**Table I: Grading of scientific evidence of protection**

<table>
<thead>
<tr>
<th>Question: Do currently available pneumococcal conjugate vaccines protect children against pneumococcal disease and carriage of serotypes included in the vaccine?</th>
<th>Rating</th>
<th>Adjustment to score</th>
</tr>
</thead>
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<tr>
<td><strong>Factors decreasing confidence</strong></td>
<td>No of studies/starting score</td>
<td>15 RCTs</td>
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<tr>
<td>Limitation in study design</td>
<td>None serious</td>
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</tr>
<tr>
<td>Inconsistency</td>
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<td>0</td>
</tr>
<tr>
<td>Indirectness</td>
<td>None serious</td>
<td>0</td>
</tr>
<tr>
<td>Imprecision</td>
<td>None serious</td>
<td>0</td>
</tr>
<tr>
<td>Publication bias</td>
<td>None serious</td>
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<tr>
<td><strong>Factors increasing confidence</strong></td>
<td>Large effect</td>
<td>No applicable</td>
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<tr>
<td>Dose-response</td>
<td>Evidence of dose response</td>
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<td>Antagonistic bias and confounding</td>
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<tr>
<td><strong>Final score</strong></td>
<td>5 (maximum score 4)</td>
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</tbody>
</table>

**Quality**

We are very confident that the true effect against IPD lies close to that of the estimate of effect on IPD.

**Conclusion**

There is strong evidence that the recommended schedules for PCV vaccines protect children against pneumococcal disease and vaccine type carriage.

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1. This GRADE table is based on 15 randomized controlled trials (RCTs) included in the systematic review by Scott P et al (2011). The authors’ summaries of these RCTs as well as of relevant observational studies are presented below.

2. In some of the RCTs the randomization sequence and/or the concealment of allocation was not described or not well described. However, collectively these limitations are not considered serious enough for downgrading the score.

3. Heterogeneity was moderate to high with regard to carriage of vaccine-type pneumococci at 9 and 12 months post vaccination, but each individual study showed a lower carrier prevalence in the vaccinated group. The inconsistencies are not considered serious enough to warrant downgrading.

4. There is evidence of a decreased risk of pneumococcal disease and bacterial carriage with increased number of doses. At the population level, there is evidence of an increasing herd immunity in the adult and elderly populations with increasing childhood vaccination coverage.
**Summary of clinical outcomes for comparisons of PCV with no PCV**

Twelve RCTs reported clinical data for a comparison of PCV receiving and no PCV-receiving groups (2-13).

Invasive pneumococcal disease (IPD) caused by vaccine-type pneumococcal strains was reduced in all five trials reporting this outcome, with little between-trial heterogeneity (pooled estimate of VE 78%, 95% CI 60,88%, I² 27%, intention to treat (ITT) analysis); for IPD caused by any pneumococcal serotype, the estimated vaccine efficacy (VE) in the USA1 7v trial was higher (VE 89%, 95% CI 73, 96%) than in all other trials (pooled VE 47%, 95% CI 31, 60%, I² 0%, ITT analysis); the detection of less severe IPD in this trial and the distribution of IPD-causing serotypes in the USA1 7v population are among the potential explanations for this result.

Estimates of VE against pneumonia were lower than estimates of VE against IPD; in part this may be due to the lack of specificity of this outcome for pneumococcal pneumonia. VE was also somewhat lower for clinical pneumonia (12%, 95% CI 4, 19%) than for WHO-defined radiologically confirmed pneumonia (25%, 95% CI 14, 35%) in ITT analyses.

VE against VT pneumococcal pneumonia (diagnosed by lung biopsy) was reported in 1 study, from a non-randomly selected subset of children with pneumonia. The reported VE against this outcome was 73% (95% CI –2.95%).

Generally few deaths were reported in trials, with only 2 trials reporting more than 25 deaths. In both these trials, fewer deaths occurred in the vaccinated group.

