Landscape analysis of pneumococcal conjugate vaccine dosing schedules: A systematic review

Sub-report on the 3-dose schedules

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Executive summary

Objectives

Pneumococcal conjugate vaccines (PCVs) are being introduced rapidly into a growing number of countries, but the optimal dosing schedule is unclear. We conducted a comprehensive, systematic review to gather available information on PCV dosing schedules that, along with other data, would guide PCV policy development in relation to the World Health Organization's Expanded Programme for Immunization schedule. The full reviewed included 6 questions on a variety of schedules related issues. This report describes available data relevant to the question about whether a three-dose series should be administered on a schedule of two primary doses with a booster (2+1) or three primary doses without a booster (3+0) schedule.

Methods

A systematic literature review was performed to collect all available data from published and selected unpublished sources on the immunogenicity, effect on NP colonization and effect (direct and indirect) on pneumonia and invasive pneumococcal disease (IPD) of various PCV schedules. Only studies published in the English language were considered for review. In addition abstracts from meetings of the International Symposium on Pneumococci and Pneumococcal Disease (ISPPD) and the Interscience Conference on Antimicrobial Agents and Chemotherapeutics (ICAAC) were searched. Titles and abstracts were reviewed twice and those with relevant content on one of the four outcomes (immunogenicity, carriage, invasive disease, and pneumonia) underwent full review using a standardized data collection instrument. Publications and abstracts from the same protocol or study system were grouped into 'families' that were represented by key 'primary studies.' For immunogenicity, we compared results across studies using multivariable regression modeling controlling for region, age of first dose, concomitant vaccines, and laboratory methods.

Results

Out of 10,205 citations reviewed, we identified 170 primary studies on immunogenicity, 99 primary studies of IPD (48 among children <2 years), 26 primary studies on carriage, and 45 on pneumonia. Of the 289 total primary studies among young children, 79 (27%) contained information on a 3+0 schedule, 35 (12%) contained information on a 2+1 schedule, and 25 (9%) evaluated 2 primary doses without a booster (2+0).

2-dose vs. 3-dose priming schedules

Comparing across immunogenicity studies (N=40 to 117, depending on serotype), the post-primary antibody response (median GMC) was generally higher for all serotypes following a 3-dose primary series compared to a 2-dose schedule. In the multivariable model, geometric mean concentrations (GMCs) for serotypes 6B, 23F, and 14 were significantly higher following 3 doses compared to 2 doses. For carriage, two published studies (in Fiji and the Gambia) showed less carriage for 3+0 vs 2+0 schedules at some but not all timepoints evaluated after vaccination; one unpublished study (Israel) had similar findings, with 6B carried less often for the schedule with three primary doses. For IPD, 2 case control studies and 3 indirect cohort studies evaluated 2+0 and 3+0 schedules within the same study; all showed benefit compared to no vaccination. One case control study directly compared 2+0 and 3+0 schedules and could not discern a difference in effectiveness, but a case series from the US found more cases of 6B disease occurring among children who received 2 doses compared to children who had 3 doses. For pneumonia, one case control study found significantly more pneumonia hospitalizations for children who had received 2 primary doses compared to those that recieved three doses in the interval between the primary series and the booster dose. When comparing vaccine effectiveness estimates

between studies, we could not discern differences between 3+0 and 2+0 schedules for carriage (2 trials evaluating 2-dose primary series and and 8 evaluating 3-dose series). No randomized controlled trials or post-licensure trend studies have been conducted for 2+0 schedules for pneumonia or IPD. For the 3+0 schedule, 5 clinical trials and 1 observational study demonstrated PCV impact against either Xray confirmed or clinical pneumonia; for IPD, 3 randomized clinical trials and 2 observational studies showed vaccine efficacy and impact.

3+0 vs. 2+1 schedules

Comparing across immunogenicity studies (N=31 to 86, depending on serotype), the modeled post-booster antibody response of a 2+1 schedule (median age at blood draw = 14.8 months) was significantly higher than the post-primary response of a 3+0 schedule (median age at blood draw = 6.3 months) for all serotypes. For carriage, no published studies directly compared 2+1 and 3+0 schedules. Comparing across studies, only one clinical trial examined a 2+1 schedule and four examined a 3+0 schedule; both schedules reduced vaccine-type carriage compared to unvaccinated controls. No published observational studies examined carriage in the population before and after introduction of a 3+0 schedule, and only one published observational study examined early impact following introduction of a 2+1 schedule, which showed a reduction in vaccine-type carriage among children with otitis media and pneumonia. For invasive disease, two case-control studies allowed for within-study comparison of 2+1 and 3+0 schedules; both showed high vaccine effectiveness against vaccine-type IPD compared to no vaccine. No discernable difference between the schedules was seen in either study. Comparing across studies for IPD, we found 7 observational surveillance/trend analysis studies that evaluated either the effect of 2+1 (n=5) or 3+0 (n=2) schedules. Despite highly variable baseline incidence rates, all studies showed a significant reduction in vaccine-type IPD after introduction of vaccine. The paucity of data on the impact of these schedules, particularly ≥1 year after vaccine introduction, did not allow for a clear determination on which regimen is superior to the other. Randomized clinical trials of 3+0 schedules showed good efficacy against invasive disease (N=2) and pneumonia (N=5) compared to no vaccination. No randomized clinical trials have been conducted for 2+1 schedules for IPD or pneumonia; one non-randomized trial of the 2+1 schedule against pneumonia found high effectiveness. For pneumonia, observational studies showing the impact of PCV after routine introduction demonstrated significant reductions for both the 2+1 schedule (3 studies) and the 3+0 schedule (1 study).

Key study findings

- Studies of immunogenicity, nasopharyngeal carriage, and pneumonia suggest that a schedule of 3 primary doses has some benefit over 2 primary doses for some serotypes (eg 6B, 23F), at least until a booster dose is given.
- The 2+1 schedule induces higher antibody levels following the third dose than those found after the third dose of a 3+0 schedule.
- Determining the relative benefits of 2+1 vs. 3+0 schedules is difficult because very few studies of clinical outcomes included head-to-head comparisons of the two schedules.
- Use of the 3+0 schedule is strongly supported by multiple randomized controlled clinical trials of pneumonia and IPD in developing country settings. No such trials have been done for a 2+1 schedule.
- Post-vaccine introduction observational studies are available from several countries that demonstrate the benefits of a 2+1 schedule, including impact on pneumonia and vaccine type IPD; only 1 country (Australia) has published studies on disease reductions following implementation of a 3+0 schedule.
- We found important limitations to the available data, including the fact that all published post-introduction studies are from high income countries, most of which

employed catch-up vaccination for children up to 2 years of age. In addition, most data are for PCV7; very few studies evaluated PCV10 and PCV13.

Conclusions

Both 2+1 and 3+0 show evidence of impact on immunogenicity, NP colonization, IPD and pneumonia, although the strength of supporting evidence differs for the two schedules by outcome. Determining the relative benefit of one over another schedule is limited by the paucity of head to head studies for clinical outcomes, by the paucity of specific data in regions where child mortality is high, and by the paucity of data on additional serotypes (i.e. the non-PCV7 serotypes) in the PCV10 and PCV13 products which are now in use. Use of the 3+0 schedule may be preferred in settings with a large proportion of pneumonia deaths occurring in the first year of life or if obtaining high coverage for routine vaccinations given late in the first year of life or in the second year (ie, measles vaccine) is challenging. A 2+1 schedule can be very effective in practice, especially if implemented with a catch-up campaign. Few data exist on the impact of 2+1 without a catch-up schedule. More data are needed, in particular for the vaccines that are now being introduced (PCV10 and PCV13) and for whether giving the third dose of PCV later would confer better protection against serotype 1 disease.

Contents

I. Introduction

Three licensed pneumococcal conjugate vaccines (PCV) contain antigens from 7, 10 or 13 pneumococcal serotypes (PCV7, PCV10 and PCV13). There is much that is known, and much more to learn, about the effects of different pneumococcal conjugate vaccine (PCV) dosing schedules. PCV has been tested in efficacy trials with pneumococcal disease outcomes using 4-dose (three primary doses plus a booster dose in the second year of life, 3+1) and 3-dose (three primary doses without a booster, 3+0) schedules. Immunogenicity studies of other PCV regimens that vary the number of doses, age at dosing, interval between doses, use of combination schedules [i.e., PCV with 23-valent pneumococcal polysaccharide vaccine (PS23)], and use of maternal pneumococcal vaccine have been published, recently completed, or are ongoing. Outcomes from these immunogenicity studies include quantitative and functional antibody measures while studies of clinical outcomes include impact on nasopharyngeal colonization, pneumonia, and invasive pneumococcal disease (IPD). Although PCV7 and PCV10 were initially licensed for use with a four-dose (3+1) regimen, PCV7, PCV10, and PCV13 were later granted licenses in Europe and elsewhere for schedules using two primary doses plus a booster (2+1), when used as part of a routine immunization program. While many early adopting countries use PCVs on the 3+1 schedule, others have introduced PCV with the 2+1 or 3+0 regimens (e.g., the UK schedule is 2, 4 and 13 months of age and Australia's schedule is 2, 4, and 6 months). Post-introduction disease impact assessments are now becoming available for PCV7 and importantly for PCV10 and PCV13; however, the impact of these reduced-dose schedules relative to a four-dose schedule is not clearly known, and the optimal schedule to deliver only three doses is not clearly known. In fact this may vary by serotype, by epidemiologic setting (i.e. mortality, community HIV prevalence, or pneumococcal burden) and by immunization program characteristics. Furthermore, the disease impact of catch-up campaigns as part of PCV introduction is not characterized or fully understood in its relationship to dosing schedule choices.

The scientific community does not have consensus on which PCV schedule(s) or which introduction strategies are optimal for a given epidemiologic setting, considering both the direct and indirect effects as well as the possibility of serotype replacement disease. Optimum schedules may vary according to the transmission dynamics in a community; a schedule that is or optimum for a setting where carriage rates are relatively low may not achieve optimum disease reduction results in a setting where carriage rates are very high and include significant colonization among those outside the pre-school age group. The optimum schedule for a particular setting may also depend on the routine immunization program, expected coverage rates and ages at actual vaccination. Furthermore, there is no consensus on what gaps remain in the evidence base that, if filled, would assist with policy development and should therefore be prioritized for funding, study development and analysis. Consequently, a comprehensive technical analysis of the published and unpublished data on PCV dosing schedules, assessing immunogenicity, effect on NP colonization, impact on disease (IPD and pneumonia) as well as indirect effects, and covariates which describe the epidemiologic setting of the study is needed to provide the evidence base on which a strategic analysis of key information gaps can be undertaken.

We conducted a comprehensive, systematic review to gather available information on PCV dosing schedules that, along with other data, would guide PCV policy development in relation to the World Health Organization's Expanded Programme for Immunization schedule. The full review was conducted with the following questions guiding the strategy:

1. What is the evidence that a 3-dose primary series is superior or inferior to a 2-dose primary series?

2. What is the evidence that a 3-dose series should be administered on a 2+1 vs. a 3+0 schedule?
3. What interval of doses should be recommended?
4. What is the optimal age for doses?
5. What is the evidence that a schedule including a booster dose is superior to one without a booster dose?
6. Do certain dosing schedules result in better indirect effects of vaccine impact?

For this sub-report, we summarize available data in support of use of PCVs on 2+1 and 3+0 schedules (i.e. question two from the above list). The specific outcomes of interest identified for the evaluation of three-dose series were as follows:

- *Immunogenicity.* Participant immune response (ELISA and OPA) as measured by geometric mean concentration (GMC) and post-vaccination concentrations above a specified cut-off (0.35 or when appropriate, 0.20).
- *Carriage*: Changes in vaccine-type pneumococcal nasopharyngeal carriage in controlled clinical trials as well as in observational studies, including 'before and after' vaccine introduction (i.e. ecologic studies).
- *Invasive pneumococcal disease*: Impact on vaccine-type invasive pneumococcal disease in controlled clinical trials and in observational studies, including 'before and after' vaccine introduction (i.e. ecologic studies).
- *Pneumonia*: Observational (before and after vaccine introduction) and randomized clinical trial data on both chest X-ray confirmed pneumonia and clinical pneumonia,
- *Indirect effects of PCV*: The indirect effects of different vaccine schedules on various clinical outcomes, including pneumonia, IPD and carriage, among groups of persons not targeted to receive vaccine or not actually receiving vaccine as described in randomized trials and observational studies.

II. Methods

A. Literature search strategy

A systematic literature review was performed to collect all available data from published and selected unpublished sources on the immunogenicity, effect on NP colonization and effect (direct and indirect) on disease of various PCV vaccination schedules for healthy children as well as children with underlying medical conditions (i.e. sickle cell disease and HIV). Data were obtained through a review of published reports of randomized controlled trials, other clinical studies (e.g. observational studies) and surveillance database analyses performed in the setting of different PCV regimens. Only studies published in the English language were considered for review because of the low likelihood that such studies had been published in non-English journals[1].

The specific search terms used to identify all potentially relevant articles for this review are shown in **Table 1**. To be identified in the search, each article had to include a minimum of one "narrow vaccine term" and one "Pneumococcal term". Terms were listed as Medical Subject Headings (MeSH) or other categories specific to each database. In addition abstracts from meetings of the International Symposium on Pneumococci and Pneumococcal Disease (ISPPD) and the Interscience Conference on Antimicrobial Agents and Chemotherapeutics (ICAAC) were searched. The following electronic databases were used in this analysis:

- EMBASE
- PubMed
- Biological Abstracts (BA)

[1] Articles that have been translated into English were also included.

- Pascal Biomed
- Global Health
- BioAbst/Reports, Reviews, Meetings
- Cochrane Library
- Regional databases
    - African Index Medicus (AIM)
    - Western Region Index Medicus (WPRIM)
    - Index Medicus for Eastern Med. Region (IMEMR)
    - Index Medicus for South-East Asia Region (IMSEAR)
    - Latin America and Caribbean Health Sciences Info. (LILACS)
    - Pan-American Health Org. (PAHO)
    - IndiaMed (IndMed)

B. Selection of studies

1. Inclusion criteria

We included all data published during or after 1994 from randomized control trials (RCTs), non-randomized trials, surveillance database analyses and observational studies of any PCV schedule on one or more outcome of interest (IPD, pneumonia, NP colonization, antibody concentrations, functional antibody measures). In addition to the direct effects of PCV introduction on groups targeted to receive vaccine, we included studies reporting indirect effects of PCV on groups not targeted to receive vaccine, i.e. unvaccinated children, older children and adult populations. Licensed or about-to-be licensed products (e.g. from Wyeth (now Pfizer) and GSK) as well as products that are not being further pursued (e.g. products from Merck and Aventis (now Sanofi-Pasteur)) were also included.[2] For nasopharyngeal carriage, data were limited to those studies reporting changes in vaccine-type pneumococcal nasopharyngeal carriage in response to vaccination (i.e. controlled trials) and in before and after vaccine introduction (i.e. ecologic studies).

2. Exclusion criteria

We excluded studies evaluating maternal doses of pneumococcal vaccine (either PS23 or PCV), dose ranging studies, and review articles. We also excluded studies published prior to 1994 as these studies are likely to evaluate preliminary product formulations which are differ too much from the final licensed products to provide relevant information for our study objectives. Studies with non-analyzable data (e.g. cross-sectional studies that only reported data before or after PCV introduction but not for both time periods) were excluded because they did not allow for calculation of impact for the outcomes of interest. Studies reporting a vaccine target group older than 15 years of age and those that used PS23 in a primary series or single dose were also excluded from the analysis.[3] For nasopharyngeal carriage, studies were excluded if the vaccination series started after 12 months of life. Pneumonia analyses for this draft report were limited to citations with clinical pneumonia, radiologically confirmed pneumonia, or mortality as the primary endpoints.

C. Data abstraction

Titles and abstracts for all citations identified by the search strategy were screened by two independent reviewers with expertise in pneumococcal disease to create a master list of

[2] The rationale for inclusion of data on products that are not headed to commercialization was based on the notion that some attributes of dosing and relative immunogenicity may be generalizable across PCV products.
[3] Fifteen years of age was selected to allow for inclusion of data on catch up schedules.

potentially relevant citations for full-text review. To identify any missing relevant articles, the list was reviewed by senior staff members and a second pass through the original title/abstract list was performed by two reviewers. Abstracts for all articles flagged for inclusion were reviewed to determine if the full report was eligible to be included in the analysis. Full text articles from all eligible citations were abstracted for a limited set of variables and data recorded directly into an electronic database. This information was used to generate "groups" based on outcome of interest: IPD, pneumonia, immunogenicity and carriage. A full text review was performed on all articles within each 'group', and detailed information on the article was abstracted into a larger standardized database. Because a given study could have multiple reports in the literature, we defined 'study families' that included abstracts or publications generated from a single protocol, surveillance system or other data collection system. For each study family we identified a single 'primary study' or main publication. Quality control was maintained at this step through double abstraction of all articles within each 'group'. Standard operating procedures and data collection forms with standardized variables were developed for the initial article review process, as well as for review of each individual outcome-related 'group' to guide the review. In addition, reviewers were trained on data abstraction methods by senior staff members. A team of five epidemiologists with expertise in pneumococcal disease reconciled the double abstractions and de-duplicated articles to identify primary data within each family of studies.

D. Statistical analysis

The published and unpublished literature we reviewed included studies performed using a variety of methods. Even when methods were similar, the analyses presented were often very different. Few studies included head-to-head comparisons of schedules within the study. This heterogeneity meant that the data collected did not lend itself to a formal meta-analysis. Data on carriage, pneumonia, and IPD were therefore summarized in descriptive analyses to provide an overview of the amount and variability of the data by schedules and outcomes. Following the descriptive analysis, biologically and epidemiologically meaningful subgroup analyses were performed to compare and contrast dosing schedules as much as the data would allow.

To provide a complete synthesis of the available data on 3+0 and 2+1 PCV dosing schedules, information on the impact of the primary series and full series on our outcomes of interest was included. The two primary series were evaluated using a 3+0 schedule as a baseline for comparison with a 2-dose primary series. Information on co-administered vaccines, the timing of the primary series (including intervals between doses and the ages at which the doses are administered) were reviewed and considered for inclusion in the analysis.

For immunogenicity, we created multivariable models that attempted to control for differences between studies while examining the relationship of dosing schedules to antibody levels. Data on serotype-specific outcomes were included only in the immunogenicity analysis and were limited to serotypes 1, 5, 6B, 14, 19F, 23F because of their particular epidemiological and/or biological interest.
Geometric mean antibody concentration (GMC) or percent above cutoff (0.35 ug/ml or 0.2 ug/ml if GSK ELISA method used) were evaluated. Effect of schedule on GMC was assessed using random effects linear regression adjusted for PCV product, co-administration with DTaP versus DTwP, lab method and geographic region.

For IPD observational studies reporting incidence over time, we calculated percent reduction by defining baseline incidence as the mean of the all data points reported prior to introduction. When annual data on post-introduction incidence was available, we calculated percent reduction from baseline using the data point given for each year reported. In cases

where only the average post-introduction incidence rate over a period of time was provided, we calculated percent reduction from baseline to the reported rate and assigned it to the median year of the date range provided. When possible, incidence rates during the year of introduction were excluded from these calculations.

E. Presentation of results

For each outcome of interest, results were presented through a variety of methods. These include descriptive tables, forest plots, scatter plots, and graphs displaying trends in disease incidence over time. A limited set of the results are presented here in this draft report to highlight the major findings.

III. Results:

A. Literature search

Results from the literature search are shown in **Figure 1.** Out of 10,205 citations reviewed, we identified 170 primary immunogenicity studies, 99 primary IPD studies, 26 primary carriage studies, and 45 primary pneumonia studies. IPD studies were further broken down to direct effects (48 primary studies among children ≤2 years of age) and indirect effects (14 primary studies among young adults 5-50 years of age). Although this total includes IPD citations that only report data on meningitis or bacteremia, these studies are subsequently excluded from the dosing schedule analyses for this report. Furthermore, this total also includes studies for all endpoints for pneumonia (clinical, radiological, pneumococcal pneumonia, ALRI, empyema); however, only studies with a clinical or radiological pneumonia endpoint are included in the direct effects analyses presented here.

B. Description of included studies

A descriptive summary of all primary studies included in the landscape analysis for immunogenicity, carriage, IPD and pneumonia outcomes is shown in **Table 2.** Across outcomes, a total of 289 primary citations were included in this PCV dosing landscape analysis. The vast majority of studies (n=221; 77%) were published after 2003; data published earlier were primarily immunogenicity (n=57; 20%) or NP carriage (n=5; 2%). Studies evaluating a 3+1 schedule were most common (n=142; 49%), with studies of 3+0 next most common (n=79, 27%); very few citations included evaluation of a 2+0 (n=25; 9%) or 2+1 (n=35; 12%) schedule. Most studies occurred in North America (n= 99; 34%) or Europe (n= 109; 38%), although studies from Africa, Asia, Oceania and Latin America/Caribbean are represented. Furthermore, most studies were of a PCV7 formulation with very few studies of PCV10 or PCV13.

C. Number of doses in the primary series (2-dose primary vs. 3-dose primary)

In this analysis we asked whether a 3-dose primary schedule is superior or equivalent to a 2-dose priming schedule.

1. Immunogenicity

Within study comparisons (n= 6 studies)

Six studies directly compared the immunogenicity of a 2- and 3-dose primary series. These within study comparisons were analyzed in the report from the University of Berne so they were not evaluated separately in our study. An additional 8 studies presented the post dose-2 results of a 3-dose primary series and were evaluated as part of the between study comparisons.

Between study comparisons (n= 68 studies)
Because a study may contribute data for more than one randomization group or may contribute data post dose 2 and post dose 3 in the same group, analyses of GMCs included data frm 61 studies and 119 study-arms. The 3-dose primary PCV schedule produced higher post-primary GMC antibody response for all serotypes except for serotype 1 when compared to 2 primary doses in a model that controlled for age at first dose, geographic region, PCV product, coadministered vaccines, and laboratory methods (**Figures 2 & 3**). GMCs for serotypes 6B, 23F, and 14 were significantly higher following 3 doses compared to 2 doses (**Figure 3**). The percent of children with titers above 0.35ug/ml (or 0.20ug/ml if studies used a GSK ELISA assay) tended to be a high for both schedules except for serotypes 6B and 23F, but those receiving a 3-dose primary schedule appeared slightly higher compared to those receiving a 2-dose primary schedule, although differences were small (**Figure 4**).

2. Nasopharyngeal carriage

Within study comparisons (n=3 studies)
Two studies directly compared the efficacy of 2- and 3-dose primary series for vaccine-type carriage. The first study, conducted in Fiji, compared 0, 1, 2, and 3 PCV7 doses given at 14 weeks, 6 and 14 weeks, or 6, 10, and 14 weeks, with and without a PPV booster at 12 months (Russell, Carapetis et al. 2010). Nasopharyngeal samples were taken at 6, 9, 12 and 17 months. The only statistically significant difference in frequency of vaccine-type carriage between the 2-dose and 3-dose groups was at 9 months, when the 3-dose group had significantly less vaccine-type carriage. However, at 6 months, 12 months, and 17 months, there were no statistically significant differences between the frequency of vaccine-type carriage between the children who received 2- and 3-doses. The second study, conducted in the Gambia, compared 1-, 2- and 3-dose regimens given at 2 months, 2 and 3 months, and 2, 3, and 4 months with a PPV booster at 10 months (Ota, Akinsola et al. 2011). Nasopharyngeal samples were taken at 5, 11, and 15 months. At 11 months, the 3-dose regimen had a borderline significant reduction in vaccine-type carriage (p=0.056) compared to the 2-dose regimen. However, at 5 and 15 months, the vaccine serotype colonization prevalence among children who received 2-dose and 3-dose regimens were equivalent.

A third study has also been conducted and has been shared with us in unpublished form (Dagan personal communication). This study from Israel compared a 2+1 schedule, given at 4, 6, and 12 months, to a 3+1 schedule, given at 2, 4, 6, and 12 months. At 7 and 12 months, before the booster dose, the vaccine-type carriage in the 2+1 group was 28.4% versus 22.6% in the 3+1 group. However, at 13 and 18 months, after the booster dose, vaccine-type carriage was almost the same at 18.8% in the 3+1 group and 19.1% in the 2+1 group.

Between study comparisons (n= 10 studies)
As compared to unvaccinated controls, only two studies examined a 2-dose primary regimen (**Figure 5**) (Van Gils, Veenhoven et al. 2009; Russell, Carapetis et al. 2010) while eight studies examined a 3-dose primary regimen (**Figure 6**) (Dagan, Muallem et al. 1997; Mbelle, Huebner et al. 1999; Obaro, Adegbola et al. 2000; Yeh, Zangwill et al. 2003; O'Brien, Millar et al. 2007; Cheung, Zaman et al. 2009; Prymula, Kriz et al. 2009; Russell, Carapetis et al. 2010). All studies of 2-dose primary series revealed a reduction in vaccine-type carriage compared with the control group (no vaccination). Most 3-dose primary regimens reduced vaccine-type carriage, although statistical significance was not always reached. One study with a 3-dose primary regimen and a PCV7 product made by Merck showed a non-significant increase of vaccine-type carriage at 7 months of age (Yeh, Zangwill et al. 2003).

3. Invasive pneumococcal disease

Within study comparisons (n=6 studies)
Two case-control studies and three indirect cohort studies allow for *within-study* comparisons of 2- and 3-dose primary series on effectiveness of PCV against IPD among children (Tables 3 and 4). All of these studies evaluated PCV7 (Wyeth). One study (Deceuninck, 2010) took place in the setting of a 2+1 national immunization schedule; the others (Whitney, 2006; De Serres, 2008; Mahon, 2005; Ruckinger, 2010) took place in the United States in the setting of a 3+1 schedule. All of these studies showed high effectiveness (≥70%) of both 2- and 3-doses when received before 7 months of age *as compared to no vaccine*; however, confidence intervals overlap and no clear difference between the two priming series regimens can be distinguished. Only one (Whitney, 2006) of these studies directly compared the effectiveness of a 2-dose to a 3-dose primary series and a difference could not be discerned, although numbers in each group were small. One observational study (Park 2010) looking at cases of vaccine type IPD occurring in vaccinated children under 5 years of age in the US demonstrated that more breakthrough cases of IPD caused by serotype 6B occurred among those who had received 2-doses as compared to 3-doses (**Table 5**).

