Pneumococcal Conjugate Vaccine (PCV) Review of Impact Evidence (PRIME)

Summary of Findings from Systematic Review

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SUMMARY FINDINGS: PRIME SYSTEMATIC REVIEW

PREFACE

This document provides a technical review of the evidence on pneumococcal conjugate vaccine (PCV) immunogenicity as well as effectiveness and impact on nasopharyngeal pneumococcal (NP) carriage, disease and mortality. This evidence was reviewed by pneumococcal experts convened by the World Health Organization (WHO) in June 2017, and has been used by the Strategic Advisory Group of Experts on Immunization (SAGE) Working Group (WG) on PCV to formulate their recommendations. The SAGE WG on PCV is presenting updated recommendations, based on the most contemporary evidence, at the October 2017 SAGE meeting. The WHO and country decision-makers may also find the document useful decisions on optimizing and sustaining PCV use.

The 2012 WHO position paper on PCV use notes that either a 2+1 or 3+0 dosing regimen should be used for PCV as part of routine national immunization programs. These recommendations were based largely on studies using the 7-valent PCV, from high income country settings. There is now substantial evidence on PCV performance from routine use settings using next generation PCVs (PCV10 and PCV13), including in low- and middle-income settings, that has motivated a review of the relative merits of each schedule in relation to overall impact and maximal herd (or indirect) effects of the vaccine. Furthermore, the availability of two pneumococcal vaccines, with overlapping but non-identical characteristics, including formulations, means that both country policy-makers and donors need information on product performance characteristics.

The document synthesizes the evidence on biologic impact, and programmatic considerations surrounding pneumococcal vaccine performance, effectiveness, and impact for current PCV products, PCV10 (Synflorix, GSK) and PCV13 (Prevenar, Pfizer) in the current WHO-recommended dosing schedules: 2 primary doses plus a booster dose at or after 9-months of age (2+1) and 3 primary doses before 9-months of age (3+0). Both products are pre-qualified by WHO.

The technical evidence provided in this document comes from *a systematic review* of published data on PCV immunogenicity, carriage and disease effectiveness and impact of currently licensed PCV products (PCV10 and PCV13) used in 3-dose schedules (2+1 and 3+0). Evidence from 4-dose schedules (3+1) is not included except for outcomes assessed during the primary series, up to the point of the booster dose. Evidence from both observational studies and clinical trials is included. Evidence reporting changes in disease incidence (pre- and post- PCV introduction) was prioritized for the sections on PCV effectiveness and impact. Case series data and studies providing disease information limited to only the post-PCV era are not included.

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List of Abbreviations and Acronyms:

CAP—Community-acquired pneumonia
CFR—Case fatality rate
CI – Confidence interval
DTaP - Diphtheria, tetanus and acellular pertussis vaccine
DTP – Diphtheria, tetanus and pertussis vaccine
FinIP - Finnish Invasive Pneumococcal Disease Vaccine Trial
Gavi – Gavi, the Vaccine Alliance
GMC – Geometric mean concentration
GSK – GlaxoSmithKline
HIC – High Income Country
HIV - Human Immunodeficiency Virus
IgG –Immunoglobulin G
IPD – Invasive pneumococcal disease
ITT—Intention to treat
IVAC – International Vaccine Access Center
LMIC—Low- and middle-income countries
MIC—Middle income country
NIP – National Immunization Program
NP – Nasopharyngeal
NTHi—Non-typeable *Haemophilus influenzae*
NVT – Non-vaccine serotype
PCV – Pneumococcal conjugate vaccine
PCV7 – 7-valent pneumococcal conjugate vaccine
PCV10 – 10-valent pneumococcal conjugate vaccine
PCV13 – 13-valent pneumococcal conjugate vaccine
PICO – Population, Intervention, Comparison, Outcome
PRIME – PCV Review of Impact Evidence
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT—Randomized controlled trial
SAGE – Strategic Advisory Group of Experts on Immunization
ST - Serotype
UK—United Kingdom
UMIC – Upper Middle-Income Country
VE—Vaccine efficacy
VT – Vaccine Type
WHO – World Health Organization
2p – 2 Primary Doses
3p – 3 Primary Doses