**Comparing PCV to no PCV with regard to effects on nasopharyngeal carriage of pneumococcal vaccine serotypes (VT)**

Six RCTs reporting VT carriage outcomes compared a PCV schedule to no PCV vaccination (3, 9, 11, 13, 14, 15).

All vaccinated groups had a lower prevalence of carriage than the unvaccinated groups. Confidence intervals around odds ratios (ORs) crossed 1 for all comparisons except for the cluster-randomized, which had an odds ratio of 0.40 (95% CI 0.23-0.67) for the analysis accounting for clustering and a similar result using raw data. There was little heterogeneity between the 2 other studies (0.0% heterogeneity), with a combined OR of 0.73 (95% CI 0.46-1.15).

Pneumococcal carriage at 9 months of age: Data were available from 3 studies (3, 11, 14). VT prevalence was lower in all vaccinated groups than in unvaccinated groups. Confidence intervals for ORs did not cross 1 for comparisons 3p vs. 0 with ORs of 0.39 (95% CI 0.24-0.62. Heterogeneity was moderate between the 3 studies in comparison (I² 38.1%).

Pneumococcal carriage at 12 months of age: Data were available from 4 studies (9, 13, 14, 15). VT results were similar in all comparisons with OR point estimates around 0.5 for combined estimates of each comparison. However, heterogeneity was high for comparison 3p vs. 0 (75.1%) and the combined estimate is less appropriate, but individual studies each had lower prevalence of VT carriage in the vaccinated group.

Pneumococcal carriage at 18 months of age: Data were available from 4 studies (9, 13, 14, 15). For VT, carriage prevalence was lower in vaccinated groups in combined estimates.

**Observational studies**

Four cohort studies (16-20) and two case control studies (21, 22) reported clinical data and/or pneumococcal nasopharyngeal carriage data comparing a group receiving a PCV schedule with a non-vaccinated group.
Effectiveness was high against vaccine type IPD for all 2 or 3 dose infant schedules examined in the case-control studies (21, 22). The case-control study (21) which estimated effectiveness of individual schedules against vaccine-type IPD, reported a VE of 73% (95% CI 43-87) for 1 dose, 96% (95% CI 88-99) for 2 doses, and 95% (95% CI 88-98) for 3 doses all doses given at less than 7 months of age (<7m).

For schedules with a booster, effectiveness against vaccine type IPD was reported to be 98% (95% CI 75-100) for 2 doses at <7m and a booster at 12-16 m, and 100% (95% CI 94-100) for 3 doses at less than 7m and a booster at 12-16m. Effectiveness of toddler schedules against vaccine-type IPD was estimated at 93% (95% CI 68-98) for 1 dose between 12 and 23 months of age, and 96% (95% CI 81-99) for 2 doses in the same time period.

A 2p+1 schedule showed a marked effectiveness against radiologically confirmed pneumonia but no protective effect was seen in the period between the primary schedule and the booster dose. The estimate of effectiveness of a 3p+1 schedule against clinical pneumonia from the first dose until the end of 2-years of follow up (after adjustment for underlying health conditions) was around 25%, but confidence intervals were wide.

Carriage of any serotype was reduced after a 3p+1 schedule with the biggest reduction seen in vaccine-type carriage. Catch-up (toddler doses) had no effect on carriage compared to unvaccinated toddlers, but the percentage of children carrying any serotype decreased in both groups.

References

1) Scott, P., et al. A systematic review of PCV schedules of data from randomized controlled trials and observational studies of childhood schedules using 7, 9, 10 and 13 valent vaccines. (WHO 2011) www.who.int/entity/immunization/sage/1_SAGE_PCV_review_Executive_summary_v3_101020.pdf


Table II: Grading of scientific evidence of safety of pneumococcal conjugate vaccine (PCV)