Between study comparisons (n= 0 studies)
Between study comparisons of a 2-dose and 3-dose primary series are not possible because there are no studies that specifically evaluate the impact of a 2-dose series on IPD independently of other dosing schedules. Studies that evaluate only a 3-dose series are described below under the section "Timing of doses in a 3-dose series (2+1 vs. 3+0)".

4. Pneumonia

Within study comparisons (n= 1 study)
There were no randomized controlled trials (RCT) and only one observational study (Pelton, 2010) that directly compared the effectiveness of two versus three primary doses against pneumonia. This observational study, conducted in the US, evaluated the rate of hospitalizations and ambulatory visits for LRTI and found that children who received three primary doses had fewer ambulatory visits and hospitalizations than those that only received two primary doses, a difference that disappeared after the booster dose was administered.

Between study comparisons (n= 14 studies)
No RCTs have evaluated the efficacy of a two-dose primary series against pneumonia. There were nine RCTs that evaluated either a 3+0 (N=5) (Klugman 2003; Cutts, 2005; Lucero, 2009; Madhi, 2005; Richmond, 2008) or a 3+1 (N=4) schedule (**Table 6**) (Black, 2002; Hansen, 2006; O'Brien, 2002; Adam, 2008). Almost all of these RCTs showed efficacy against clinical and/or radiologically confirmed pneumonia in general pediatric populations (**Figure 7**).

Five observational studies evaluated a three dose primary series on clinical pneumonia- one study from Australia utilized a 3+0 schedule in non-indigenous populations (Jardine, 2010) and four studies from the US evaluated a 3+1 schedule on general populations (**Table 9**) (Grijalva, 2007; Nelson, 2008; Simonsen, 2011 ;Zhou, 2007). Almost all studies showed evidence of effectiveness of PCV use on the reduction of pneumonia rates (**Figure 8**).

D. Timing of doses in a 3-dose series (2+1 vs. 3+0)

1. Immunogenicity

Within study comparisons (n= 5 studies)
Five studies directly compared 2+1 vs. 3+0 schedules. These within study comparisons were analyzed in the University of Berne report so a within-study analysis was not separately

conducted in our analysis. However, these studies are included in our meta-analysis of all studies that have either data for a 2+1 or 3+0 schedule. Note that because they were listed in the Berne Report, we excluded them from reference lists and listings of individual studies in summary tables.

Between study comparisons (n= 67 studies)
As expected, comparing the two 3-dose schedules in the 62 studies with GMC results, the post-booster antibody response (median age at blood draw = 14.8 months) of a 2+1 schedule was significantly higher than the post-primary response (median age at blood draw = 6.3 months) of a 3+0 schedule for all serotypes (**Figures 9 & 10**). The post-booster median GMC response (in µg/ml) compared to the post-primary GMC response, ignoring confounders such as geographic region, DtaP verus DTwP as a co-administered vaccine and PCV product, was 8.3 v 2.7, 4.3 v 2.7, 6.7 v 1.3, 12.0 v 4.5, 8.1 v 3.8, and 4.5 v 1.7 for serotypes 1, 5, 6B, 14, 19F, and 23F respectively.

2. Nasopharyngeal carriage

Within study comparisons (n= 0 studies)
No published studies directly compared 2+1 and 3+0 schedules.

Between study comparisons (n= 10 studies)
As compared to unvaccinated controls, only one clinical trial examined a 2+1 schedule (**Figure 11**) (Van Gils, Veenhoven et al. 2009), and four studies examined a 3+0 schedule (**Figure 12**) (Madhi, Adrian et al. 2007; Nohynek, Makela et al. 2008; Cheung, Zaman et al. 2009; Russell, Carapetis et al. 2010). When compared to controls, both 2+1 and 3+0 schedules reduced vaccine-type carriage.(Madhi, Adrian et al. 2007; Nohynek, Makela et al. 2008; Cheung, Zaman et al. 2009; Van Gils, Veenhoven et al. 2009; Russell, Carapetis et al. 2010) (**Table 7**).

No published observational studies examined carriage in the population before and after introduction of a 3+0 schedule, and only one published observational study examined impact following introduction of a 2+1 schedule (Muhlemann and Aebi 2008). In this study in Switzerland using an 2+1 schedule given at 2, 4, and 12 months, 57.1% of children less than 2 years of age with acute otitis media or pneumonia carried vaccine-type pneumococci prior to PCV7 introduction (Muhlemann and Aebi 2008). One year following introduction, 37.1% of vaccinated children less than 2 years with acute otitis media or pneumonia carried vaccine-type pneumococci (**Figure 13**) (Muhlemann and Aebi 2008). Additionally, two Australian studies and a British study showed reductions in vaccine-type pneumococci following PCV7 introduction with 3+1PPV schedules,(Mackenzie, Carapetis et al. 2006; Mackenzie, Carapetis et al. 2006; Alexander, Telfer et al. 2008), while one Australian study with a 3+1PPV schedule did not show a reduction in vaccine-type during the first year after introduction (**Figure 13**).(Hare, Morris et al. 2006) Effects on vaccine-type carriage from a 3+1PPV schedule likely approximate the effects 3+0 schedules as PPV appears to have no effect on carriage.(Russell, Carapetis et al. 2010)

3. Invasive pneumococcal disease

Within study comparisons (n= 2 studies)
Of the two case-control studies that allow for *within-study* comparison of 2 primary doses (received at ≤7 months of age) with a booster and 3 primary doses (received ≤7 months of age) without a booster, both showed high vaccine effectiveness against vaccine-type IPD *when compared to no vaccine* (**Table 8**). No discernable difference between the schedules was seen in either study.

Between study comparisons (n=9 studies)
No clinical trials were identified in our search on the efficacy of a 2+1 schedule against IPD in children; however, two clinical trials in the Gambia and South Africa report data on the efficacy of PCV9 (Wyeth) using a 3+0 schedule (**Table 9**). Both of these studies demonstrate that the vaccine was efficacious against vaccine-type IPD among healthy children; the South African trial also demonstrated efficacy among HIV-infected children.

Seven observational surveillance/trend analysis studies evaluated the effect of 2+1 (n=5) and 3+0 (n=2) schedules on vaccine-type IPD in children ≤2 years of age (**Figure 14**). . Despite highly variable baseline incidence rates, all of these studies show a significant reduction in vaccine-type IPD after introduction of vaccine. Although impact can be seen early after introduction, the largest reduction can be seen in mature programs ≥3 years after vaccine introduction. The paucity of data on the impact of these schedules in young children, particularly ≥1 year after vaccine introduction, does not allow for a clear determination on which regimen is superior or inferior to the other.

4. Pneumonia

Within study comparisons (n= 0 studies)
There were no studies with a pneumonia endpoint that directly evaluated the timing of doses for a three dose series within a single study.

Between study comparisons (n = 10 studies)
There were five RCTs that evaluated a 3+0 schedule (Cutts, 2005; Madhi, 2005; Lucero, 2009; Richmond, 2008; Klugman, 2003). There was one clinical trial that evaluated a 2+1 study (Esposito, 2007). This study, conducted in Italy, showed impact of PCV use on pneumonia, however, the study was non- randomized with single blinding. There were three observational studies evaluating a 2+1 schedule (Ansaldi 2008; de Wals, 2008; Patrzalek, 2010) and one observational study evaluating a 3+0 schedule in a national immunization program (Jardine, 2010). All of these studies showed effectiveness of PCV against clinical and radiologically confirmed pneumonia after PCV introduction into the national immunization program (**Table 10**).

E. Indirect effects

1. Nasopharyngeal carriage

Within study comparisons (n= 0 studies)
No studies directly compared the indirect effects of a 2+1 schedule with a 3+0 schedule.

Between study comparisons (n= 4 studies)
One controlled trial examined the indirect effect of a 2+1 schedule,(van Gils, Veenhoven et al. 2008; Van Gils, Veenhoven et al. 2009) and one study examined indirect effects of a 3+0 schedule (**Table 11**).(Cheung, Zaman et al. 2009) The individually-randomized trial conducted in the Netherlands examined the indirect effects of a 2+1 schedule, given at 2, 4, and 11 months, on parents of vaccinated children at 1 and 13 months after the booster dose and on siblings of vaccinated children at 1 month after the booster dose. No significant indirect effects were seen among parents or siblings of children vaccinated with a 2+1 dosing schedule at any time when compared to unvaccinated controls.(van Gils, Veenhoven et al. 2008; Van Gils, Veenhoven et al. 2009). Additionally, the individually-randomized trial conducted in the Gambia examined the indirect effects of a 3+0 schedule given at 2.5, 4, and 5.6 months on younger unvaccinated siblings and found no significant indirect effects.(Cheung, Zaman et al. 2009) Finally, one observational study among Australian Aboriginal adults examined the effect of a 3+1PPV schedule, given at 2, 4, 6 and 18 months,(Mackenzie, Carapetis et al. 2006) which could be considered to approximate a 3+0 schedule as PPV appears to have no effect on carriage.(Russell, Carapetis et al. 2010)

Before vaccine introduction, 11.3% of Aboriginal adults carried vaccine-type pneumococcus, while after introduction 6.1% of adults had vaccine-type pneumococcus, although this difference was not statistically significant when the proportion of vaccine-type isolates among all pneumococcal isolates was compared before and after introduction.

2. Invasive pneumococcal disease

Within study comparisons (n= 0 studies)
We did not identify any within-study comparisons or randomized trials in the literature that demonstrate the impact of vaccine introduction on IPD among on groups not targeted to receive vaccine.

Between study comparisons (n= 5 studies)
Five observational studies included in this analysis document the impact of vaccine introduction on the incidence of vaccine-type IPD among young adults aged 5-50 years. Two of these studies occur in the setting of a 2+1 national program (Miller 2011 and Verstheim 2010) and three occur in the setting of a 3+0 schedule (Hanna 2006; Hanna 2008; Roche 2008; Lehmann 2010). All of these studies demonstrated a reduction in vaccine-type IPD among young adult groups, however the degree of impact varies by specific age group and the number of years post introduction (**Figures 15 and 16**). The paucity of data on both 2+1 and 3+0 vaccine schedules does not allow for a distinction to be made between these schedules on their relative indirect impact on invasive disease.

3. Pneumonia and Mortality

Within study comparisons (n= 0 studies)
There were no studies with a pneumonia endpoint that directly evaluated various dosing schedules on indirect populations.

Between study comparisons (n= 9 studies; n= 3 studies on adult mortality)
There were no RCTs that evaluated the impact of PCV on pneumonia in unvaccinated populations (i.e. indirect effect). However, there were a number of observational studies that evaluated the effectiveness of various dosing schedules on clinical and radiologically confirmed pneumonia as well as IPD mortality (**Table 12**). The studies utilizing 2+1 (Patrzalek, 2010) and 3+0 (Jardine, 2010) schedules showed no impact while some of the studies using a 3+1 schedule (Ardunuy, 2009; Lin, 2010; Grijalva, 2007; Nelson, 2008; Simonsen, 2011) showed some impact on pneumonia. There were three studies, all using a 3+1 schedule, that evaluated PCV impact on adult mortality (**Table 13**) (Pulido, 2010; Simonsen, 2011; Tsigrelis, 2008). All of these studies showed a reduction in mortality rates after implementation of PCV into the national childhood immunization program.

This analysis also found two case-control studies evaluating PCV impact on unvaccinated populations (**Table 14**). One study, conducted in South Africa, evaluated the impact of a 3+0 schedule on adults residing with children enrolled in an RCT for PCV9 (Albrich, 2007). This study found no impact against pneumonia in adults during a clinical trial. Another case-control study conducted in the US after implementation of PCV into the national immunization program showed an 80% reduction in odds of getting bacteremic pneumococcal pneumonia in adults that resided with a vaccinated child (Metlay, 2006).

IV. Discussion

A. Main findings

Immunogenicity:
A 3-dose primary series schedule tends to provide a greater antibody response compared to a 2-dose primary series schedule for most serotypes that were evaluated. By contrast, the

2+1 schedule post-booster response is consistently greater than the post-primary response following a 3-dose primary series. These trends remained after adjustment for covariates in our model which include age at first dose, geographic region, lab method for measuring ELISA antibody concentration, use of DtaP or DTwP, and vaccine product. Each of these has an independent effect on post-PCV antibody responses and were adjusted for when possible.

IPD
Direct effects: Both a 2+1 and the 3+0 schedule have demonstrated impact on vaccine-type IPD among children targeted to receive vaccine. The relative benefit of one schedule over the other is limited by the data paucity and by head to head studies. One study showed more breakthrough cases for serotype 6B with 2 primary doses as compared to 3 primary doses.

Indirect effects: No within-study comparisons of indirect impact of vaccine introduction regiments on young adult groups exist. Between-study comparisons show that both 2+1 and 3+0 schedules have some indirect effect on adults in this age group.

Pneumonia
Direct effects: Three primary doses are superior to two doses against hospitalizations for LRTI before a booster and in an observational study of an immature immunization program. There are no RCT data on two dose primary schedules for pneumonia outcome. There is evidence of efficacy against clinical and CXR pneumonia using three-dose primary schedules (3+0 and 3+1) in RCTs from general pediatric populations. There is evidence of impact on clinical and CXR pneumonia using 2+1 and 3+1 schedules in observational studies. There is only one observational study using a 3+0 schedule; findings show a decline in pneumonia hospitalizations after PCV7 introduction.

Indirect effects on pneumonia and mortality: One case- control study of pneumonia in adults showed a reduction in disease risk for adults exposed to vaccinated children in the household in a setting routinely using a 3+1 schedule, but no impact was seen for adults living with a vaccinated child in the setting of an RCT evaluating a 3+0 schedule. Studies to date have not shown any reduction of pneumonia in indirect (unvaccinated) populations in settings using 2+1 or 3+0 schedules in immunization programs. Use of a 3+1 schedule shows impact on pneumonia and IPD mortality in indirect populations.

Nasopharyngeal carriage
Direct: In head-to-head comparisons, 3 doses result in a slightly improved reduction in vaccine-type carriage compared with 2 doses in the few months following the primary series. However, 2 and 3 dose primary schedules appear to be equivalent in terms of reduction in vaccine-type carriage with longer times since vaccination. In between study comparisons, both 2-dose and 3-dose schedules reduced vaccine-type carriage, but differences between the schedules are difficult to discern.

There are no published direct comparisons of 2+1 and 3+0 schedules, however, one unpublished study (Dagan, Israel) has been conducted showing that point estimates for reduction in VT carriage compared to the no PCV arm is nearly equivalent for the 2+1 and 3+0 schedule. In controlled trials, both 2+1 and 3+0 schedules show reduction in vaccine-type carriage over controls, but differences between the schedules are difficult to discern.

There are no published observational studies evaluating the effect of introduction of a 3+0 schedule on carriage. Only one observational study examines a 2+1 schedule with limited post-introduction data, but shows a reduction in vaccine-type carriage among children less than 2 years. Observational data with 3+1PPV schedules, which in terms of nasopharyngeal carriage effects likely approximate 3+0 schedules, show reduction in vaccine-type carriage.

Indirect: Individually-randomized trials did not demonstrate indirect effects for either 2+1 or 3+0 schedules, but this study design would not be expected to demonstrate these effects. Indirect effects were suggested among Australian Aboriginal adults with a 3+1PPV schedule that may approximate a 3+0 schedule in terms of nasopharyngeal carriage, although this result did not meet statistical significance.

B. Strengths and limitations

Immunogenicity

There is a wealth of immunogenicity data on 2 vs. 3 primary doses and on 2+1 vs. 3+0 schedules beyond the more limited number of studies with intra-study schedule comparisons. The findings from the limited number of head-to-head comparisons are reviewed in detail by the University of Berne systematic review of PCV dosing schedules which focused on these head-to-head randomized controlled trials. In the immunogenicity domain our review included those head-to-head studies but then focused more so on studies without intra-study comparisons. There were 170 studies that report immunogenicity data and of these, 136 study arms contributed data to our analysis. Univariate descriptive analyses from our review of geometric mean concentrations reinforce the findings from the head-to-head analyses of RCTs that 3 primary doses provide improved immunogenicity compared with 2 primary doses for most serotypes. When the metric for assessment is the proportion of subjects with an antibody concentration above 0.35 mcg/mL (or 0.20 mcg/mL for those studies which used the GSK assay), the same trend is observed but with less differentiation between the 2-dose and 3-dose schedule. It is our assessment that the use of GMC rather than the proportion meeting the 0.35 mcg/mL threshold is a more finely differentiating metric of the various dosing schedules. Although the 0.35 mcg/mL threshold has been derived as the value that correlates with efficacy demonstrated in the four trials which contributed to the threshold analysis, we emphasize the GMC values for several reasons.

First, the population level effects are dependent on NP colonization. Prevention or reduction of pneumococcal transmission is arguably the most important public health outcome of pneumococcal vaccination. Current evidence supports the notion that PCV effects on NP pneumococcal colonization are not related primarily with the height of circulating serum antibody but instead are mediated by effector cells at the level of the mucosa, which in turn are likely more fully developed through a greater number of primary series doses.

Second, the prevention of pneumococcal pneumonia is the primary syndrome of concern for PCV programs given that this syndrome constitutes the large majority of pneumococcal deaths in young children globally. The GMC threshold for prevention of pneumococcal pneumonia is estimated to be significantly higher than 0.35 mcg/mL (unpublished data from O'Brien and Goldblatt). Furthermore, given the mucosal nature of pneumococcal pneumonia (as compared with IPD syndromes) it is not entirely clear whether circulating antibody or mucosal cells are the more important effector molecule for its prevention, although passive antibody studies (i.e. BPIG studies) would argue for a role of circulating pneumococcal serum antibody.

Because much of the data considered for the immunogenicity analysis was from between-study comparisons, controlling for potential confounders of immunogenicity is essential when drawing inferences of the differential effect of dosing schedules. It is important to be aware that, for some analyses, covariates such as co-administration of DTaP and DTwP or the timing of doses (e.g. 6, 10, and 14 weeks) could not be adjusted for in the models because these factors are region specific. Furthermore, when stratified by region, we could only compare studies using 2+1 and 3+0 schedules within the North America, Europe, and Australia region because there were no 2+1 schedule studies from Africa, South America, and Asia & Oceania among the included studies.

In summary then, the primary findings from the University of Berne meta-analysis of head-to-head 2+1 vs. 3+0 studies are supported by our analysis of this larger body of evidence. Specifically, our analyses illustrate improved immunogenicity for 3- compared with 2-doses for most serotypes when the geometric mean concentration is used as the metric for comparison. As expected, the 2+1 schedule leads to significantly higher antibody concentrations following the booster dose when compared with those among age-matched children who received a 3+0 schedule. The tradeoff therefore is between higher antibodies following the booster with a 2+1 schedule and a greater immune response from a primary schedule with 3 doses compared with 2 doses.

IPD

The IPD analysis shows us that both 3+0 and 2+1 schedules have an impact on vaccine serotype IPD in the target age group. Differentiating the relative magnitude of these effects is not possible except from very limited data because of the imperative to make cross setting comparisons. The within-study setting comparisons that can be made are from case-control studies that only compare the efficacy of a given schedule to no vaccine. There are no direct 3+0 vs. 2+1 comparisons. However the data from both case control studies and from observational surveillance data demonstrate clearly that both schedules are effective *in the settings where they have been used*. We emphasize this latter point because this does not necessarily imply that they will be equally effective in all settings. Notably, the settings where 2+1 regimens have been used and from which we have impact data are those that are low mortality and, from a global perspective, low pneumococcal diseaseIn addition, the 2+1 schedules have usually been implemented in conjunction with a catch-up schedule, which is likely to speed up the effects of the vaccination program. Furthermore, the only impact data on a 3+0 schedule comes from Australia which has similar attributes to the countries with 2+1 impact data and also used a catch-up program. There will be preliminary data from an IPD case control study in South Africa on a 2+1 schedule which can be compared to the efficacy trial data from the 3+0 schedule that was tested in the same study setting. There will also be IPD impact data on 3+0 schedules from a number of African countries including The Gambia and Kenya in the near future.

The strengths of this analysis are in the diversity of countries, diversity of study designs and the larger amount of data than is seen from the two head-to-head studies. Clearly there are very few pieces of data that directly compare 2+1 with 3+0 schedules or 2- vs. 3- primary doses. Considering the observational data that includes studies of single schedules is important. The single schedule data include surveillance data from countries where these schedules are in routine use and therefore inform the impact these schedules may have over the longer term when indirect effects are contributing to overall program benefits. Inclusion of observational surveillance studies from countries that have introduced vaccine allows for better understanding of whether differences between schedules exist in 'real-life' scenarios.

The IPD analysis presented here has limitations; these include confounding in the inter-study comparisons, little of which can be controlled because measures of the relevant potential confounders are not provided by the study sites. We were also not able to account for vaccine coverage in the analyses to address the contribution of indirect effects or calibrate the impact observed relative to the expected impact. Further limitations are those noted above which include no data on 2+1 regimens without a catch-up campaign, and no data on 2+1 impact in developing world settings except for preliminary data from South Africa (personal communication).

Pneumonia

This analysis found evidence of impact on both clinical and radiologically confirmed pneumonia in the targeted age group for vaccination using 2+1, 3+0 and 3+1 schedules. However, there was only one study that directly compared two different schedules within a study. The remaining studies made comparisons between one vaccine schedule versus no

vaccination. Despite this lack of within-study comparisons, there were still a number of randomized controlled trials that demonstrated efficacy against pneumonia. However, the vast majority of these RCTs were for three dose primary schedules. This analysis also found a large number of observational studies that showed impact of a schedule on pneumonia burden. These studies are important because they demonstrate the effectiveness of PCV in a routine immunization setting.

This analysis has a number of strengths. It includes all of the present literature on the impact of PCV on pneumonia and provides a broad landscape of the evidence for various dosing schedules. The analysis took into account all studies with within study dosing schedule comparisons as well as studies that evaluated a single dosing schedule. Furthermore, the studies included in this analysis represent a number of different settings and populations.

There are a few limitations to this analysis. Due to the heterogeneity between studies, and the lack of necessary data to control for potential confounders, we were unable to directly compare evidence across different studies. Furthermore, there was a paucity of data for studies that directly compared 2+1 to 3+0 schedules or 2 to 3 primary doses within a study. Our analysis also found no studies on 2+0 schedule and only a few studies that evaluated 2+1 or 3+0 schedules. Lastly, most of the studies in our analysis represent impact in low disease burden and higher income countries.

Nasopharyngeal carriage

Similar to IPD, the NP carriage analysis shows that both 3+0 and 2+1 schedules reduce carriage of vaccine-serotypes in the target age group. Differentiating the relative magnitude of these effects is not possible, as there are no direct 3+0 vs. 2+1 comparisons. However, both clinical trials and observational data show that 2+1 and 3+0 schedules are effective in the settings where they have been used. Data supporting a 2+1 schedule comes from Europe (Netherlands and Switzerland), whereas data supporting a 3+0 schedule comes from developing countries (Philippines, Fiji, The Gambia, and South Africa). Geographic region, socioeconomic level, and other factors affect carriage of pneumococci, and limit the generalizability of the studies and our ability to compare schedules across studies.

The strengths of this analysis are in the diversity of countries and the diversity of study designs. At this point, no head-to-head comparisons of 2+1 and 3+0 schedules exist for NP carriage and only two head-to-head studies that compare 2- and 3-dose primary regimens. This analysis allows for these evidence supporting each of these regimens to be considered.

The NP carriage analysis includes the following limitations: confounding in the inter-study comparisons, inability to account for vaccine coverage, and limited observational data. Inter-study comparisons have many potential confounders, little of which can be controlled for because the data from various studies are too heterogeneous to be combined into a meta-analysis. Additionally, we were unable account for vaccine coverage in the study target populations or the presence of a catch-up campaign, due to limited information in the citations.

Indirect Effects

Many factors contribute to the indirect impact of a vaccine schedule. This analysis was unable to fully address the wide variability in study settings that may contribute to the relative impact of a 2+1 or 3+0 schedule (e.g. vaccine coverage, proportion of the population under 5 years of age, HIV prevalence). Some of the studies presented here were small and/or were sub-studies of clinical trials and therefore may not accurately represent the herd immunity of vaccine introduction in a broad population. In addition, few data points exist for any outcome. Nevertheless, the strengths of this analysis are the diversity of settings and study designs included, both for high risk and non-high risk populations.

