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Review

The short-term impact of each primary dose of pneumococcal conjugate vaccine on nasopharyngeal carriage: Systematic review and meta-analyses of randomised controlled trials

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A B S T R A C T

Background: Early onset of persistent otitis media is a priority issue for Australian Indigenous populations. The objective is to determine the direct and short-term impact of one, two and three doses of any pneumococcal conjugate vaccine (PCV) formulation on nasopharyngeal (NP) carriage of Streptococcus pneumoniae (Spn) and non-typeable Haemophilus influenzae (NTHi), the otopathogens targeted by current PCVs.

Methods: We searched MEDLINE (PubMed) and CENTRAL (Cochrane Library) to 29 September 2015. We also scanned reference lists of recent reviews and contacted authors. We included randomised controlled trials (RCTs) with a PCV schedule commencing ≤3 months of age that reported controlled non-cumulative group-specific prevalence data for carriage of Spn or NTHi at age <12 months. We performed a standard risk of bias assessment. We estimated the pooled relative risk (RR) and 95% confidence interval (95%CI) for each vaccine dose on NP carriage by meta-analysis.

Results: We included 16 RCTs involving 14,776 participants. The PCVs were conjugated to diptheria toxin CRM197, diptheria toxoid, tetanus toxoid or NTHi protein D and varied in valency (4–13). Controls were non-PCVs, placebo or no vaccine. The earliest carriage outcome was from 2 to 9 months of age. Compared to controls, there were no significant differences between one or two doses of PCV on vaccine-type (VT) pneumococcal carriage at ~4 and ~6 months respectively. However, VT carriage was significantly lower at ~7 months RR 0.67 95%CI 0.56–0.81 from 9 studies and 7613 infants and non-vaccine type (NVT) carriage was higher RR 1.23 95%CI 1.09–1.40 from 8 studies and 5861 infants. No impact on overall pneumococcal or NTHi carriage was found.

Conclusions: The primary PCV schedule had no significant short-term impact on overall pneumococcal or NTHi NP carriage and a limited impact on VT pneumococcal carriage before the third dose.

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1. Introduction

Carriage of bacteria in the nasopharynx can lead to invasive disease, pneumonia and otitis media [1]. In remote Aboriginal communities in Australia, almost all babies have otitis media within weeks of birth following nasopharyngeal (NP) colonisation with both Streptococcus pneumoniae (Spn) and non-typeable Haemophilus influenzae (NTHi), which increases the risk of otitis media 33-fold [2]. In one remote community, 72% of Aboriginal children developed otitis media by two months of age [3]. Vaccines that have an early and direct impact on acquisition or density of NP carriage, following early first dose or accelerated schedules, are needed. The risk of conductive hearing loss, impaired language development and educational disadvantage [4] throughout formative years may be partly addressed by vaccination. For developing countries, where NP carriage also occurs early in life [5], reduced dose schedules that are protective early could provide an affordable option. Huebner et al. [6] has indicated that an immune response (IgG > 0.15 µg/mL) is mounted to all 9 serotypes after a single dose of vaccine in 70% of children at 10 weeks of age. However, efficacy for carriage prevention was not assessed at this age. Indirect protection of non-vaccinees occurs following direct impacts of vaccination on NP carriage in vaccinees [7,8].

Abbreviations: RCT, randomised controlled trial; PCV, pneumococcal conjugate vaccine; Spn, Streptococcus pneumoniae; NTHi, non-typeable Haemophilus influenzae; NP, nasopharyngeal; VT, vaccine-type; NVT, non-vaccine-type.

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Three systematic reviews [9–11] have been published recently on the impact of PCVs on NP carriage. Fleming-Dutra's [9] search to 2010 assessed vaccine-type (VT) carriage following two or three-dose primary and booster schedules. Randomised and non-randomised studies were included and results were not statistically combined. Both two and three-dose schedules reduced VT pneumococcal carriage. Non-vaccine type (NVT) replacement and post single dose outcomes were not reported. Scott’s [10] search to 2010 focused on immunogenicity and included two studies for the carriage component. No difference between two and three-dose schedules was found at six months of age. Davis’s [11] search to 2005 examined the indirect effect on non-target populations. A contemporaneous relationship between VT invasive pneumococcal disease and VT carriage was found, supporting the inclusion of NP carriage in vaccine licensure processes.

