (2). The current evidence on comparative efficacy of acellular pertussis vaccines with different antigen components has been cited by the most recent WHO position paper on pertussis vaccines (3).

We are conscious that the clinical implication of any possible superiority of multi-component vaccines over mono- and bivalent vaccines in the efficacy demonstrated by RCTs needs to consider the transferability of this conclusion to whole countries and vaccine delivery systems. The effectiveness of vaccination programmes on a national scale for controlling infectious disease depends not only on the efficacy of the vaccine but also other factors such as the vaccination schedule and adherence, and transportation and storage of the vaccine. Moreover, indirect effects in producing herd immunity in the population may also contribute to the effectiveness of large-scale vaccination in controlling infectious diseases (4,5). Therefore, successful control of pertussis infections by two-component vaccines in Japan and in other countries (5-7) does not necessarily exclude the potential additional benefits of large-scale vaccination with multi-component vaccines.

This is a systematic review of RCTs, so we did not included observational studies in the review. In the next update, we will devote a special paragraph in the discussion to compare the results from RCTs and observational studies, and to address the potential contribution of follow-up duration for the heterogeneity across the studies, as suggested by André and Johnson. We will also modify the conclusion to be "Currently available evidence suggests that multi-component vaccines confer better protection against both classical whooping cough and mild pertussis infection than vaccines containing only one or two components".

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Contributors

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WHAT'S NEW

Date	Event	Description
20 September 2014	Amended	Abstract and Plain language summary corrected in reporting the efficacy of one- and two-component vaccines against typical whooping cough and against mild pertussis disease.

HISTORY

Review first published: Issue 2, 1999

Date	Event	Description
20 January 2014	New search has been performed	Searches updated. We did not identify any new trials for inclusion or exclusion.
20 January 2014	New citation required but conclusions have not changed	Our conclusions remain unchanged.
9 January 2012	New search has been performed	Searches conducted. No new included or excluded trials found
17 May 2011	New citation required but conclusions have not changed	Our conclusions remain unchanged in this update
18 April 2011	Feedback has been incorporated	Feedback comment added to review
21 April 2009	New search has been performed	Searches conducted. Three trials were excluded and seven additional trials were included
21 April 2009	New citation required but conclusions have not changed	New team of review authors updated this previously withdrawn review
13 December 2007	Amended	Converted to new review format
23 March 2006	Amended	Review withdrawn from *The Cochrane Library*, Issue 3, 2006

Date	Event	Description
22 January 1998	New search has been performed	Searches conducted

CONTRIBUTIONS OF AUTHORS

Inge Axelsson (IA) contributed to updating the Background section and the section "Agreements and disagreements with other studies or reviews" in the Discussion section.
Silvio Prietsch (SP) was responsible for updating the Background section. He participated in study selection, quality assessment and data collection for the updated review. He also provided input to updating the section Risk of bias in included studies.
Linjie Zhang (LZ) was responsible for study selection, quality assessment, data collection and data analysis for the updated review. He was also responsible for updating the Abstract, Methods, Results, Discussion and References. He contributed to updating the Background section.
Scott Halperin (SH) performed a critical review of the manuscript and provided input to updating the Discussion section.
The final version of the updated review was approved by all review authors.

DECLARATIONS OF INTEREST

Inge Axelsson was in part paid by the Research and Development Unit, Jämtland County Council, Östersund, Sweden. "In the last 10 years, I have been a Clinical Investigator in a trial of an infant combination vaccine containing acellular pertussis (aP) vaccine from Sanofi Pasteur MSD but I have not received any fee from any pharmaceutical company".

Scott A Halperin has undertaken clinical trials of acellular pertussis vaccines for most manufacturers of these products including GlaxoSmithKline, Sanofi Pasteur, Novartis and Wyeth. He has given Continuing Medical Education talks (not as part of a manufacturers' speakers bureau) for which an honorarium has been paid. He has served on occasional ad hoc advisory boards of vaccine manufacturers but does not have any ongoing consultancies.

Linjie Zhang: none known.

Sílvio OM Prietsch: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- UK Department of Health Cochrane Incentive Scheme 2008, UK.

  This updated review received an award from the UK Department of Health Cochrane Incentive Scheme 2008

NOTES

This review was previously withdrawn from *The Cochrane Library* in Issue 3, 2006. The electronic searches had been conducted in 1998 and the lead author was unable to update the review. In May 2008 this review was taken over and updated by a new team of review authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Age Factors; Diphtheria-Tetanus-Pertussis Vaccine [adverse effects] [*therapeutic use]; Diphtheria-Tetanus-acellular Pertussis Vaccines [adverse effects] [therapeutic use]; Pertussis Vaccine [therapeutic use]; Randomized Controlled Trials as Topic; Whooping Cough [*prevention & control]

MeSH check words

Child; Child, Preschool; Humans; Infant