C. Implications for policy changes

This systematic review of all available evidence on PCV dosing schedules and response for immunogenicity, invasive pneumococcal disease, pneumonia, nasopharyngeal colonization and indirect effects reveals a number of conclusions that are policy relevant. We address these conclusions from the perspective of the existing WHO/SAGE recommendation for use of PCV in all countries. A 3-dose schedule is recommended based on efficacy trials and a large body of supportive evidence. Many industrialized countries have included a booster dose (i.e. 3+1) as this is the schedule used in the initial efficacy trials in developed world settings. The policy implications of this review, which aimed to reveal what is known or unknown about use of 2+1 as an alternate to the 3+0 schedule, are as follows:

- The available data have important limitations.
    - The large majority of the data available is on the comparisons and use of PCV7; very few (for some outcomes or some schedules, no data) data are available for the PCV10 and PCV13 products which include very important serotypes for developing world settings
    - The large majority of routine use impact data is available from developed world settings, most of which employed catch-up campaigns along with routine infant immunization; very little routine use impact data is yet available from developing world settings but there are studies ongoing which will soon be providing results
- All schedules (2+1, 3+0 and 3+1) show evidence of impact on immunogenicity, NP colonization, IPD and pneumonia
- There is significant immunogenicity data on the 3+0 and 2+1 schedules, including head-to-head data. Three, compared with two, primary doses results in improved antibody concentrations after the primary series for most serotypes. A booster dose provides higher antibody concentrations following that dose than a schedule without the booster.
- Knowledge of the relative benefit of the 3+0 or the 2+1 schedule for clinical outcomes is limited by data paucity of head to head studies and of impact studies of these regimens in epidemiologically relevant settings and for important serotypes. The limited data on 2+1 schedules is in the context of catch-up regimens and is almost entirely in developed world settings. There is an important need therefore for data on 2+1 disease impact in relevant epidemiologic settings, caution should be expressed about the lack of data on the impact of this schedule absent a catch-up regimen.
- For serotypes important in developing world settings (i.e. types 1, 5 in particular) there are little to no data on the relative choice between 2+1 and 3+0 regimens. Given the disease distribution of serotype 1 by age strata in the first 5 years of life (i.e. relative predominance in the second year of life and later), consideration of the benefit of a booster dose is important. However, there is a cost to this regimen, which is the potential risk of failing to deliver three doses to the child (in which case we are considering 2-dose vs. 3-dose regimens) and the risk of reduced immunogenicity in the first year of life while awaiting the booster dose.
- The relative benefit on disease and mortality prevention of either strategy must be weighed relative to pneumococcal disease epidemiology by age strata, serotype specific burden by age, operational issues (i.e. likelihood of timely vaccination and success of coverage) and vaccine introduction plans (catch-up or no catch-up)

Policy relevant research is needed to further optimize the use of PCV in various epidemiologic settings, particularly high disease burden settings where the impact of vaccine on NP colonization might be most important for overall success of the PCV program.

Table 1. Detailed search strategy utilized in the Dosing Landscape analysis literature search.

Search terms	
Pneumococcal Terms: 1. Pathogen terms "Streptococcus pneumoniae"[mesh] ("Diplococcus"[all fields] AND "pneumoniae"[all fields]) ("micrococcus"[all fields] AND "pneumoniae"[all fields]) "Pneumococcus"[all fields] "pneumococcal"[all fields] "s. pneumoniae"[all fields] "pneumococci"[all fields] Pneumococc*[all fields] "Streptococcus" [mesh] "Streptococcal"[mesh] 2. Outcome-related terms "Pneumonia, Pneumococcal"[mesh] "Meningitis, Pneumococcal"[mesh] "Meningitis, Streptococcal"[mesh] "Pneumococcal Infections"[mesh] "Streptococcal Infections"[mesh] "Otitis Media"[mesh] ("lobar"[all fields] AND "pneumonia"[all fields]) ("Nasopharyngeal"[all fields] AND "carriage"[all fields]) ("Nasopharyngeal"[all fields]AND "colonization"[all fields]) (" nasopharyngeal"[all fields] AND "colonisation"[all fields]) ("Community acquired"[all fields] AND "pneumonia"[all fields]) ("community acquired"[all fields] AND "pneumonias"[all fields]) ("Bacteraemic"[all fields] AND "pneumonia"[all fields]) ("bacteraemic"[all fields] AND "pneumonias"[all fields]) ("Bacteremic"[all fields] AND "pneumonia"[all fields]) ("bacteremic"[all fields] AND "pneumonias"[all fields]) "Anti-pneumococcal"[all fields] "antipneumococcal"[all fields] ("lower respiratory tract infection"[all fields]) ("lower respiratory tract infections"[all fields]) ("Invasive disease" [all fields]) ("invasive pneumococcal disease" [all fields])	**Narrow Vaccine Terms:** "Vaccines, conjugate"[mesh] "Pneumococcal Vaccines"[mesh] "streptococcal vaccines"[mesh] (("conjugate" OR "conjugated" OR "pneumococcal"[all fields] OR "streptococcal"[all fields]) AND ("vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab] OR "vaccinated"[tiab] OR "immunization"[tiab] OR "immunisation"[tiab] OR "immunized"[tiab] OR "immunised"[tiab])) (("Pneumococcal"[all fields] OR "pneumococcus"[all fields] OR "capsular"[all fields]) AND ("polysaccharide"[all fields]) AND ("vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab] OR "vaccinated"[tiab] OR "immunization"[tiab] OR "immunisation"[tiab] OR "immunized"[tiab] OR "immunised"[tiab])) "PncCRM197"[all fields] "PCV"[all fields] "Pneumovax"[all fields] "Pnu-Imune" [all fields] "Pnu Imune"[all fields] "PnuImune"[all fields] "pneu immune"[all fields] "pnu immune"[all fields] "pneumo 23"[all fields] "pneumopur"[all fields] "streptopur"[all fields] "streptorix"[all fields] "PncOMPC vaccine" [Substance Name] "PncOMPC"[all fields] ("Pneumococcal"[all fields] AND "polysaccharide"[all fields] AND "meningococcal"[all fields] AND "outer"[all fields] AND "membrane"[all fields] AND "protein"[all fields] AND "complex"[all fields]) "five-valent pneumococcal conjugate vaccine" [Substance Name]

(“invasive bacterial disease” [all fields]) (“Bacterial pneumonia”[all fields]) (“Bacterial pneumonias”[all fields]) (“Otitis Media”[all fields]) (“inner ear infection”[all fields]) (“inner ear infections”[all fields])	“five-valent”[all fields] “5-valent”[all fields] “PCV5”[all fields] “PCV-5”[all fields] “heptavalent pneumococcal conjugate vaccine” [Substance Name] “heptavalent”[all fields] “PNCRM7”[all fields] “PNCRM-7”[all fields] “PCV7”[all fields] “PCV-7”[all fields] “seven-valent”[all fields] ” 7-valent”[all fields] “Prevenar”[all fields] “Prevnar”[all fields] “10-valent pneumococcal vaccine” [Substance Name] “Ten-valent”[all fields] “10-valent”[all fields] “PCV10”[all fields] “PCV-10”[all fields] “13-valent pneumococcal vaccine” [Substance Name] “Thirteen-valent”[all fields] “13-valent”[all fields] “PCV13”[all fields] “PCV-13”[all fields] “nine-valent”[all fields] “9-valent”[all fields] “PCV9”[all fields] “PCV-9”[all fields] “two-valent”[all fields] “2-valent”[all fields] “PCV2”[all fields] “PCV-2”[all fields] “three-valent”[all fields] “3-valent”[all fields] “PCV3”[all fields] “PCV-3”[all fields] “four-valent”[all fields] “4-valent”[all fields] “PCV4”[all fields] “PCV-4”[all fields] “six-valent”[all fields] “6-valent”[all fields] “PCV6”[all fields] “PCV-6”[all fields] “7vPnC”[all fields] “7vCRM”[all fields] “PHiD-CV”[all fields] ((“23-valent”[all fields] “23vPPV”[all fields] “PPV23”[all fields] “PPSV23”[all fields] “23-valent pneumococcal capsular

	polysaccharide vaccine"[substance name] "pneumococcal surface protein" [all fields] "pneumococcal surface proteins"[all fields] "pneumococcal protein"[all fields] "pneumococcal proteins"[all fields] "streptococcal surface protein"[all fields] "streptococcal surface proteins"[all fields] "streptococcal protein"[all fields] "streptococcal proteins"[all fields]
Additional search elements: Additional controlled vocabulary used in EMBASE (pathogen/outcome terms): • 'streptococcus pneumonia'[EMTREE term] • 'lower respiratory tract infection' [EMTREE term] • 'bacterial pneumonia' [EMTREE term] • 'lobar pneumonia' [EMTREE term] • 'community acquired pneumonia' [EMTREE term] Additional controlled vocabulary in EMBASE (vaccine terms): • 'Pneumococcus vaccine' [EMTREE term] • 'Streptococcus vaccine' [EMTREE term] • 'Pneumococcus polysaccharide' [EMTREE term] Adjacency Searching (near 5) used in: EMBASE Global Health Biological Abstracts Biological Abstracts/RRM Pascal BioMed Cochrane Library Animal Limits used in: PubMed EMBASE Biological Abstracts Biological Abstracts/RRM Other limits: English language Date: 1994 - current Not needed – pneumococcal/streptococcal finds that did not yield additional material: *Pneumococcal Pneumonia* *Pneumococcal Pneumonias*	

Pneumococcal Meningitis *Pneumococcal Infection* *Pneumococcal Infections* *Pneumococcal mortality* *Pneumococcal mortalities* *Streptococcal infection* *Streptococcal infections*	

Table 2. Descriptive summary of primary studies included in the PCV dosing landscape analysis, by outcome of interest

	Number of primary studies			
Variable	**Immunogenicity N=170**	**Carriage N=26**	**IPD N=48**	**Pneumonia N= 45**
Study Publication date				
1994-1998	26 (15%)	2 (8%)	0	1 (2%)
1999-2002	31 (18%)	3 (12%)	3 (6%)	2 (5%)
2003-2006	40 (24%)	6 (23%)	16 (33%)	13 (30%)
2007-present	73 (43%)	15 (58%)	29 (61%)	29 (65%)
Dosing Schedule				
2+0	21 (14%)	4 (15%)	0	0
2+1	20 (13%)	2 (8%)	7 (15%)	6 (13%)
3+0	52 (34%)	12 (46%)	7 (15%)	8 (18%)
3+1	58 (38%)	16 (62%)	34 (70%)	34 (76%)
U.N. Region [α]				
Africa	12 (7%)	5 (19%)	2 (4%)	4 (9%)
Asia	27 (15%)	3 (12%)	1 (2%)	1 (2%)
Oceania	7 (4%)	3 (12%)	5 (11%)	6 (14%)
Europe	75 (43%)	9 (35%)	15 (31%)	10 (23%)
Latin America/Caribbean	9 (5%)	0 (0%)	0	0 (0%)
North America	45 (26%)	6 (23%)	25 (52%)	23 (52%)

Table 3. Case-control studies reporting vaccine effectiveness (VE) against vaccine-type IPD among children using 2 or 3 doses compared to no vaccine.

Country	Citation	Study design	PCV product	Sample size (case: control)	Population	Dose	VE* (95% CI)
Canada	Deceuninck (PIDJ 2010)	Active lab surveillance, Community controls	PCV7	180:897	2-59m	2+0	99% (90-100)
						3+0	90% (24-100)
USA	Whitney (Lancet 2006)	Active lab surveillance, Community controls	PCV7	782:2512	3-36m healthy	2+0	96% (88-99)
						3+0	95% (88-98)

* Adjusted

Table 4. Indirect cohort studies reporting PCV effectiveness (VE) against vaccine-type IPD among children using 2 or 3 doses compared to no vaccine.

Country	Citation	PCV product	NIP Schedule	Sample size	Population	Dose	VE (95% CI)
USA	De Serres (ISPPD6 2008)	PCV7	3+1 (2m, 4m, 6m, 12-15m)	400	3-59 month old, no high risk	2+0	96% (93-98)
						3+0	98% (95-99)
USA	Mahon (Vaccine 2005)	PCV7	3+1 (2m, 4m, 6m, 12-15m)	553	<5 years old	2+0	70.5%* (28.0, 87.9)
						3+0	76.6%* (50.4, 88.9)
Germany	Ruckinger (Vaccine 2010)	PCV7	3+1 (2m, 3m, 4m, 11-14m)	102	3-59 month old	2+0	89.8% (20.6-100.0)
						3+0	94.6% (69.7-99.5)

* Adjusted

Table 5. Observational data demonstrating vaccine-type IPD breakthrough cases caused by serotype 6B. (Park 2010)

Serotype	Number of cases (%) by number of doses				Total N (%)
	1	2	3	4	
Total VT	**69 (45%)**	**37 (24%)**	**41 (26%)**	**8 (5%)**	**155**
4	1	0	5	1	7 (5%)
6B	23	19	8	0	50 (32%)
9V	2	2	3	2	9 (6%)
14	10	2	1	1	14 (9%)
18C	6	2	3	0	11 (7%)
19F	15	9	18	3	45 (29%)
23F	12	3	4	1	19 (12%)
NonVT	114 (19%)	149 (25%)	241 (40%)	94 (16%)	598

Table 6. Summary of characteristics for PCV clinical trials with a pneumonia outcome, by dosing schedule

Country	Reference	Study Design	Dosing schedule for PCV (product)	Total Participants	Population	Endpoint and Case Definition	Vaccine Efficacy (95% CI)	
							Intent to Treat	Per Protocol
2+1 schedules								
Italy	Esposito, S (Resp Res 2007)	Non-randomized, single-blind	3, 5, 11m (PCV7 Wyeth)	1,555	Children(75-105 d) Followed to 29 months of age	CXR pneumonia (non- WHO Clinical reading)	65% (47% to 78%)	—
3+0 schedules								
Papua New Guinea	Richmond, P (ISPPD 2008)	Randomized, non-blind	0, 1, 2m 1, 2, 3m (PCV7 Wyeth)	Not stated	Neonates Infants Followed to 18 months of age	Clinical pneumonia (syndromic diagnosis)	18% (4% to 31%)*	—
Philippines	Lucero, M (PIDJ 2009)	Randomized, double-blind	6, 10, 14w (PCV11 Sanofi)	12,191	Children (<2 y) Followed to 24 months of age	Clinical pneumonia (WHO IMCI), CXR pneumonia (WHO reading)	Clinical:-0.8% (-9.6% to 7.4%) CXR: 16% (-7.3%to 34.2%)	Clinical: 0.1% (-9.4% to 8.7%) CXR: 22.9% (-1.1 to 41.2%)
South Africa	Klugman, K (NEJM 2003)	Randomized, double-blind	6, 10, 14w (PCV9 Wyeth)	39,836	HIV- and HIV+ Children (<2 y)	CXR pneumonia (WHO reading)	HIV-: 20% (2% to 35%) HIV+: 13% (-7% to 29%)	—
South Africa	Madhi, S (CID 2005)	Randomized, double-blind	6, 10, 14w (PCV9 Wyeth)	39,836	HIV- and HIV+ Children (<2 y)	Clinical pneumonia (WHO IMCI)	HIV-: 17% (7% to 26%) HIV+: 15% (5% to 24%)	HIV-: 23% (11% to 33%) HIV+: 14% (-4% to 28%)
The Gambia	Cutts, F (Lancet 2005)	Randomized, double-blind	11, 15, 24w (PCV9 Wyeth)	16,340	Children (6-51 w) Followed for 2 years	Clinical pneumonia (WHO IMCI), CXR pneumonia (WHO reading)	Clinical: 6% (1% to 11%) CXR: 35% (26% to 43%)	Clinical: 7% (1% to 12%) CXR: 37% (27% to 45%)
3+1 schedules								
USA	Black (PIDJ 2002)	Randomized, double-blind	2, 4, 6, 12-15m (PCV7 Wyeth)	37,868	Children (<3 y)	Clinical pneumonia (study defined)	6.0% (-1.5% to 11.0%)	4.3% (-3.5% to 11.5%)
USA	Hansen, J (PIDJ 2006)	Randomized, double-blind	2, 4, 6, 12-15m (PCV7 Wyeth)	37,868	Children (<3 y)	CXR pneumonia (WHO reading)	25.5% (6.5% to 40.7%)	30.3% (10.7% to 45.7%)
USA	O' Brien, K (ISPPD 3)	Randomized	2, 4, 6, 12-15m (PCV7 Wyeth)	8,292	Native American children	CXR pneumonia (non- WHO Clinical reading)	-21.2% (-61.5% to 9%)	—
Germany	Adam, D (Vaccine 2008)	Non-randomized, non-blind	2, 4, 6, 12-15m (PCV7 Wyeth)	5,984	Children (2-6m) Followed until 1 year after booster	Clinical pneumonia (syndromic diagnosis)	6.3% (-15.9% to 23.7%)	—

* VE= 1-IRR

Table 7. Direct Effects Clinical Trials, Nasopharyngeal Carriage

Country	Primary author	PCV product	Schedule	Age at doses	Mean / median age at swab	Risk group	Number swabbed PCV group	Number swabbed control group	Percent carriage of VT carriage among study population for PCV group	Percent carriage of VT carriage among study population for control group	Vaccine efficacy for vaccine type carriage (95% CI)
Czech Republic	Prymula, R(Prymula, Kriz et al. 2009)	PCV11GSK	3 + 1	13w, 17w, 22w, 12m	6	General Population			7.0	8.0	-12.5%
					12	General Population			11.0	11.5	-4.3%
					13	General Population			12.0	14.0	-14.3%
					15	General Population	177	175	6.2	10.9	-42.8% (-71.9 – 16.7%)
					19	General Population			9.5	12.5	-24.0%
					24	General Population			9.5	13.0	-26.9%
Fiji	Russell, F(Russell, Carapetis et al. 2010)	PCV7Wyeth	2 + 0	6w, 14w	6	General Population	148	127	10.8	12.6	-14.2%
					9	General Population	146	126	10.3	15.9	-35.3%
					12	General Population	143	125	6.3	16.0	-60.7%
					17	General Population	68	63	5.0	18.0	-72.2%
		PCV7Wyeth	2+1PPV	6w, 14w, 12m	17	General Population	67	63	4.0	18.0	-77.8%
		PCV7Wyeth	3 + 0	6w, 10w, 14w	6	General Population	127	127	10.2	12.6	-39.0% (-74.0 – 42.0%)

Country	Primary author	PCV product	Schedule	Age at doses	Mean / median age at swab	Risk group	Number swabbed PCV group	Number swabbed control group	Percent carriage of VT carriage among study population for PCV group	Percent carriage of VT carriage among study population for control group	Vaccine efficacy for vaccine type carriage (95% CI)
					9	General Population	122	126	3.3	15.9	-82.0% (-94.0 – -46.0%)
					12	General Population	114	125	7.0	16.0	-64.0% (-85.0 – -13.0%)
					17	General Population	60	63	2.5	18.0	-86.1%
		PCV7Wyeth	3+1PPV	6w, 10w, 14w,12 m	17	General Population	49	63	5.0	18.0	-72.2%
		PCV7Wyeth	1+0	14w	6	General Population	122	127	11.5	12.6	-8.9%
					9	General Population	118	126	6.8	15.9	-57.3%
					12	General Population	115	125	8.7	16.0	-45.7%
					17	General Population	49	63	10.0	18.0	-44.4%
		PCV7Wyeth	1+1PPV	14w, 12m	17	General Population	59	63	9.0	18.0	-50.0%
		PPV only	0+1PPV	12m	17	General Population	57	63	12.5	18.0	-30.6%
Finland	Palmu, A(Palmu, Verho et al. 2002)	PCV7Wyeth	3 + 1	2m, 4m, 6m, 12m	54	General Population	401	353	8.5	13.6	-38.0% (-59.0 – -5.0%)

Country	Primary author	PCV product	Schedule	Age at doses	Mean / median age at swab	Risk group	Number swabbed PCV group	Number swabbed control group	Percent carriage of VT carriage among study population for PCV group	Percent carriage of VT carriage among study population for control group	Vaccine efficacy for vaccine type carriage (95% CI)
Israel	Dagan, R(Dagan, Muallem et al. 1997)	PCV4Sanofi-tetanus toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	2	General Population			9.0	4.0	125.0%
		PCV4Sanofi-diptheria toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	2	General Population			6.0	4.0	50.0%
		PCV4Sanofi-tetanus toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	4	General Population			4.0	9.0	-55.6%
		PCV4Sanofi-diptheria toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	4	General Population			5.0	9.0	-44.4%
		PCV4Sanofi-tetanus toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	6	General Population			9.0	18.0	-50.0%
		PCV4Sanofi-diptheria toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	6	General Population			16.0	18.0	-11.1%
		PCV4Sanofi-tetanus toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	7	General Population			4.3	21.7	-80.0%
		PCV4Sanofi-diptheria toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	7	General Population			9.1	21.7	-58.2%

Country	Primary author	PCV product	Schedule	Age at doses	Mean / median age at swab	Risk group	Number swabbed PCV group	Number swabbed control group	Percent carriage of VT carriage among study population for PCV group	Percent carriage of VT carriage among study population for control group	Vaccine efficacy for vaccine type carriage (95% CI)
		PCV4Sanofi-tetanus toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	12	General Population			12.0	30.4	-60.6%
		PCV4Sanofi-diptheria toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	12	General Population			4.8	30.4	-84.4%
		PCV4Sanofi-tetanus toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	13	General Population			12.5	29.2	-57.1%
		PCV4Sanofi-diptheria toxoid	3+1PPV	2.1m, 3.9m, 6m, 12.2m	13	General Population			0.0	29.2	-100.0%
Israel	Dagan, R(Dagan, Zamir et al. 2000)	PCV11Sanofi	3 + 1	2m, 4m, 6m, 12m	18	General Population	141	57	15.6	31.6	-50.6%
Netherlands	Van Gils, E(Van Gils, Veenhoven et al. 2009)	PCV7Wyeth	2 + 0	2m, 4m	12	General Population	333	319	24.6	38.2	-36.0% (-49.0 – -19.0%)
					18	General Population	327	317	24.2	37.5	-36.0% (-49.0 – -18.0%)
					24	General Population	332	321	14.8	35.5	-58.0% (-69.0 – -44.0%)
		PCV7Wyeth	2 + 1	2m, 4m, 11m	12	General Population	335	319	20.0	38.2	-48.0%
					18	General Population	329	317	15.5	37.5	-59.0% (-69.0 – -45.0%)

Country	Primary author	PCV product	Schedule	Age at doses	Mean / median age at swab	Risk group	Number swabbed PCV group	Number swabbed control group	Percent carriage of VT carriage among study population for PCV group	Percent carriage of VT carriage among study population for control group	Vaccine efficacy for vaccine type carriage (95% CI)
					24	General Population	333	321	14.1	35.5	-60.0% (-71.0 – -46.0%)
Philippines	Nohynek, H(Nohynek, Makela et al. 2008)	PCV11Sanofi	3 + 0	6w, 10w, 14w	24	General Population					-35.0% (-8.0 – -54.0%)
South Africa	Mbelle, N(Mbelle, Huebner et al. 1999)	PCV9Wyeth	3 + 0	45d, 76d, 106d	9	General Population	242	239	17.8	36.4	-51.2%
South Africa	Madhi, S.(Madhi, Adrian et al. 2007)	PCV9Wyeth	3 + 0	6w, 10w, 14w	67.2	General Population	121	150	13.2	19.3	-31.6%
						HIV-infected	32	49	50.0	40.8	22.5%
The Gambia	Cheung, YB(Cheung, Zaman et al. 2009)	PCV9Wyeth	3 + 0	2.5m, 4m, 5.6m	12	General Population	1078	1061	22.6	40.0	-44.0% (-51.0 – -35.0%)
					22	General Population	967	961	24.9	41.2	-39.0% (-47.0 – -31.0%)
The Gambia	Obaro, S(Obaro, Adegbola et al. 1996)	PCV5Wyeth	2+1PPV	2m, 3m, 18m	24	General Population	30	160	66.7	90.0	-78.0% (-92.0 – -39.0%)
		PCV5Wyeth	3+1PPV	2m, 3m, 4m, 18m	24	General Population	26	160	50.0	90.0	-89.0% (-96.0 – -69.0%)
The Gambia	Obaro, S.(Obaro, Adegbola et al. 2000)	PCV9Wyeth	3 + 0	2m, 3m, 4m	5	General Population	100	102	54.0	62.7	-13.9%
					9	General Population	98	99	62.2	74.7	-16.7%

Country	Primary author	PCV product	Schedule	Age at doses	Mean / median age at swab	Risk group	Number swabbed PCV group	Number swabbed control group	Percent carriage of VT carriage among study population for PCV group	Percent carriage of VT carriage among study population for control group	Vaccine efficacy for vaccine type carriage (95% CI)
The Gambia	Ota, M(Ota, Akinsola et al. 2011)	PCV7Wyeth	2+1PPV	2m, 3m, 10m	5	General Population	218		18.3		
					11	General Population	198		16.7		
					15	General Population	196		15.3		
		PCV7Wyeth	3+1PPV	2m, 3m, 4m, 10m	5	General Population	215		13.5		
					11	General Population	200		10.0		
					15	General Population	194		12.4		
		PCV7Wyeth	1+1PPV	2m, 10m	5	General Population	217		19.8		
					11	General Population	203		20.2		
					15	General Population	205		18.5		
UK	Lakshman, R(Lakshman, Murdoch et al. 2003)	PCV7Wyeth	3+1PPV	2m, 3m, 4m, 13m	35	General Population	150	126	10.0	13.5	-25.9%
					40	General Population	143	188	30.0	31.5	-4.8%
USA	Yeh, S(Yeh, Zangwill et al. 2003)	PCV7Merck	3 + 1	2m, 4m, 6m, 12m	2	General Population	49	32	2.0	6.3	-67.3%
					6	General Population	47	29	17.0	10.3	64.5%

Country	Primary author	PCV product	Schedule	Age at doses	Mean / median age at swab	Risk group	Number swabbed PCV group	Number swabbed control group	Percent carriage of VT carriage among study population for PCV group	Percent carriage of VT carriage among study population for control group	Vaccine efficacy for vaccine type carriage (95% CI)
					7	General Population	46	28	10.9	7.1	52.2%
					12	General Population	41	28	17.1	17.9	-4.4%
					13	General Population	39	28	10.3	21.4	-52.1%
USA	Millar, E(Millar, P'Brien et al. 2006)	PCV7Wyeth	3 + 1	2.1m, 4.6m, 6.9m, 12.5m	40.8	Indigenous	468	281	10.3	17.1	-45.0% (-64.0 – -15.0%)
USA	O'Brien, K(O'Brien, Millar et al. 2007)	PCV7Wyeth	3 + 1	2m, 4m, 6m, 13.5m	7	Indigenous	227	226	14.1	27.9	-60.0% (-77.0 – -33.0%)
					12	Indigenous	226	208	10.6	25.0	-49.0% (-66.0 – -22.0%)
					18	Indigenous	239	219	15.5	24.7	-19.0% (-49.0 – 31.0%)

Table 8. Case-control studies reporting PCV effectiveness (VE) against vaccine-type IPD among children using 2+1 or 3+0 doses compared to no vaccine.

