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Systematic review of the effects of pertussis vaccines in children

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Abstract

Objective: To assess the efficacy and safety of whole-cell and acellular pertussis vaccines administered to children singly or within diphtheria, tetanus and pertussis (DTP) vaccines. *Data sources*: We searched the Cochrane Library, MEDLINE, EMBASE, Biological Abstracts and Science Citation Index to December 2001. Specialised websites and bibliographies of retrieved articles and reviews were assessed. Vaccine manufacturers and investigators were contacted for additional data. *Review methods*: We included randomised and cohort studies comparing efficacy and/or safety of pertussis vaccines with placebo, DT, no intervention or each other. *Results*: We included 52 studies (49 randomised controlled trials (RCTs), 3 cohort studies). All tested whole-cell and acellular vaccines were significantly more effective than placebo against pertussis. Absolute efficacy of whole-cell DTP varied from 37 to 92%. One- and two-component acellular vaccines had lower absolute efficacy (67–70%), than vaccines with ≥3 components (80–84%). Whole-cell vaccines were associated with significantly higher incidences of swelling and induration (odds ratio (OR) 11.67, 95% confidence interval (CI) 8.83–15.44), fever (OR for fever >39 °C 3.36, 95% CI 2.06–5.49) and crying for >2 h (OR 4.72, 95% CI 2.94–7.59) than placebo or DT. Differences in incidence of hypotonic hyporesponsive episodes (HHE) and convulsions were not statistically significant. Acellular pertussis vaccines did not cause a higher incidence of local signs, fever, convulsions, HHE or prolonged crying than placebo or DT. *Conclusion*: All tested pertussis vaccines were efficacious. Whole-cell vaccines show variable efficacy, making interpretation of direct comparisons unreliable. Acellular vaccines with ≥3 antigenic components showed higher efficacy than one- and two-component vaccines. The adverse event profile of acellular vaccines was similar to that of placebo and considerably better than that of whole-cell vaccines.

Keywords: Pertussis vaccines; Systematic review; Meta-analysis; Effectiveness; Safety

1. Introduction

Vaccination against pertussis (whooping cough) is widely practised and coverage with DTP (pertussis combined with diptheria and tetanus toxoids) is almost universal in Europe [1]. Whole-cell vaccines against pertussis (wP) were developed in the 1940s but concerns about possible associations with infantile spasms, convulsions and epilepsy led to the development of acellular vaccines (aP) in the 1970s [2,3]. These contain up to five of the *Bordetella pertussis* antigens: pertussis toxin, filamentous heamagglutinin, pertactin and three serotypes of fimbrial antigens or agglutinogens. Identification of the best pertussis vaccines is important to ensure effective prevention and to ensure efficient use of healthcare resources, since whole-cell vaccines are considerably cheaper than acellular vaccines. However, the array of pertussis vaccines within DTP, differences in case definitions, ascertainment procedures and vaccination schedules have made it difficult to review the evidence about their relative efficacy [4–11]. We report a systematic review of studies assessing the efficacy and safety of DTP vaccines.

2. Methods

2.1. Searching

We searched the Cochrane Library, MEDLINE, EMBASE, Biological Abstracts, Science Citation Index and OLDMEDLINE up to December 2001. We also searched the bibliographies of retrieved articles and reviews and the Vaccine Adverse Event Reporting System website [12]. Vaccine manufacturers and authors of relevant studies were contacted to identify further published or unpublished studies and to answer queries about the conduct or outcome of studies.

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2.2. Selection

We included randomised and quasi-randomised controlled trials (RCT) of the efficacy and safety and cohort studies of the safety of vaccination with pertussis or DTP given in any dose, preparation or time schedule to healthy individuals aged ≤15 years. Given the published variability in efficacy and safety of DTP, we selected studies comparing the effects of DTP with DT or placebo or no intervention and those assessing their relative performance in head-to-head comparisons. We included studies of vaccines which are no longer licensed, those which are not yet licensed or are no longer being developed. We excluded studies of whole-cell vaccines performed before the potency of the pertussis component was standardised using the mouse protection test (MPT) in the 1940s [7,9,10].