<table>
<thead>
<tr>
<th>Question: Do 10-valent and 13-valent PCV have safety profiles similar to that of 7-valent PCV* following 3 primary doses or 2 primary doses plus one booster dose?</th>
<th>Rating</th>
<th>Adjustment to quality level</th>
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<td>No of Studies/Starting Score</td>
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<tr>
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<td>Limitation in study design</td>
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</tr>
<tr>
<td>Inconsistency</td>
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</tr>
<tr>
<td>Indirectioness</td>
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</tr>
<tr>
<td>Imprecision</td>
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<td>Publication Bias</td>
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<tr>
<td>Factors increasing confidence</td>
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<td>Does-Response</td>
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<tr>
<td>Final Score</td>
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</table>

Summary of Findings

- Quality: We are very confident that the true effect lies close to that of the estimate of effect on health outcome
- Conclusion: PCV10 and PCV13 have safety profiles comparable to that of PCV7 following 3 primary doses or 2 primary doses plus one booster dose.

*PCV7 is known to be a very safe vaccine. (WHO’s Global Advisory Committee on Vaccine Safety (GACVS). Weekly Epidemiological Record (WER) 2007,82,17-24.

PCV 10-valent

Two randomized controlled trials (RCTs) evaluated the non inferiority of PCV 10-valent compared to the PCV 7-valent vaccine in terms of post-immunization febrile reactions with rectal temperature >39°C [1-4]. Parents or guardians recorded specified local (pain, redness, and swelling at the injection site) or systemic (fever, irritability, and loss of appetite) adverse events occurring 0–3 days after each dose of PCV 10-valent or PCV 7-valent vaccine following primary and booster vaccination, and symptoms were graded 0–3 in intensity[5] In addition, unsolicited adverse events, that occurred within 31 days of vaccination, were also recorded together with any serious adverse events that occurred during the entire study period. The tolerability profile of PCV 10-valent was generally similar to that of PCV 7-valent, when both vaccines were co-administered with other commonly used pediatric vaccines[5]. Post-immunization febrile reactions with rectal temperature >39°C were seen in 2.0–6.1% of PCV 10-valent versus 2.1–5.0% of PCV 7-valent vaccinees after primary vaccination and 1.6–2.8% versus 1.0–3.1%, respectively, after booster vaccination (primary endpoint). The most common solicited local adverse event of any grade was redness, and the most common solicited systemic adverse event of any grade was irritability. Approximately one-third of PCV 10-valent and PCV 7-valent primary or booster vaccine doses were followed by fever of ≥38°C when co-administered with DTPw-based combination vaccines, which increased to ≈60% for both treatment groups when co-administered with a DTPw-based combination vaccine. A fever of >40°C was observed following ≤1.1% of all PCV 10-valent vaccine doses compared with ≤2.2% of PCV 7-valent vaccine doses. Drowsiness and irritability of any grade occurred with a higher numerical frequency in PCV 10-valent than in PCV 7-valent vaccinees when co-administered with meningococcal conjugate vaccines after primary or booster vaccinations. Similarly, irritability and loss of appetite of any grade occurred with a higher numerical frequency in PCV 10-valent than in PCV 7-valent vaccinees when co-administered with a DTPw-based vaccine. For solicited systemic adverse events of grade 3 intensity, no increased incidence was observed for PCV 10-valent versus PCV 7-valent vaccinees. Of the 194 vaccinees with serious adverse events, six had events considered to be treatment-related and were withdrawn from the study. Serious adverse events leading to treatment withdrawal in PCV 10-valent recipients included pneumonia, gastroenteritis, and nephritic syndrome (n = 1), febrile convulsions (n = 1), and post-vaccination crying (n = 2) and in PCV 7-valent recipients included irritability and anorexia (n = 1), and fever (n = 1). The incidence of solicited local
and general adverse events reported within 4 days after each vaccination dose of PCV 10-valent was within the same range as after vaccination with the 7-valent PCV vaccine.