Country	Citation	Study Design	PCV Product	Sample Size (case: control)	Population	Dose	VE*(95 % CI)
Canada	Deceuninck (PIDJ 2010)	Active lab surveillance, Community controls	PCV7	180:897	2-59m	2+1	100% (15-100)
						3+0	90% (24-100)
USA	Whitney (Lancet 2006)	Active lab surveillance, Community controls	PCV7	782:2512	3-36m healthy	2+1	98% (75-100)
						3+0	95% (88-98)

* Adjusted

Table 9. Randomized controlled trials reporting PCV efficacy (VE) against vaccine-type IPD among children using a 3+0 dosing regimen.

Country	Citation	Study Design	Schedule and Product	Sample Size	Population	VE (95% CI) ITT
Gambia	Cutts (Lancet 2005)	Randomized, double-blind	11, 15, 24w (PCV9, Wyeth)	17,437	Healthy children ages 6-51 weeks	71% (46-86)
South Africa	Klugman (NEJM 2003)	Randomized, double-blind	6, 10, 14w (PCV9, Wyeth)	39,836	HIV-infected	65% (24-86)
					HIV-uninfected	83% (39-97)

Table 10. Summary of characteristics for PCV observational studies with a pneumonia outcome (direct effects) in children <5 years, by dosing schedule

Country	Reference	Study design	Dosing Schedule for PCV7 (Wyeth)*	Age groups	Endpoints evaluated	Findings	Change in pneumonia Rates
2+1 schedules							
Canada	De Wals, P (PIDJ 2008)	Passive, sentinel surveillance	2, 4, 12 m	Children <5 years	Clinical pneumonia, CXR- pneumonia, Empyema	Significant decrease in hospitalizations for clinical and CXR pneumonia after implementation of PCV	↓
Italy	Ansaldi, F J Int Med Res 2008)	Sentinel surveillance	3, 5, 11-12 m	Children <5 years	Clinical pneumonia	Significant reductions in clinical and pneumococcal pneumonia rates after PCV introduction	↓
Poland	Patrzalek, M (Eur J Clin Microbiol Infect Dis 2010)	Sentinel surveillance	3, 5, 12m	Children <5 years (<1, 2-4 years)	CXR-pneumonia, All-cause hospitalizations	Significant decrease in pneumonia hospitalizations among <1 year (65% reduction) and 2-4 years (23% reduction)	↓
3+0 schedules							
Australia	Jardine, A (PIDJ 2010)	Population-based surveillance	2, 4, 6 m	Children <5 years (<2, 2-4 years)	Clinical pneumonia	Significant reductions in pneumonia rates in children <2 years (38% reduction) and children 2-4 years (29% reduction)	↓
3+1 schedules							
USA	Nelson, J (Vaccine 2008)	Cohort study	2, 4, 6, 12-15 m	Children <5 years	Clinical pneumonia, CXR pneumonia	No significant reductions in pneumonia hospitalization rates in children <5 years	←
USA	Simonsen, L (Mbio 2011)	Population-based surveillance	2, 4, 6, 12-15 m	Children <5 years	All- cause pneumonia, pneumococcal pneumonia	Found significant reductions in hospitalizations for all- cause pneumonia in children <2 years	↓
USA	Grijalva, C (Lancet 2007)	Passive, population-based surveillance	2, 4, 6, 12-15 m	Children <2 years	Clinical pneumonia, Other	Significant reductions in all-cause pneumonia in children <2 years after PCV introduction (39% reduction)	↓
USA	Zhou, F (Am Journal Epid 2006)	Cohort study	2, 4, 6, 12-15 m	Children <2 years	Clinical pneumonia	Significant reductions in all- cause pneumonia in children <2 years (52.4% reduction)	↓

Table 11. Indirect Effect Outcome from PCV Clinical Trials, Nasopharyngeal Carriage

		Vaccinees							
Country	Primary author	PCV product	Schedule	Age at doses	Age of vaccinee at time of study swab	Mean/median age at swab in months	Percent carriage of VT carriage among study population for PCV group	Percent carriage of VT carriage among study population for control group	Vaccine efficacy for vaccine type carriage (95% CI)
The Gambia	Cheung, YB(Cheung, Zaman et al. 2009)	PCV9Wyeth	3 + 0	2.5m, 4m, 5.6m (75d, 122d, 169d)	9-15 m	3 months	35.2	37.1	-5.0% (-22.0 – 16.0%)
Netherlands	Van Gils, E(Van Gils, Veenhoven et al. 2009)	PCV7Wyeth	2 + 0	2m, 4m	12m	Adults	8.2	9.5	-14.0% (-48.0 – 42.0%)
			2 + 1	2m, 4m, 11m,	12m	Adults	8.8	9.5	-7.0% (-43.0 – 52.0%)
			2 + 0	2m, 4m	24m	Adults	5.2	8.4	-39.0% (-67.0 – 12.0%)
			2 + 1	2m, 4m, 11m,	24m	Adults	5.6	8.4	-34.0% (-63.0 – 19.0%)
Netherlands	Van Gils, E(van Gils, Veenhoven et al. 2008)	PCV7Wyeth	2 + 0	2m, 4m	12m	36 months	24.0	29.0	
			2 + 1	2m, 4m, 11m	12m	36 months	25.0	29.0	
USA	O'Brien, K(O'Brien, Millar et al. 2007)	PCV7Wyeth	3 + 1	2m, 4m, 6m, 13.5m	Vaccinations 4/97-10/00	1.8 months	10.7	13.6	-52.0% (-67.0 – 5.0%)
					7m	47 months*	29.1	30.4	-6.0% (-34.0 – 34.0%)
					12m	51.5 months*	30.0	28.2	63.0% (-15.0 – 214.0%)
					18m	53.5 months*	26.6	31.8	6.0% (-16.0 – 34.0%)
USA	Millar, E(Millar, Watt et al. 2008)	PCV7Wyeth	3 + 1	2m, 4m, 6m, 13.5m	3.3 years (1-7)	Adults*	2.4	4.1	-43.0% (-67.0 – -1.0%)
					3.3 years (1-7)	5 – 17 years*	7.5	8.0	-16.0% (-44.0 – 29.0%)
					3.3 years (1-7)	≤5 years*	12.0	19.2	-43.0% (-74.0 – -2.0%)

***Indigenous populations**

Table 12. Summary of characteristics for PCV observational studies with a pneumonia outcome (indirect effects), by dosing schedule

Country	Reference	Study design	Dosing schedule for PCV7 (Wyeth)*	Endpoints evaluated	Indirect groups evaluated	Detailed findings for clinical pneumonia	Change in clinical pneumonia rates
2+1 schedules							
Poland	Patrzalek, M (Eur J Clin Microbiol Infect Dis 2010)	Sentinel surveillance	3, 5, 12m	CXR-pneumonia, All-cause hospitalizations	30-49 years 50-64 years ≥65 years	No evidence that PCV7 intro decreased incidence in age groups >4 years; risk of pneumonia in unvaccinated remained unchanged	←
3+0 schedules							
Australia	Jardine, A (PIDJ 2010)	Population-based surveillance	2, 4, 6 m	Clinical pneumonia, pneumococcal pneumonia	5-17 years 18-39 years 40-64 years	3-11% reduction (borderline significant) observed in age groups >4 years	↙
3+1 schedules							
Spain	Ardunuy, C (CID 2009)	Sentinel surveillance	2, 4, 6, 12-15 m	Pneumococcal pneumonia	Adults	39% overall increase (significant); due to 27% reduction in PCV7 types and 81% increase in non-PCV7 types	↑
Taiwan	Lin, S (J Am Geriatr Soc 2010)	Passive, sentinel surveillance	Unknown	Clinical pneumonia, All-cause mortality	5-64 years ≥65 years	No significant reduction in 5-64 years; significant reduction in 65+ (64.1%) but greater use of PPV23 in 65+	↙
USA	Grijalva, C (Lancet 2007)	Sentinel surveillance	2, 4, 6, 12-15 m	Clinical pneumonia, pneumococcal pneumonia, empyema	18-39 years	26% reduction in clinical pneumonia in 18-39 years, rates seemed to decline in other older groups but not significant; 30% reduction in pneumococcal pneumonia	↓
USA	Nelson, J (Vaccine 2008)	Cohort study	2, 4, 6, 12-15 m	Clinical pneumonia, CXR pneumonia	18-49 years living with children	No reductions seen; >18 years had increased rates after PCV intro	←

USA	Simonsen, L (Mbio 2011)	Population-based surveillance	2, 4, 6, 12-15 m	All- cause pneumonia, pneumococcal pneumonia	5-17 years 18-39 years 40-64 years ≥65 years	Significant reductions in all-cause pneumonia hospitalizations (5-17 and 18-39 years); 90-95% modeled reductions in pneumococcal pneumonia due to >18 years	↓

Table 13. Summary of characteristics for PCV obsevational studies with an IPD mortality outcome (indirect effects), by dosing schedule

Country	Reference	Study design	Vaccine product	Dosing schedule	Age groups evaluated	Mortality endpoints evaluated	Detailed findings IPD mortality	Change in mortality rates
USA	Pulido, M (Vaccine 2010)	Population-based database	PCV7	3+1 (2, 4, 6, 12-15m)	5-14, 15-24, 25-34, 45-54, 55-64, 65-74, 75-84, ≥85years	IPD mortality	Decrease in IPD mortality across most age groups after PCV7 introduction	↓
USA	Simonsen, L (Mbio 2011)	Population-based database	PCV7	3+1 (2, 4, 6, 12-15m)	5-17, 18-39, 40-64, ≥65years	IPD mortality rate, pneumococcal pneumonia mortality, pneumonia-specific mortality	Reductions in IPD, pneumococcal pneumonia, and all-cause pneumonia mortality after PCV7 introdcution	↓
USA	Tsigrelis, C (CID 2008)	Population-based surveillance	PCV7	3+1 (2, 4, 6, 12-15m)	5-19, 20-39, 40-64, ≥65years	IPD case fatality rate IPD mortality rate	Significant decline in overall IPD case fatality, driven largely by ≥65 population; significant decline in overall IPD mortality	↓

Table 14. Summary of characteristics for PCV case-control studies with a pneumonia outcome (indirect effects)

Country	Reference	Study design	Vaccine product	Dosing schedule for PCV	N Participants	Population	Endpoint	Odds Ratio (95% CI)
South Africa	Albrich, W (Lancet 2007)	Sub-study of PCV9 clinical trial	PCV9 (Wyeth)	6, 10, 14w	Total:158	Adults (residing with child from PCV9 trial)	All-cause pneumonia	1.07 (0.79-1.45) (Crude)
							Pneumococcal pneumonia	1.00 (0.39-2.59) (Crude)
USA	Metlay, J (Vaccine 2006)	Risk factor analysis	PCV7 (Wyeth)	2, 4, 6, 12-15m	Cases:233 Controls:609	Adults (Controls from random digit dialing)	Bacteremic pneumococcal pneumonia	0.2 (0.1 – 0.8) (Adjusted)

Table 15. Summary of studies included in NP analysis – PCV pre-post studies comparing childhood schedules or estimating vaccine effectiveness, direct and indirect

Study author and PCV valency	Country	Comparison	Schedules, age in months	Number of participants	Age group of participants	Outcomes reported	Years since introduction reported[§¥]			Main results*
			Actual age at administration				Clinical	Carriage	Immuno.	
Hare, K(Hare, Morris et al. 2006) PCV7Wyeth	Australia	Pre-vaccine introduction	2m, 4m, 6m, (18m PPV)	996	Children in daycare	Carriage		0.5		Baseline VT carriage: 25.6% Post-intro VT carriage: 27.1% Percent change: 5.6%[β]
MacKenzie, G (Mackenzie, Carapetis et al. 2006) PCV7Wyeth	Australia	Pre-vaccine introduction	2m, 4m, 6m, (18m PPV)	481	4 – 13 years	Carriage		2		Median baseline VT carriage: 25% Median post-intro VT carriage: 13.8% Percent change: -44.8%[€]
				538	Adults					Median baseline VT carriage: 11.3% Median post-intro VT carriage: 6.1% Percent change: -45.4%[†]
MacKenzie, G (Mackenzie, Carapetis et al. 2006) PCV7Wyeth	Australia	Pre-vaccine introduction	2m, 4m, 6m, (18m PPV)	137	7 – 10m	Carriage		1.5		Median baseline VT carriage: 47.2% Median post-intro VT carriage: 8.5% Percent change: -81.9%[€]

				107	12 – 17m					Median baseline VT carriage: 55.6% Median post-intro VT carriage: 24.5% Percent change: -55.8%[€]
Cohen, R(Cohen, Levy et al. 2009) PCV7Wyeth	France	Pre-vaccine introduction	2m, 3m, 4m, 13.5m	3,278	6 – 24 months with acute otitis media	Carriage		2.5		Median baseline VT carriage: 43.1% Post-intro VT carriage: 17.3% Percent change: -59.8%[β]
Dunais, B(Dunais, Bruno et al. 2008) UPD031 PCV7Wyeth	France	Pre-vaccine introduction	2m, 3m, 4m, 13.5m	1,261	3 – 39 months	Carriage		3		Median baseline VT carriage: 42.4% Post-intro VT carriage: 10.7% Percent change: -74.7%[β]
Sa-Leao, R(Sa-Leao, Nunes et al. 2009) PCV7Wyeth	Portugal	Pre-vaccine introduction	3m, 5m, 7m, 12m	1,288	4 months – 6 years	Carriage				Baseline VT carriage: 34.4% Post-intro VT carriage: 7.7% Percent change: -77.6%[€]
Mühlemann, K (Muhlemann and Aebi 2008) PCV7Wyeth	Switzerland	Pre-vaccine introduction	2m, 4m, 12m	Not reported	<2 years with acute otitis media or pneumonia	Carriage		1		Baseline VT carriage: 57.1% Post-intro VT carriage among vaccinated children: 37.1% Percent change: -35.0%[β]

Alexander, E(Alexander, Telfer et al. 2008) PCV7Wyeth	United Kingdom	Pre-vaccine introduction	2m, 3m, 4m (2y PPV)	106	1 – 59m Children with sickle cell disease	Carriage		2		Baseline VT carriage: 15.9% Post-intro VT carriage: 2.3% Percent change: -85.3%[†]
Hammitt, L(Hammitt, Bruden et al. 2006) PCV7Wyeth	USA	Pre-vaccine introduction	2m, 4m, 6m, 13.5m	1,030	<5 years	Carriage		3		Baseline VT carriage: 55.4% Post-intro VT carriage: 4.8% Percent change: -91.4%[β]
				1,597	Adults					Baseline VT carriage: 28.4% Post-intro VT carriage: 4.5% Percent change: -84.1% [β]
Park, S(Park, Moore et al. 2008) PCV7Wyeth	USA	Pre-vaccine introduction	2m, 4m, 6m, 13.5m	2,250	3 – 59 months	Carriage		3		Baseline VT carriage: 20.4% Post-intro VT carriage: 4.0% Percent change: -80.4%[€]
Samore, M(Samore, Alder et al. 2004) PCV7Wyeth	USA	Pre-vaccine introduction	2m, 4m, 6m, 13.5m		≤6 years	Carriage		3		Baseline VT carriage: 62.0% Post-intro VT carriage: 26.0% Percent change: -58.1%[β]
Sharma, D(Sharma, Thomas et al. 2010) PCV7Wyeth	USA	Pre-vaccine introduction	2m, 4m, 6m, 13.5m	728	<5 years	Carriage		9		Baseline VT carriage: 60.2% Post-intro VT carriage: 0.7% Percent change: -98.8%[β]

Scott, J(Scott, Millar et al. 2011) PCV7Wyeth	USA	Pre-vaccine introduction	2m, 4m, 6m, 13.5m		<5 years	Carriage		8		Baseline VT carriage: 24.1% Post-intro VT carriage: 1.0% Percent change: -94.2% β
Wenger, J(Wenger, Bruden et al. 2010) PCV7Wyeth	USA	Pre-vaccine introduction	2m, 4m, 6m, 13.5m	683	<5 years	Carriage		8		Baseline VT carriage: 21.0% Post-intro VT carriage: 1.0% Percent change:-95.2% β
				600	All ages					Baseline VT carriage: 18.7% Post-intro VT carriage: 0% Percent change: -100%£

§ Only last time point reported after introduction is reported, and percent change is calculated based on latest time point.
¥ If the percent vaccine-type carriage is presented for multiple baseline or post-introduction years reported together, e.g. 2001-2004, then the number of years since introduction is reported using the median year.
* Percent vaccine-type carriage calculated per number of individuals tested
β Significance not reported in citation at this time point for this value
€ Significant reduction in vaccine-type carriage reported when percent vaccine-type carriage calculated per number of pneumococcal isolates
† Non-significant change in vaccine-type carriage reported when percent vaccine-type carriage calculated per number of pneumococcal isolates
£ Significant at $p<0.05$

Table 16. Summary of studies included in immunogenicity analysis - Immunological outcome data from randomized controlled trials

a. Post-primary (2p or 3p) geometric antibody concentration (GMC) and percent above 0.35ug/ml (or 2.0 if GSK lab method used)

Serotype 1, dose 2p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB071-21	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	156	0.80 (. - .)	N/A
BB097-21	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	12.80 (10.20-16.00)	N/A
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	1.00 (0.80- 1.20)	86.3
LC109-21	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	233	5.60 (. - .)	N/A
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	2.20 (2.00- 2.60)	N/A

Serotype 1, dose 3p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
02MYP052-1	Yaich, M (2000)	Israel	Aventis-11	2, 4, 6	No	DTwP	Wyeth	59	1.80 (. - .)	N/A
02MYP052-2	Yaich, M (2000)	Finland	Aventis-11	2, 4, 6	No	DTwP	Wyeth	60	1.60 (. - .)	N/A
02MYP052-3	Yaich, M (2000)	Iceland	Aventis-11	3, 4, 6	No	DTwP	Wyeth	73	2.60 (. - .)	N/A
AC030-1	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	35	6.80 (5.40- 8.60)	N/A
AC030-2	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	4.40 (3.00- 6.60)	N/A
AC030-3	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	6.00 (5.00- 7.20)	N/A
BB071-1	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	169	1.20 (1.00- 1.40)	90.5
BB071-2	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	175	1.00 (1.00- 1.20)	88.5
BB071-3	Wysocki, J (2009)	Germany, Poland,	GSK-10	2, 4, 6, 14	No	DTaP	GSK	173	1.00 (0.80- 1.20)	84.4

		Spain								
BB093-1	Prymula, R (2006)	Czech Republic, Slovakia	GSK-11	3, 5, 6, 12	No	DTaP	GSK	140	1.60 (1.40- 1.80)	N/A
BB097-1	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	15.20 (12.80- 18.20)	N/A
BB846-1	Lucero, MG (2004)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	56	11.20 (9.40- 13.40)	N/A
BBJL603-2	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 4, 5, 12	No	DTaP	GSK	154	1.20 (1.00- 1.40)	90.7
JL065-1	Bermal, N (2009)	North America	GSK-10	1.5, 2.5, 3.5	No	DTwP	GSK	285	3.20 (3.00- 3.60)	99.6
JL065-3	Bermal, N (2009)	Poland	GSK-10	2, 4, 6	No	DTwP	GSK	285	1.00 (1.00- 1.20)	91.9
JL097-1	Buttery, J (2005)	United Kingdom	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	100	1.40 (1.20- 1.80)	N/A
LC019-1	Dagan, R (2004)	Finland	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	91	2.00 (1.60- 2.60)	N/A
LC019-2	Dagan, R (2004)	Israel	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	125	2.80 (2.40- 3.20)	N/A
LC109-1	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	205	5.40 (. - .)	N/A
MR266-1	Soininen, Anu (2009)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	479	5.40 (4.80- 5.80)	N/A
MR301-2	Vesikari, T. (2009)	Finland, France, Poland	GSK-10	2, 3, 4	No	DTaP	GSK	1107	1.00 (1.00- 1.20)	90.2
MR818-1	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	2.40 (2.00- 3.00)	N/A
MR818-2	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	2.80 (2.20- 3.60)	N/A
MR824-1	Obaro, S. (2000)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	96	7.00 (5.60- 8.40)	N/A
MR825-2	Obaro, Stephen (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	60	3.60 (2.80- 4.40)	N/A
MR825-3	Obaro, Stephen (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	53	4.00 (3.20- 5.00)	N/A
UPD012-1	Bryant, K (2010)	United States	Wyeth-13	2, 4, 6, 14	No	DTaP	Wyeth	102	2.60 (2.20- 3.00)	N/A
UPD117-1	GSK (2008)	Taiwan	GSK-10	2, 3, 6	No	DTaP	GSK	219	3.00 (2.60- 3.20)	N/A
UPD118-1	GSK (2009)	Mali	GSK-10	1.5, 2.5, 3.5	Yes	DTwP	GSK	141	2.40 (2.20- 2.80)	N/A
UPD122-1	GSK (2009)	South Korea	GSK-10	2, 4, 6	No	DTaP	GSK	344	3.40 (3.20- 3.80)	N/A

Serotype 5, dose 2p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB071-21	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	156	1.20 (. - .)	N/A
BB097-21	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	12.40 (10.00-15.20)	N/A
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	1.40 (1.20- 1.60)	94.7
LC109-21	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	233	5.40 (. - .)	N/A
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	1.20 (1.20- 1.40)	N/A

Serotype 5, dose 3p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
02MYP052-1	Yaich, M (2000)	Israel	Aventis-11	2, 4, 6	No	DTwP	Wyeth	59	2.00 (. - .)	N/A
02MYP052-2	Yaich, M (2000)	Finland	Aventis-11	2, 4, 6	No	DTwP	Wyeth	60	1.60 (. - .)	N/A
02MYP052-3	Yaich, M (2000)	Iceland	Aventis-11	3, 4, 6	No	DTwP	Wyeth	73	1.80 (. - .)	N/A
AC030-1	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	35	4.80 (3.80- 6.20)	N/A
AC030-2	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	3.00 (2.00- 4.40)	N/A
AC030-3	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	3.40 (2.60- 4.20)	N/A
BB071-1	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	169	2.00 (1.80- 2.20)	98.8
BB071-2	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	175	1.80 (1.60- 2.00)	98.9
BB071-3	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	173	1.60 (1.40- 2.00)	97.1
BB093-1	Prymula, R (2006)	Czech Republic, Slovakia	GSK-11	3, 5, 6, 12	No	DTaP	GSK	143	2.00 (1.60- 2.20)	N/A
BB097-1	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	12.40 (10.80-14.40)	N/A

BB846-1	Lucero, MG (2004)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	56	11.40 (9.40-14.00)	N/A
BBJL603-2	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 4, 5, 12	No	DTaP	GSK	154	1.80 (1.60- 2.00)	99.3
JL065-1	Bermal, N (2009)	North America	GSK-10	1.5, 2.5, 3.5	No	DTwP	GSK	285	4.80 (4.60- 5.20)	100.0
JL065-3	Bermal, N (2009)	Poland	GSK-10	2, 4, 6	No	DTwP	GSK	285	1.60 (1.40- 1.80)	96.1
JL097-1	Buttery, J (2005)	United Kingdom	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	100	0.80 (0.60- 0.80)	N/A
LC019-1	Dagan, R (2004)	Finland	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	91	2.00 (1.60- 2.60)	N/A
LC019-2	Dagan, R (2004)	Israel	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	125	2.00 (1.80- 2.40)	N/A
LC109-1	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	204	6.20 (. - .)	N/A
MR266-1	Soininen, Anu (2009)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	479	8.40 (7.80- 9.20)	N/A
MR301-2	Vesikari, T. (2009)	Finland, France, Poland	GSK-10	2, 3, 4	No	DTaP	GSK	1107	1.80 (1.60- 1.80)	95.5
MR818-1	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	1.40 (1.20- 1.80)	N/A
MR818-2	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	1.80 (1.60- 2.20)	N/A
MR824-1	Obaro, S. (2000)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	97	5.80 (4.80- 7.20)	N/A
MR825-2	Obaro, Stephen (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	60	4.20 (3.40- 5.20)	N/A
MR825-3	Obaro, Stephen (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	53	5.20 (4.00- 6.80)	N/A
UPD012-1	Bryant, K (2010)	United States	Wyeth-13	2, 4, 6, 14	No	DTaP	Wyeth	101	2.40 (2.00- 2.80)	N/A
UPD117-1	GSK (2008)	Taiwan	GSK-10	2, 3, 6	No	DTaP	GSK	219	4.60 (4.20- 5.00)	N/A
UPD118-1	GSK (2009)	Mali	GSK-10	1.5, 2.5, 3.5	Yes	DTwP	GSK	141	3.80 (3.40- 4.40)	N/A
UPD122-1	GSK (2009)	South Korea	GSK-10	2, 4, 6	No	DTaP	GSK	344	4.60 (4.20- 4.80)	N/A

Serotype 6b, dose 2p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB045-1	Kayhty, H (2005)	Sweden	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	75	0.40 (0.20- 0.40)	61.0
BB053-21	Kim, N-H (2007)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	181	0.60 (0.40- 0.80)	78.8