1.0. BACKGROUND:

A systematic review, referred to as the PCV Dosing Landscape Study [1] conducted in 2010, informed the scientific community and Strategic Advisory Group of Experts (SAGE) on Immunizations at WHO on PCV schedule(s) with a focus on the differences in immunogenicity and colonization/disease impact between 3- and 4-dose schedules using the 7-valent PCV (PCV-7) product. The PCV Dosing Landscape Study provided evidence for SAGE's recommendation for the use of a PCV series consisting of 3 primary doses without a booster or 2 primary doses with a booster given at 9 months of age or later. WHO adopted this recommendation in its 2012 PCV Position Paper, which replaced the 2007 PCV Positions Paper. Currently the WHO recommendation is for all countries to adopt PCV and to implement a schedule containing a minimum of three doses, which may be administered either as 3 primary doses without a booster (3p+0) or as 2 primary doses with one booster (2p+1). Some national immunization programmes use a 3p+1 schedule, which is also considered as acceptable.

Additional immunogenicity and post-introduction disease and colonization impact assessments are now more widely available than in 2010, in particular from low-and-middle-income countries (LMIC) which are known to have pneumococcal epidemiologic characteristics that differ from those in higher income settings. Furthermore, 10-valent (PCV-10) and 13-valent PCV (PCV-13) products are both available; PCV-7 is no longer supplied. The majority of the recent data are from these two expanded serotype WHO prequalified products, and these data have yet to be summarized for decision-making on the optimal use of PCV globally. Annex A of this document provides a summary of the programmatic aspects of each PCV product to complement this technical evidence review and to support decision-making.

Providing clear information to countries on the optimal regimens for PCV aims to support continued PCV use in national immunization programs (NIP) through clear demonstration of the impact and value of these vaccines. In that context, the relative merits of providing or not providing a booster dose, within a 3-dose schedule (i.e. 2-dose primary series plus booster dose) must be evaluated. In addition, due to increasing demands and limited resources, there is interest in understanding the available evidence to support the use of reduced dose schedules (i.e. 2 doses) once a PCV program has matured to the point where disease and colonization has largely been controlled (i.e. a vaccine maintenance phase which might occur 5 or more years following PCV introduction) as evidenced by near elimination of vaccine-type (VT)-carriage and disease.

An update to the previous, 2010 PCV review provides further evidence to the scientific community and policy makers regarding which PCV schedule(s) are optimal, considering both the direct and indirect effects of the vaccines. The impact of PCVs on colonization and disease has not previously been comprehensively evaluated by product; currently there are 2 products licensed: PCV-10 (GSK) and PCV-13 (Pfizer). Countries therefore make decisions without having a systematic evidence base to inform them on which PCV product and schedule to use in their NIP. A comprehensive technical analysis of the published and unpublished data on PCV dosing schedules and PCV products, assessing immunogenicity, effect on nasopharyngeal (NP) colonization, and impact on pneumonia, invasive pneumococcal disease (IPD) and mortality is needed to further optimize the use of the vaccines and promote their sustained use in the future. Critical remaining evidence gaps that may be strategically targeted for future research are identified.

2.0. METHODS:

The PCV Review of Impact Evidence (PRIME) systematic review protocol is registered with PROSPERO (CRD42017058664), and follows PRISMA systematic review reporting guidelines [2].

A systematic literature review of 14 databases (EMBASE, PubMed, Biological Abstracts (BA), Pascal Biomed, Global Health, BioAbst/Reports, Reviews, Meetings, Cochrane Library, 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), and, IndiaMed (IndMed)), was conducted to include relevant data published in English from January 1, 2010-December 31, 2016, with ad-hoc additions through June 2017. All relevant citations (evaluating PCV-10 and/or PCV-13) included in the PCV Dosing Landscape Study systematic review (1994-2010) were also brought into this analysis and summary document [1]. Relevant unpublished data was considered and cited as "personal communication" throughout the report.

A set of core exclusion criteria were established for all outcomes in order to ensure that effectiveness and impact estimates were comparable across studies and technically relevant to address the proposed research questions on optimal use of PCV globally.