**PCV 13-valent**

Safety was evaluated in 13 clinical trials in which 4,729 infants and toddlers received at least one dose of PCV 13-valent and 2,760 infants and toddlers received at least one dose of PCV 7 valent. Safety data for the first three doses are available for all 13 infant studies; dose 4 data are available for 10 studies; and data for the 6-month follow-up are available for 7 studies. No statistically significant increase in risk was observed after the three infant doses or the toddler dose for systemic events, fever, antipyretic medications, and adverse events[6-10].

A meta-analysis of safety data from 13 infant studies concluded that PCV13 has a safety profile similar to that of PCV7 [11, 12]. Overall, rates of local reactions after any dose of the infant series were similar between PCV13 and PCV7 groups (tenderness [46.7 vs 44.8%], swelling [28.5 vs 26.9%], redness [36.4 vs 33.9%] respectively). After the toddler dose, tenderness was significantly higher (p = 0.005) among PCV7 (54.4%) subjects than PCV13 (48.8%) subjects. Frequencies of fever (≥38°C) were similar in both groups, most were mild (<39°C); incidence of moderate fever (39°-40°C) with PCV13 was ≤2.8% after any infant dose and 5% after the toddler dose compared to ≤2.6% and 7.3% with PCV7. Fever >40°C was uncommon in both groups. Frequencies of decreased appetite, irritability, and sleep disturbances were similar in both groups. Reported AEs were types of conditions and symptoms expected in infants and children. Few subjects discontinued study vaccine because of AEs: 22 subjects (0.47%) in the PCV13 group and 17 subjects (0.62%) in the PCV7 group.


Table III. Grading of the scientific evidence that with pneumococcal conjugate vaccine (PCV), 3 primary doses (3p) is superior to a 2p or a 2p+1 schedule in terms of inducing immunogenicity and for the prevention of pneumococcal disease and carriage\(^1\)

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Rating</th>
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<td>No of studies/starting score</td>
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<td>Factors decreasing confidence</td>
<td>Limitation in study design</td>
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<td>Inconsistency</td>
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<td>Indirectness</td>
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<tr>
<td></td>
<td>Imprecision</td>
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<td>Final numerical score of quality of evidence</td>
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<td>3</td>
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</table>

Summary of Findings

- We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.
- There is no definitive evidence that 3p schedule is superior to a 2p+1 schedule with regard to clinical disease or carriage outcomes. The clinical relevance of differences found in immunological outcomes is unclear.

Summary of studies included in the GRADE assessment

The studies used to compare 3 primary (3p) versus 2p include 3 RCTs with data on disease outcomes; 2 RCTs with data on nasopharyngeal carriage of vaccine types and; five RCTs with data on immunological outcomes. One observational study with data on invasive pneumococcal disease (IPD) and one RCT with data on immunological outcomes were used to compare 3p versus 2p+1 (two primary doses plus one booster).

**Iceland 9v (1)**

RCT that assessed immunogenicity in infants with a pneumococcal–meningococcal conjugate vaccine in 2p versus 3p with a booster. Infants (N=223) received 9vPnC–MnCC (CRM197-conjugated pneumococcal serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F combined with meningococcal C conjugate vaccine) either at 3 and 5 or 3, 4 and 5 months and a booster with either 9vPnC–MnCC or 23-valent pneumococcal-polysaccharide vaccine (23vPPS) and CRM197-MnCC, at 12 months. IgG measured at 3, 6, 12 and 13 months in all subjects and serum bactericidal activity (SBA) in half. One in the two-dose group had septicaemia 7 days after the second dose, caused by streptococcal serotype 7F. The 9vPnC–MnCC vaccine induced significant IgG to all components. Three doses induced higher antibody GMCs (geometric mean concentrations) at 6 months to seven of nine pneumococcal serotypes. This was most significant for 6B and 23F (p < 0.001), that also showed lower rate of responders >0.35 (6B, 23F) and >0.5 µg/mL (6B). Antibody GMCs remained lower following 9vPnC–MnCC booster in subjects primed with two doses although significant for serotype 18C. Significant memory responses were observed 1 week after the 23vPPS toddler dose. MnCC–IgG GMC was lower after two doses, however with comparable SBA.

