

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 to 0.62). MenACWY-CRM boosted Hib antibody responses by 22% (GMR 1.22, 95% CI 1.06 to 1.41) whilst pneumococcal CRM conjugate vaccines had no impact on Hib antibody responses (GMR 0.91, 95%CI 0.68 to 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

24 either positive or negative effects on Hib antibody responses. These inconsistencies suggest
25 that CRM itself may not be the main driver of variability in Hib responses, and challenge
26 current perspectives on this issue.

27

28 **Introduction**

29 Encapsulated bacteria such as *Haemophilus influenzae* type b (Hib), *Streptococcus*
30 *pneumoniae* and *Neisseria meningitidis* can cause substantial invasive disease and death due
31 to septicaemia, meningitis and pneumonia, particularly in infants. The development and
32 deployment of glyconjugate vaccines in infant immunisation programmes has substantially
33 reduced the incidence of these diseases [1-3]. Administration of a capsular polysaccharide
34 conjugated to a carrier protein induces T cell dependent antibody responses and the
35 differentiation of B cells into long-lived plasma and memory cells. As a result of this,
36 protein-polysaccharide conjugate vaccines induce immunological memory, longer lasting
37 protection and enable boosting of antibody responses with further doses – these advantages
38 are not found with plain polysaccharide vaccines which do not engage T cells in the immune
39 response. Different proteins are used as the carriers for different vaccine antigens, and when
40 multiple conjugate vaccines are administered to infants, the resulting interactions between
41 different carrier-proteins may enhance or restrict the immune response. Various mechanisms
42 by which this may occur have been postulated [4-7]. The most common carrier proteins are
43 tetanus toxoid (TT) and cross reacting material-197 (CRM), a mutant form of diphtheria
44 toxoid.

45 Co-administration of a polysaccharide (particularly for capsular group C *Neisseria*
46 *meningitidis*) conjugated to CRM protein has been reported to suppress antibody responses to
47 Hib vaccine conjugated to tetanus toxoid (Hib-TT) [4, 8]. Reviews of this phenomenon,
48 referred to as bystander interference, have suggested that interference increases as the amount
49 of co-administered CRM increases [9]. New conjugate vaccines are in development (e.g.
50 against Group B *Streptococcus*), some of which include the same carrier proteins as those in
51 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 and 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.

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) 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 (PD); 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, PCV13, 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 τ^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.

Results

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 (Figure 1). Two dose schedules of MenC-CRM resulted in a 48% reduction in Hib anti-PRP GMCs (GMR 0.52, 95% CI 0.41 to 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 to 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 to 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 to 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 ($p=0.39$) (Figure 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 ($p=0.044$) (Figure 2).

One study compared 2 doses MenC-CRM with no MenC with a GMR of 0.61 (0.32 to 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 to 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 $p=0.58$.

138 Quadrivalent meningococcal ACWY vaccine

139 Four estimates from two studies measuring anti-PRP IgG one month after priming with 3
140 doses of MenACWY-CRM compared with no meningococcal vaccine were available (Figure
141 3). There was no heterogeneity in estimates of the effect of MenACWY-CRM which overall
142 boosted anti-PRP IgG responses by 23% (GMR 1.23, 95% CI 1.06 to 1.41; heterogeneity:
143 $I^2=0\%$, $p=0.63$, $\tau=0.000$).

144 In addition, two studies using different conjugate proteins compared a 3 dose priming
145 schedule of MenACWY with a 2 dose schedule and found no differences in anti-PRP IgG
146 (MenACWY-CRM (3 vs 2) GMR 1.02, 0.59 to 1.78, [21], and MenACWY-TT (3 vs 2) GMR
147 1.12, 0.85 to 1.49 [22]).

148 Pneumococcal vaccines

149 There were two studies in which the 7-valent CRM conjugate pneumococcal vaccine (PCV7)
150 was compared with no pneumococcal vaccine. The combined estimate from the network
151 meta-analysis (Figure 4) showed no difference in anti-PRP antibody responses due to
152 administration of the CRM conjugate (GMR 0.91, 95%CI 0.68 to 1.22). Studies of 13 valent
153 CRM conjugate PCV compared with 7 valent also revealed no change in anti-PRP IgG (0.95,
154 0.73 to 1.24).

155 Studies in which infants were randomised to receive the 10 valent pneumococcal vaccine
156 (PHiD-CV) conjugated to *Haemophilus influenzae* protein D for 8 serotypes, and TT and
157 diphtheria toxoid (DT) for one serotype each, had higher anti-PRP antibody responses
158 compared with no vaccine (1.41, 1.05 to 1.89) and were also higher compared with PCV7
159 (1.54, 1.28 to 1.86).

160 No studies were available in which PCV13 was compared with no vaccine however the
161 indirect estimate derived from the network meta-analysis indicates that no difference in anti-
162 PRP antibody responses would be expected (indirect GMR 0.96, 95% CI 0.65 to 1.42).
163 There was no evidence of inconsistency in the network model ($\chi^2=0.89$, $p=0.3445$).

164

165

Discussion

This is the first systematic review and meta-analysis of studies comparing the effect of different protein-polysaccharide conjugate vaccines on Hib-TT vaccine antibody responses and reveals that the effect of CRM protein conjugates on Hib antibody responses varies greatly between vaccines. Whilst MenC-CRM administration does appear to reduce Hib antibody responses, MenACWY-CRM enhances them and PCV-CRM has no effect.