BB071-21	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	156	0.20 (. - .)	53.6
BB097-21	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	0.40 (0.20- 0.40)	N/A
BB815-23	Miernyk , KM (2000)	United States	Merck-7	2, 4, 6, 15	No	DTaP	Wyeth	32	0.20 (0.20- 0.20)	N/A
BBJL601-1	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	114	0.20 (0.20- 0.20)	46.0
BBJL601-2	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	170	0.40 (0.40- 0.40)	69.0
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	0.20 (0.20- 0.20)	45.0
JL038-21	Anderson, E (1996)	United States	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	24	1.60 (1.00- 2.80)	N/A
LC048-21	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	26	0.60 (0.40- 1.00)	N/A
LC048-22	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	24	0.40 (0.20- 0.80)	N/A
LC059-2	Esposito, S (2005)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	46	1.00 (0.00-12.80)	N/A
LC109-21	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	231	1.80 (. - .)	N/A
MR207-21	Rennels, M (1998)	United States	Wyeth-7	2, 4, 6, 14	Yes	DTwP	Wyeth	90	0.20 (0.20- 0.40)	N/A
MR817-21	Nurkka, A (2001)	Finland	Aventis-8	2, 4, 6, 15	No	DTwP	Wyeth	.	0.40 (. - .)	N/A
MR817-22	Nurkka, A (2001)	Finland	Aventis-8	2, 4, 6, 15	No	DTwP	Wyeth	.	0.20 (. - .)	N/A
MR917-21	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	1.00 (0.60- 1.60)	N/A
MR917-22	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	1.00 (0.60- 1.60)	N/A
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	0.40 (0.40- 0.40)	N/A

Serotype 6b, dose 3p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
02IJP039-1	Jonsdottir, I (2000)	Iceland	Aventis-8	3, 4, 6	No	DTwP	Wyeth	.	1.20 (. - .)	N/A
02IJP039-2	Jonsdottir, I (2000)	Iceland	Aventis-8	3, 4, 6	No	DTwP	Wyeth	.	1.00 (. - .)	N/A
02MYP052-1	Yaich, M (2000)	Israel	Aventis-11	2, 4, 6	No	DTwP	Wyeth	59	1.00 (. - .)	N/A
02MYP052-2	Yaich, M (2000)	Finland	Aventis-11	2, 4, 6	No	DTwP	Wyeth	60	0.60 (. - .)	N/A
02MYP052-3	Yaich, M (2000)	Iceland	Aventis-11	3, 4, 6	No	DTwP	Wyeth	73	0.80 (. - .)	N/A

07KK2158-2	Kim, KH (2010)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	129	N/A	98.4
AC022-1	Knuf, M (2006)	Germany	Wyeth-7	2, 3, 4, 14	No	DTaP	Wyeth	115	3.20 (2.60- 3.80)	N/A
AC030-1	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	35	10.40 (7.40-14.40)	N/A
AC030-2	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	11.20 (8.40-15.40)	N/A
AC030-3	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	6.00 (3.80- 9.20)	N/A
AC034-1	Lee, H (2009)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	31	4.80 (3.20- 7.00)	N/A
BB053-1	Kim, N-H (2007)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	177	5.60 (4.80- 6.40)	100.0
BB071-1	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	169	1.00 (0.80- 1.20)	87.0
BB071-2	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	175	0.80 (0.80- 1.00)	91.1
BB071-3	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	173	0.80 (0.60- 0.80)	75.7
BB071-4	Wysocki, J (2009)	Germany, Poland, Spain	Wyeth-7	2, 4, 6, 13	No	DTaP	GSK	170	1.40 (1.20- 1.60)	87.0
BB076-1	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	56	1.20 (. - .)	N/A
BB076-2	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	51	0.60 (. - .)	N/A
BB076-3	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	50	0.40 (. - .)	N/A
BB076-4	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	42	0.40 (. - .)	N/A
BB093-1	Prymula, R (2006)	Czech Republic, Slovakia	GSK-11	3, 5, 6, 12	No	DTaP	GSK	133	0.60 (0.60- 0.80)	N/A
BB097-1	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	1.20 (0.80- 1.60)	N/A
BB815-3	Miernyk , KM (2000)	United States	Merck-7	2, 4, 6, 15	No	DTaP	Wyeth	32	0.40 (0.40- 0.60)	N/A
BB837-1	Li, RC (2008)	China	Wyeth-7	3, 4, 5, 14	Yes	DTaP	Wyeth	64	3.00 (2.20- 4.40)	N/A
BB837-2	Li, RC (2008)	China	Wyeth-7	3, 4, 5, 14	Yes	DTaP	Wyeth	66	1.20 (0.80- 1.60)	N/A
BB846-1	Lucero, MG (2004)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	56	1.20 (0.80- 1.60)	N/A
BBJL603-2	Silfverdal, SA (2009)	Denmark, Norway, Slovakia,	GSK-10	3, 4, 5, 12	No	DTaP	GSK	154	0.40 (0.20- 0.40)	49.0

		Sweden								
JL038-1	Anderson, E (1996)	United States	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	25	3.40 (1.80- 6.20)	N/A
JL045-1	Anttila, M (1999)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	28	1.40 (. - .)	N/A
JL045-2	Anttila, M (1999)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	25	1.40 (. - .)	N/A
JL065-1	Bermal, N (2009)	North America	GSK-10	1.5, 2.5, 3.5	No	DTwP	GSK	285	1.20 (1.00- 1.40)	81.8
JL065-2	Bermal, N (2009)	North America	Wyeth-7	1.5, 2.5, 3.5	No	DTwP	GSK	95	1.00 (0.80- 1.40)	81.1
JL065-3	Bermal, N (2009)	Poland	GSK-10	2, 4, 6	No	DTwP	GSK	285	0.80 (0.60- 0.80)	78.2
JL065-4	Bermal, N (2009)	Poland	Wyeth-7	2, 4, 6	No	DTwP	GSK	96	1.20 (1.00- 1.60)	91.7
JL097-1	Buttery, J (2005)	United Kingdom	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	100	1.20 (1.00- 1.60)	N/A
JLMR202-1	Reinert, P (2003)	France	Wyeth-7	2, 3, 4	Yes	DTwP	Wyeth	53	3.00 (2.00- 4.40)	N/A
JLMR251-1	Shapiro, E (1997)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	40	1.20 (. - .)	N/A
JLMR251-2	Shapiro, E (1997)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	40	2.80 (. - .)	N/A
JLMR254-1	Shinefield, H (1999)	United States	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	81	1.20 (1.00- 1.60)	N/A
JLMR254-2	Shinefield, H (1999)	United States	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	75	1.20 (1.00- 1.60)	N/A
LC019-1	Dagan, R (2004)	Finland	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	91	0.80 (0.60- 1.00)	N/A
LC019-2	Dagan, R (2004)	Israel	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	125	1.20 (1.00- 1.60)	N/A
LC048-1	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	26	2.00 (1.20- 3.20)	96.2
LC048-2	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	24	1.40 (0.80- 2.40)	95.8
LC049-1	Ekstrom, N (2005)	Finland	Wyeth-7	2, 4, 6, 12	Yes	DTwP	Wyeth	55	2.00 (1.40- 3.00)	N/A
LC049-2	Ekstrom, N (2005)	Finland	Merck-7	2, 4, 6, 12	Yes	DTwP	Wyeth	53	0.40 (0.20- 0.60)	N/A
LC109-1	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	203	5.80 (. - .)	N/A
MR207-1	Rennels, M (1998)	United States	Wyeth-7	2, 4, 6, 14	Yes	DTwP	Wyeth	90	1.40 (1.00- 1.80)	N/A
MR223-2	Ruggeberg, J (2007)	United Kingdom	Wyeth-7	2, 3, 4, 12	No	DTwP	Wyeth	62	1.00 (0.60- 1.40)	92.0
MR250-1	Shao, Pei-Lan (2004)	Taiwan	Wyeth-7	2, 4, 6	No	DTwP	Wyeth	60	5.40 (4.00- 7.20)	N/A
MR266-1	Soininen, Anu (2009)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	479	1.00 (0.80- 1.20)	N/A
MR282-1	Tichmann-Schumann, I. (2005)	Germany	Wyeth-7	2, 3, 4, 13	No	DTaP	GSK	141	1.00 (0.80- 1.20)	N/A
MR301-1	Vesikari, T. (2009)	Finland, France,	Wyeth-7	2, 3, 4	No	DTaP	GSK	375	0.60 (0.60- 0.60)	70.7

		Poland								
MR301-2	Vesikari, T. (2009)	Finland, France, Poland	GSK-10	2, 3, 4	No	DTaP	GSK	1107	0.40 (0.40- 0.40)	54.8
MR816-1	Nurkka, A (2001)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	29	1.40 (1.20- 1.80)	N/A
MR816-2	Nurkka, A (2001)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	30	1.40 (1.20- 1.80)	N/A
MR818-1	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	1.20 (1.00- 1.80)	N/A
MR818-2	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	1.60 (1.00- 2.20)	N/A
MR824-1	Obaro, S. (2000)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	91	5.00 (3.60- 6.80)	N/A
MR825-2	Obaro, S (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	60	2.40 (1.60- 3.80)	N/A
MR825-3	Obaro, S (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	53	4.20 (2.80- 6.20)	N/A
MR912-3	O'Brien, K. (2000)	United States	Wyeth-7	2, 4, 6	No	DTwP	Wyeth	9	3.00 (0.80-10.40)	N/A
MR914-1	Olivier, C (2008)	France, Germany	Wyeth-7	2, 3, 4, 14	No	DTaP	Wyeth	125	1.20 (1.00- 1.60)	N/A
MR917-1	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	14.00 (10.80-18.00)	N/A
MR917-2	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	12.80 (9.80-16.60)	N/A
MRJL087-1	Block, S (1997)	United States	Merck-7	2, 4, 6	No	DTwP	Wyeth	68	0.40 (. - .)	N/A
MRJL087-2	Block, S (1997)	United States	Merck-7	2, 4, 6	No	DTwP	Wyeth	31	0.60 (. - .)	N/A
UPD012-1	Bryant, K (2010)	United States	Wyeth-13	2, 4, 6, 14	No	DTaP	Wyeth	102	2.80 (2.00- 3.60)	N/A
UPD012-2	Bryant, K (2010)	United States	Wyeth-7	2, 4, 6, 14	No	DTaP	Wyeth	113	3.00 (2.20- 4.00)	N/A
UPD054-1	Kieninger, D (2010)	Germany	Wyeth-13	2, 3, 4, 12	No	DTaP	Wyeth	.	1.00 (0.80- 1.20)	N/A
UPD054-2	Kieninger, D (2010)	Germany	Wyeth-7	2, 3, 4, 12	No	DTaP	Wyeth	.	1.40 (1.20- 1.80)	N/A
UPD068-1	Moss, S (2010)	United Kingdom	Wyeth-7	2, 3, 4	No	DTaP	Wyeth	53	0.20 (0.20- 0.40)	N/A
UPD117-1	GSK (2008)	Taiwan	GSK-10	2, 3, 6	No	DTaP	GSK	219	1.60 (1.40- 2.00)	N/A
UPD118-1	GSK (2009)	Mali	GSK-10	1.5, 2.5, 3.5	Yes	DTwP	GSK	141	0.60 (0.60- 1.00)	N/A
UPD122-1	GSK (2009)	South Korea	GSK-10	2, 4, 6	No	DTaP	GSK	344	1.40 (1.20- 1.60)	N/A
UPD122-2	GSK (2009)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	GSK	123	2.00 (1.80- 2.40)	N/A
UPD128-1	Scott (2011)	Kenya	Wyeth-7	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	.	3.20 (2.60- 4.20)	N/A
UPD128-2	Scott (2011)	Kenya	Wyeth-7	0, 2.5, 3.5, 9	No	DTwP	Wyeth	.	3.60 (2.60- 5.00)	N/A

Serotype 14, dose 2p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB045-1	Kayhty, H (2005)	Sweden	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	75	3.40 (2.60- 4.40)	N/A
BB053-21	Kim, N-H (2007)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	181	8.80 (7.20-11.00)	99.3
BB071-21	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	156	2.20 (. - .)	97.4
BB097-21	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	1.20 (1.00- 1.80)	N/A
BB815-23	Miernyk , KM (2000)	United States	Merck-7	2, 4, 6, 15	No	DTaP	Wyeth	32	1.60 (1.00- 2.20)	N/A
BBJL601-1	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	114	2.60 (2.00- 3.20)	97.0
BBJL601-2	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	170	4.40 (3.60- 5.20)	99.0
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	1.80 (1.40- 2.00)	90.8
JL038-21	Anderson, E (1996)	United States	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	24	3.60 (2.00- 6.40)	N/A
LC048-21	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	26	2.60 (1.60- 4.40)	N/A
LC048-22	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	24	1.20 (0.80- 1.80)	N/A
LC059-2	Esposito, S (2005)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	46	6.00 (0.00-174.4)	N/A
LC109-21	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	232	2.20 (. - .)	N/A
MR207-21	Rennels, M (1998)	United States	Wyeth-7	2, 4, 6, 14	Yes	DTwP	Wyeth	90	2.00 (1.60- 2.60)	N/A
MR817-21	Nurkka, A (2001)	Finland	Aventis-8	2, 4, 6, 15	No	DTwP	Wyeth	.	2.40 (. - .)	N/A
MR817-22	Nurkka, A (2001)	Finland	Aventis-8	2, 4, 6, 15	No	DTwP	Wyeth	.	1.20 (. - .)	N/A
MR917-21	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	1.60 (1.00- 2.80)	N/A
MR917-22	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	1.40 (0.80- 2.20)	N/A
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	2.80 (2.40- 3.40)	N/A

Serotype 14, dose 3p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
02IJP039-1	Jonsdottir, I (2000)	Iceland	Aventis-8	3, 4, 6	No	DTwP	Wyeth	.	3.00 (. - .)	N/A
02IJP039-2	Jonsdottir, I (2000)	Iceland	Aventis-8	3, 4, 6	No	DTwP	Wyeth	.	3.60 (. - .)	N/A
02MYP052-1	Yaich, M (2000)	Israel	Aventis-11	2, 4, 6	No	DTwP	Wyeth	59	1.80 (. - .)	N/A
02MYP052-2	Yaich, M (2000)	Finland	Aventis-11	2, 4, 6	No	DTwP	Wyeth	60	1.00 (. - .)	N/A
02MYP052-3	Yaich, M (2000)	Iceland	Aventis-11	3, 4, 6	No	DTwP	Wyeth	73	2.80 (. - .)	N/A
07KK2158-2	Kim, KH (2010)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	129	N/A	100.0
AC022-1	Knuf, M (2006)	Germany	Wyeth-7	2, 3, 4, 14	No	DTaP	Wyeth	115	6.80 (5.80- 8.20)	N/A
AC030-1	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	35	7.60 (5.40-10.40)	N/A
AC030-2	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	7.00 (4.80-10.00)	N/A
AC030-3	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	6.40 (4.60- 9.00)	N/A
AC034-1	Lee, H (2009)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	31	10.40 (7.40-14.80)	N/A
BB053-1	Kim, N-H (2007)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	177	14.20 (12.00-17.00)	100.0
BB071-1	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	169	3.80 (3.20- 4.40)	98.2
BB071-2	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	175	3.80 (3.40- 4.20)	99.4
BB071-3	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	173	3.40 (3.00- 3.80)	98.3
BB071-4	Wysocki, J (2009)	Germany, Poland, Spain	Wyeth-7	2, 4, 6, 13	No	DTaP	GSK	170	6.00 (5.00- 7.00)	97.0
BB076-1	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	56	3.20 (. - .)	N/A
BB076-2	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	51	2.60 (. - .)	N/A
BB076-3	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	50	1.60 (. - .)	N/A
BB076-4	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	42	1.60 (. - .)	N/A
BB093-1	Prymula, R (2006)	Czech Republic, Slovakia	GSK-11	3, 5, 6, 12	No	DTaP	GSK	143	3.00 (2.60- 3.60)	N/A

BB097-1	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	2.20 (1.60- 2.80)	N/A
BB815-3	Miernyk , KM (2000)	United States	Merck-7	2, 4, 6, 15	No	DTaP	Wyeth	32	3.00 (2.20- 4.20)	N/A
BB837-1	Li, RC (2008)	China	Wyeth-7	3, 4, 5, 14	Yes	DTaP	Wyeth	64	17.80 (13.60-23.20)	N/A
BB837-2	Li, RC (2008)	China	Wyeth-7	3, 4, 5, 14	Yes	DTaP	Wyeth	66	13.40 (10.40-17.20)	N/A
BB846-1	Lucero, MG (2004)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	56	2.80 (2.00- 4.00)	N/A
BBJL603-2	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 4, 5, 12	No	DTaP	GSK	154	2.60 (2.20- 3.00)	98.0
JL038-1	Anderson, E (1996)	United States	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	25	5.40 (3.20- 9.20)	N/A
JL045-1	Anttila, M (1999)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	28	5.20 (. - .)	N/A
JL045-2	Anttila, M (1999)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	25	5.20 (. - .)	N/A
JL065-1	Bermal, N (2009)	North America	GSK-10	1.5, 2.5, 3.5	No	DTwP	GSK	285	6.40 (5.60- 7.40)	98.2
JL065-2	Bermal, N (2009)	North America	Wyeth-7	1.5, 2.5, 3.5	No	DTwP	GSK	95	5.80 (4.80- 7.40)	98.9
JL065-3	Bermal, N (2009)	Poland	GSK-10	2, 4, 6	No	DTwP	GSK	285	3.40 (3.00- 3.60)	98.2
JL065-4	Bermal, N (2009)	Poland	Wyeth-7	2, 4, 6	No	DTwP	GSK	96	5.20 (4.40- 6.20)	99.0
JL097-1	Buttery, J (2005)	United Kingdom	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	100	2.40 (2.00- 3.20)	N/A
JLMR202-1	Reinert, P (2003)	France	Wyeth-7	2, 3, 4	Yes	DTwP	Wyeth	53	5.60 (4.00- 7.80)	N/A
JLMR251-1	Shapiro, E (1997)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	40	3.80 (. - .)	N/A
JLMR251-2	Shapiro, E (1997)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	40	3.00 (. - .)	N/A
JLMR254-1	Shinefield, H (1999)	United States	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	81	3.80 (3.20- 4.40)	N/A
JLMR254-2	Shinefield, H (1999)	United States	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	75	3.80 (3.20- 4.40)	N/A
LC019-1	Dagan, R (2004)	Finland	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	91	1.40 (1.00- 2.00)	N/A
LC019-2	Dagan, R (2004)	Israel	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	125	2.00 (1.60- 2.40)	N/A
LC048-1	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	26	5.60 (3.60- 8.80)	100.0
LC048-2	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	24	2.60 (1.60- 4.60)	100.0
LC049-1	Ekstrom, N (2005)	Finland	Wyeth-7	2, 4, 6, 12	Yes	DTwP	Wyeth	55	6.20 (4.80- 8.20)	N/A
LC049-2	Ekstrom, N (2005)	Finland	Merck-7	2, 4, 6, 12	Yes	DTwP	Wyeth	53	3.00 (2.00- 4.20)	N/A

LC109-1	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	199	3.60 (. - .)	N/A
MR207-1	Rennels, M (1998)	United States	Wyeth-7	2, 4, 6, 14	Yes	DTwP	Wyeth	90	3.40 (2.80- 4.60)	N/A
MR223-2	Ruggeberg, J (2007)	United Kingdom	Wyeth-7	2, 3, 4, 12	No	DTwP	Wyeth	62	4.20 (3.20- 5.60)	98.0
MR250-1	Shao, Pei-Lan (2004)	Taiwan	Wyeth-7	2, 4, 6	No	DTwP	Wyeth	60	11.00 (8.60-13.80)	N/A
MR266-1	Soininen, Anu (2009)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	479	3.40 (3.00- 3.80)	N/A
MR282-1	Tichmann-Schumann, I. (2005)	Germany	Wyeth-7	2, 3, 4, 13	No	DTaP	GSK	141	4.60 (4.00- 5.40)	N/A
MR301-1	Vesikari, T. (2009)	Finland, France, Poland	Wyeth-7	2, 3, 4	No	DTaP	GSK	375	4.40 (4.00- 5.00)	97.9
MR301-2	Vesikari, T. (2009)	Finland, France, Poland	GSK-10	2, 3, 4	No	DTaP	GSK	1107	3.00 (2.80- 3.00)	99.0
MR816-1	Nurkka, A (2001)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	29	5.20 (4.00- 7.00)	N/A
MR816-2	Nurkka, A (2001)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	30	5.20 (4.00- 7.00)	N/A
MR818-1	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	4.60 (3.60- 6.00)	N/A
MR818-2	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	5.00 (3.60- 6.80)	N/A
MR824-1	Obaro, S. (2000)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	94	4.40 (3.40- 5.80)	N/A
MR825-2	Obaro, Stephen (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	60	3.00 (2.00- 4.60)	N/A
MR825-3	Obaro, Stephen (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	53	3.60 (2.60- 5.40)	N/A
MR912-3	O'Brien, K. (2000)	United States	Wyeth-7	2, 4, 6	No	DTwP	Wyeth	9	4.80 (2.80- 7.80)	N/A
MR914-1	Olivier, C (2008)	France, Germany	Wyeth-7	2, 3, 4, 14	No	DTaP	Wyeth	125	6.80 (5.80- 8.00)	N/A
MR917-1	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	11.40 (9.20-14.20)	N/A
MR917-2	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	9.20 (6.80-12.20)	N/A
MRJL087-1	Block, S (1997)	United States	Merck-7	2, 4, 6	No	DTwP	Wyeth	68	2.80 (. - .)	N/A
MRJL087-2	Block, S (1997)	United States	Merck-7	2, 4, 6	No	DTwP	Wyeth	31	4.00 (. - .)	N/A
UPD012-1	Bryant, K (2010)	United States	Wyeth-13	2, 4, 6, 14	No	DTaP	Wyeth	102	4.20 (3.40- 5.20)	N/A
UPD012-2	Bryant, K (2010)	United States	Wyeth-7	2, 4, 6, 14	No	DTaP	Wyeth	113	5.40 (4.20- 6.60)	N/A
UPD054-1	Kieninger, D (2010)	Germany	Wyeth-13	2, 3, 4, 12	No	DTaP	Wyeth	.	4.20 (3.60- 4.60)	N/A

UPD054-2	Kieninger, D (2010)	Germany	Wyeth-7	2, 3, 4, 12	No	DTaP	Wyeth	.	4.60 (4.00- 5.20)	N/A
UPD068-1	Moss, S (2010)	United Kingdom	Wyeth-7	2, 3, 4	No	DTaP	Wyeth	53	3.80 (2.80- 5.20)	N/A
UPD117-1	GSK (2008)	Taiwan	GSK-10	2, 3, 6	No	DTaP	GSK	219	5.60 (5.00- 6.40)	N/A
UPD118-1	GSK (2009)	Mali	GSK-10	1.5, 2.5, 3.5	Yes	DTwP	GSK	141	3.20 (2.60- 3.80)	N/A
UPD122-1	GSK (2009)	South Korea	GSK-10	2, 4, 6	No	DTaP	GSK	344	5.60 (5.00- 6.20)	N/A
UPD122-2	GSK (2009)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	GSK	123	8.60 (7.20-10.00)	N/A
UPD128-1	Scott (2011)	Kenya	Wyeth-7	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	.	3.40 (2.80- 4.40)	N/A
UPD128-2	Scott (2011)	Kenya	Wyeth-7	0, 2.5, 3.5, 9	No	DTwP	Wyeth	.	3.60 (2.80- 4.40)	N/A

Serotype 19F, dose 2p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB045-1	Kayhty, H (2005)	Sweden	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	75	5.00 (3.80- 6.80)	N/A
BB053-21	Kim, N-H (2007)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	181	7.60 (6.40- 9.40)	98.0
BB071-21	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	156	2.00 (. - .)	90.4
BB097-21	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	4.60 (3.40- 6.20)	N/A
BB815-23	Miernyk , KM (2000)	United States	Merck-7	2, 4, 6, 15	No	DTaP	Wyeth	32	0.60 (0.40- 0.80)	N/A
BBJL601-1	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	114	2.00 (1.60- 2.40)	99.0
BBJL601-2	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	170	2.20 (2.00- 2.60)	100.0
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	2.40 (2.00- 3.00)	91.4
JL038-21	Anderson, E (1996)	United States	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	24	4.00 (2.60- 6.40)	N/A
LC048-21	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	26	5.20 (3.20- 8.20)	N/A
LC048-22	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	24	2.40 (1.60- 3.80)	N/A
LC059-2	Esposito, S (2005)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	46	5.80 (0.00-89.60)	N/A
LC109-21	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	232	3.20 (. - .)	N/A

MR207-21	Rennels, M (1998)	United States	Wyeth-7	2, 4, 6, 14	Yes	DTwP	Wyeth	90	2.20 (1.80- 2.80)	N/A
MR817-21	Nurkka, A (2001)	Finland	Aventis-8	2, 4, 6, 15	No	DTwP	Wyeth	.	3.00 (. - .)	N/A
MR817-22	Nurkka, A (2001)	Finland	Aventis-8	2, 4, 6, 15	No	DTwP	Wyeth	.	1.60 (. - .)	N/A
MR917-21	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	2.40 (1.60- 4.00)	N/A
MR917-22	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	2.00 (1.40- 3.00)	N/A
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	3.40 (3.00- 4.00)	N/A