Currently, the impact of each dose of the primary PCV schedule on NP carriage, with the pooled estimate derived solely from randomised controlled trials (RCT), is not known. Our aim was to review RCTs of PCVs to determine whether infants receiving 1, 2 or 3 doses of PCV in a primary schedule commencing <3 months of age have reduced NP carriage of Spn and NTHi in the short term.

2. Methods

2.1. Eligibility criteria

We used the following eligibility criteria: (a) RCTs of any PCV schedule commencing <3 months of age; (b) NP carriage was measured <12 months of age, after at least one dose of PCV and prior to the booster; and (c) controlled non-cumulative group-specific prevalence data for carriage of Spn and/or NTHi.

2.2. Information sources

We searched the MEDLINE (PubMed) and CENTRAL (Cochrane Library) databases to 29 Sept 2015. We also reviewed the reference lists of recent reviews and contacted authors.

2.3. Search terms


2.4. Study selection

One review author [TN] manually screened the citations in three stages: (1) titles, (2) abstract and (3) full text. Citations that failed to meet our eligibility criteria were excluded at each stage. The articles that could not immediately be excluded were discussed with a second review author [PM or AJL].

2.5. Data collection process

Two review authors [TN, AJL] independently extracted the relevant data from the included studies. Where carriage data were aggregated across scheduled visits or groups or where carriage data had not yet been published, we contacted the authors for raw data or used online trial databases.

2.6. Data items

The following data items were extracted from each included paper or the primary publication of the RCT: year, author, risk of bias items (below); study population, number of participants randomised for NP carriage, randomisation age, vaccine formulation, vaccine schedule, nasopharyngeal swab schedule and prevalence of Spn and NTHi at the earliest time point given <12 months for each dose comparison. We did not extract data on acquisition or cumulative incidence of carriage.

To extract data for meta-analysis, the following techniques were employed. For the NP carriage denominator, we assumed that all children assessed at each time point also had an NP swab, unless explicit numbers were provided. For overall, VT and NVT Spn carriage, we assumed that VT + NVT = overall Spn carriage. We combined allocated groups when appropriate.

We assumed that H. influenzae and NTHi were synonymous across studies. Where both were given, we reported NTHi. For NTHi, we only extracted data from the PHiD-CV10 and 11Pn-PD RCTs, as we were interested in direct effects. We reported pneumococcal VT carriage as per the author’s definition. If not specified, cross-protected serotypes were defined as NVTs.

2.7. Risk of bias

We assessed risk of bias for the methodology reported in each included paper or the primary publication of the RCT. We applied the principles of the Cochrane ‘Risk of Bias’ tool. Two review authors [TN, AJL] independently assessed each component and discussed their findings until consensus was reached. The components assessed were: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessor; incomplete outcome data and selective reporting. These components addressed risk of bias due to selection, performance, detection, attrition and reporting. We also assessed reporting of baseline characteristics to address selection bias. If the information provided was inadequate but it appeared that the component was appropriately performed or if the author had set precedence by performing the component appropriately in a previous trial without explicitly reporting so in the paper [12], we deemed the information unclear but ‘probably low’ risk of bias. Where participants and personnel were not blinded or blinding was not explicitly stated, clinical care such as antibiotic use may have affected the carriage outcome. However, we considered this to be uncommon and deemed these studies as ‘probably low’ risk of bias. For each study, we also extracted information on the funding source, the compliance with WHO recommendations for NP carriage studies [13,14] and the population naivety to PCV exposure. Populations that had hosted previous pneumococcal trials but were otherwise naïve were considered to be naïve. These study characteristics may contribute to clinical heterogeneity but do not necessarily infer higher risk of bias. Therefore, they were not formally included in our risk of bias summary.

2.8. Methods of analysis

The meta-analyses were generated with Stata 14. We pooled relative risks using the random-effects model. For each dose comparison, a relative risk (RR) and 95% confidence interval (95%CI) were estimated. We determined the associated statistical heterogeneity using the I2 test.

2.9. Risk of bias across studies

We used funnel plots to assess possible small study bias (including publication bias). Plots were generated for three versus zero
dose overall, VT and NVT pneumococcal meta-analyses and the two versus zero dose overall pneumococcal meta-analysis. Other dose comparisons had too few studies. To assess within study selective reporting, we used the principles of the Cochrane ‘Risk of Bias’ Tool. Sensitivity analyses were done by removing studies which contributed high risk of bias for any component of the Cochrane’s ‘Risk of Bias’ tool.