Administration of 2 or 3 doses of MenC-CRM reduced Hib responses by 45% compared with MenC-TT. The reduction in Hib reported in studies comparing MenC-CRM with MenC-TT has variously been attributed to either a suppression of Hib responses due to bystander interference with CRM conjugate vaccines, or alternatively, a boosting effect on Hib due to the co-administration of two vaccines which are both conjugated to tetanus toxoid (MenC-TT and Hib-TT) resulting in carrier-specific enhancement of T cell help [6, 9-11]. Only one study compared MenC-CRM with no MenC vaccine, and observed a similar effect on Hib responses as was seen with the CRM vs TT comparisons. This suggests that the differences observed are more likely to be reductions in Hib response due to administration of MenC-CRM rather than increases in Hib response due to a MenC-TT booster effect, although further studies comparing MenC-CRM and/or MenC-TT to no MenC vaccine would be needed to provide definitive evidence.

There does not appear to be a direct relationship between Hib antibody response and amount of CRM in co-administered vaccines. MenC-CRM vaccine contains 10µg of oligosaccharide conjugated to approximately 12-25 µg of CRM protein. In comparison, the MenACWY-CRM vaccine contains 25µg of oligosaccharide and 32.7 to 64.1 µg CRM. If total CRM content were responsible for the suppression of Hib observed, it might be expected that a higher CRM content vaccine would have a greater suppressive effect than a lower dose one.

In this meta-analysis, however, the opposite is observed, with high dose MenACWY-CRM boosting Hib responses rather than reducing them. Similarly, administration of PCV7, containing 20 µg of CRM, had no effect on Hib responses, and the additional 14 µg of CRM in PCV13 vaccine (containing 34 µg of CRM), had no effect on Hib responses when compared with PCV7.

Administration of additional doses of CRM conjugate vaccines in our review did not result in increased interference, whether in a positive or negative direction. Two dose schedules of MenC-CRM reduced Hib antibody responses by a similar magnitude as did three dose schedules. Similarly, in the one trial in which 2 dose and 3 dose priming schedules of MenACWY-CRM were compared, Hib responses were very similar.

It is thus unlikely that the total CRM content of a vaccine, or of a series of vaccinations, is the sole source of interference in Hib antibody responses and other causes need to be considered.

Hib vaccines in these studies were administered in combination with diphtheria-tetanus-pertussis-(HepB)-polio combination vaccines made by two different manufacturers. Although both vaccines contained the same dose of Hib-TT and were both made by carbodiimide coupling chemistry, the Hib-TT molecules in the two vaccines are very different in size. The 5 component acellular pertussis combination vaccine (DTaP5-IPV/Hib) has a larger Hib-TT molecule than the three-component acellular pertussis vaccines (DTaP-HBV-IPV/Hib) with a weight-average molecular mass for the 5 component vaccine of 7.16×10^6 g/mol compared with only 2.60×10^6 g/mol for the 3 component vaccine [23, 24]. The 5 component vaccine also has a lower total PRP saccharide content [23]. In addition, the 3 component vaccine also contains hepatitis B. In our meta-analysis suppression of Hib responses was observed when MenC-CRM was administered with either vaccine, however subgroup comparisons revealed the degree of interference was significantly greater with the vaccine that had the larger Hib-

214 TT molecule, lower saccharide content and no hepatitis B component. The potential for
215 interference in responses to a saccharide-TT conjugate vaccine may therefore be related to
216 the saccharide: protein ratio, size of the molecule and presence or absence of other specific
217 components.

218 Consistent evidence that PHiD-CV boosted Hib responses was observed. There are three
219 different carrier proteins in the PHiD-CV vaccine and the effect on Hib responses has been
220 attributed to the TT component of the vaccine [25]. It is however possible that protein D
221 might influence Hib responses, however there is no licensed vaccine which uses protein D as
222 the sole conjugate so this remains theory only.

223 Carrier-specific enhancement of T cell help would explain the observed boosting effect of
224 PHiD-CV due to the co-administration of two vaccines which both contain a TT conjugate
225 protein. Although such enhancement has been noted in studies of MenC-TT [8] and studies of
226 PHiD-CV [4, 25] it has not been universally observed. Dagan *et al* reported a study of
227 tetravalent pneumococcal vaccine conjugated to TT and delivered at different doses. Infants
228 were randomised to receive vaccines with either 1, 3 or 10 µg of pneumococcal
229 polysaccharide per serotype and the ratio of TT to polysaccharide was held constant across
230 the different dose vaccines [26]. Larger reductions in both anti-PRP as well as anti-TT
231 antibodies were observed with higher dose vaccines. These findings are therefore the
232 opposite to the more commonly cited boosting effect of TT conjugates. It is possible that a
233 vaccine which can induce higher antibody responses with smaller amounts of saccharide may
234 have advantages.

235 The boosting of Hib responses with MenACWY administration was surprising considering
236 the significant suppression of Hib responses seen with MenC-CRM. The oligosaccharide in
237 both types of MenC vaccine (MenC-CRM and MenC-TT) is adsorbed on aluminium

hydroxide 0.3 to 0.4 mg Al³⁺ whereas MenACWY vaccine contains no adjuvant and this may be a factor in the differences seen between these two different vaccines.

This review contains some limitations. As with all systematic reviews, it is limited by the fact that studies in which vaccines with different carrier proteins were compared did not all measure or report Hib antibody responses. Anti-PRP IgG is not the primary outcome for any study comparing meningococcal or pneumococcal vaccines, and is thus not always reported therefore the existence of publication or reporting bias in this review cannot be ruled out.