Serotype 19F, dose 3p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
02IJP039-1	Jonsdottir, I (2000)	Iceland	Aventis-8	3, 4, 6	No	DTwP	Wyeth	.	3.40 (. - .)	N/A
02IJP039-2	Jonsdottir, I (2000)	Iceland	Aventis-8	3, 4, 6	No	DTwP	Wyeth	.	4.00 (. - .)	N/A
02MYP052-1	Yaich, M (2000)	Israel	Aventis-11	2, 4, 6	No	DTwP	Wyeth	59	5.00 (. - .)	N/A
02MYP052-2	Yaich, M (2000)	Finland	Aventis-11	2, 4, 6	No	DTwP	Wyeth	60	4.60 (. - .)	N/A
02MYP052-3	Yaich, M (2000)	Iceland	Aventis-11	3, 4, 6	No	DTwP	Wyeth	73	6.20 (. - .)	N/A
05AS249-1	Soininen, A (2006)	Finland	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	46	3.60 (2.80- 4.80)	N/A
05AS249-2	Soininen, A (2006)	Finland	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	46	4.60 (3.40- 6.20)	N/A
05AS249-3	Soininen, A (2006)	Finland	Aventis-11	2, 4, 6, 14	No	DTwP	Wyeth	60	5.80 (4.40- 7.80)	N/A
05AS249-4	Soininen, A (2006)	Finland	Aventis-11	2, 4, 6, 14	No	DTwP	Wyeth	60	6.00 (4.40- 8.20)	N/A
05AS249-5	Soininen, A (2006)	Finland	GSK-11	2, 4, 6, 14	No	DTaP	GSK	48	5.20 (4.00- 6.60)	N/A
07KK2158-2	Kim, KH (2010)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	129	N/A	100.0
AC022-1	Knuf, M (2006)	Germany	Wyeth-7	2, 3, 4, 14	No	DTaP	Wyeth	115	4.40 (4.00- 5.00)	N/A
AC030-1	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	35	3.40 (2.60- 4.20)	N/A
AC030-2	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	2.80 (2.00- 3.60)	N/A
AC030-3	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	2.40 (1.80- 3.00)	N/A
AC034-1	Lee, H (2009)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	31	3.80 (3.00- 4.80)	N/A
BB053-1	Kim, N-H (2007)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	177	4.80 (4.20- 5.80)	97.9
BB071-1	Wysocki, J (2009)	Germany,	GSK-10	2, 4, 6, 14	No	DTaP	GSK	169	5.00 (4.20- 5.60)	98.2

		Poland, Spain								
BB071-2	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	175	4.80 (4.00- 5.40)	98.9
BB071-3	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	173	3.80 (3.40- 4.40)	97.7
BB071-4	Wysocki, J (2009)	Germany, Poland, Spain	Wyeth-7	2, 4, 6, 13	No	DTaP	GSK	170	2.60 (2.20- 2.80)	99.4
BB076-1	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	56	2.20 (. - .)	N/A
BB076-2	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	51	1.80 (. - .)	N/A
BB076-3	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	50	1.60 (. - .)	N/A
BB076-4	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	42	1.60 (. - .)	N/A
BB093-1	Prymula, R (2006)	Czech Republic, Slovakia	GSK-11	3, 5, 6, 12	No	DTaP	GSK	143	2.60 (2.20- 3.00)	N/A
BB097-1	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	16.20 (12.80-20.20)	N/A
BB815-3	Miernyk , KM (2000)	United States	Merck-7	2, 4, 6, 15	No	DTaP	Wyeth	32	1.40 (1.00- 2.00)	N/A
BB837-1	Li, RC (2008)	China	Wyeth-7	3, 4, 5, 14	Yes	DTaP	Wyeth	64	11.80 (9.00-15.60)	N/A
BB837-2	Li, RC (2008)	China	Wyeth-7	3, 4, 5, 14	Yes	DTaP	Wyeth	66	5.60 (4.40- 7.00)	N/A
BB846-1	Lucero, MG (2004)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	56	16.00 (11.60-22.40)	N/A
BBJL603-2	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10		No	DTaP	GSK	154	4.40 (3.60- 5.40)	94.7
JL038-1	Anderson, E (1996)	United States	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	25	7.20 (4.60-11.40)	N/A
JL045-1	Anttila, M (1999)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	28	7.20 (. - .)	N/A
JL045-2	Anttila, M (1999)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	25	7.20 (. - .)	N/A
JL065-1	Bermal, N (2009)	North America	GSK-10	1.5, 2.5, 3.5	No	DTwP	GSK	285	10.40 (9.40-11.80)	99.6
JL065-2	Bermal, N (2009)	North America	Wyeth-7	1.5, 2.5, 3.5	No	DTwP	GSK	95	4.60 (4.00- 5.40)	97.9
JL065-3	Bermal, N (2009)	Poland	GSK-10	2, 4, 6	No	DTwP	GSK	285	5.40 (4.80- 5.80)	97.9
JL065-4	Bermal, N (2009)	Poland	Wyeth-7	2, 4, 6	No	DTwP	GSK	96	2.40 (2.00- 2.80)	96.9

JL097-1	Buttery, J (2005)	United Kingdom	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	100	1.80 (1.60- 2.20)	N/A
JLMR202-1	Reinert, P (2003)	France	Wyeth-7	2, 3, 4	Yes	DTwP	Wyeth	53	4.20 (3.20- 5.60)	N/A
JLMR251-1	Shapiro, E (1997)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	40	2.40 (. - .)	N/A
JLMR251-2	Shapiro, E (1997)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	40	2.40 (. - .)	N/A
JLMR254-1	Shinefield, H (1999)	United States	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	81	2.00 (1.60- 2.40)	N/A
JLMR254-2	Shinefield, H (1999)	United States	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	75	2.00 (1.60- 2.40)	N/A
LC019-1	Dagan, R (2004)	Finland	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	91	4.60 (3.60- 6.00)	N/A
LC019-2	Dagan, R (2004)	Israel	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	125	5.80 (3.60- 7.20)	N/A
LC048-1	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	26	7.00 (4.80-10.40)	100.0
LC048-2	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	23	7.60 (4.80-11.80)	100.0
LC049-1	Ekstrom, N (2005)	Finland	Wyeth-7	2, 4, 6, 12	Yes	DTwP	Wyeth	55	3.20 (2.60- 4.20)	N/A
LC049-2	Ekstrom, N (2005)	Finland	Merck-7	2, 4, 6, 12	Yes	DTwP	Wyeth	53	3.60 (2.80- 4.60)	N/A
LC109-1	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	201	3.00 (. - .)	N/A
MR207-1	Rennels, M (1998)	United States	Wyeth-7	2, 4, 6, 14	Yes	DTwP	Wyeth	90	3.40 (2.80- 4.40)	N/A
MR223-2	Ruggeberg, J (2007)	United Kingdom	Wyeth-7	2, 3, 4, 12	No	DTwP	Wyeth	62	3.80 (3.20- 4.60)	100.0
MR250-1	Shao, Pei-Lan (2004)	Taiwan	Wyeth-7	2, 4, 6	No	DTwP	Wyeth	60	4.40 (3.80- 5.00)	N/A
MR266-1	Soininen, Anu (2009)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	479	13.80 (12.40-15.40)	N/A
MR282-1	Tichmann-Schumann, I. (2005)	Germany	Wyeth-7	2, 3, 4, 13	No	DTaP	GSK	141	3.80 (3.20- 4.40)	N/A
MR301-1	Vesikari, T. (2009)	Finland, France, Poland	Wyeth-7	2, 3, 4	No	DTaP	GSK	375	3.40 (3.20- 3.80)	98.1
MR301-2	Vesikari, T. (2009)	Finland, France, Poland	GSK-10	2, 3, 4	No	DTaP	GSK	1107	18.40 (1.80- 2.00)	89.1
MR816-1	Nurkka, A (2001)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	29	7.00 (5.80- 8.80)	N/A
MR816-2	Nurkka, A (2001)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	30	7.00 (5.80- 8.80)	N/A
MR818-1	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	3.80 (3.00- 4.60)	N/A
MR818-2	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	4.40 (3.40- 5.60)	N/A

MR824-1	Obaro, S. (2000)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	94	3.00 (2.20- 3.80)	N/A
MR825-2	Obaro, Stephen (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	60	2.00 (1.40- 3.00)	N/A
MR825-3	Obaro, Stephen (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	53	3.20 (2.20- 4.80)	N/A
MR912-3	O'Brien, K. (2000)	United States	Wyeth-7	2, 4, 6	No	DTwP	Wyeth	9	2.00 (1.00- 4.00)	N/A
MR914-1	Olivier, C (2008)	France, Germany	Wyeth-7	2, 3, 4, 14	No	DTaP	Wyeth	125	3.60 (3.20- 4.20)	N/A
MR917-1	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	5.80 (4.40- 7.80)	N/A
MR917-2	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	5.60 (4.40- 7.20)	N/A
MRJL087-1	Block, S (1997)	United States	Merck-7	2, 4, 6	No	DTwP	Wyeth	68	2.40 (. - .)	N/A
MRJL087-2	Block, S (1997)	United States	Merck-7	2, 4, 6	No	DTwP	Wyeth	31	8.60 (. - .)	N/A
UPD012-1	Bryant, K (2010)	United States	Wyeth-13	2, 4, 6, 14	No	DTaP	Wyeth	102	2.20 (1.80- 2.40)	N/A
UPD012-2	Bryant, K (2010)	United States	Wyeth-7	2, 4, 6, 14	No	DTaP	Wyeth	111	2.60 (2.20- 3.00)	N/A
UPD054-1	Kieninger, D (2010)	Germany	Wyeth-13	2, 3, 4, 12	No	DTaP	Wyeth	.	1.80 (1.60- 2.00)	N/A
UPD054-2	Kieninger, D (2010)	Germany	Wyeth-7	2, 3, 4, 12	No	DTaP	Wyeth	.	2.80 (2.60- 3.20)	N/A
UPD068-1	Moss, S (2010)	United Kingdom	Wyeth-7	2, 3, 4	No	DTaP	Wyeth	53	2.60 (2.00- 3.40)	N/A
UPD117-1	GSK (2008)	Taiwan	GSK-10	2, 3, 6	No	DTaP	GSK	219	8.00 (7.40- 8.80)	N/A
UPD118-1	GSK (2009)	Mali	GSK-10	1.5, 2.5, 3.5	Yes	DTwP	GSK	141	7.20 (6.00- 8.60)	N/A
UPD122-1	GSK (2009)	South Korea	GSK-10	2, 4, 6	No	DTaP	GSK	344	7.40 (6.60- 8.20)	N/A
UPD122-2	GSK (2009)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	GSK	123	2.80 (2.40- 3.20)	N/A
UPD128-1	Scott (2011)	Kenya	Wyeth-7	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	.	6.40 (5.40- 7.40)	N/A
UPD128-2	Scott (2011)	Kenya	Wyeth-7	0, 2.5, 3.5, 9	No	DTwP	Wyeth	.	3.60 (3.00- 4.20)	N/A

Serotype 23F, dose 2p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compari-son vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB045-1	Kayhty, H (2005)	Sweden	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	75	0.80 (0.60- 1.20)	N/A
BB053-21	Kim, N-H (2007)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	181	1.60 (1.40- 2.00)	95.9
BB071-21	Wysocki, J (2009)	German, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	156	0.40 (. - .)	60.9
BB097-21	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	0.80 (0.60- 1.20)	N/A
BB815-23	Miernyk , KM (2000)	United States	Merck-7	2, 4, 6, 15	No	DTaP	Wyeth	32	0.20 (0.00- 0.20)	N/A
BBJL601-1	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	114	0.20 (0.20- 0.20)	51.0
BBJL601-2	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	170	0.60 (0.40- 0.60)	78.0
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	0.40 (0.40- 0.40)	55.6
JL038-21	Anderson, E (1996)	United States	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	24	1.00 (0.60- 1.60)	N/A
LC048-21	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	26	1.00 (0.60- 1.60)	N/A
LC048-22	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	24	0.40 (0.20- 0.60)	N/A
LC059-2	Esposito, S (2005)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	46	1.20 (0.00-15.60)	N/A
LC109-21	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	232	1.20 (. - .)	N/A
MR207-21	Rennels, M (1998)	United States	Wyeth-7	2, 4, 6, 14	Yes	DTwP	Wyeth	90	0.40 (0.20- 0.40)	N/A
MR817-21	Nurkka, A (2001)	Finland	Aventis-8	2, 4, 6, 15	No	DTwP	Wyeth	.	0.40 (. - .)	N/A
MR817-22	Nurkka, A (2001)	Finland	Aventis-8	2, 4, 6, 15	No	DTwP	Wyeth	.	0.20 (. - .)	N/A
MR917-21	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	1.80 (1.00- 3.20)	N/A
MR917-22	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	1.00 (0.60- 1.60)	N/A
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	0.60 (0.60- 0.80)	N/A

Serotype 23F, dose 3p

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
02IJP039-1	Jonsdottir, I (2000)	Iceland	Aventis-8	3, 4, 6	No	DTwP	Wyeth	.	1.00 (. - .)	N/A
02IJP039-2	Jonsdottir, I (2000)	Iceland	Aventis-8	3, 4, 6	No	DTwP	Wyeth	.	1.00 (. - .)	N/A
02MYP052-1	Yaich, M (2000)	Israel	Aventis-11	2, 4, 6	No	DTwP	Wyeth	59	1.40 (. - .)	N/A
02MYP052-2	Yaich, M (2000)	Finland	Aventis-11	2, 4, 6	No	DTwP	Wyeth	60	1.00 (. - .)	N/A
02MYP052-3	Yaich, M (2000)	Iceland	Aventis-11	3, 4, 6	No	DTwP	Wyeth	73	1.40 (. - .)	N/A
07KK2158-2	Kim, KH (2010)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	129	N/A	98.4
AC022-1	Knuf, M (2006)	Germany	Wyeth-7	2, 3, 4, 14	No	DTaP	Wyeth	115	2.00 (1.60- 2.40)	N/A
AC030-1	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	35	4.20 (2.60- 6.60)	N/A
AC030-2	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	4.20 (3.20- 5.40)	N/A
AC030-3	Lagos, R (2009)	Chile	Wyeth-9	2, 4, 6	Yes	DTwP	Wyeth	40	2.80 (2.00- 4.00)	N/A
AC034-1	Lee, H (2009)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	31	3.00 (2.20- 4.20)	N/A
BB053-1	Kim, N-H (2007)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	Wyeth	177	3.80 (3.20- 4.40)	97.9
BB071-1	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	169	1.20 (1.20- 1.40)	94.1
BB071-2	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	175	1.20 (1.00- 1.40)	88.6
BB071-3	Wysocki, J (2009)	Germany, Poland, Spain	GSK-10	2, 4, 6, 14	No	DTaP	GSK	173	1.00 (0.80- 1.20)	83.8
BB071-4	Wysocki, J (2009)	Germany, Poland, Spain	Wyeth-7	2, 4, 6, 13	No	DTaP	GSK	170	2.40 (2.00- 3.00)	91.1
BB076-1	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	56	0.80 (. - .)	N/A
BB076-2	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	51	0.60 (. - .)	N/A
BB076-3	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	50	0.40 (. - .)	N/A
BB076-4	Zangwill, K (2003)	United States	Merck-7	2, 4, 6, 12	No	DTwP	Wyeth	42	0.40 (. - .)	N/A
BB093-1	Prymula, R (2006)	Czech Republic, Slovakia	GSK-11	3, 5, 6, 12	No	DTaP	GSK	139	0.80 (0.80- 1.00)	N/A

BB097-1	Puumalainen, T (2002)	North America	Aventis-11	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	47	3.80 (2.80- 5.40)	N/A
BB815-3	Miernyk , KM (2000)	United States	Merck-7	2, 4, 6, 15	No	DTaP	Wyeth	32	0.40 (0.20- 0.80)	N/A
BB837-1	Li, RC (2008)	China	Wyeth-7	3, 4, 5, 14	Yes	DTaP	Wyeth	64	4.60 (3.20- 6.80)	N/A
BB837-2	Li, RC (2008)	China	Wyeth-7	3, 4, 5, 14	Yes	DTaP	Wyeth	66	2.20 (1.60- 3.00)	N/A
BB846-1	Lucero, MG (2004)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	56	3.20 (2.00- 4.80)	N/A
BBJL603-2	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 4, 5, 12	No	DTaP	GSK	154	0.60 (0.40- 0.60)	64.5
JL038-1	Anderson, E (1996)	United States	Merck-7	2, 4, 6, 14	No	DTwP	Wyeth	25	2.40 (1.40- 3.80)	N/A
JL045-1	Anttila, M (1999)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	28	4.00 (. - .)	N/A
JL045-2	Anttila, M (1999)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	25	4.00 (. - .)	N/A
JL065-1	Bermal, N (2009)	North America	GSK-10	1.5, 2.5, 3.5	No	DTwP	GSK	285	2.20 (2.00- 2.60)	94.7
JL065-2	Bermal, N (2009)	North America	Wyeth-7	1.5, 2.5, 3.5	No	DTwP	GSK	95	2.20 (1.80- 3.00)	91.6
JL065-3	Bermal, N (2009)	Poland	GSK-10	2, 4, 6	No	DTwP	GSK	285	1.20 (1.00- 1.20)	88.8
JL065-4	Bermal, N (2009)	Poland	Wyeth-7	2, 4, 6	No	DTwP	GSK	96	2.20 (1.80- 2.60)	96.9
JL097-1	Buttery, J (2005)	United Kingdom	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	100	1.20 (1.00- 1.40)	N/A
JLMR202-1	Reinert, P (2003)	France	Wyeth-7	2, 3, 4	Yes	DTwP	Wyeth	53	1.60 (1.20- 2.40)	N/A
JLMR251-1	Shapiro, E (1997)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	40	0.80 (. - .)	N/A
JLMR251-2	Shapiro, E (1997)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	40	1.20 (. - .)	N/A
JLMR254-1	Shinefield, H (1999)	United States	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	81	2.60 (2.20- 3.00)	N/A
JLMR254-2	Shinefield, H (1999)	United States	Wyeth-7	2, 4, 6, 14	No	DTwP	Wyeth	75	2.60 (2.20- 3.20)	N/A
LC019-1	Dagan, R (2004)	Finland	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	91	1.20 (0.80- 1.60)	N/A
LC019-2	Dagan, R (2004)	Israel	Aventis-11	2, 4, 6, 12	No	DTwP	Wyeth	125	1.60 (1.20- 2.00)	N/A
LC048-1	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	26	1.40 (0.80- 2.20)	92.3
LC048-2	Eick, A (2004)	United States	Aventis-8	2, 4, 6	No	DTwP	Wyeth	24	1.40 (0.60- 2.60)	87.5
LC049-1	Ekstrom, N (2005)	Finland	Wyeth-7	2, 4, 6, 12	Yes	DTwP	Wyeth	55	2.60 (1.80- 3.40)	N/A
LC049-2	Ekstrom, N (2005)	Finland	Merck-7	2, 4, 6, 12	Yes	DTwP	Wyeth	53	0.60 (0.40- 0.80)	N/A

LC109-1	Huebner, R (2002)	South Africa	Wyeth-9	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	202	2.80 (. - .)	N/A
MR207-1	Rennels, M (1998)	United States	Wyeth-7	2, 4, 6, 14	Yes	DTwP	Wyeth	90	1.80 (1.20- 2.60)	N/A
MR223-2	Ruggeberg, J (2007)	United Kingdom	Wyeth-7	2, 3, 4, 12	No	DTwP	Wyeth	62	2.20 (1.60- 3.00)	95.0
MR250-1	Shao, Pei-Lan (2004)	Taiwan	Wyeth-7	2, 4, 6	No	DTwP	Wyeth	60	3.20 (2.40- 4.40)	N/A
MR266-1	Soininen, A (2009)	North America	Aventis-11	1.5, 2.5, 3.5	Yes	DTwP	Wyeth	479	1.60 (1.40- 1.80)	N/A
MR282-1	Tichmann-Schumann, I. (2005)	Germany	Wyeth-7	2, 3, 4, 13	No	DTaP	GSK	141	2.00 (1.80- 2.60)	N/A
MR301-1	Vesikari, T. (2009)	Finland, France, Poland	Wyeth-7	2, 3, 4	No	DTaP	GSK	375	1.40 (1.20- 1.60)	87.2
MR301-2	Vesikari, T. (2009)	Finland, France, Poland	GSK-10	2, 3, 4	No	DTaP	GSK	1107	0.60 (0.60- 0.60)	66.6
MR816-1	Nurkka, A (2001)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	29	4.20 (3.60- 5.20)	N/A
MR816-2	Nurkka, A (2001)	Finland	Wyeth-7	2, 4, 6, 15	No	DTwP	Wyeth	30	4.20 (3.60- 5.20)	N/A
MR818-1	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	1.40 (1.00- 1.80)	N/A
MR818-2	Nurkka, A. (2004)	Finland	GSK-11	2, 4, 6, 14	Yes	DTaP	Wyeth	51	1.60 (1.20- 2.20)	N/A
MR824-1	Obaro, S. (2000)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	93	2.80 (2.20- 3.80)	N/A
MR825-2	Obaro, S (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	60	1.20 (0.80- 1.60)	N/A
MR825-3	Obaro, S (2002)	The Gambia	Wyeth-9	2, 3, 4	No	DTwP	Wyeth	53	2.40 (1.60- 3.40)	N/A
MR912-3	O'Brien, K. (2000)	United States	Wyeth-7	2, 4, 6	No	DTwP	Wyeth	9	2.20 (1.00- 4.60)	N/A
MR914-1	Olivier, C (2008)	France, Germany	Wyeth-7	2, 3, 4, 14	No	DTaP	Wyeth	125	1.40 (1.20- 1.80)	N/A
MR917-1	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	6.60 (4.80- 9.20)	N/A
MR917-2	Osendarp, S (2007)	Bangladesh	Wyeth-7	4, 5, 6	No	DTwP	Wyeth	53	6.60 (5.40- 8.20)	N/A
MRJL087-1	Block, S (1997)	United States	Merck-7	2, 4, 6	No	DTwP	Wyeth	68	0.60 (. - .)	N/A
MRJL087-2	Block, S (1997)	United States	Merck-7	2, 4, 6	No	DTwP	Wyeth	31	0.60 (. - .)	N/A
UPD012-1	Bryant, K (2010)	United States	Wyeth-13	2, 4, 6, 14	No	DTaP	Wyeth	102	1.40 (1.20- 1.60)	N/A
UPD012-2	Bryant, K (2010)	United States	Wyeth-7	2, 4, 6, 14	No	DTaP	Wyeth	114	1.80 (1.60- 2.20)	N/A
UPD054-1	Kieninger, D (2010)	Germany	Wyeth-13	2, 3, 4, 12	No	DTaP	Wyeth	.	1.20 (1.20- 1.40)	N/A
UPD054-2	Kieninger, D (2010)	Germany	Wyeth-7	2, 3, 4, 12	No	DTaP	Wyeth	.	1.40 (1.20- 1.60)	N/A

UPD068-1	Moss, S (2010)	United Kingdom	Wyeth-7	2, 3, 4	No	DTaP	Wyeth	53	1.40 (1.00- 2.00)	N/A
UPD117-1	GSK (2008)	Taiwan	GSK-10	2, 3, 6	No	DTaP	GSK	219	2.80 (2.40- 3.20)	N/A
UPD118-1	GSK (2009)	Mali	GSK-10	1.5, 2.5, 3.5	Yes	DTwP	GSK	141	0.80 (0.60- 1.00)	N/A
UPD122-1	GSK (2009)	South Korea	GSK-10	2, 4, 6	No	DTaP	GSK	344	2.00 (1.80- 2.20)	N/A
UPD122-2	GSK (2009)	South Korea	Wyeth-7	2, 4, 6	No	DTaP	GSK	123	4.00 (3.20- 4.80)	N/A
UPD128-1	Scott (2011)	Kenya	Wyeth-7	1.5, 2.5, 3.5, 9	No	DTwP	Wyeth	.	3.00 (2.60- 3.60)	N/A
UPD128-2	Scott (2011)	Kenya	Wyeth-7	0, 2.5, 3.5, 9	No	DTwP	Wyeth	.	2.80 (2.20- 3.60)	N/A

b. Post-booster (2p+1) geometric antibody concentration (GMC) and percent above 0.35ug/ml (or 2.0 if GSK lab method used)

Serotype 1, dose 2p+1

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	1.80 (1.60- 2.20)	95.5
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	5.80 (5.20- 6.40)	N/A

Serotype 5, dose 2p+1

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compari-son vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	2.60 (2.40- 3.00)	98.7
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	3.60 (3.20- 4.00)	N/A

Serotype 6b, dose 2p+1

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB045-1	Kayhty, H (2005)	Sweden	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	83	5.00 (3.40- 7.00)	N/A
BBJL601-1	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	107	8.20 (6.40-10.40)	N/A
BBJL601-2	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	90	7.40 (5.60- 9.80)	N/A
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	1.20 (0.80- 1.40)	87.2
BBJL604-1	Rodenburg, GD (2010)	Netherlands	Wyeth-7	2, 4, 11	No	DTaP	Wyeth	72	2.20 (1.60- 3.20)	N/A
LC046-1	Durando, P (2009)	Italy	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	146	6.80 (5.60- 8.20)	N/A
LC059-2	Esposito, S (2005)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	46	15.60 (1.20-163.2)	N/A

UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	10.00 (8.80-11.40)	N/A
UPD033-2	Esposito, S (2010)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	.	10.40 (9.20-11.80)	N/A

Serotype 14, dose 2p+1

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB045-1	Kayhty, H (2005)	Sweden	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	83	11.60 (9.60-14.20)	N/A
BBJL601-1	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	53	18.40 (15.40-21.80)	N/A
BBJL601-2	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	116	16.00 (12.80-19.80)	N/A
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	4.20 (3.60- 4.80)	98.7
BBJL604-1	Rodenburg, GD (2010)	Netherlands	Wyeth-7	2, 4, 11	No	DTaP	Wyeth	72	9.40 (7.80-11.40)	N/A
LC046-1	Durando, P (2009)	Italy	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	146	12.20 (10.40-14.40)	N/A
LC059-2	Esposito, S (2005)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	46	13.80 (0.20-168.2)	N/A
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	10.40 (9.20-11.40)	N/A
UPD033-2	Esposito, S (2010)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	.	12.00 (10.80-13.40)	N/A

Serotype 19F, dose 2p+1

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB045-1	Kayhty, H (2005)	Sweden	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	83	5.00 (3.40- 7.40)	N/A
BBJL601-1	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	53	7.60 (6.40- 9.20)	N/A
BBJL601-2	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	116	6.00 (5.00- 7.40)	N/A
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	5.60 (4.60- 6.60)	95.5
BBJL604-1	Rodenburg, GD (2010)	Netherlands	Wyeth-7	2, 4, 11	No	DTaP	Wyeth	72	3.40 (2.80- 4.20)	N/A
LC046-1	Durando, P (2009)	Italy	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	146	10.20 (8.60-12.20)	N/A
LC059-2	Esposito, S (2005)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	46	8.40 (0.40-89.00)	N/A

UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	9.00 (7.80-10.40)	N/A
UPD033-2	Esposito, S (2010)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	.	8.00 (7.00- 9.20)	N/A

Serotype 23F, dose 2p+1

Study ID	Author (Year)	Country	PCV product valency	Vaccination schedule (months)	Compar-ison vs. no PCV	Co-admin. DTP Vaccine	ELISA method	No. analyzed	GMC (95% CI)*	% Above cutoff**
BB045-1	Kayhty, H (2005)	Sweden	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	83	4.60 (3.40- 6.20)	N/A
BBJL601-1	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	53	5.60 (4.40- 7.00)	N/A
BBJL601-2	Goldblatt, D (2010)	United Kingdom	Wyeth-7	2, 3, 13	No	DTaP	Wyeth	116	6.40 (5.00- 7.80)	N/A
BBJL603-1	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	GSK-10	3, 5, 12	No	DTaP	GSK	158	2.40 (2.00- 3.00)	92.2
BBJL604-1	Rodenburg, GD (2010)	Netherlands	Wyeth-7	2, 4, 11	No	DTaP	Wyeth	72	2.60 (2.20- 3.20)	N/A
LC046-1	Durando, P (2009)	Italy	Wyeth-7	3, 5, 12	No	DTaP	Wyeth	146	4.40 (3.80- 5.20)	N/A
LC059-2	Esposito, S (2005)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	46	9.00 (0.20-289.0)	N/A
UPD033-1	Esposito, S (2010)	Italy	Wyeth-13	3, 5, 11	No	DTaP	Wyeth	.	3.40 (3.00- 3.80)	N/A
UPD033-2	Esposito, S (2010)	Italy	Wyeth-7	3, 5, 11	No	DTaP	Wyeth	.	4.80 (4.40- 5.60)	N/A

*The 95% confidence interval is included where available.
**If ELISA method=GSK then cutoff=0.20 ug/ml; if ELISA method = Wyeth or other lab then cutoff=0.35 ug/ml.
Notes: Lab method “Wyeth” includes all lab methods except GSK method (i.e., WHO, KTL, etc.). When PCV is co-administered with DTwP, it tends to produce higher antibody responses than when co-administered with DTaP.