3. Results

3.1. Study selection

A total of 16 RCTs involving 14,776 participants were included in the systematic review and meta-analyses (Table 1) [15–30]. To assess study characteristics and risk of bias, the primary publication of the RCT was also referred to for seven of the included studies [31–37]. Similarly, we referred to an additional methods paper for one included study [38] and the published protocol for another [27].

The MEDLINE search (Fig. 1) provided 426 citations and 12 studies met our eligibility criteria [15–23, 26, 29, 30]. Two of these studies reported carriage data in online databases, ClinicalTrials.gov and GSK Clinical Trials Register [29, 30]. The CENTRAL search identified no additional eligible studies.

Our manual search provided four additional studies—two of which [24, 25] were found by reviewing reference lists of recent reviews and one (abstract) [28] by corresponding with a senior author. The fourth study is our ongoing RCT for which we analysed the unpublished dataset [27].

3.2. Study characteristics

3.2.1. Participants

Study populations and the number of infants randomised for carriage (n) varied across the included studies. Four studies took place in Europe; two (n = 780, 1005) took place in the Netherlands [17, 19], one (n = 381) in the Czech Republic & Slovakia [22] and one (n = 5093) in Finland [30]. Twelve studies took place outside Europe. Four took place in Africa—two (n = 500, 300) in South Africa [25, 28] and two (n = 684, 207) in the Gambia [20, 24]. Three studies (n = 1866, 733, 75) took place in Israel [16, 18, 26], one (n = 566) in Navajo and White Mountain Apache reservations [23], one (n = 1628 infants for Spn, 1644 for NTHi) in Argentina, Panama and Columbia [29], one (n = 552) in Fiji [21], one (n = 390) in Nepal [15] and one (recruitment ongoing) in Australia [27].

Of the 16 studies, there were nine naïve study populations [15–20, 26–29], three were naïve to serotypes 1, 4, 7F and NTHi [17, 28, 30], one was naïve to serotypes 3, 6A and 19A [16] and one naïve to NTHi [27]. Two populations were not naïve [18, 19], Dagan [18] approximated a 25% vaccine uptake in the population. van Gils’ 2009 [19] enrolment started on 7 July 2005, PCV7 was introduced nationwide on 31 March 2006 and follow up ended 14 February 2008. It was the author’s view that a herd effect was unlikely to have interfered.

3.3. Intervention

The vaccine formulation and valency varied across the included studies. Four studies compared two vaccines—PCV13 versus PCV7 [16], PHID-CV10 versus PCV7 [17], PHID-CV10 versus PCV13 [27] and Pnc-T versus Pnc-D versus placebo [26]. Seven studies used a pneumococcal vaccine with polysaccharides conjugated to CRM197. Five used a 7-valent vaccine [18–21, 23] and two used a 9-valent vaccine [24, 25]. Five studies used a pneumococcal vaccine with the majority of polysaccharides conjugated to NTHi protein D; four used PHID-CV10 [15, 28–30] and one used 11Pn-PD [22].

![Fig. 1. Flow diagram: a systematic search for randomised controlled trials comparing the short-term impact of one, two and three primary doses of pneumococcal conjugate vaccine on nasopharyngeal carriage of Streptococcus pneumoniae and non-typeable Haemophilus influenzae.](image)
Table 1
Characteristics of randomised controlled trials comparing the short-term impact of one, two and three primary doses of PCV on nasopharyngeal carriage of Streptococcus pneumoniae and non-typeable Haemophilus influenzae.