**Europe 10v: (2)**
RCT that evaluated the immunogenicity of the 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) using a simplified 2-dose priming and a 3-dose priming both followed by a booster dose. A total of 351 healthy subjects were primed with PHiD-CV at either 3 and 5 or 3, 4 and 5 months of age followed in all subjects by a booster dose at 11 to 12 months of age. Serotype-specific pneumococcal responses were measured 1 month following primary and booster vaccinations. Depending on the serotype, the percentages of subjects reaching the ELISA antibody threshold of 0.2 µg/mL were 92.8% to 98.0% following 2 primary doses and 96.1% to 100% following 3 primary doses except for serotype 6B (55.7% and 63.1%, respectively) and serotype 23F (69.3% and 77.6%, respectively). Opsonophagocytic activity (OPA) could be measured in 74.4% to 100% and 88.9% to 100% of the subjects after the 2-dose or 3-dose priming, respectively, except for serotype 1 (60.8% and 62.9%, respectively). In both groups, robust increases in ELISA antibodies and OPA titers were observed for all serotypes after the booster dose. Higher post primary and post booster ELISA antibody levels and OPA titers were observed for most serotypes following the 3 plus 1 schedule.

Fiji 7v (3)
RCT that evaluated the effect of a reduced-dose 7-valent pneumococcal conjugate vaccine (PCV) primary series followed by a 23-valent pneumococcal polysaccharide vaccine (23vPPS) booster on nasopharyngeal (NP) pneumococcal carriage. Infants aged 6 weeks were randomized to receive 0, 1, 2, or 3 PCV doses. Within each group, half received 23vPPS at 12 months. NP swabs were taken at 6, 9, 12, and 17 months. Isolates were serotyped by multiplex PCR and a reverse line blot assay. There were no significant differences in PCV vaccine type (VT) carriage between the 3- and 2-dose groups at 12 months. NP VT carriage was significantly higher (P < 0.01) in the unvaccinated group than in the 3-dose group at the age of 9 months. There appeared to be a PCV dose effect in the cumulative proportion of infants carrying the VT, with less VT carriage occurring with more doses of PCV. Non-PCV serotype (NVT) carriage rates were similar for all PCV groups. When groups were pooled by receipt or non receipt of 23vPPS at 12 months, there were no differences in pneumococcal, VT, or NVT carriage rates between the 2 groups at the age of 17 months. In conclusion, there appeared to be a PCV dose effect on VT carriage, with less VT carriage occurring with more doses of PCV. By the age of 17 months, NVT carriage rates were similar for all groups. 23vPPS had no impact on carriage, despite the substantial boosts in antibody levels.

Gambia 7v (4)
The immunogenicity and impact on carriage of fewer doses of pneumococcal conjugate vaccine (PCV7) followed by booster with pneumococcal polysaccharide vaccine (PPV) were investigated. 684 infants were assigned randomly to one of the three groups that received one (A), two (B) or three (C) doses of PCV7 between 2 and 4 months of age, plus PPV at 10 months. Following primary vaccination protective antibody titers of >0.35 µg/ml against the PCV7 serotypes combined increased significantly with the number of PCV7 doses, 44% vs. 77% vs. 94% (p < 0.001), and correlated positively with the opsonophagocytic indices, but negatively with nasopharyngeal carriage of pneumococcus. The differences in antibody responses and pneumococcal carriage between the groups diminished following booster with PPV.

Israel 7v (5)
An open-label RCT evaluating two different schedules: 3+1 (primary 2, 4, 6m [n=353]; booster 12m [n=163]); and 2+1 (primary 4, 6m [n=188]; booster 12m [n=169]). Nasopharyngeal cultures were obtained at 2, 4, 6, 7, 12, 13, 18, 19, 24, 30m (total=3798). Serum serotype-specific IgG ELISA was obtained at 2, 7, 13, 19m. At 7 months, antibody concentrations and % ≥0.35µg/ml were significantly lower in the 2+1 vs. 3+1 groups, mainly for serotypes 6B and 23F; this persisted after booster (age=12m). After ≥1 PCV7 dose, during 1st year, PCV7-serotype carriage was significantly higher in the 2+1 groups, mainly due to 6B and 6A carriage. However, this was reversed after booster, and thus for the entire period of 4-30m, no significant difference between the groups was observed. The effect of the 2+1 reduced-dose regimen on NP-Pnc-Carr was similar to that of the 3+1.