Table 17. Quality Indicators for Immunogenicity Clinical Trials

Study ID	Author(year)	Country	Randomized	Blinded	2p	3p	2p+1
BB053	Kim, N-H (2007)	South Korea	No	Not Stated	Y	Y	N
BB071	Wysocki, J (2009)	German, Poland, Spain	Yes	Double	Y	Y	N
BB097	Puumalainen, T (2002)	North America	No	No	Y	Y	N
BB815	Miernyk , KM (2000)	United States	No	No	Y	Y	N
BBJL603	Silfverdal, SA (2009)	Denmark, Norway, Slovakia, Sweden	Yes	No	Y	Y	Y
BBJL604	Rodenburg, GD (2010)	Netherlands	Yes	Not Stated	Y	Y	Y
LC048	Eick, A (2004)	United States	No	No	Y	Y	N
LC109	Huebner, R (2002)	South Africa	Yes	Double	Y	Y	N
MR207	Rennels, M (1998)	United States	Yes	Double	Y	Y	N
MR917	Osendarp, S (2007)	Bangladesh	Yes	Double	Y	Y	N
BB045	Kayhty, H (2005)	Sweden	No	No	Y	N	Y
BBJL601	Goldblatt, D (2010)	United Kingdom	Yes	Not Stated	Y	N	Y
LC046	Durando, P. (2009)	Italy	Not Stated	No	Y	N	Y
LC059	Esposito, S (2005)	Italy	No	Not Stated	Y	N	Y
MR817	Nurkka, A. (2001)	Finland	.		Y	N	N
UPD033	Esposito, S (2010)	Italy	Yes	Double	Y	N	Y
02IJP039	Jonsdottir, I (2000)	Iceland	Not Stated	Not Stated	N	Y	N
02MYP052	Yaich, M (2000)	Iceland	Not Stated	Not Stated	N	Y	N
05AS249	Soininen, A (2006)	Finland	Not Stated	Not Stated	N	Y	N
07KK2158	Kim, KH (2010)	South Korea	Yes	Single	N	Y	N
AC022	Knuf, M (2006)	Germany	Yes	Double	N	Y	N
AC030	Lagos, R (2009)	Chile	Yes	Single	N	Y	N
AC034	Lee, H (2009)	South Korea	No	Not Stated	N	Y	N
BB076	Zangwill, K (2003)	United States	Yes	Not Stated	N	Y	N
BB093	Prymula, R (2006)	Czech Republic, Slovakia	Yes	Double	N	Y	N
BB837	Li, RC (2008)	China	Yes	No	N	Y	N
BB846	Lucero, MG (2004)	North America	Yes	Double	N	Y	N
BBJL208	McNeely, TB (1997)	United States	Yes	Not Stated	N	Y	N
JL038	Anderson, E (1996)	United States	No	Not Stated	N	Y	N
JL045	Anttila, M (1999)	Finland	Not Stated	Not Stated	N	Y	N
JL065	Bermal, N (2009)	Poland	Yes	Double	N	Y	N

JL097	Buttery, J (2005)	United Kingdom	Yes	No	N	Y	N
JLMR202	Reinert, P (2003)	France	Yes	No	N	Y	N
JLMR251	Shapiro, E (1997)	United States	Not Stated	Not Stated	N	Y	N
JLMR254	Shinefield, H (1999)	United States	Yes	Double	N	Y	N
LC019	Dagan, R (2004)	Israel	Not Stated	Not Stated	N	Y	N
LC049	Ekstrom, N (2005)	Finland	Not Stated	Not Stated	N	Y	N
MR223	Ruggeberg, J (2007)	United Kingdom	Not Stated	Not Stated	N	Y	N
MR250	Shao, Pei-Lan (2004)	Taiwan	No	Double	N	Y	N
MR266	Soininen, Anu (2009)	North America	Yes	Double	N	Y	N
MR282	Tichmann-Schumann, I. (2005)	Germany	Yes	No	N	Y	N
MR301	Vesikari, T. (2009)	Finland, France, Poland	Yes	Not Stated	N	Y	N
MR816	Nurkka, A (2001)	Finland	Not Stated	Not Stated	N	Y	N
MR818	Nurkka, A. (2004)	Finland	Yes	Single	N	Y	N
MR824	Obaro, S. (2000)	The Gambia	Yes	Double	N	Y	N
MR825	Obaro, Stephen (2002)	The Gambia	Yes	Double	N	Y	N
MR912	O'Brien, K. (2000)	United States	Not Stated	Not Stated	N	Y	N
MR914	Olivier, C (2008)	France, Germany	Yes	No	N	Y	N
MRJL087	Block, S (1997)	United States	No	No	N	Y	N
UPD012	Bryant, K (2010)	United States	Yes	Not Stated	N	Y	N
UPD054	Kieninger, D (2010)	Germany	Yes	Not Stated	N	Y	N
UPD068	Moss, S (2010)	United Kingdom	No	Not Stated	N	Y	N
UPD117	GSK (2008)	Taiwan	No	Not Stated	N	Y	N
UPD118	GSK (2009)	Mali	Yes	Not Stated	N	Y	N
UPD122	GSK (2009)	South Korea	Yes	Single	N	Y	N
UPD128	Scott (2011)	Kenya	Yes	No	N	Y	N

Note: "2p", "3p", and "2p+1" indicates where study contributed to analysis of 2 primary doses, 3 primary doses or 2 primary doses plus booster dose.

Figure 1. PCV Dosing landscape analysis literature search results

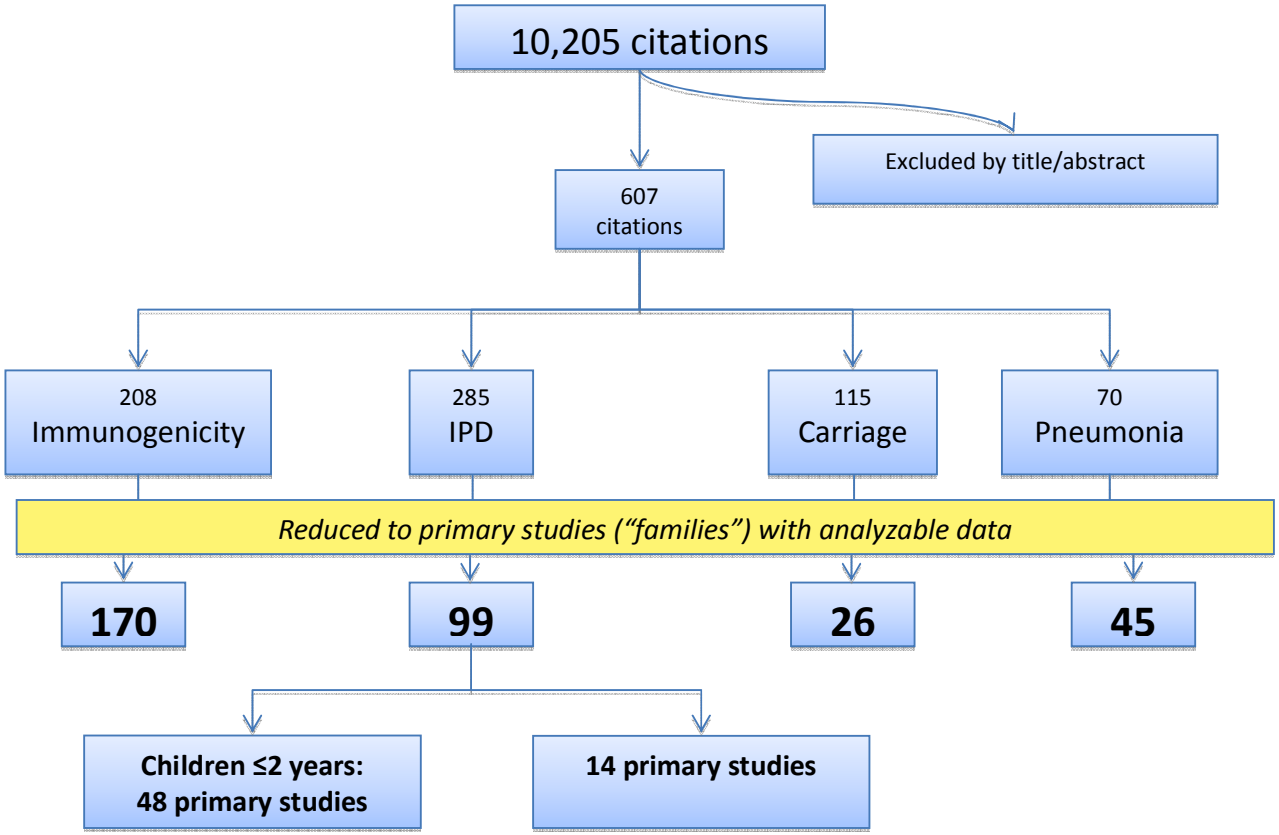
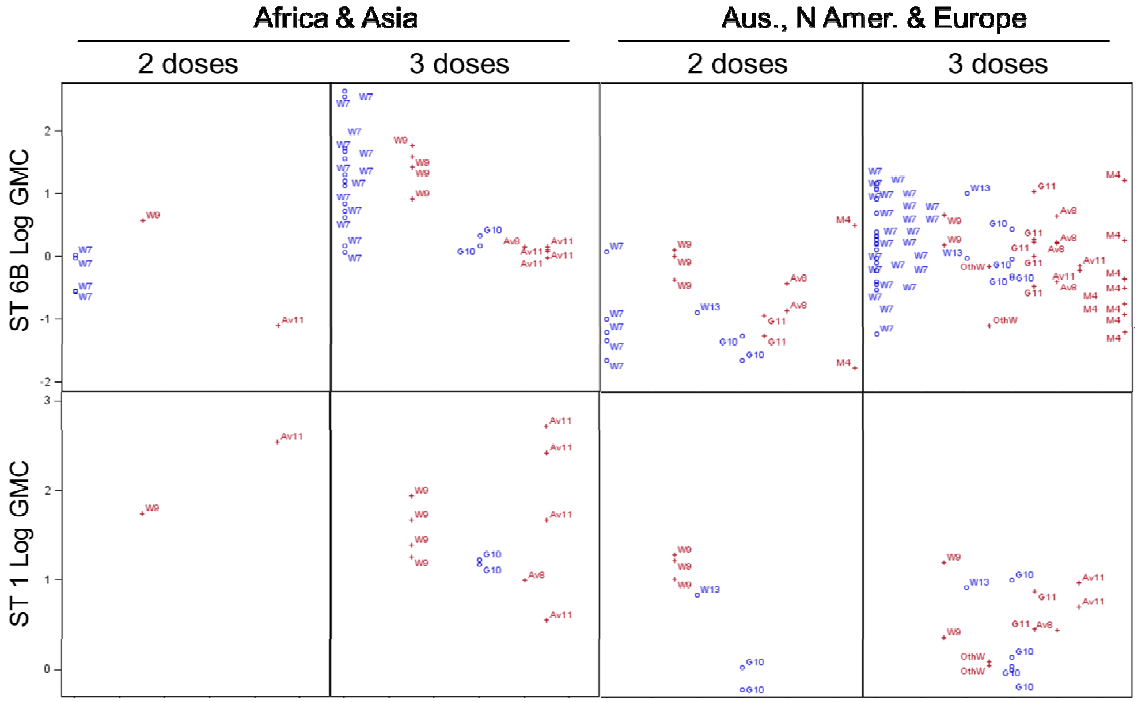
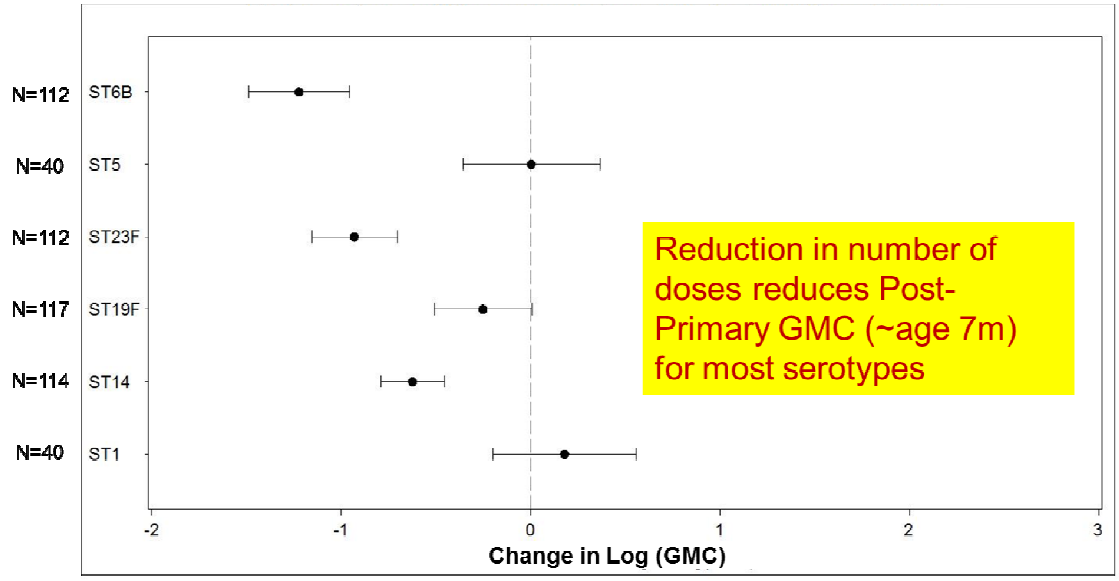


Figure 2. Serotypes 1 and 6B Log GMC by region and number of primary PCV doses (product indicated)



Note: blue indicates licensed product or precursor; red indicates unlicensed product.

Figure 3. Effect on post-primary log GMC when changing from a 3-dose to a 2-dose PCV primary schedule



Adjusted for: Age at first dose, geographic region, PCV product, co-administration of DTaP v DTwP, Lab method (GSK v Wyeth/other)

Figure 4. Effect of 2 vs. 3 PCV doses in primary series on percent of children with titers above 0.35ug/ml (0.2ug/ml if GSK ELISA used)

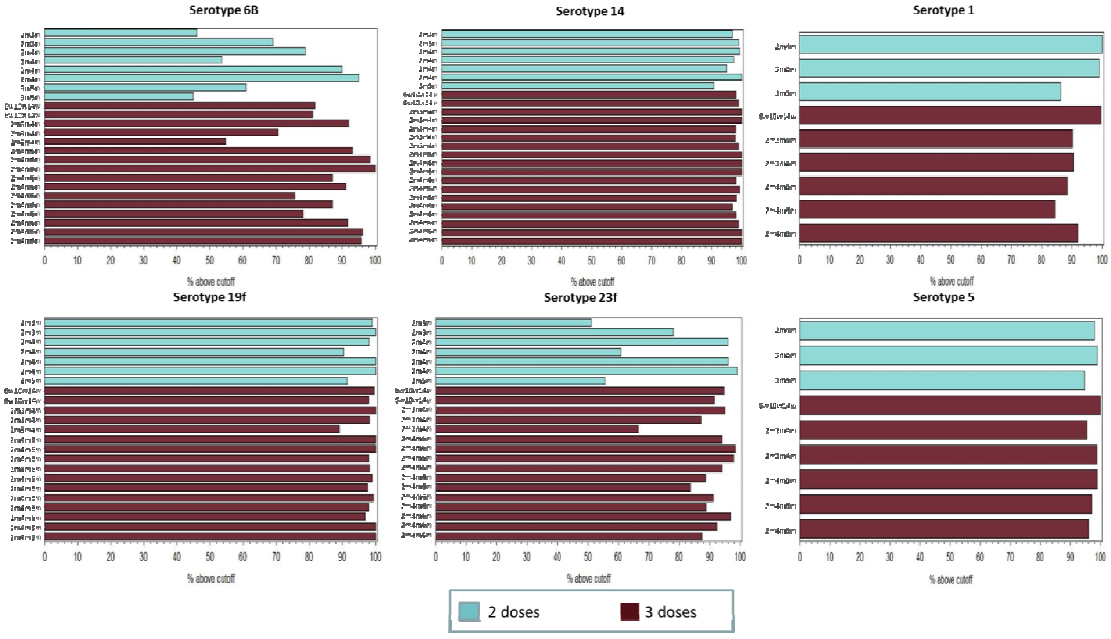
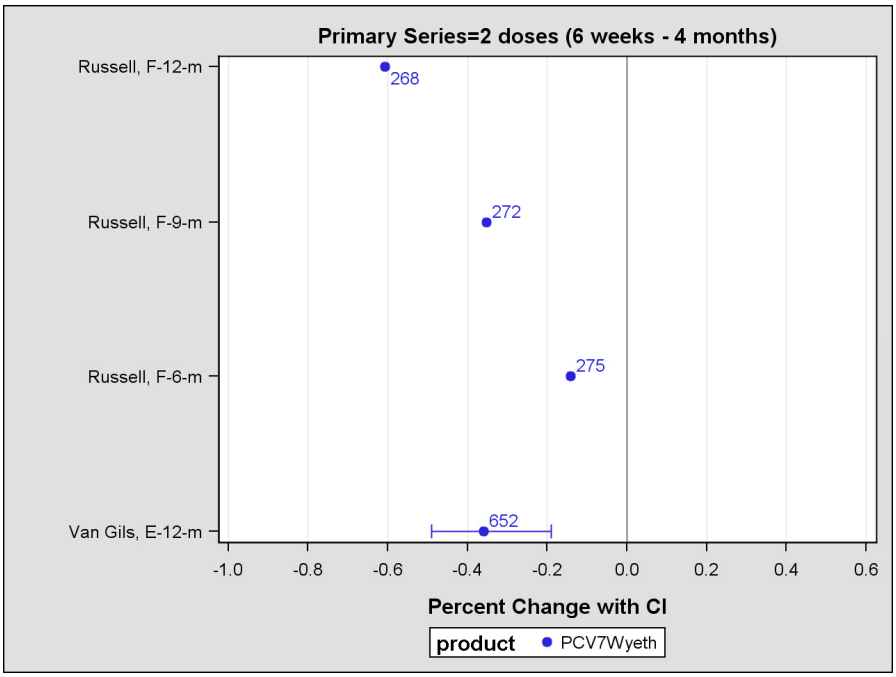
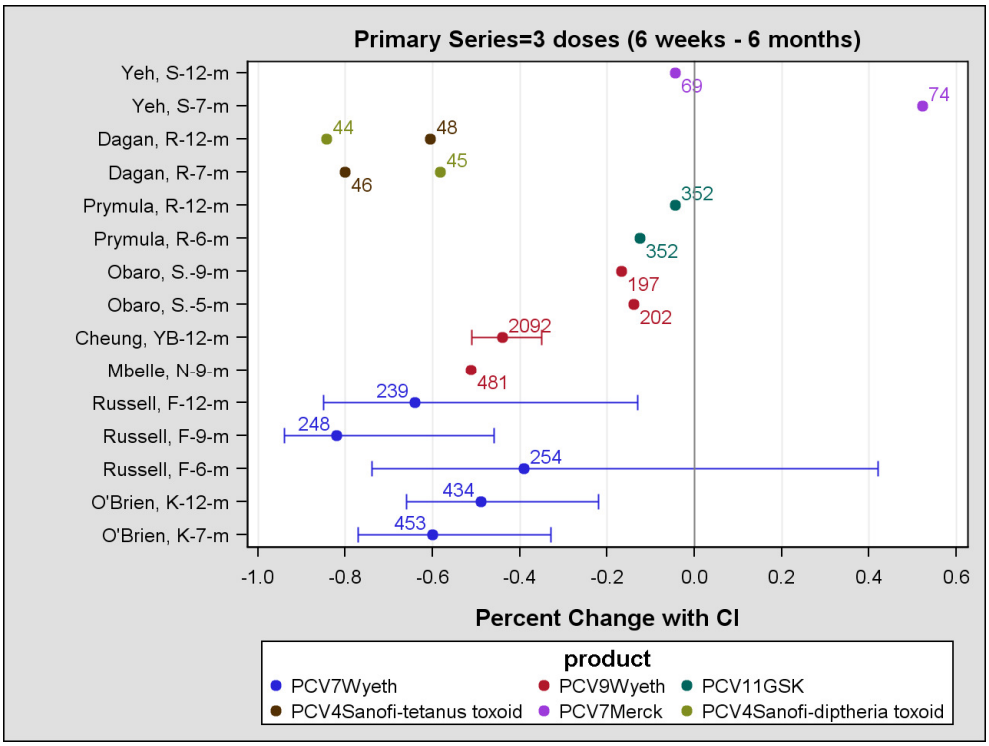


Figure 5. Vaccine-type nasopharyngeal carriage in controlled trials with a 2-dose primary series, given between 6 weeks and 4 months



*Numbers above dots are the sample size. Study labels contain first author's last name, first initial, and age at time of nasopharyngeal swab.

Figure 6. Vaccine-type nasopharyngeal carriage in controlled trials with a 3-dose primary series, given between 6 weeks and 6 months



*Numbers above dots are the sample size. Study labels contain first author's last name, first initial, and age at time of nasopharyngeal swab.