<table>
<thead>
<tr>
<th>Country</th>
<th>Number randomised for carriage</th>
<th>Vaccine</th>
<th>Schedule</th>
<th>NP swab timing</th>
<th>Outcomes reported from the RCT&lt;sup&gt;3,4&lt;/sup&gt;</th>
<th>Which meta-analyses?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamaluba [15]</td>
<td>Nepal</td>
<td>PHID-CV10</td>
<td>2 + 1: 6,14 wk, 9 m 3 + 0: 6,10,14 wk 0 + 2: 10,11 m</td>
<td>9 m</td>
<td>Immunogenicity, OPA, safety, carriage (Spn O)</td>
<td>2 vs 0 (Spn O&lt;sup&gt;3&lt;/sup&gt;) 3 vs 0 (Spn O)</td>
</tr>
<tr>
<td>Dagan [16]</td>
<td>Israel</td>
<td>PCV13, PCV7</td>
<td>3 + 1: 2,4,6,12 m</td>
<td></td>
<td>Immunogenicity, safety, carriage (Spn VT, NVT)</td>
<td>3 vs 0 (Spn VT)</td>
</tr>
<tr>
<td>van den Bergh [17]</td>
<td>Netherlands</td>
<td>PHID-CV10, PCV7</td>
<td>3 + 1: 2,3,4,11–13 m 2 + 1: 4,6,12 m 3 + 1: 2,4,6,12 m 0 + 2: 12,18 m</td>
<td>5,11,14,18,24 m</td>
<td>Carriage (NTHi) Immunogenicity, carriage (Spn O, VT, NVT)</td>
<td>3 vs 0 (NTHi) 1 vs 0 (Spn O, VT, NVT) 2 vs 1 (Spn O, VT, NVT) 2 vs 0 (Spn O, VT, NVT) 3 vs 2 (Spn O, VT, NVT) 3 vs 0 (Spn O, VT, NVT) 2 vs 0 (Spn O)</td>
</tr>
<tr>
<td>Dagan [18]</td>
<td>Israel</td>
<td>PCV7</td>
<td>3 + 1: 2,3,4,11–13 m 2 + 1: 4,6,12 m 3 + 1: 2,4,6,12 m 0 + 2: 12,18 m</td>
<td>5,11,14,18,24 m</td>
<td>Carriage (NTHi) Immunogenicity, carriage (Spn O, VT, NVT)</td>
<td>3 vs 0 (NTHi) 1 vs 0 (Spn O, VT, NVT) 2 vs 1 (Spn O, VT, NVT) 2 vs 0 (Spn O, VT, NVT) 3 vs 2 (Spn O, VT, NVT) 3 vs 0 (Spn O, VT, NVT) 2 vs 0 (Spn O)</td>
</tr>
<tr>
<td>van Gils [19,31]</td>
<td>Netherlands</td>
<td>PCV7</td>
<td>Zero doses 2 + 0: 2,4 m 2 + 1: 2,4,11 m 1 + PPV: 2,10 m 2 + PPV: 2,3,10 m 3 + PPV: 2,3,4,10 m</td>
<td>6 wk, 6,12,18,24 m</td>
<td>Immunogenicity, OPA, carriage (Spn O, NTHi)</td>
<td>2 vs 0 (Spn O)</td>
</tr>
<tr>
<td>Ota [20]</td>
<td>Gambia</td>
<td>PCV7</td>
<td>0 + 0: 14 wk 2 + 0: 6,14 wk 3 + 0: 6,10,14 wk Booster to 1/2 per group</td>
<td>6,9,12,17 m</td>
<td>Immunogenicity, OPA, safety, carriage (Spn O, VT, NVT)</td>
<td>2 vs 0 (Spn O, VT, NVT) 3 vs 1 (Spn O, VT, NVT) 3 vs 2 (Spn O, VT, NVT)</td>
</tr>
<tr>
<td>Russell [21,32]</td>
<td>Fiji</td>
<td>PCV7</td>
<td>3 + 1: 3,4,5,12–15 m</td>
<td>6,12–15,13–16,15–18, 19–22,24–27 m</td>
<td>Clinical, immunogenicity, OPA, safety, carriage (Spn O, VT, NVT, NTHi)</td>
<td>1 vs 0 (Spn O, VT, NVT) 2 vs 1 (Spn O, VT, NVT) 3 vs 1 (Spn O, VT, NVT) 3 vs 2 (Spn O, VT, NVT) 3 vs 0 (Spn O, VT, NVT) 3 vs 0 (Spn O, VT, NTHi) 3 vs 0 (NTHi)</td>
</tr>
<tr>
<td>Prymula [22,33]</td>
<td>Czech Republic and Slovakia</td>
<td>PCV7, MnCC</td>
<td>3 + 1: 2,4,6,12–15 m</td>
<td>7,12,18 m</td>
<td>Clinical, safety, immunogenicity, carriage (Spn O, VT, NVT)</td>
<td>3 vs 0 (Spn O, VT, NVT)</td>
</tr>
<tr>
<td>O'Brien [23,34]</td>
<td>Navajo and White Mountain Apache reservations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Region</td>
<td>Recruitment</td>
<td>Vaccine</td>
<td>Time Points</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-------------</td>
<td>---------</td>
<td>-------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Obaro [24]</td>
<td>Gambia</td>
<td>207</td>
<td>PCV9, IPV</td>
<td>3 + 0: 2,3,4 m</td>
<td>Safety, immunogenicity, carriage (Spn O, VT, NVT)</td>
<td></td>
</tr>
<tr>
<td>Mbelle [25]</td>
<td>South Africa</td>
<td>500</td>
<td>PCV9, placebo</td>
<td>3 + 0: 6,10,14 wk</td>
<td>6,10,14,18 wk, 9 m</td>
<td></td>
</tr>
<tr>
<td>Dagan 1997 [26,35]</td>
<td>Israel</td>
<td>75</td>
<td>PCV10, PCV13</td>
<td>3 + 1: 2,4,6, 12 m (non-conjugate booster)</td>
<td>2,4,6,7,12,13 m</td>
<td></td>
</tr>
<tr>
<td>Leach (Menzies data) [27]</td>
<td>Australia</td>
<td>Recruitment ongoing</td>
<td>PHiD-CV10, PCV13</td>
<td>PCV10: 2,4,6 m PCV13: 2,4,6 m Both: PCV10, 1,2,4 m PCV13 6 m</td>
<td>2,4,6,7 m</td>
<td></td>
</tr>
<tr>
<td>Madhi (ESPID abstract) [28]</td>
<td>South Africa</td>
<td>300</td>
<td>PHiD-CV10</td>
<td>2 + 1: 6,14 wk, 9–10 m</td>
<td>6–12, 18 wk, 9–10, 10–11, 12–13, 15–18, 16–19, 24–27 m</td>
<td></td>
</tr>
<tr>
<td>COMPAS (Clinical trials.gov) [29,36]</td>
<td>Argentina, Colombia, Panama</td>
<td>Spn: 1628 NTHi: 1644</td>
<td>PHiD-CV10, HepB (Hep A for control booster)</td>
<td>3 + 1: 2,4,6,15–18 m</td>
<td>5, 10–13, 13–16, 14–17, 16–19, 22–25</td>
<td></td>
</tr>
<tr>
<td>FinIP Nested (GSK Clinical Study Register) [30,37]</td>
<td>Finland</td>
<td>5093 (6 wk–6 mth)</td>
<td>PHiD-CV10, HBV</td>
<td>If enrolled 6 wk–6 m: 3 + 1, 2 + 1</td>
<td>3,6,11–12,14–15,18–22 m</td>
<td></td>
</tr>
</tbody>
</table>