The estimates in our meta-analyses report relative rather than absolute changes thus the clinical significance of these findings will differ depending on the setting. Even though GMRs did not vary greatly between studies, there was a very large degree of difference in anti-PRP GMCs across all studies (tables 1 – 3), presumably due in part to inter-laboratory variation, but also due to differences in co-administered vaccines as well as inter-country variation. It is not possible to adjust an analysis for all co-administered vaccines or country differences as these factors varied for almost every trial however it is notable that generally higher GMCs were observed in studies conducted in countries where whole-cell pertussis vaccines were co-administered. In settings where antibody titres are generally well above protective thresholds, relative changes of the magnitude observed in this report may have no impact on disease incidence, however in settings with poorer responses in general, such alterations could be critical.

Conclusion

We need a new paradigm. Previous theories about CRM conjugate vaccines suppressing Hib responses via the mechanism of bystander interference are not supported by the data available in the medical literature to date. Responses to Hib-TT vaccine in the presence of a CRM conjugate vaccine differ greatly for different vaccines and are potentially influenced by other

262 co-administered vaccines, the size of the Hib-TT molecule itself, the presence or absence of
263 adjuvant in the CRM conjugate vaccine, and the dose of oligosaccharide. This suggests that
264 CRM itself may not be the main driver of variability in Hib responses.

265 It is important to investigate vaccine interactions prior to introducing new vaccines into an
266 immunisation schedule to minimise the possibility of unexpected effects on disease incidence
267 and to monitor ongoing incidence. The measurement and reporting of responses to
268 concomitant vaccines in clinical trials provides important information for decision making in
269 this area.

Contributions

MV analysed the data and drafted the manuscript which was reviewed and edited by all other authors. All authors approved the final manuscript prior to submission.

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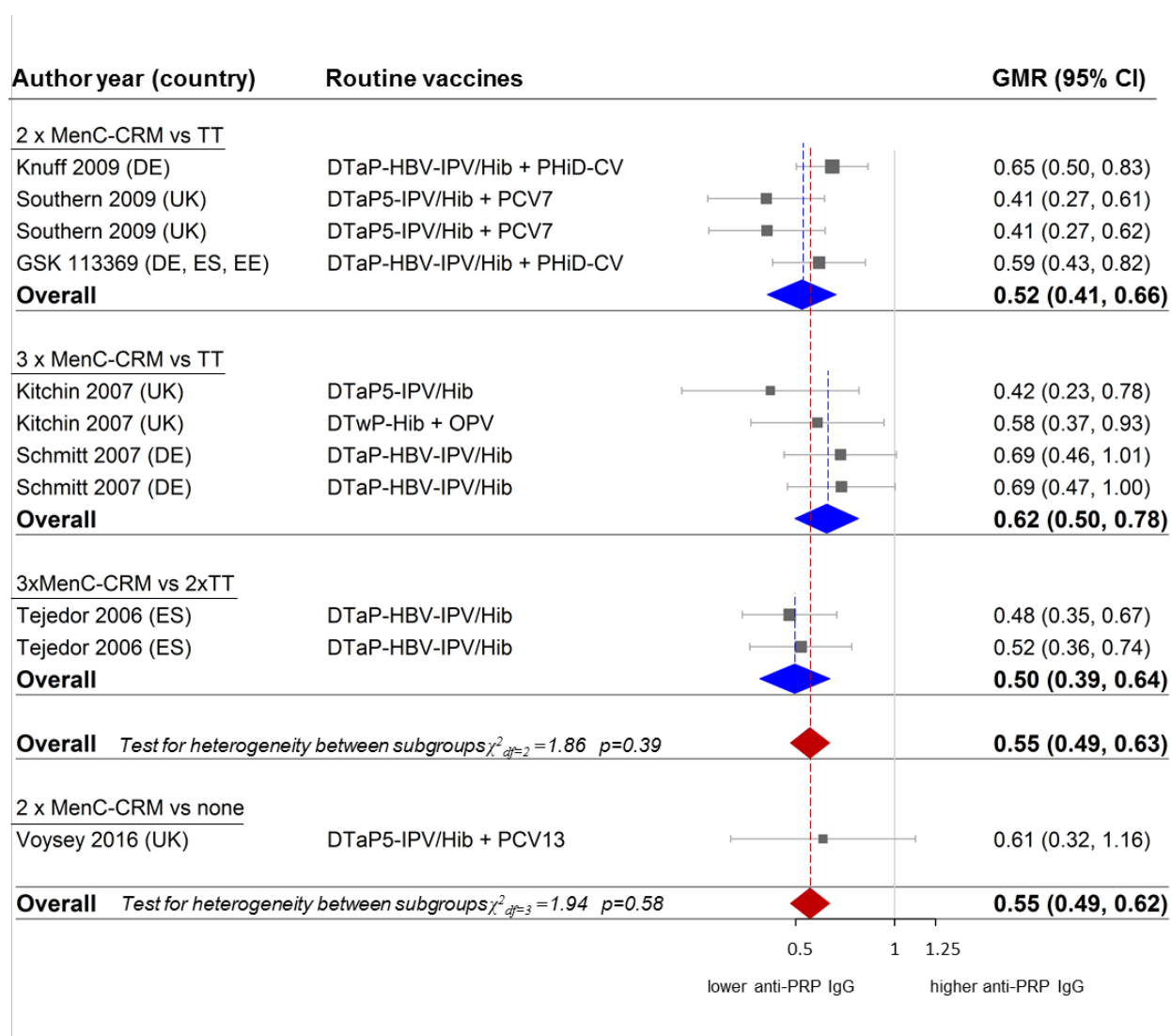
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Declarations of interests

AJP has previously conducted studies on behalf of Oxford University funded by vaccine manufacturers, but currently does not undertake industry funded clinical trials. AJP chairs the UK Department of Health's (DH) Joint Committee on Vaccination and Immunisation (JCVI); the views expressed in this manuscript do not necessarily reflect the views of JCVI or DH.