USA 7v (6)
A case control study analysed data on invasive pneumococcal disease among children 3–59 months identified through the US Centers for Disease Control and Prevention’s Active Bacterial Core surveillance. Three
controls, matched for age and zip code were selected for each case. The matched odds ratio for vaccination were calculated using conditional logistic regression, controlling for underlying conditions. Vaccine effectiveness was calculated as one minus the adjusted matched odds ratio times 100%. The study included 782 cases and 2512 controls. Effectiveness of one or more doses against vaccine serotypes was 96% (95% CI 93–98) in healthy children and 81% (57–92) in those with coexisting disorders. It was 76% (63–85) against infections that were not susceptible to penicillin. Compared with no vaccine, point estimates for effectiveness of two, three, or four doses when given on an infant schedule were close to each other, with widely overlapping CI and were more effective than a single dose. Effectiveness of two, three, and four-dose schedules was similar up to 6 months after vaccination (97% [87–99] for 2 doses, 100% [96–100] for 3 doses, and 100% [58–100] for 4 doses) and 6 or more months following vaccination (95% [71–99] for 2 doses, 87% [64–95] for 3 doses, and 100% [93–100] for 4 doses). Vaccination prevented disease caused by all seven vaccine serotypes, and by vaccine-related serotype 6A. Several schedules were more protective than no vaccination; three infant doses with a booster were more protective against vaccine-type disease than were three doses alone (p=0.0323).

USA 7v cohort (7,8)
A retrospective matched-cohort study design and health insurance claims data, this study compared rates of lower respiratory tract infections (LRTD) between children who were born in 2002 and received 2 versus 3 PCV7 doses in the primary series, both before and after receipt of the booster dose. Two-dose and 3-dose children were matched (1:1) using propensity scoring. Cumulative rates of hospital admissions and outpatient visits for LRTD were tallied during the post-primary/pre-booster period and the post-booster period (to age 3 years), respectively. During the post-primary/pre-booster period, 3-dose children (n = 3293) had 7.8 (95% CI: 0.8 to 14.8) fewer LRTD-related hospital admissions (per 1000 children) and 57 (95% CI: −6 to 128) fewer LRTD-related outpatient visits (per 1000 children) than matched 2-dose subjects (n = 3293). During the post-booster period, the numbers of LRTD-related hospital admissions and outpatient visits did not differ significantly between 3-dose and 2-dose children.

UK 9v (9)
A cohort study in the U.K evaluated 2p or 3p schedules in infants (at 2 and 4 or 2/3/4 months of age) of a 9-valent pneumococcal conjugate vaccine (9VPCV) followed by boosting at 12 months of age. For infants, serotype-specific IgG geometric mean concentrations were similar post-primary immunization between the groups with both showing avidity maturation and similar booster responses. For toddlers, the primary response to 4 of the 9 serotypes was lower in the 1-compared with the 2-dose group (type 6B, 0.77 versus 7.1; type 14, 4.67 versus 14.98; type 19F, 5.05 versus 7.75; type 23F, 2.48 versus 5.05), although for all serotypes booster responses were similar between groups, and the post primary responses in the 1-dose group were at least as high as those after infant immunization. The 2-dose infant priming schedule of 9VPCV is comparable with the 3-dose schedule. The comparison groups in this cohort study were different counties in the United Kingdom and during different time periods (2000-2001 or 2001-2003). This could have introduced bias if systematic differences existed between locations and time periods, such as recruitment processes or exposure to Streptococcus pneumoniae.

References