Figure 7. PCV efficacy against clinical and radiologically confirmed pneumonia for Randomized Clinical Trials with a 3+0 dosing schedule

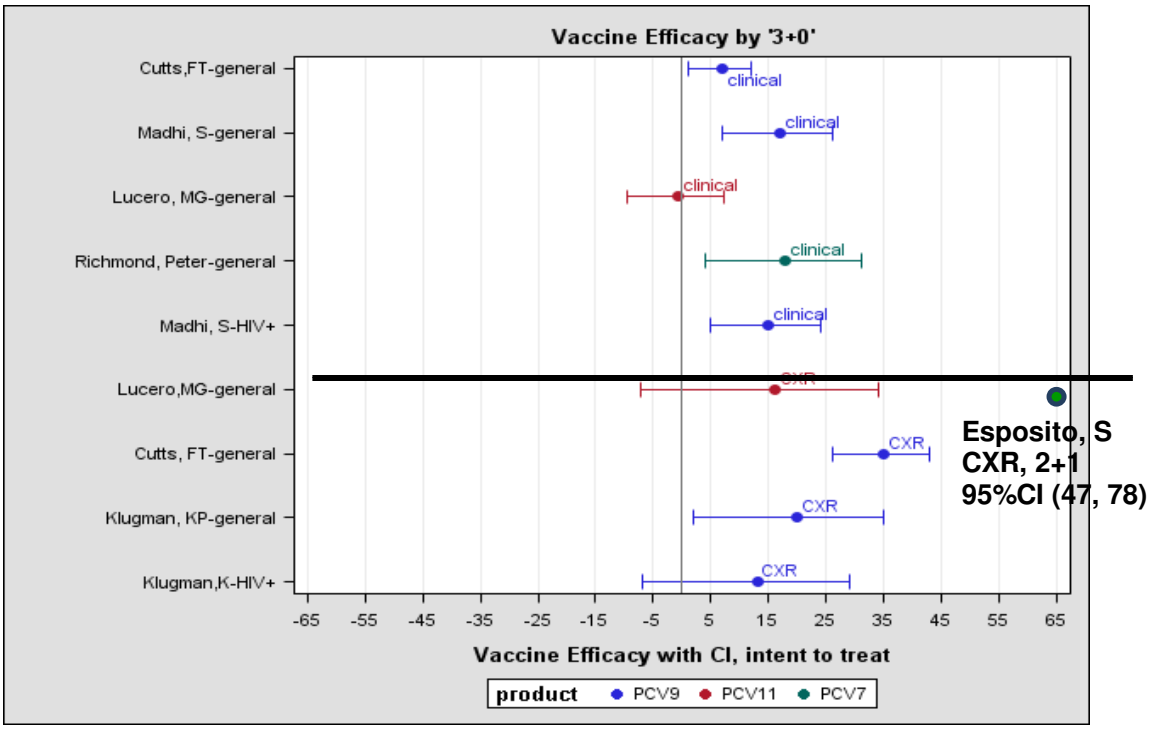


Figure 8. PCV effectiveness against clinical pneumonia in children <5 years, 3+1 schedule

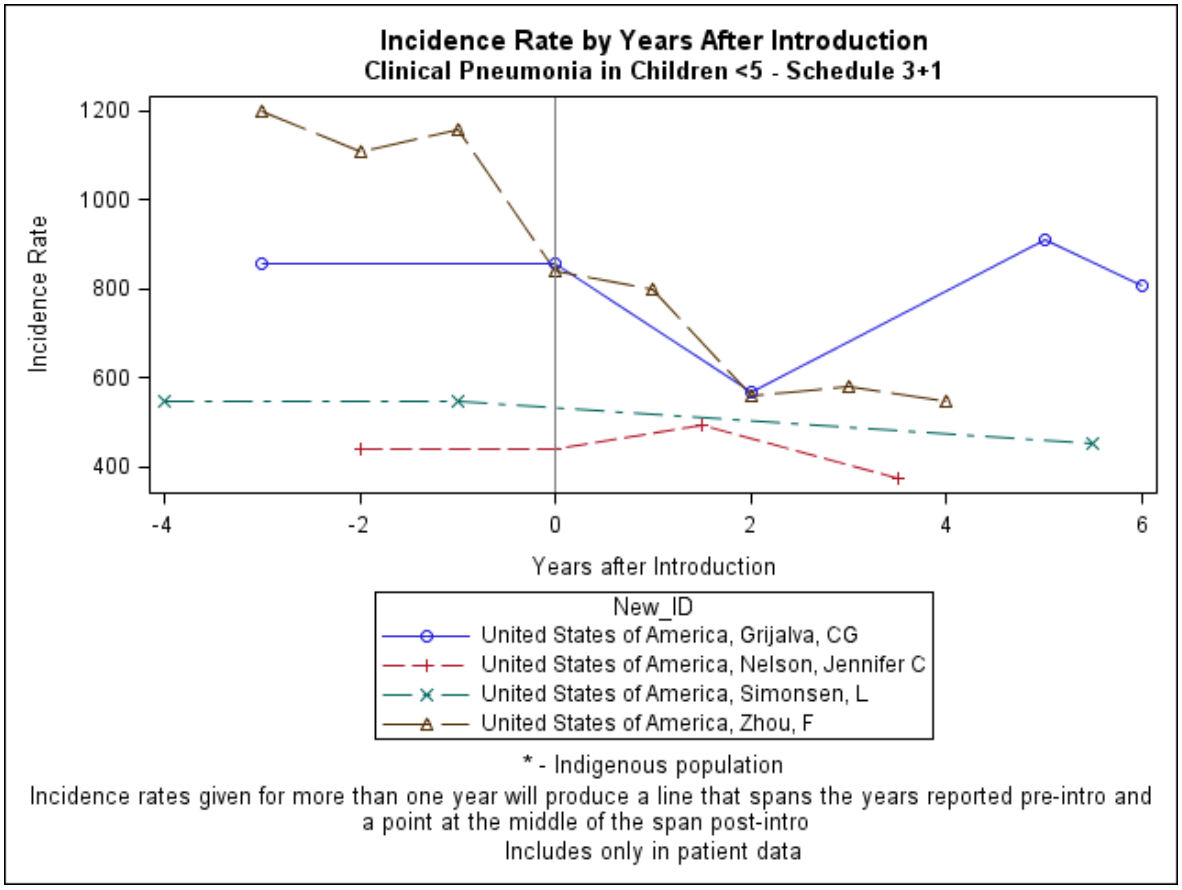
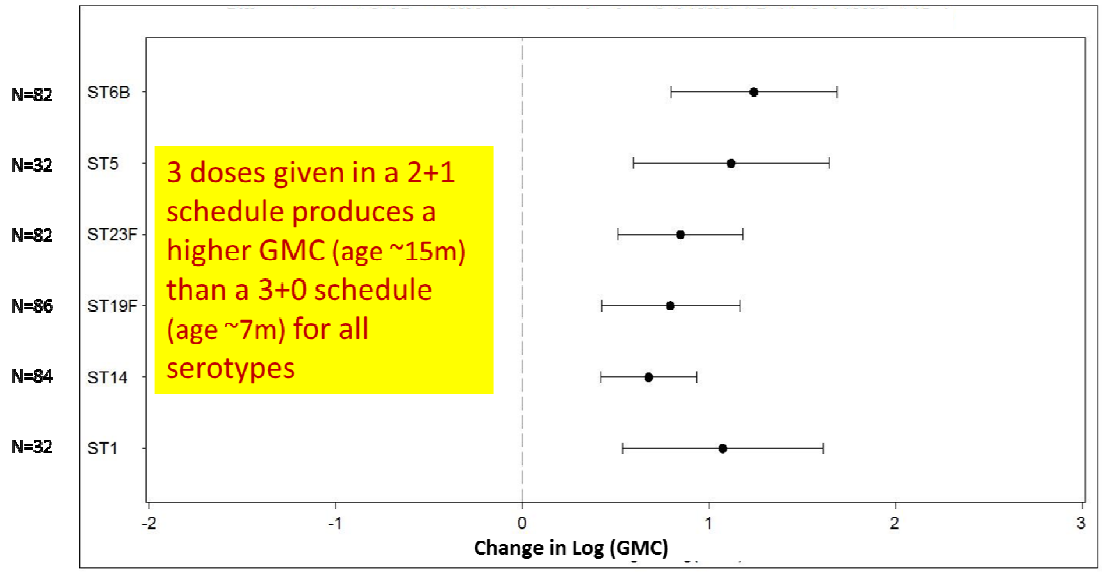
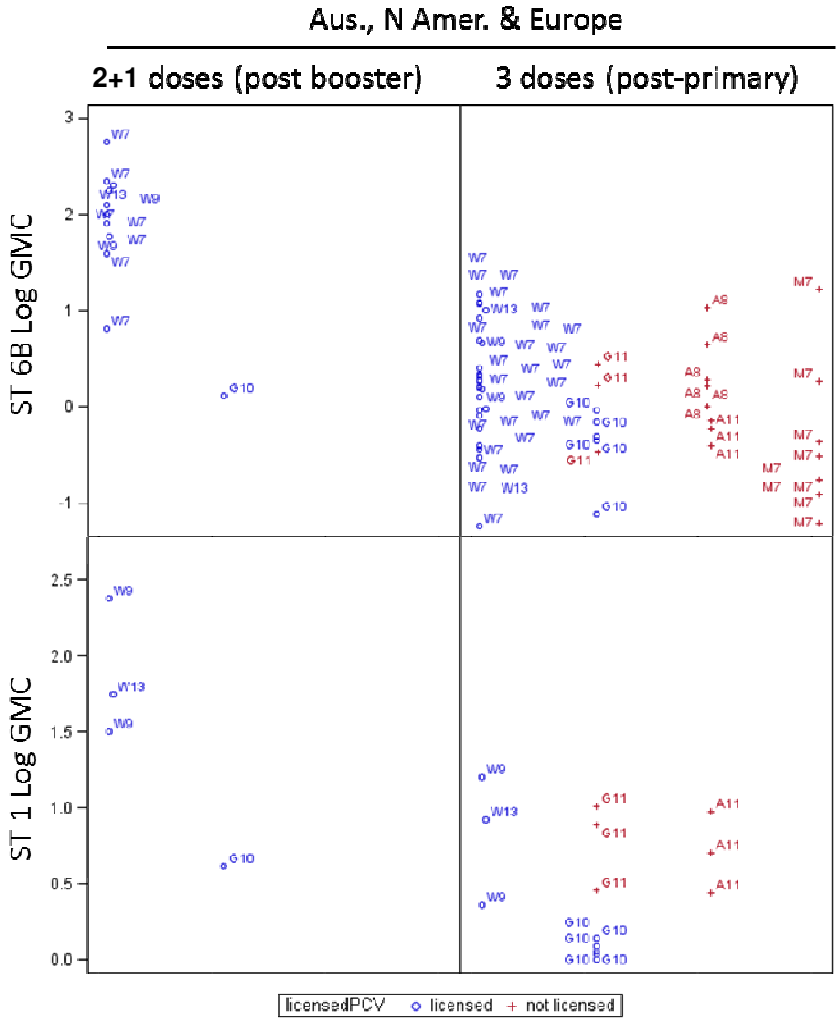


Figure 9. Difference in post-3rd dose GMC when changing from 3+0 (GMC at 7m) to 2+1 (GMC at 15m) PCV schedule



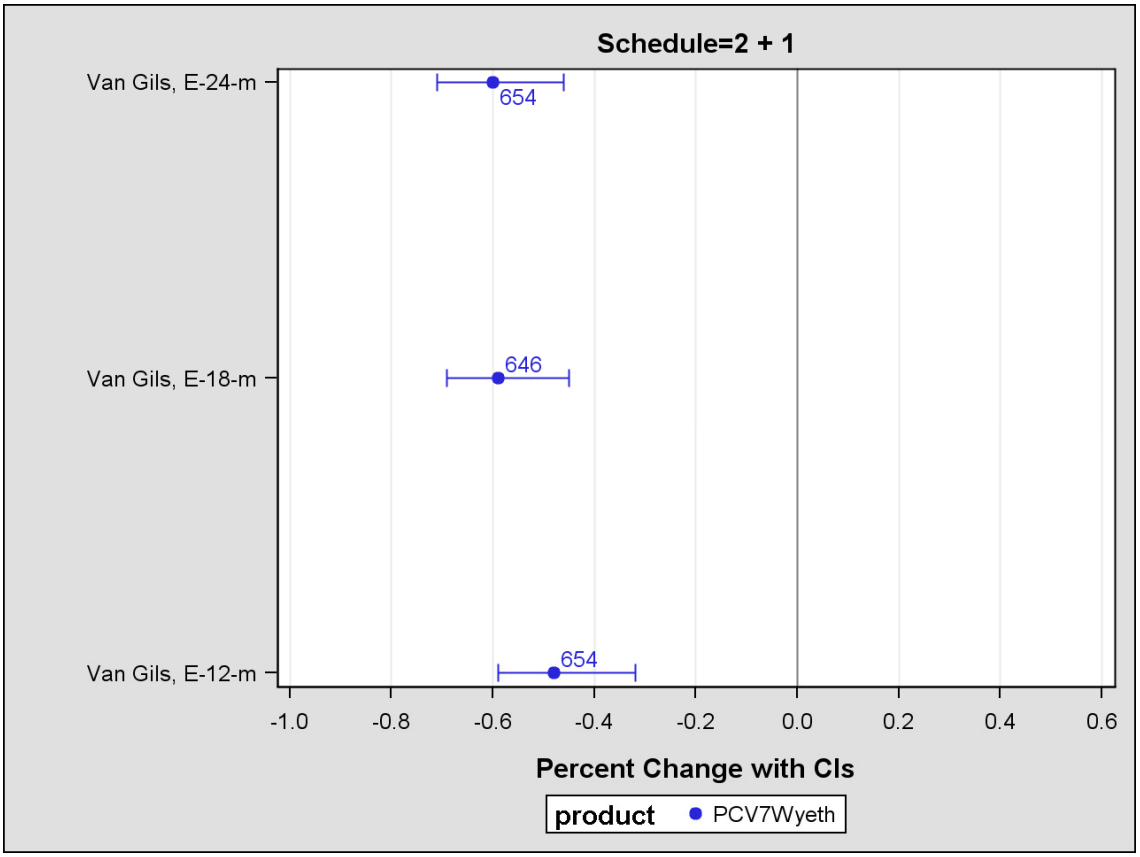
Adjusted for: Age at first dose, geographic region, PCV product, co-administration of DTaP v DTwP, Lab method (GSK v Wyeth/other)

Figure 10. Log GMC for Serotypes 1 and 6B by PCV schedule: 2+1 (post-booster) v 3+0 (post-primary)



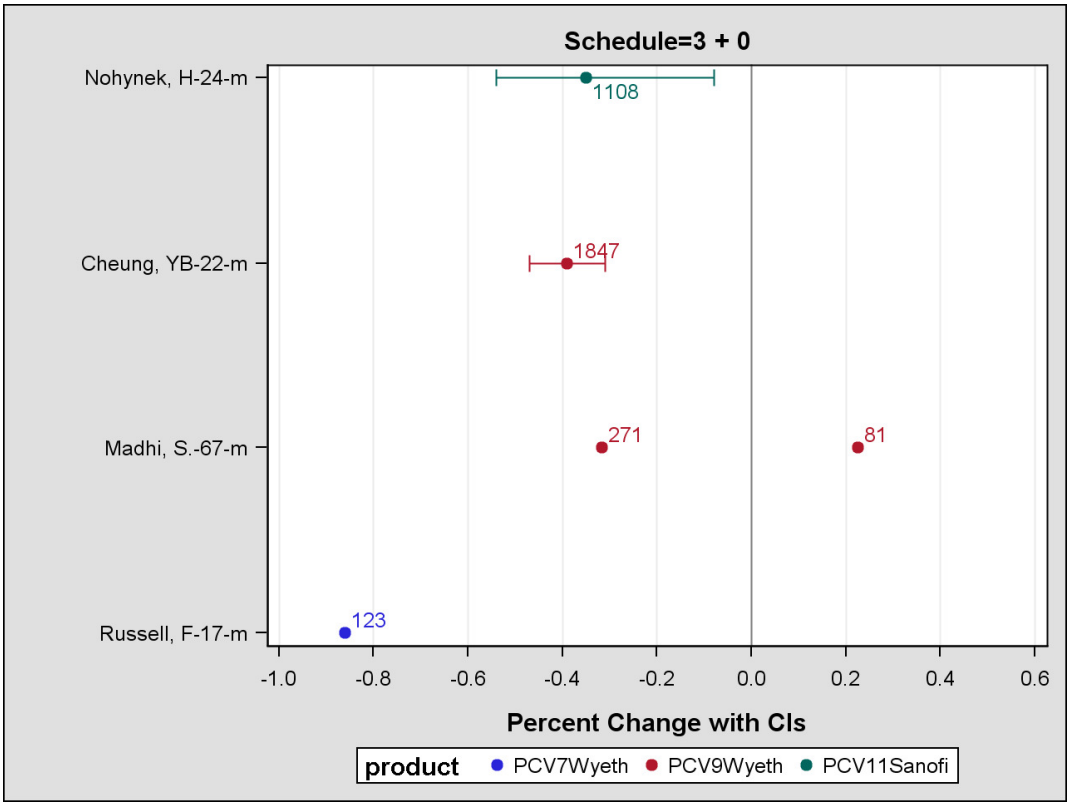
Note: product is noted (e.g., “W-7“ is Wyeth 7-valent PCV product.

Figure 11. Vaccine-type nasopharyngeal carriage in 2+1 schedules at post-booster sampling



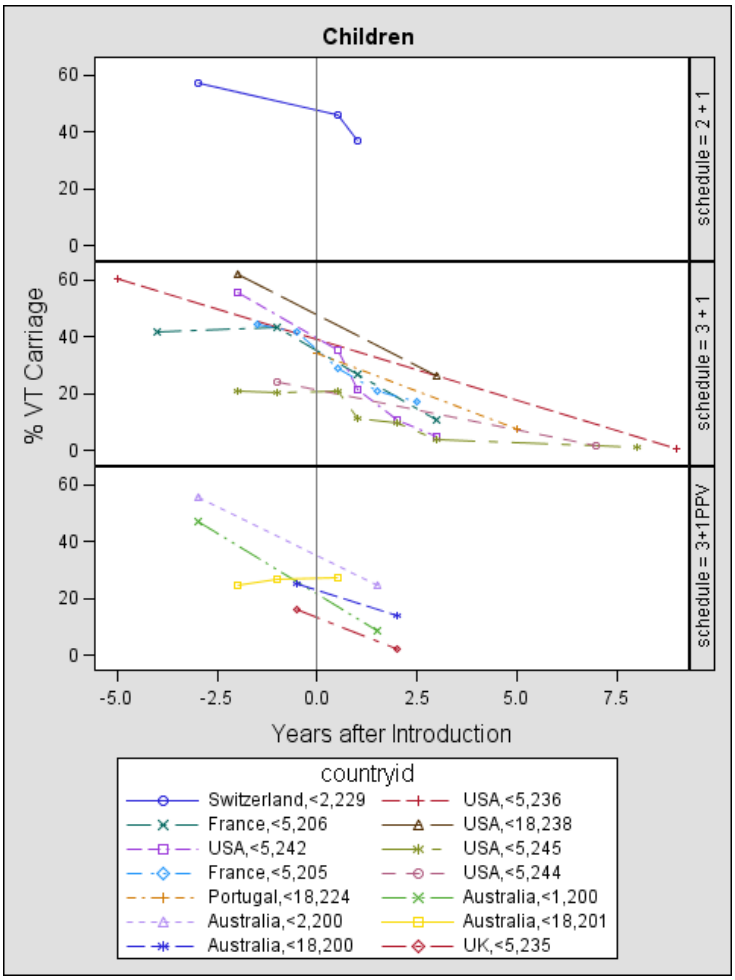
*Numbers above dots are the sample size. Study labels contain first author's last name, first initial, and age at time of nasopharyngeal swab.

Figure 12. Vaccine-type nasopharyngeal carriage in 3+0 schedules at post-booster sampling



*Numbers above dots are the sample size. Study labels contain first author's last name, first initial, and age at time of nasopharyngeal swab.

Figure 13. Percent vaccine-type nasopharyngeal carriage among children in observational studies by schedule



* Study labels contain first country, age in years, and a study identification number

Figure 14. PCV observational studies reporting the incidence of vaccine-type IPD among children ≤2 years of age before and after vaccine introduction.

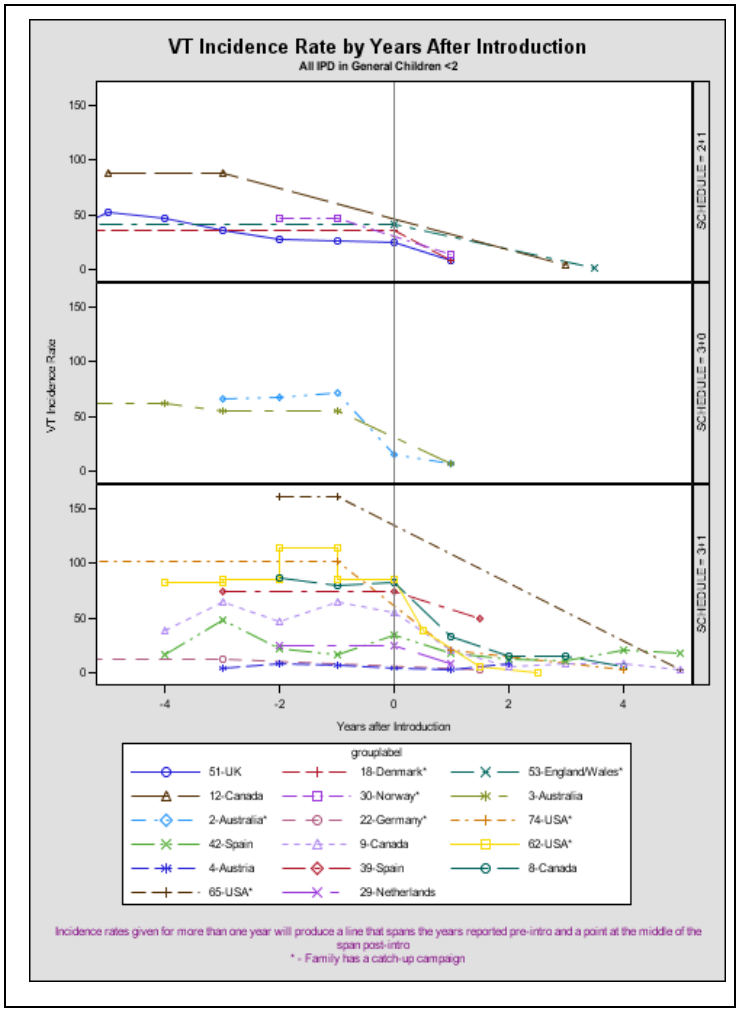


Figure 15. Observational studies reporting the incidence of vaccine-type IPD among young adults (ages 5-50 years) before and after vaccine introduction.

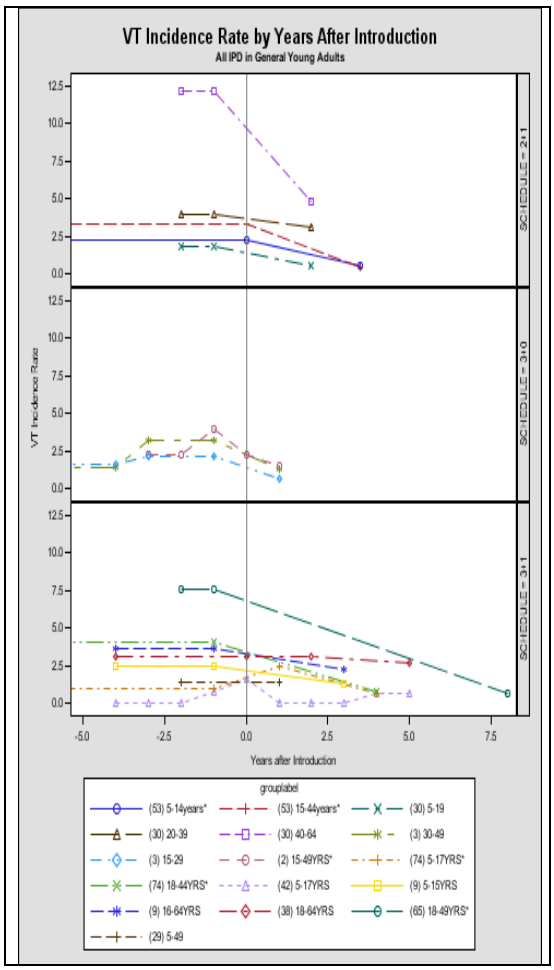
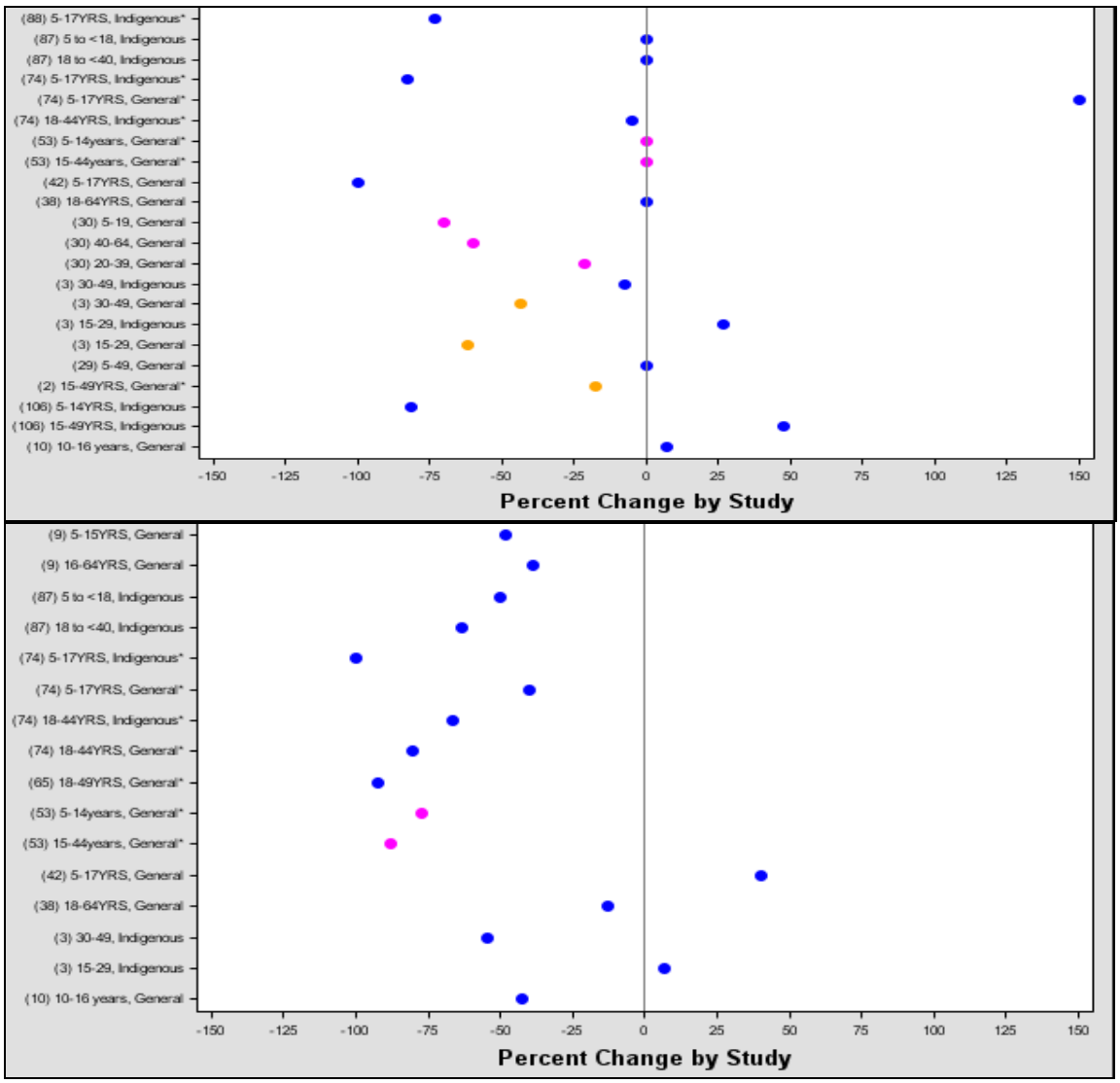


Figure 16. Percent change in the incidence of vaccine-type IPD among young adults (ages 5-50 years) ≤ 3 years after introduction (top box) and >3 years after introduction after vaccine introduction (bottom box).



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