The other authors have no conflicts of interest.

Figure 1 Meta-analysis of studies measuring anti-PRP IgG responses one month after priming with meningococcal C vaccines



PRP: polyribosylribitol phosphate; IgG: immunoglobulin G; GMR: geometric mean ratio (CRM vs TT or CRM vs none as indicated), values less than 1.0 indicated lower anti-PRP responses in those receiving CRM conjugate vaccines; CI: confidence interval; CRM: cross-reacting material; TT: tetanus toxoid; PHiD-CV: 10-valent pneumococcal conjugate vaccine (Synflorix, GSK); PCV7: 7-valent pneumococcal conjugate vaccine (Prevenar, Pfizer); DTaP: diphtheria, tetanus, acellular pertussis; DTwP: diphtheria, tetanus, whole cell pertussis; HBV: hepatitis b; IPV: inactivated polio vaccine; Hib: *Haemophilus influenzae*

type b; OPV: oral polio vaccine; MenC: group C meningococcal vaccine; MenC-CRM: Meningitec (Pfizer) or Menjugate (GSK); MenC-TT: NeisVac-C (Pfizer) or an unlicensed formulation (GSK); DTaP5-IPV/Hib-TT: Pediacel (Sanofi Pasteur); DTaP-HBV-IPV/Hib: Infanrix Hexa (GSK); DTwP-Hib: Act-Hib DTP (Sanofi Pasteur).

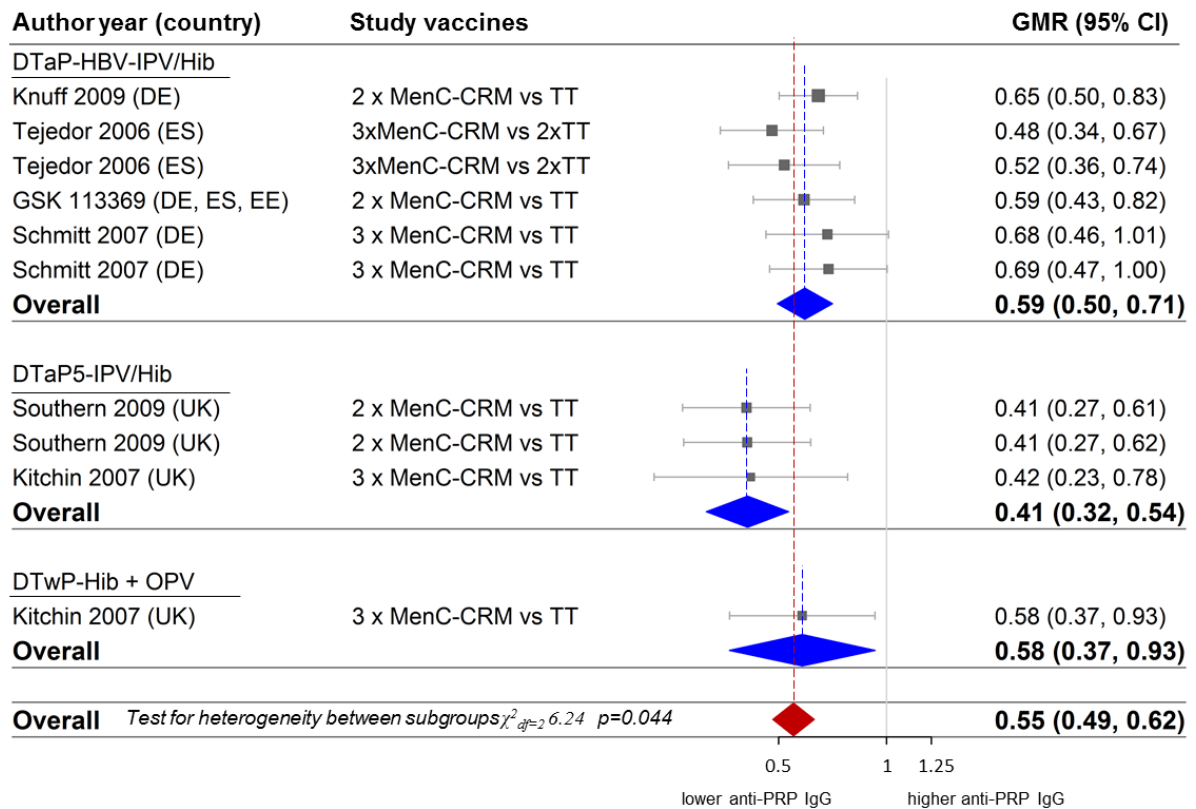
Southern 2009: children received two different MenC-CRM vaccines (Meningitec, Pfizer and Menjugate, GSK) or MenC-TT (NeisVac-C, Pfizer).

Kitchin 2007: children were randomised to two strata in which different vaccines were administered.

Schmidt 2007: children were randomised to receive one of two different MenC-TT vaccines (one with adjuvant and one without) or MenC-CRM vaccine (Meningitec).

Tejedor 2006: children who received MenC-TT were randomised to receive HBV at birth or no HBV.