* Bolded swab time-points indicate which swab data was used for the meta-analyses.
* Outcomes listed were only those found in studies and databases during our search.
* Carriage outcomes listed are only for prevalence <12 months and serotype-specific carriage.
* Overall (O).
and three were not stated [28–30]. Use of a calibrated inoculum size for culture was reported by four studies [20,21,23,27]; eight studies reported direct plating [16,18–20,22,24–26]. Selective media for pneumococcus (blood agar with gentamicin) was used by ten studies [16,18–25] and incubation in up to 10% CO2 was reported by eight studies [15,16,19,21–24,27]. Good overall adherence to WHO recommendations was reported by four studies [20,21,23,27].

### 3.5. Risk of bias within studies

Overall, the risk of bias within each study was very low (Table 2). Twelve studies [15–17,19–24,27,29,30] described appropriate random sequence generation and four [18,25,26,28] were unclear but deemed probably low risk of bias. Randomisation was lost in O’Brien’s carriage subset [23] which was selected from clusters.

---

**Table 2**: Risk of bias within each study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Vaccine</th>
<th>Carriage</th>
<th>No carriage</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 vs 0 - Overall Pneumococcus</td>
<td>Dagan 2012</td>
<td>PCV7</td>
<td>4m</td>
<td>58/18</td>
<td>168/34</td>
</tr>
<tr>
<td>Russell 2010</td>
<td>PCV7</td>
<td>6m</td>
<td>67/122</td>
<td>53/127</td>
<td>1.32 (1.01, 1.75)</td>
</tr>
<tr>
<td>O’Brien 2007</td>
<td>144wks</td>
<td>112/185</td>
<td>105/230</td>
<td>1.01 (0.83, 1.23)</td>
<td>18.49</td>
</tr>
<tr>
<td>Leadon (unpublished)</td>
<td>PHDC-V7</td>
<td>2m</td>
<td>4/79</td>
<td>11/155</td>
<td>1.31 (1.02, 1.67)</td>
</tr>
<tr>
<td>Subtotal (i-squared = 31.0%, p = 0.226)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.14 (1.00, 1.30)</td>
</tr>
</tbody>
</table>

**Fig. 2**: A meta-analysis of randomised controlled trials comparing the short-term impact of one, two and three primary doses of pneumococcal conjugate vaccine to zero doses on nasopharyngeal carriage of Streptococcus pneumoniae and non-typeable Haemophilus influenzae.