Exclusion Criteria:

- Study did not adequately report characteristics of the population evaluated to determine the approximate coverage of PCV, making it impossible to decipher if the observed effects were due to PCV or another intervention
    - Years post-PCV introduction could not be determined
        1) E.g. no dates of surveys decipherable, introduction year of vaccine not ascertainable
    - Did not report ages sampled
    - Did not distinguish between vaccinated and unvaccinated groups
- Assessment was of more than one schedule and/or more than one product which could not be distinguished and thus effects from either schedule and/or product could not be distinguished
- Less than 50% (insufficient proportion) of the sampled population was vaccinated with PCV
    - Assessment requires that the data adequately reflect populations directly immunized: e.g., at least 6 months' post introduction if assessing children <1 year of age; at least 18 months' post introduction if assessing children <2 years of age; at least 2 years post introduction if assessing children <5 years of age.
- Only provided prevalence of pneumococcal carriage or disease in the post-PCV period (no impact data available)
    - However, as these results can provide anecdotal evidence regarding persistence in serotype-specific carriage if assessed several years (e.g., 5 years) post introduction and with high coverage (e.g., 70% of birth cohort), they were recorded for quality assurance and validation purposes
- Did not distinguish (i.e. aggregated data) between pre- and post- PCV introduction periods
- Study population is not representative of general population (e.g.., colonization data was only among cases with respiratory symptoms, AOM or pneumonia cases)
- For the PICO III assessment (catch-up) studies were additionally excluded if they reported only data from 2 or more years after the catch-up campaign or if they had prior PCV7 use. However, countries that had prior PCV7 use were only included if non-PCV7 serotypes were evaluated at the time of a PCV10/13 catch-up.

Types of Studies:

- Included: Randomized control trials (RCTs), non-randomized trials, and observational studies reporting **pre (baseline) and post** vaccine introduction incidence rates for disease outcomes or prevalence for carriage
- Excluded: Incidence data from only the PCV post-introduction era, and case-series data for disease outcomes (pre-post or post- only)

Outcomes:

- Included: invasive pneumococcal disease (IPD), pneumonia (syndromic outcome), pneumococcal nasopharyngeal (NP) carriage, and pneumococcal serotype specific immunogenicity [measured by serotype specific IgG antibody geometric mean concentration (GMC) and proportion achieving the correlate of protection (using assay specific correlates)]
- Excluded: otitis media (syndromic outcome), pneumococcal immunogenicity measured by opsonophagocytic activity or avidity

Intervention & Comparators:

- Products: PCV-13 & PCV-10
- Schedules: 3+0 and 2+1 dosing schedules
    - 2+0 and 3+1 schedule studies were included where technically relevant (ie. Post-primary IGG GMC data for immunogenicity using a 2+0 or 3+1 schedule; Serotype specific invasive disease data for 3+1 due to data paucity)
    - Excluded: Studies evaluating other dosing schedules and/or other PCV products were excluded

Deduplication:

- Studies that published data from the same population(s) over time were identified (termed 'family of studies') and duplicates were removed so that the most recent, comprehensive data were included. This allowed for maximum time for PCV impact to be evaluated and prevented a PCV impact in a particular population from being reported in the summary data multiple times.
    - A parent paper was chosen as representing the family of studies for that population, and used as the citation for PCV impact in that population within figures and tables

Citations:

- All included studies are described in Annex B by outcome.

Specific methods for direct effects section:

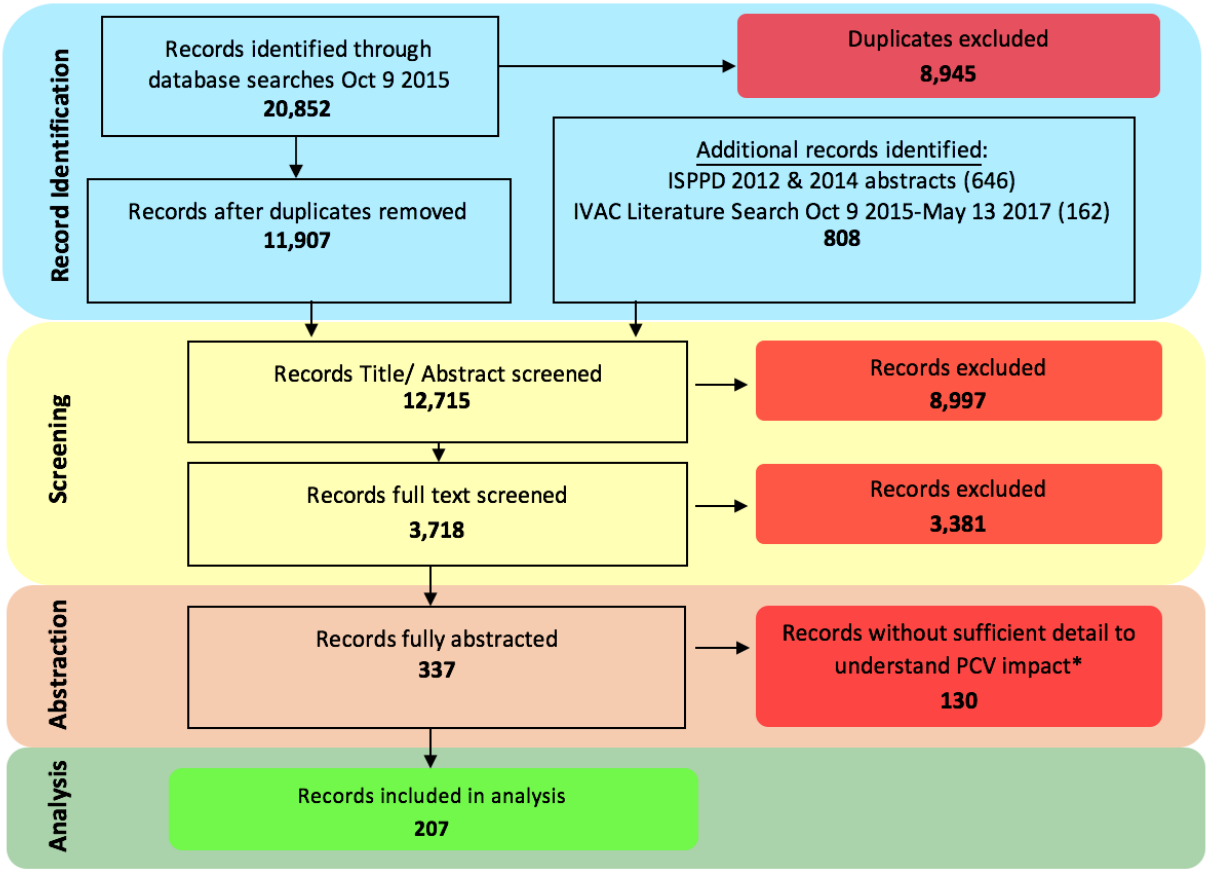
At least 1 year of pre-PCV and 1 year of post-PCV data were required for observational studies to be included in analyses.

Specific methods for indirect effects section:

At least 3 years of post-introduction data were required for studies to be included in the indirect effects assessment. Studies had to report on an age group that represented indirect effects only rather than a mix of direct and indirect effects.

Selection of Studies:

Figure 1. PRISMA Inclusion/Exclusion Report



*Exclusion criteria with justification detailed in section 2.0 Methods

Data extraction:

Trained PRIME team data abstractors (public health graduate students) extracted data into web-based data extraction forms from full-text articles that remained eligible for inclusion after screening. Data extraction forms were designed for each outcome of interest and piloted by PRIME team epidemiologists prior to implementation. All quantitative data underwent double independent extraction.

Quality control and assurance were employed throughout data extraction by PRIME team epidemiologists. Activities included weekly re-training and review of extraction tools with PRIME team abstractors, daily interaction with abstractors to provide necessary direction on accurate data to extract, regular review of extracted data to ensure accuracy and resolve discordant results, and re-extraction of full-text articles when high levels of errors and inconsistencies were noted in data review. When necessary, changes to data extraction forms were made to improve the quality of extractions and ensure the integrity of data used for analysis.

Data analysis:

Descriptive analyses reveal the amount and variability of the data by product, schedule and outcome evaluated, whether or not a meta-analysis was done with the data. We aimed to conduct meta-analyses for all outcomes of interest when designing the PRIME systematic review. However, heterogeneity in included studies by outcome, and thus the data available, did not allow for a valid (or valuable) pooling of impact estimates. Thus, meta-analyses were done only where appropriate, and not for all outcomes of interests. A narrative synthesis is based on the information summarized in tables with the characteristics and findings of the included studies: country, year of publication, number of participants, age range, name of vaccine, immunization schedule, comparator, study design, outcomes, magnitude of effect, and confidence interval.