Figure 2 Meta-analysis of studies measuring anti-PRP IgG responses one month after priming with meningococcal C vaccines according to subgroups of routinely administered diphtheria-tetanus-pertussis vaccines



PRP: anti-polyribosylribitol phosphate; IgG: immunoglobulin G; GMR: geometric mean ratio (CRM vs TT or CRM vs none as indicated), values less than 1.0 indicated lower anti-PRP responses in those receiving CRM conjugate vaccines; CI: confidence interval; CRM: cross-reacting material; TT: tetanus toxoid; PHiD-CV: 10-valent pneumococcal conjugate vaccine (Synflorix, GSK); DTaP: diphtheria, tetanus, acellular pertussis; DTwP; diphtheria, tetanus, whole cell pertussis; HBV: hepatitis b; IPV: inactivated polio; Hib: *Haemophilus influenzae* type b; OPV: oral polio vaccine; MenC: group C meningococcal vaccine; MenC-CRM: Meningitec (Pfizer) or Menjugate (GSK); MenC-TT: NeisVac-C (Pfizer); DTaP5-IPV/Hib-TT: Pediacel (Sanofi Pasteur); DTaP-HBV-IPV/Hib: Infanrix Hexa (GSK); DTwP-Hib: Act-Hib DTP (Sanofi Pasteur).

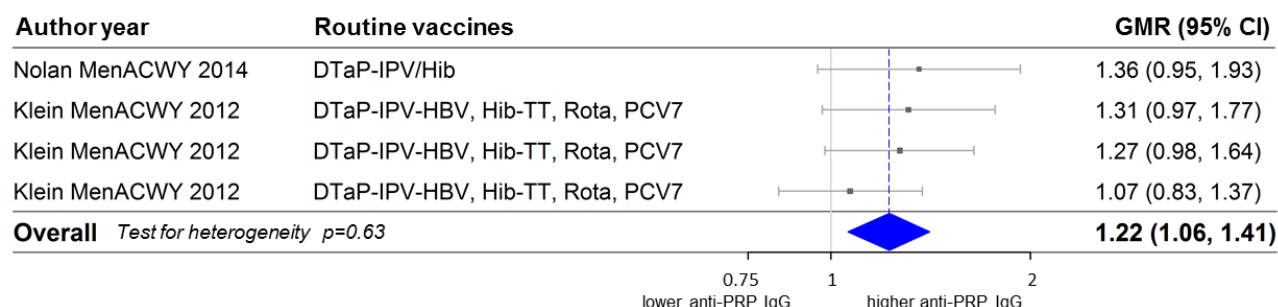
Southern 2009: children received two different MenC-CRM vaccines (Meningitec, Pfizer and Menjugate, GSK) or MenC-TT (NeisVac-C, Pfizer).

Kitchin 2007: children were randomised to two strata in which different vaccines were administered.

Schmidt 2007: children were randomised to receive one of two different MenC-TT vaccines (one with adjuvant and one without) or MenC-CRM vaccine (Meningitec).

Tejedor 2006: children who received MenC-TT were randomised to receive HBV at birth or no HBV.

Figure 3 Meta-analysis of studies measuring anti-PRP IgG responses one month after priming with meningococcal ACWY vaccines compared with no meningococcal vaccine

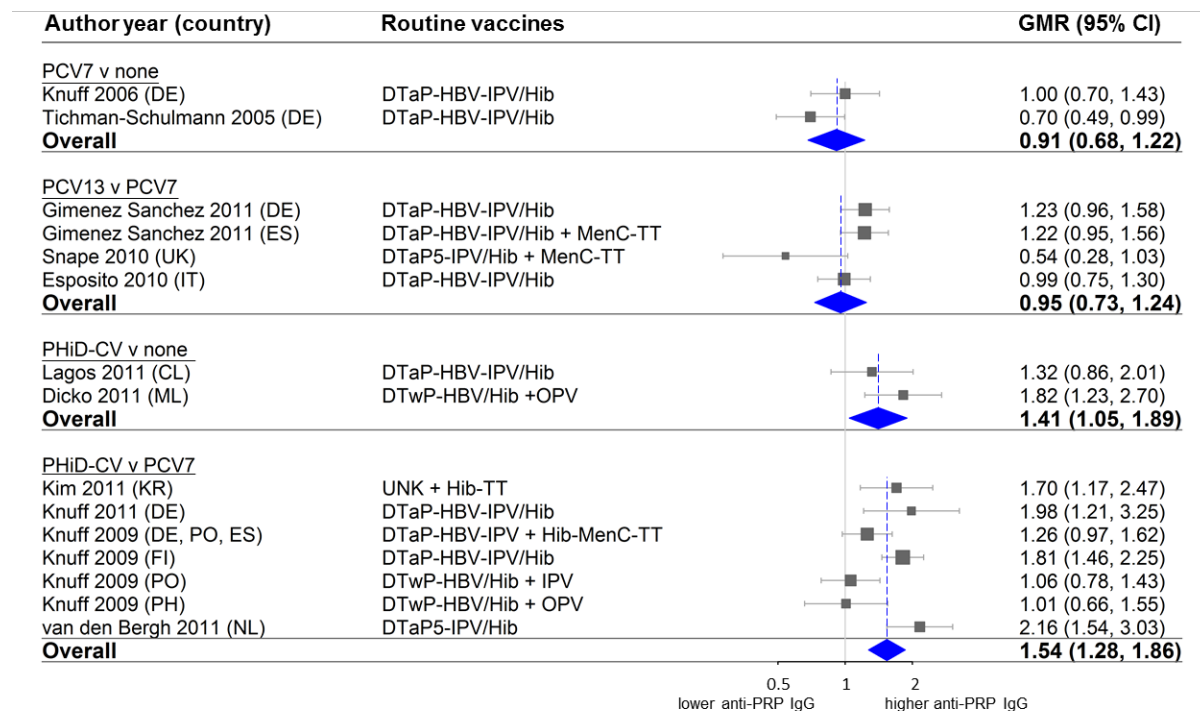


PRP: anti-polyribosylribitol phosphate; IgG: immunoglobulin G; GMR: geometric mean ratio (MenACWY vs none), values less than 1.0 indicated lower anti-PRP responses in those receiving meningococcal group ACWY conjugate vaccines; CI: confidence interval; TT: tetanus toxoid; DTaP: diphtheria, tetanus, acellular pertussis; HBV: hepatitis b; IPV: inactivated polio vaccine; Hib: *Haemophilus influenzae* type b; MenACWY: quadrivalent group ACWY meningococcal vaccine (Menveo, Novartis); PCV7: 7 valent pneumococcal conjugate vaccine (Prevenar, Pfizer); Rota: Oral rotavirus vaccine (RotaTeq, Merck); DTaP5-IPV/Hib-TT: Pediacel (Sanofi Pasteur); DTaP-HBV-IPV: Pediarix (GSK); Hib-TT: ActHIB (Sanofi Pasteur).