---
Table 2
Risk of bias assessment of randomised controlled trials comparing the short-term impact of one, two and three primary doses of pneumococcal conjugate vaccine on nasopharyngeal carriage of Streptococcus pneumoniae and non-typeable Haemophilus influenzae.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamaluba [15]</td>
<td>Low</td>
<td>Low</td>
<td>Not blinded probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Dagan [16]</td>
<td>Low</td>
<td>Low</td>
<td>Unclear probably low</td>
<td>Unclear probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>van den Bergh [17]</td>
<td>Low</td>
<td>Low</td>
<td>Not blinded probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Dagan [18]</td>
<td>Unclear probably low</td>
<td>Unclear probably low</td>
<td>Not blinded probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>van Gils [19,31]</td>
<td>Low</td>
<td>Unclear probably low</td>
<td>Not blinded probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Ota [20]</td>
<td>Low</td>
<td>Unclear probably low</td>
<td>Not blinded probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Russell [21,32]</td>
<td>Low</td>
<td>Low</td>
<td>Not blinded probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Prymula [22,33]</td>
<td>Low</td>
<td>Unclear probably low</td>
<td>Not blinded probably low</td>
<td>Unclear probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>O’Brien [23,34,38]</td>
<td>Low for trial high for carriage</td>
<td>Low</td>
<td>Low</td>
<td>Unclear probably low</td>
<td>Low</td>
<td>Unclear probably low</td>
<td>Low</td>
</tr>
<tr>
<td>Obaro [24]</td>
<td>Low</td>
<td>Unclear probably low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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according to adherence to a per-protocol vaccination schedule. We therefore performed a sensitivity analysis excluding this study (Supplementary Table 1). Allocation concealment was unclear in seven studies [18–20,22,24,25,28] but probably low risk. Nine studies [15–17,21,23,26,27,29,30] reported sound concealment of allocation.

Six studies blinded participants and personnel [23–26,29,30], eight studies were not blinded [15–17,21,27,28] and two were unclear, stating that they were double blind without further detail [16,22]. For blinding of outcome assessment, ten studies [15–17,21,23,26,27,30] described masking of the laboratory staff (low risk of bias). Six studies [16,22,24,25,28,29] were unclear but deemed probably low risk.

Follow-up of participants for nasopharyngeal swabs was performed well and described appropriately in thirteen studies [15–22,24–26,28,30]. Two studies [23,29] were unclear but were deemed probably low risk and one was not available [27]. As for selective reporting, all studies reported according to protocol or pre-specified outcomes [15–30]. Baseline characteristics were reported in text or table in all studies except Madhi [28] and Leach [27] which were not available in the abstract or protocol, respectively.

Eleven studies were funded by drug companies [15–19,22,23,25,28–30]. Four studies were not funded by drug companies [20,21,24,27], two of whom received vaccine donations [20,21]. One study did not report funding source [26].

3.6. Risk of bias across studies

The funnel plots generated did not indicate a difference between the reporting of small and large studies (Supplementary Fig. 1).

3.7. Results of individual studies

Prior to pooling data in the meta-analyses, we applied our data extraction rules. We used the COMPAS swab data at 5 months of age but excluded data at 10–13 months [29], since our inclusion criteria were that swabs be collected at <12 months of age. We selected the outcome data at 7 months of age from Dagan’s [18] combined 7 + 12 month data, using a provided dataset. Data from 4 and 6 month swabs were also extracted from this dataset. In Dagan [26], the numerator and denominator were not reported for 2, 4 & 6 month prevalence data so we were only able to include the outcomes at 7 months of age. In Dagan [16], cross-protective serotypes were included as vaccine types.

For our RCT [27] which is still recruiting, we analysed the available 2 and 4 month NP carriage data. To maintain blinding, only aggregate data for each scheduled visit and allocated group were provided to authors by the data manager.

The relative risks for individual studies and dose comparisons are presented in the meta-analyses (Figs. 2 and 3).