The qualitative synthesis for each outcome of interest addresses the strengths and limitations of individual studies and the relationship with their reported findings and patterns across studies. Following the descriptive analysis, biologically and epidemiologically meaningful subgroup analyses were formulated by outcome, comparing and contrasting products and/or dosing schedules as much as the data allowed. Qualitative syntheses and descriptive analyses were framed by the key policy issues of interest, which were constructed in the form of PICO questions (Population, Intervention, Comparison, Outcome).

3.0. PICO I: Dosing Schedule (2+1 vs 3+0) Effectiveness and Impact of WHO Prequalified PCV Products:

Executive Summary:

I. Immunogenicity and Dosing Schedule:

Head to Head studies of dosing schedules (n=10 studies):

- A two-dose primary schedule elicits lower post-primary antibody concentrations (geometric mean concentrations, GMC) than a three-dose primary schedule for most vaccine serotypes but there is little difference between these schedules in the proportion of subjects with antibody concentrations above the correlate of protection. For serotypes (ST) 6A and 6B, antibody responses are better after a three-dose primary series using both outcome measures.
- For both products, post-dose 3 antibody concentrations are higher for infants receiving a 2+1 schedule than those receiving a 3+0 schedule for most serotypes. However, this does not lead to significant differences in the proportion of subjects with antibody concentrations above the correlate of protection, with exception of serotype 6B.

Single arm and non-randomized studies of dosing schedules (n=67 study arms)

- A two-dose primary schedule (most, but not all studies, with 8-weeks between doses)[1] elicits a lower post-primary immune response than a three-dose primary schedule, as measured by antibody concentration and proportions of infants with antibody concentration above the correlate of protection; these differences vary by product and are statistically significant only for certain serotypes and outcome measures. At the pre-booster time point, antibody concentrations have waned from the post-primary peak concentrations, so little difference is observed in GMCs for the two-dose and three-dose schedules for both products and for most serotypes.
- For both products, post-dose 3 antibody concentrations are higher for children receiving a 2+1 schedule than those receiving a 3+0 schedule for most serotypes. However, this does not lead to substantial differences in the proportion of subjects with antibody concentrations above the assay-specific correlate of protection.

[1] Among 41 study arms included, 35 had 8 weeks between doses 1 and 2, 4 had only 4 weeks and 2 had 4 months.

II. NP Carriage and Dosing Schedule

Vaccine Type:

- Two underpowered head-to-head trials (both PCV10) directly compared schedules; although not statistically significant, directionality favored the 2+1 schedule.
- Single schedule trials for indirect comparisons included 4 trials evaluating 3+0 schedules and 3 trials evaluating 2+1 schedules. Although not statistically significant, on average the 2+1 regimens had greater reduction in VT carriage than 3+0 regimens.
- Of 18 observational arms (10 of 3+0 and 8 of 2+1) identified evaluating PCV impact in routine use, only 5 described impact after long-term (3+ years) PCV use (1 of 3+0 and 4 of 2+1); neither schedule consistently performed better. Persistent carriage of PCV13-types after 4.5 years of high immunization coverage with PCV13 using a 3+0 schedule suggests that in high burden settings a 3+0 schedule may not eliminate vaccine-type carriage; no long-term (3+ years) data was found from high burden settings using a 2+1 schedule.
- **Caveats:** most evidence came from low carriage settings and there was confounding by product (although no effect of product was noted in PICO2 in regard to their respective impact on vaccine-type carriage), by previous PCV7 use, by use of catch-up strategy, and in the proportion of children age-eligible to receive PCV10/13.

Serotype 1:

- *The impact of schedule on serotype 1 carriage was not assessed because it rarely carried and therefore any data would be unstable due to very low sample size.*

Serotype 3

- **Availability of data:** We identified 14 studies evaluating impact in 16 arms of 3+0 (n=9) or 2+1 (n=7) schedules: 3 arms from single-schedule trials (two 2+1 and one 3+0) and 13 arms in observational studies evaluating routine use (8 of 3+0 and 5 of 2+1).
- **Results:** Neither schedule impacted ST3 carriage, regardless of product used. No decreases were seen in any clinical trial, but ST3 carriage was low.