Klein 2012: results from children in USA, Argentina, and Columbia reported separately.

Results obtained from clinicaltrials.gov as geometric means are not reported in the published paper for this outcome.

Figure 4 Network meta-analysis of studies measuring anti-PRP IgG responses one month after priming with pneumococcal conjugate



PRP: anti-polyribosylribitol phosphate; IgG: immunoglobulin G; GMR: geometric mean ratio; CI: confidence interval; TT: tetanus toxoid; PHiD-CV: 10-valent pneumococcal conjugate vaccine (Synflorix, GSK); PCV7: 7-valent pneumococcal conjugate vaccine (Prevenar, Pfizer); PCV13: 13-valent pneumococcal conjugate vaccine (Prevenar 13, Pfizer); DTaP: diphtheria, tetanus, acellular pertussis; DTwP: diphtheria, tetanus, whole cell pertussis; HBV: hepatitis b; IPV: inactivated polio vaccine; Hib: *Haemophilus influenzae* type b; OPV: oral polio vaccine (Polio Sabin, GSK); MenC-TT: NeisVac-C (Pfizer); Hib-MenC-TT: Menitorix (GSK); UNK: unknown; DTaP5-IPV/Hib-TT: Pediacel (Sanofi Pasteur); DTwP-HBV/Hib-TT: Zilbrix Hib (GSK); DTaP-HBV-IPV: Pediarix (GSK). Knuff 2009 and Gimenez-Sanchez 2011 report on multiple studies in different countries.

SUPPLEMENTARY MATERIALS

Supplementary Table 1 Studies of capsular group C meningococcal vaccines measuring anti-PRP IgG GMCs one month after priming

<i>Author, Year (country)</i>	<i>Schedule (months)</i>	<i>Randomised study vaccine</i>	<i>PCV vaccine</i>	<i>Routine vaccines</i>	<i>N</i>	<i>Anti-PRP GMC (µg/mL)</i>	<i>LCL</i>	<i>UCL</i>	<i>Ref</i>
<i>Knuff 2009 (DE, PO, ES)</i>	2,4,6	MenC-CRMx2	PHiD-CV	DTaP-HBV-IPV/Hib	168	4.343	3.556	5.304	[25]
	2,4,6	MenC-TTx2	PHiD-CV	DTaP-HBV-IPV/Hib	174	6.708	5.762	7.81	
<i>Southern 2009 (UK)</i>	2,3,4	MenC-CRMx2	PCV7	DTaP5-IPV/Hib-TT	126	1.75	1.29	2.38	[27]
	2,3,4	MenC-CRMx2	PCV7	DTaP5-IPV/Hib-TT	126	1.76	1.29	2.39	
	2,3,4	MenC-TTx2	PCV7	DTaP5-IPV/Hib-TT	115	4.29	3.27	5.62	
<i>Voysey 2016 (UK)</i>	2,3,4	MenC-CRMx2	PCV13	DTaP5-IPV/Hib-TT	140	0.309	0.218	0.439	[20]
	2,3,4	No MenC	PCV13	DTaP5-IPV/Hib-TT	57	0.509	0.296	0.875	
<i>Kitchin 2007 (UK)</i>	2,3,4	MenC-CRMx3		DTaP5-IPV/Hib-TT	50	2.17	1.34	3.53	[8]
	2,3,4	MenC-TTx3		DTaP5-IPV/Hib-TT	53	5.17	3.53	7.58	
	2,3,4	MenC-CRMx3		DTwP-Hib + OPV	51	4.38	3.08	6.22	
	2,3,4	MenC-TTx3		DTwP-Hib + OPV	49	7.51	5.54	10.19	
<i>Tejedor 2006 (ES)</i>	2,4,6	MenC-CRMx3		DTaP-HBV-IPV/Hib	114	3.813	2.932	4.959	[19]
	2,4,6	MenC-TTx2		DTaP-HBV-IPV/Hib	107	7.933	6.495	9.691	
	2,4,6	MenC-TTx2		DTaP-HBV-IPV/Hib +HBV@ birth	106	7.341	5.766	9.345	
<i>GSK 113369 (DE, ES, EE)</i>	2,3,4	MenC-CRMx2	PHiD-CV	DTaP-HBV-IPV/Hib	123	2.752	2.144	3.534	[22]
	2,3,4	MenC-TTx2	PHiD-CV	DTaP-HBV-IPV/Hib	114	4.662	3.788	5.739	
<i>Schmitt 2007 (DE)</i>	2,3,4	MenC-TTx3		DTaP-HBV-IPV/Hib	90	4.06	3.06	5.39	[28]
	2,3,4	MenC-TTx3 + Adj		DTaP-HBV-IPV/Hib	99	4.03	3.11	5.23	
	2,3,4	MenC-CRMx3		DTaP-HBV-IPV/Hib	105	2.78	2.11	3.65	

