



# The impact of administration of conjugate vaccines containing cross reacting material on *Haemophilus influenzae* type b antibody responses in infants: A systematic review and meta-analysis of randomised controlled trials



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## ABSTRACT

**Background:** Protein-polysaccharide conjugate vaccines such as *Haemophilus influenzae* type b (Hib), meningococcal, and pneumococcal vaccine, induce immunological memory and longer lasting protection than plain polysaccharide vaccines. The most common proteins used as carriers are tetanus toxoid (TT) and cross reacting material-197 (CRM), a mutant form of diphtheria toxoid. CRM conjugate vaccines have been reported to suppress antibody responses to co-administered Hib-TT vaccine.

**Methods:** We conducted a systematic review and meta-analysis of randomised controlled trials in which infants were randomised to receive meningococcal or pneumococcal conjugate vaccines along with Hib-TT. Trials of licensed vaccines with different carrier proteins were included for group C meningococcal (MenC), quadrivalent ACWY meningococcal (MenACWY), and pneumococcal vaccines.

**Results:** Twenty-three trials were included in the meta-analyses. Overall, administration of MenC-CRM in a 2 or 3 dose schedule resulted in a 45% reduction in Hib antibody concentrations (GMR 0.55, 95% CI 0.49–0.62). MenACWY-CRM boosted Hib antibody responses by 22% (GMR 1.22, 95% CI 1.06–1.41) whilst pneumococcal CRM conjugate vaccines had no impact on Hib antibody responses (GMR 0.91, 95% CI 0.68–1.22).

**Conclusions:** The effect of CRM protein-polysaccharide conjugate vaccines on Hib antibody responses varies greatly between vaccines. Co-administration of a CRM conjugate vaccine can produce either positive or negative effects on Hib antibody responses. These inconsistencies suggest that CRM itself may not be the main driver of variability in Hib responses, and challenge current perspectives on this issue.

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## 1. Introduction

Encapsulated bacteria such as *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis* can cause substantial invasive disease and death due to septicaemia, meningitis and pneumonia, particularly in infants. The development and deployment of glyconjugate vaccines in infant immunisation programmes has substantially reduced the incidence of these diseases [1–3]. Administration of a capsular polysaccharide conjugated to a carrier protein induces T cell dependent antibody responses and the

differentiation of B cells into long-lived plasma and memory cells. As a result of this, protein-polysaccharide conjugate vaccines induce immunological memory, longer lasting protection and enable boosting of antibody responses with further doses – these advantages are not found with plain polysaccharide vaccines which do not engage T cells in the immune response. Different proteins are used as the carriers for different vaccine antigens, and when multiple conjugate vaccines are administered to infants, the resulting interactions between different carrier-proteins may enhance or restrict the immune response. Various mechanisms by which this may occur have been postulated [4–7]. The most common carrier proteins are tetanus toxoid (TT) and cross reacting material-197 (CRM), a mutant form of diphtheria toxoid.

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Co-administration of a polysaccharide (particularly for capsular group C *N. meningitidis*) conjugated to CRM protein has been reported to suppress antibody responses to Hib vaccine conjugated to tetanus toxoid (Hib-TT) [4,8]. Reviews of this phenomenon, referred to as bystander interference, have suggested that interference increases as the amount of co-administered CRM increases [9]. New conjugate vaccines are in development (e.g. against Group B *Streptococcus*), some of which include the same carrier proteins as those in currently administered vaccines. If clear evidence of bystander interference can be demonstrated it would suggest that different carrier proteins may be beneficial in future vaccines and should be a priority in the development of new conjugate vaccines.

Whilst some have attempted to review the evidence of bystander interference in the literature, no meta-analyses of the effect of administration of CRM conjugate vaccines on Hib responses have been conducted. Reports on the existence of bystander interference have included as evidence, results from non-randomised comparisons of different studies, uncontrolled studies [9–11], or have reviewed studies from only one pharmaceutical company [12], methodologies which are prone to bias. Confounding factors such as laboratory procedures, different vaccine regimes, and different levels of circulating Hib carriage in the community in different years, can all affect responses to Hib vaccines in trials conducted with infants thus making between-trial comparisons problematic.

Randomised controlled trials provide the only unbiased estimates in which all confounding factors, whether known or unknown, are balanced via the process of randomisation. Meta-analysis is a well-established method of combining information from multiple clinical trials to obtain more precise estimates of effects and is thus the gold-standard for evidence synthesis [13]. We present herein, a systematic review and meta-analysis of randomised controlled trials of pneumococcal and meningococcal CRM conjugate vaccines and their effect on antibody responses to co-administered Hib-TT conjugate vaccines.