2.3. Validity assessment, data abstraction and study characteristics

Two reviewers (TJ and MR) applied inclusion criteria independently and disagreements were referred to a third reviewer (CD). We used standardised definitions to classify study designs to enhance comparability [13]. Methodological quality was assessed using the Cochrane Reviewers' Handbook criteria for RCTs [14] and the Newcastle–Ottawa Scales (NOS) for cohort studies [15]. Data were extracted onto electronic templates.

2.4. Quantitative data synthesis

Homogeneity of participants, vaccines and outcomes were assessed before inclusion in the meta-analysis. We excluded serological outcome data. All comparisons were stratified by vaccine type. Efficacy was stratified by the pertussis definition used in the study (Table 1).

Efficacy estimates were expressed as relative risk (RR) of pertussis with 95% confidence intervals (95% CI). Absolute vaccine efficacy (VE) was expressed as a percentage using the formula: VE = 1 − RR. Safety was expressed as the Mantel Haenszel odds ratio (OR) and 95% CI for the occurrence of: temperature >38 °C, temperature >39 °C, local induration or swelling, convulsions, crying >2 h and hypotonic hyporesponsive episodes (HHE) for up to 72 h following immunisation stratified by dose when details were available.

Table 1
Pertussis outcome definitions

Outcome used—efficacy	Cough duration	Laboratory confirmation
Pertussis—mild	≥1 week	+
Pertussis—moderate	≥2 weeks	+
Pertussis	Variable duration and severity	±
Pertussis (WHO definition)	≥3 weeks with paroxysms and whoops	+

We calculated both fixed and random effect model RR and OR and calculated the Peto OR for rare events. The presence and effects of heterogeneity were tested using chi-square on pooled estimates of effect. We used both fixed and random effect models to assess between-study variance. We assessed publication bias using funnel plots and Egger's test for plot symmetry [16,17].

Differences in efficacy estimates between DTaP3, DTaP4 and DTaP5 were tested using a test for indirect comparisons [18].

The meta-analysis shows the number of observations rather than numbers of participants.

Data from RCTs and cohort studies were synthesised separately.

3. Results

3.1. Study flow

After screening 223 studies likely to fulfil our criteria, we included 52 studies (including 8 unpublished datasets) in our meta-analysis. These comprised 49 reports of RCTs [19–67], 3 cohort studies [68–70] and 1 study incorporating both designs [62]. The most frequent reason for exclusion was non-comparative design (26 studies) (Fig. 1).

3.2. Study characteristics

Of the 52 studies, 7 scored highly on all quality criteria [23–26,41,50,61] and 20 had adequate randomisation. Treatment allocation was adequately concealed in 27 trials, 16 used an open design and 6 reported unclear or inadequate procedures. Masking was adequate in 4, insufficient in 10 and unclear in 25. Withdrawn participants were excluded from analyses in 27 trials, but reports contained sufficient data for us to perform intention to treat (ITT) analyses. Results of the meta-analyses are shown in Table 2.

3.3. Quantitative data synthesis

3.3.1. Absolute efficacy of pertussis vaccines

Whole-cell vaccines show higher efficacy than placebo against pertussis (using the WHO definition) (pooled VE 78%), but efficacy varies significantly between vaccines. VE for DTwP vaccines ranged from 46% (RR 0.54, 95% CI 0.46 to 0.63) [41,42] to 92% (RR 0.08, 95% CI 0.05–0.13) [62]. VE for wP ranged from 61% (RR 0.39, 95% CI 0.27–0.57) to 89% (RR 0.11, 95% CI 0.08–0.15) [23].

One preparation (Connaught DTwP) has been tested for efficacy against mild pertussis [41,42]. Combined VE was 37%, significantly higher than placebo.

Pooled absolute VE for acellular vaccines was 73%, VE was 67–70% for one-or two-component vaccines, 84% for three-component, 80% for four-component and 84% for