PRP: polyribosylribitol phosphate; IgG: immunoglobulin G; GMC: geometric mean concentration; LCL: lower confidence limit of 95% confidence interval; UCL: upper confidence limit of 95% confidence interval; CRM: cross-reacting material; TT: tetanus toxoid; PHiD-CV: 10-valent pneumococcal conjugate vaccine (Synflorix, GSK); PCV7: 7-valent pneumococcal conjugate vaccine (Prevenar, Pfizer); DTaP: diphtheria, tetanus, acellular pertussis; DTwP; diphtheria, tetanus, whole cell pertussis; HBV: hepatitis b; IPV: inactivated polio vaccine; Hib: *Haemophilus influenzae* type b; OPV: oral polio vaccine; MenC: group C meningococcal vaccine; MenC-CRM: Meningitec (Pfizer) or Menjugate (GSK); MenC-TT: NeisVac-C (Pfizer); DTaP5-IPV/Hib-TT: Pediacel (Sanofi Pasteur); DTaP-HBV-IPV/Hib: Infanrix Hexa (GSK); DTwP-Hib: Act-Hib DTP (Sanofi Pasteur).

Supplementary Table 2 Studies of quadrivalent capsular groups ACWY meningococcal vaccines measuring anti-PRP IgG GMCs one month after priming

<i>Author, Year (country)</i>	<i>Schedule (months)</i>	<i>Randomised study vaccine</i>	<i>PCV vaccine</i>	<i>Routine vaccines</i>	<i>N</i>	<i>Anti-PRP GMC (µg/mL)</i>	<i>LCL</i>	<i>UCL</i>	<i>Ref</i>
<i>Nolan MenACWY 2014 (AU)</i>	2,4,6	MenACWYx3	PCV7 or 13	DTaP5-IPV/Hib-TT	187	3.75	2.92	4.82	[29]
	2,4,6	none	PCV7 or 13	DTaP5-IPV/Hib-TT	194	2.76	2.16	3.53	
<i>Klein MenACWY 2012 (US)</i>	2,4,6	MenACWYx3	PCV7	DTaP-HBV-IPV + Hib-TT, rota	213	4.64	3.9	5.53	[30, 31]
	2,4,6	none	PCV7	DTaP-HBV-IPV + Hib-TT, rota	101	3.56	2.77	4.58	
<i>Klein MenACWY 2012 (AR)</i>	2,4,6	MenACWYx3	PCV7	DTaP-HBV-IPV + Hib-TT, rota	287	7.64	6.63	8.8	[30, 31]
	2,4,6	none	PCV7	DTaP-HBV-IPV + Hib-TT, rota	123	6.01	4.84	7.47	
<i>Klein MenACWY 2012 (CO)</i>	2,4,6	MenACWYx3	PCV7	DTaP-HBV-IPV + Hib-TT, rota	283	7.19	6.23	8.29	[30, 31]
	2,4,6	none	PCV7	DTaP-HBV-IPV + Hib-TT, rota	137	6.74	5.49	8.28	

PRP: polyribosylribitol phosphate; IgG: immunoglobulin G; GMC: geometric mean concentration; LCL: lower confidence limit of 95% confidence interval;

UCL: upper confidence limit of 95% confidence interval; PCV7: 7-valent pneumococcal conjugate vaccine (Prevenar, Pfizer); PCV13: 13-valent pneumococcal

conjugate vaccine (Prevenar 13, Pfizer); DTaP: diphtheria, tetanus, acellular pertussis; IPV: inactivated polio vaccine; Hib: *Haemophilus influenzae* type b;

MenACWY: quadrivalent group ACWY meningococcal vaccine conjugated to diphtheria cross reacting material (CRM), (Menveo, Novartis); rota: Oral

rotavirus vaccine (RotaTeq, Merck); DTaP5-IPV/Hib-TT: Pediacel (Sanofi Pasteur); DTaP-HBV-IPV: Pediarix (GSK); Hib-TT: ActHIB (Sanofi Pasteur).

Klein 2012: results from children in USA, Argentina, and Columbia reported separately. Results obtained from clinicaltrials.gov as geometric means are not reported in the published paper for this outcome.

Supplementary Table 3 Studies of pneumococcal vaccines measuring anti-PRP IgG GMCs one month after priming