3.8. Syntheses of results

We generated meta-analyses comparing the short-term impact of one, two and three doses of PCV with zero doses (Fig. 2) and comparing more doses with fewer doses (Fig. 3) on nasopharyngeal carriage. We used the earliest swab data reported for each comparison.

The meta-analyses comparing one versus zero doses (Fig. 2) generated non-significant pooled results for overall pneumococcus, VT pneumococcus and NTHi carriage at ~4 months but significantly higher relative risk of NVT pneumococcal carriage RR 1.36 95%CI 1.08–1.72 from 3 studies and 1000 infants swabbed. A single study contributed data to the NTHi carriage comparison RR 0.77 95%CI 0.57–1.04 from 234 infants swabbed.

The meta-analyses comparing two versus zero doses (Fig. 2) generated non-significant pooled results for pneumococcal and NTHi outcomes at ~6 months.

The meta-analyses comparing three versus zero doses (Fig. 2) generated significant pooled results for VT pneumococcal carriage at ~7 months RR 0.67 95%CI 0.56–0.81 from 9 studies and 7613 infants swabbed and non-vaccine type pneumococcal carriage RR 1.23 95%CI 1.09–1.40 from 8 studies and 5861 infants swabbed. However, NTHi carriage was not significantly different RR 1.13 95%CI 0.95–1.35 from 3 studies and 4843 infants swabbed.

The meta-analyses comparing more with fewer doses (Fig. 3) generated non-significant pooled results for all carriage outcomes from 4 to 7 months. The three dose schedule had a reduced risk of VT carriage compared to both the one and two-dose schedules, but the reductions did not reach statistical significance RR 0.73 95%CI 0.51–1.06 and RR 0.81 95%CI 0.64–1.02 from 2 studies and 681 infants swabbed and 4 studies and 1333 infants swabbed respectively. The two-dose schedule had a reduced risk of VT carriage compared to one dose, but did not reach statistical significance RR 0.86 95%CI 0.66–1.13 from 4 studies and 1188 infants swabbed. The relative risk of NVT pneumococcal carriage was not significantly increased for any of these comparisons. NTHi carriage was reduced following a two-dose schedule compared to a single dose RR 0.82 95%CI 0.63–1.07 from 1 study and 147 infants swabbed, but this did not reach statistical significance.

Within each meta-analysis, clinical heterogeneity was related to; population naiveté to PCV, vaccine formulation, NP swab age and NP swab collection method. However, statistical heterogeneity was <50% for all meta-analyses except one; the three versus zero dose comparison of VT pneumococcal carriage meta-analysis (Fig. 2) which generated an I² of 52.1% from 9 studies with 7613 infants swabbed.

3.9. Sensitivity analyses

The sensitivity analyses excluding O’Brien [23] from the three versus zero dose meta-analyses (overall, VT and NVT pneumococcal carriage) showed no substantial difference to the original relative risks or confidence intervals (Supplementary Table 1).

4. Discussion

To determine the potential for PCVs to reduce early-onset polymicrobial otitis media, we assessed the direct and short-term impact of each dose of primary PCV schedules on NP carriage of Spn and NTHi.

Our findings are consistent with previous systematic reviews for the impact of PCV on NP carriage [9–11]. However, our review includes an additional seven RCTs, is the first to include a single dose comparison and the first to include NTHi carriage. We statistically combined our results with meta-analysis and identified several new findings for the short-term effect of PCVs on NP carriage of Spn and NTHi following each dose of the primary schedule in infancy.

We found that three doses of PCV was the only dosing schedule to significantly reduce VT pneumococcal carriage when compared to no PCV. More doses were consistently superior to fewer doses and although these differences did not reach statistical significance, they reflect a dose response that could be clinically useful.

NVT pneumococcal carriage (replacement) was significant after one and three doses of vaccine and the point estimate for the two-dose comparison was not inconsistent with this.

NTHi carriage was also not significantly reduced by primary vaccination with HiD-containing vaccines. Compared to no HiD controls, NTHi carriage was lower following a single dose (one study), was not different follow two doses (three studies) and was
increased following three doses (three studies). This observation that NTHi NP carriage is increased following a three-dose schedule compared to no dose is potentially concerning. Although statistically non-significant, the point prevalence for each of the three studies showed the same trend. Interestingly, the one versus zero dose and two versus one-dose comparisons showed lower NTHi carriage with more doses. More data on NTHi carriage would assist in clarifying these trends.