Serotype 6A

- **Availability of data:** We identified 2 head-to-head trials directly comparing impact of schedule plus 20 additional single-schedule evaluations: n=12 arms of 3+0 schedules (4 from trials and 8 from observational studies of routine use, one of which was a post-only long-term use study) and 8 arms of 2+1 schedules (3 from trials and 5 observational studies of routine use).
- **Results:** Head-to-head trial results were inconsistent (no impact for either schedule in one and greater impact for 3+0 in the other, both non-significant). In single-schedule clinical trials, schedules had similar impact when there was similar carriage in the controls. In routine use, reductions were seen for both schedules and there was no evidence that one schedule performed better than the other, but conclusions are heavily confounded by differences in pre-PCV10/13 carriage levels, prior use of PCV7, and use of PCV10 (vs. PCV13) which does not contain ST6A.

Serotype 6B:

- **Availability of data:** No head to head data were found. Three single-schedule trial arms (1 of 3+0 and 2 of 2+1) evaluating impact were found, and 10 observational studies (4 of 3+0 and 6 of 2+1).
- **Results:** In single-schedule controlled trials, ST6B carriage was lower in children vaccinated with a 2+1 schedule (one each of PCV10 and PCV13) compared to controls (Vietnam, non-significant), while carriage was higher (not significant) in children vaccinated using a 3+0 schedule compared to controls (Nepal). In observational studies, declines in all studies were seen for both schedules. Although all observational studies of 2+1 were in the context of previous PCV7 use which protects against ST6B, declines were seen during the PCV7 period with a 2+1 schedule and further declines were seen after switch to PCV13 in studies that still had 6B carriage.

Serotype 6C

- **Availability of data:** No head-to-head trials directly comparing schedules or single-schedule trials were identified for ST6C. We identified 6 observational studies of routine use (1 of 3+0 and 5 of 2+1).
- **Results:** There was insufficient data to compare schedules. Schedule could not be compared in PCV13 studies as there were no 3+0 arms; for the 2+1 schedule arms, two had no change and two decreased (neither was significant). In PCV10 studies which are unlikely to have an impact on ST6C, there was no impact for either the 3+0 arm or 2+1 arm (both increased).

Serotype 19A

- **Availability of data:** We identified 2 head-to-head trials, both PCV10 which does not contain ST19A antigen but might have cross-protection from ST19F. There were 23 additional arms that evaluated a single schedule: 13 of 3+0 (6 single-schedule trials and 7 observational studies of routine use that included one post-only long-term study) and 10 of 2+1 (3 single-schedule trial and 7 observational studies of routine use).
- **Results:** There was no consistent evidence to favor either schedule over the other. Because PCV13 contains ST19A while PCV10 does not, comparison of schedule is shown separately by product:
    - PCV13: There were 4 studies of 3+0 and 6 of 2+1. No clear evidence for either schedule was seen in single-schedule trials as carriage was similar to that in their respective control arms. In the observational studies, declines for both schedules were similar but only one 3+0 study had pre-PCV13 carriage sufficient to assess impact.
    - PCV10: The two head-to-head trials were inconclusive and inconsistent: carriage was too low to assess impact in one, while in the other both schedules had higher carriage than the control arm (non-significant). All 3 single-schedule PCV10 arms used 3+0 so no comparison to 2+1 was possible. Among observational studies, 19A carriage in all four 3+0 studies increased and observed reductions in the two 2+1 studies could not be attributed to PCV10 because of temporal changes observed in non-PCV10 vaccinated children.

Serotype 19F:

- **Availability of data:** No head to head data were found. Three single-schedule trials (1 of 3+0 and 2 of 2+1) and 10 observational studies (4 of 3+0 and 6 of 2+1) were found.

- **Results:** In single-schedule controlled trials, ST19F carriage was lower (non-significant) in vaccinated children using a 2+1 schedule (one each PCV10 and PCV13) than in controls, while carriage was similar (but very low) in the 3+0 trial compared to controls. In observational studies, declines were seen for both schedules, including those conducted in the context of previous PCV7 use, which protects against ST19F.

III. NP Carriage Indirect Effects and Dosing Schedule:

Vaccine Type:

- There are very limited data with which to evaluate any difference between a 2+1 and 3+0 schedule. Both schedules had relative reductions in VT NP carriage in the same general range, but significance was reported only for one study (PCV10 used in a 3+0 schedule in Kenya).