<i>Author, Year (country)</i>	<i>Schedule (months)</i>	<i>PCV vaccine</i>	<i>Routine vaccines</i>	<i>N</i>	<i>Anti-PRP GMC (µg/mL)</i>	<i>LCL</i>	<i>UCL</i>	<i>Ref</i>
<i>Knuff 2006 (DE)</i>	2,3,4	PCV7	DTaP-HBV-IPV/Hib	115	1.16	0.92	1.47	[32]
	2,3,4	none	DTaP-HBV-IPV/Hib	111	1.16	0.89	1.51	
<i>Tichman-Schulmann 2005 (DE)</i>	2,3,4	PCV7	DTaP-HBV-IPV/Hib	141	1.59	1.232	2.052	[33]
	2,3,4	none	DTaP-HBV-IPV/Hib	138	2.274	1.783	2.901	
<i>Gimenez-Sanchez 2011 (DE)</i>	2,3,4	PCV13	DTaP-HBV-IPV/Hib	267	1.23	1.03	1.46	[34]
	2,3,4	PCV7	DTaP-HBV-IPV/Hib	252	1	0.83	1.2	
<i>Gimenez-Sanchez 2011 (ES)</i>	2,4,6	PCV13	DTaP-HBV-IPV/Hib + MenC-TT	247	1.88	1.57	2.24	[34]
	2,4,6	PCV7	DTaP-HBV-IPV/Hib + MenC-TT	250	1.54	1.29	1.83	
<i>Snape 2010 (UK)</i>	2,3,4	PCV13	DTaP5-IPV/Hib-TT + MenC-TT	114	2.4	2.65	4.37	[35]
	2,3,4	PCV7	DTaP5-IPV/Hib-TT + MenC-TT	102	4.44	3.5	5.62	
<i>Esposito 2010 (IT)</i>	3,5	PCV13	DTaP-HBV-IPV/Hib	275	0.99	0.8	1.21	[36]
	3,5	PCV7	DTaP-HBV-IPV/Hib	279	1	0.83	1.2	
<i>Lagos 2011 (CL)</i>	2,4,6	PHiD-CV	DTaP-HBV-IPV/Hib	63	13.835	10.918	17.532	[37]
	2,4,6	HAV	DTaP-HBV-IPV/Hib	56	10.488	7.384	14.899	
<i>Dicko 2011 (ML)</i>	6,10,14 wk	PHiD-CV	DTwP-HBV/Hib + OPV	110	18.461	14.256	23.907	[38]
	6,10,14 wk	none	DTwP-HBV/Hib + OPV	112	10.137	7.515	13.673	
<i>Kim 2011 (KR)</i>	2,4,6	PHiD-CV	Hib-TT (Hiberix) + UNK	175	20.131	16.775	24.158	[39]
	2,4,6	PCV7	Hib-TT (Hiberix) + UNK	60	11.844	8.542	16.424	
<i>Knuff 2011 (DE)</i>	2,3,4	PHiD-CV	DTaP-HBV-IPV/Hib	59	2.323	1.744	3.096	[40]
	2,3,4	PCV7	DTaP-HBV-IPV/Hib	55	1.172	0.784	1.752	
<i>Knuff 2009 (DE)</i>	2,4,6	PHiD-CV	DTaP-HBV-IPV + Hib-MenC-TT	172	13.746	11.406	16.567	[25]
	2,4,6	PCV7	DTaP-HBV-IPV + Hib-MenC-TT	170	10.947	9.165	13.077	
<i>Knuff 2009 (FI)</i>	2,3,4	PHiD-CV	DTaP-HBV-IPV/Hib-TT	542	2.132	1.925	2.362	[25]
	2,3,4	PCV7	DTaP-HBV-IPV/Hib-TT	178	1.176	0.973	1.423	

<i>Knuff 2009 (PO)</i>	2,4,6	PHiD-CV	DTwP-HBV/Hib-TT + IPV	140	9.376	7.941	11.071	[25]
	2,4,6	PCV7	DTwP-HBV/Hib-TT + IPV	47	8.86	6.87	11.427	
<i>Knuff 2009 (PH)</i>	6,10,14 wk	PHiD-CV	DTwP-HBV/Hib-TT + OPV	140	26.001	21.196	31.894	[25]
	6,10,14 wk	PCV7	DTwP-HBV/Hib-TT + OPV	49	25.758	17.669	37.548	
<i>Van den Bergh 2011 (NL)</i>	2,3,4	PHiD-CV	DTaP5-IPV/Hib-TT	180	4.796	3.829	6.007	[41]
	2,3,4	PCV7	DTaP5-IPV/Hib-TT	189	2.219	1.724	2.857	

PRP: anti-polyribosylribitol phosphate; IgG: immunoglobulin G; GMC: geometric mean concentration; LCL: lower confidence limit of 95% confidence interval; UCL: upper confidence limit of 95% confidence interval; TT: tetanus toxoid; PHiD-CV: 10-valent pneumococcal conjugate vaccine (Synflorix, GSK); PCV7: 7-valent pneumococcal conjugate vaccine (Prevenar, Pfizer); PCV13: 13-valent pneumococcal conjugate vaccine (Prevenar 13, Pfizer); DTaP: diphtheria, tetanus, acellular pertussis; DTwP: diphtheria, tetanus, whole cell pertussis; HBV: hepatitis b vaccine; IPV: inactivated polio vaccine; Hib: *Haemophilus influenzae* type b; Hib-TT: Hiberix (GSK); OPV: oral polio vaccine (Polio Sabin, GSK); MenC-TT: NeisVac-C (Pfizer); Hib-MenC-TT: Menitorix (GSK); UNK: unknown; DTaP5-IPV/Hib-TT: Pediacel (Sanofi Pasteur); DTaP-IPV-HBV: Pediarix (GSK); DTwP-HBV/Hib-TT: Zilbrix Hib (GSK).

Knuff 2009 and Gimenez-Sanchez 2011 report on multiple studies in different countries.

Supplementary Table 4 Saccharide and carrier protein content of study vaccines

Vaccine	Saccharide content	Carrier protein content
MenC-CRM	10 µg of group C oligosaccharide	12-25 µg of <i>Corynebacterium diphtheriae</i> (CRM197) protein
MenC-TT	10 µg of group C oligosaccharide	10-20 µg of tetanus toxoid protein
MenACWY-CRM	10 µg of group A, 5 µg each of groups C, W and Y	32.7 to 64.1 µg CRM197
PCV7-CRM	2.2 µg of polysaccharide for serotypes 4, 9V, 14, 18C, 19F and 23F. 4.4 µg of serotype 6B.	20 µg of CRM197
PCV13-CRM	2.2 µg of polysaccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F. 4.4 µg of serotype 6B.	34 µg of CRM197
PHiD-CV	1µg of polysaccharide for each of serotypes 1, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. 3µg of serotype 4	8 serotypes conjugated to <i>Haemophilus Influenzae</i> protein D. Serotype 18C conjugate to tetanus toxoid. Serotype 19F conjugated to diphtheria toxoid

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