Fleming-Dutra’s review [9] concluded that both 2 and 3 dose primary schedules reduced VT pneumococcal carriage compared to zero doses. When directly comparing VT carriage post two to three primary doses, Fleming-Dutra found three trials with pre-booster comparisons [18,20,21], of which one [21] found a significant difference at 9 months of age. Scott’s review [10] found no significant difference at 6 months between two and three doses for overall, VT or NVT pneumococcal carriage.

4.1. Limitations

We found few studies that reported NTHi carriage data or reported data following a single dose. Adherence to WHO recommendations for NP carriage was also poor across studies. We used unpublished, non-peer reviewed data for five of our included studies [18,27–30]. Within included studies, the overall risk of bias was very low, the sensitivity analyses did not substantially change the effect size and no evidence of small study bias was found. While there was a degree of clinical heterogeneity within each meta-analysis, the statistical heterogeneity was generally low.

4.2. Implications for research

RCTs evaluating NP carriage are encouraged to publish findings following each dose of PCV, particularly for high risk settings. Future trials should investigate an earlier vaccine schedule. Scott [39] found no significant difference between a 6–10–14 wk and 0–10–14 wk schedule at 18 or 36 weeks, differences at earlier ages were not reported. We are awaiting publication of the carriage outcomes from Pomat’s 2013 birth dose trial from Papua New Guinea (completed and manuscript in preparation) [40]. Maternal vaccination could also be further investigated. Binks et al. [41] showed that maternal 23-valent pneumococcal polysaccharide vaccine (23PPV)
did not reduce prevalence of all-cause otitis media in Aboriginal infants at age 7 months, but a post-hoc analysis found that otitis media associated with NP carriage of several 23PV serotypes was reduced in the vaccinated cohort compared to non-vaccinated. In a recently published study, Daly 2014, maternal PCV9 vaccination increased the infant risk of acute otitis media in the first 6 months of life [42]. Carriage outcomes were not assessed. We suggest that further research on social determinants, particularly overcrowding and hygiene will be important to understanding how best to reduce pathogen transmission and early NP carriage.

Ecological studies that have compared NP carriage before and after introduction of PHiD-CV10 into the national immunisation programs have had inconsistent findings. In Kenya [43] a significant reduction in NTHi carriage was reported. In the Northern Territory of Australia no significant impact on NTHi carriage was found, although significantly fewer PHiD-CV10-vaccinated children had NTHi cultured from middle ear infections compared to PCV7-vaccinated children [44]. A lack of impact on NTHi carriage contrasts with immunogenicity data for H. influenzae protein D one month after the third dose of primary vaccination [29]. More research is needed to determine appropriate (immune) correlates of protection for NTHi (and other) protein antigens.

4.3. Implications for practice

Based on our findings, in a high risk population naïve to PCVs (if we assume carriage ~80% with 1/2 VTs), three primary doses of PCV would reduce VT pneumococcal carriage from ~40% to 27% and increase NVT carriage from ~40% to 50% at ~7 months of age. This means that overall carriage would fall from ~80% to 77%. This is unlikely to have a clinical impact unless NVTs are less virulent in causing disease. A less expensive single-dose or two-dose schedule is unlikely to affect nasopharyngeal colonisation within this short time frame. However, small reductions may have a cumulative effect over time and as indirect effects accumulate as vaccine uptake increases. With a longer follow up period of 9–12 months, two of our included trials found that a significant protection occurred for VT pneumococcal carriage after one dose RR 0.38 95%CI 0.16–0.91 at 9 months [21] and two doses RR 0.64 95%CI 0.51–0.81 at 12 months [31]. This will be important for sustained protection throughout infancy.

In our setting, we are most concerned by early-onset otitis media. By the time Aboriginal infants reach ~7 months of age, when the third primary dose will offer protection for NP carriage, most are already colonised and affected by otitis media. Multiple cross-sectional studies have demonstrated that herd immunity does occur and this may help to protect young infants [45]. However, to substantially reduce the burden of early-onset otitis media—each dose of the primary PCV schedule needs to have a direct impact on NP carriage prevention, particularly where herd effects are absent or weak, such as for NTHi [17]. Our findings will be important for the evaluation of future vaccines and their application in high-risk settings.

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Conflict of interest statement

AJL and PSM have received research funding from GlaxoSmithKline (protocol codes 113313 and 116164) Biologicals and Pfizer (reference no. Ws2382560).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.12.048.

References