## 2. Methods

We conducted a systematic review of randomised controlled trials in which healthy infants aged 3 months old or younger were randomised to receive a primary immunisation course with two or three doses of meningococcal or pneumococcal conjugate vaccines along with Hib-TT, and anti-polyribosylribitol phosphate (PRP) immunoglobulin G (IgG) responses to the Hib-TT vaccine were measured one month post-priming (Supplementary Tables 1–3). Studies were included in which infants were randomised to receive Hib-TT along with either: (i) monovalent capsular group C meningococcal vaccine (MenC) conjugated to CRM or TT; or (ii) quadrivalent ACWY meningococcal vaccine (MenACWY) conjugated to CRM or TT; or (iii) pneumococcal vaccine conjugated to CRM or *H. influenzae* protein D (PHiD-CV); or (iv) in which the control arm participants received no meningococcal or pneumococcal vaccine. Studies were excluded in which children in different randomised arms did not receive the same Hib-TT vaccine or in which other differences in co-administered vaccines confounded the randomised comparison of interest to this review. For example, trials which studied the effect of two co-administered vaccines (Hib-TT and MenC-CRM) compared with a combination vaccine (Hib-MenC-TT) were excluded, as were trials which studied the effect of a MenC vaccine compared with a PCV vaccine on responses to other co-administered routine vaccines.

Anti-PRP IgG geometric mean concentration (GMC) and 95% confidence intervals (CI) were obtained from published papers, pharmaceutical company websites, or trial registration databases. Where estimates from different sources were discrepant, the estimate from the peer-reviewed published journal article was used. Estimates from studies which did not report anti-PRP IgG

responses but did report a trial registration number were sought from the appropriate trial database if available. Where a paper reported on more than one study, or reported a study which had more than two arms, these were included as separate estimates.

For each study the geometric mean ratio (GMR) comparing randomised vaccine arms was computed from the ratio of the GMCs and the standard error for this was derived from the log-transformed CIs of the GMCs.

The analyses of MenC and MenACWY vaccines compared the CRM vaccines with a control (TT or no vaccine). Meta-analyses were conducted using Stata version 14.0 'metaan' function [14]. For the analysis of pneumococcal vaccines, four different vaccine groups were compared (PCV7-CRM, PCV13-CRM, PHiD-CV and no vaccine). A network meta-analysis was therefore conducted using the Stata 'network meta' function which combined all vaccine comparisons in the one model [15,16]. All analyses used a restricted maximum-likelihood random effects model. Statistical heterogeneity was assessed using  $\tau^2$  and  $I^2$  statistics [17,18].

Subgroup comparisons were conducted according to the number and type of vaccine administered as the randomised study vaccines in the clinical trials. Additionally, a second meta-analysis of capsular group C meningococcal vaccine trials was conducted in which subgroups of the type of routine vaccines administered concurrently within the trial (three component acellular pertussis, five component acellular pertussis, and whole cell pertussis combination vaccines) were compared.

Randomised vaccine immunogenicity trials which have antibody measures as the outcome of interest are not prone to selection, reporting or detection biases as antibody responses cannot be observed nor influenced by study personnel with knowledge of the vaccines a child received. Thus all included studies were considered to be at low risk of bias.

## 3. Results

### 3.1. Capsular group C meningococcal vaccines

Six studies in which a priming schedule of 2 or 3 doses of MenC-CRM was compared with MenC-TT reported 10 possible comparisons (Fig. 1). Two dose schedules of MenC-CRM resulted in a 48% reduction in Hib anti-PRP GMCs (GMR 0.52, 95% CI 0.41–0.66) and a similar reduction was observed for 3 dose priming schedules in which anti-PRP IgG was reduced by 38% (0.62, 0.50–0.78). Tejedor *et al.* reported on a 3-arm study in which 3 doses of MenC-CRM were compared with 2 doses of MenC-TT [19] with a resulting combined 50% reduction in anti-PRP antibody responses (0.50, 0.39–0.64).

Overall, the combined estimate of the effect of administration of 2 or 3 priming doses of MenC-CRM compared with MenC-TT on anti-PRP IgG was a reduction of 45% (0.55, 0.49–0.63) with no substantial heterogeneity between studies ( $I^2 = 11\%$ ,  $\tau = 0.001$ ).

Subgroup analysis according to the type and number of MenC vaccines showed no heterogeneity between groups ( $p = 0.39$ ) (Fig. 1) however subgroup analysis according to the type of routinely administered concomitant vaccines revealed a significantly greater degree of interference in Hib responses when co-administered with five component acellular pertussis combination vaccines compared to three component or whole cell pertussis vaccines ( $p = 0.044$ ) (Fig. 2).

One study compared 2 doses MenC-CRM with no MenC with a GMR of 0.61 (0.32–1.16) [20]. When added to the meta-analysis this did not alter the overall estimate of a reduction of 45% (0.55, 0.49–0.62). There was no evidence that the estimate from this trial differed from the estimates obtained from other trials as the test for heterogeneity resulted in  $p = 0.58$ .

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