IV. IPD Direct Effects and Dosing Schedule:

Vaccine Type:

- There are no head to head studies comparing the two schedules and data are limited for 3+0 schedules.
- Both schedules elicited reductions in IPD caused by serotypes within each vaccine; however, quantitative comparisons in disease reduction across studies should not be made due to differences in duration of PCV use, age groups studied, vaccine coverage, serotype distribution, and analytic methods used.

Serotype 1:

- There is limited evidence available for analyzing impact of a 3+0 dosing schedule on ST 1 IPD. The majority of studies evaluating 2+1 dosing schedule show an impact on ST 1 in vaccine age-eligible cohorts.

Serotype 3:

- There is limited evidence for 3+0 schedule, and inconsistent evidence for 2+1 schedule, with the majority of studies showing no impact on type 3 IPD in vaccine age-eligible cohorts or in indirect age strata.

Serotype 6A:

- The comparison of PCV impact by schedules on ST 6A IPD is difficult to discern since most studies were conducted in countries with previous PCV7 use and therefore little ST 6A disease left to prevent.

Serotype 19A:

- Reductions in 19A IPD were observed with PCV13 use for both 2+1 and 3+0 schedules in all but one study. No distinction could be made in the magnitude of the 19A impact by schedule. For indirect impact on 19A IPD, no conclusions can be drawn on distinctions by schedule because of data limitations.

Serotype 19F

- Reductions in ST 19F IPD were observed in countries using 2+1 schedule; however, studies were conducted in countries with previous PCV7 use where reductions post-PCV7 in ST 19F IPD were already observed and little disease remained for prevention.

Serotypes 6B and 23F:

- In countries using 2+1 schedule, all with prior PCV7 use, reductions post-PCV7 were already observed and little disease remained to measure PCV13 impact.

Serotype 6C:

- Data are not sufficient to conclude that either schedule with either PCV10 or PCV13 has an impact on ST 6C disease. Therefore, no assessment can be done of PCV schedules on the 6C IPD outcome.

V. IPD Indirect Effects and Dosing Schedule:

Vaccine Type IPD:

- There are more data available on the 2+1 schedule compared to the 3+0 schedule. The data do not indicate an obvious difference between the magnitude of VT IPD impact in 3+0 countries compared to settings using a 2+1 schedule.

VI. Pneumonia Direct Effects of Dosing Schedule:

- This review identified 35 studies evaluating 3-dose schedules (2+1 or 3+0) using PCV10 or PCV13: one clinical trial [3], five case-control studies [4-8], and 29 pre/post observational studies [9-37] (Table 1). The majority of studies were from Europe (n=17) [3, 6, 8, 12, 13, 15, 16, 20, 23, 27-30, 32-34, 36] or the Americas region (n=11) [9-11, 14, 17, 21, 22, 24, 26, 31, 35]; 5 studies were from Africa [4, 5, 7, 25, 37] and two studies from Oceania, both from Fiji [18, 19]. There were no studies identified from Asia or the North America; however, the review was limited to 3-dose schedules, and therefore excluded many countries using a 3+1 schedule including the U.S.
- The review found evidence of impact from both schedules (2+1 and 3+0) for clinical and chest X-ray confirmed (CXR) pneumonia. Evidence of impact for pneumococcal pneumonia was found, but only using a 2+1 schedule. The evidence regarding impact of schedule on prevention of empyema was only available for 2+1 schedules. There is no systematic evidence that one schedule is better than another.

VII. Pneumonia Indirect Effects of Dosing Schedule:

- The data are more robust for the 2+1 schedule, coming from 7 high income strata countries. There is only one low income strata country with data for a 3+0 schedule. The paucity of evidence makes it difficult to draw firm conclusions between schedules.

FINDINGS:

3.1 IMMUNOGENICITY AND DOSING SCHEDULE:

3.1.1 IMMUNOGENICITY BACKGROUND:

In support of the clinical development of extended valency pneumococcal conjugate vaccines (i.e. those licensed after PCV7), the WHO developed a route for licensure based on the immunologic outcomes comparing a novel PCV with a licensed PCV product in head-to-head studies. An immunological correlate of protection (% of subjects with serotype specific IgG above 0.35 mcg/mL following a 3 dose primary series when IgG is measured using the Pfizer assay or equivalent without 22F adsorption) was estimated from large randomized controlled efficacy trials from the late 1990's and early 2000's of 7- and 9- valent PCV. This correlate of protection is a specified concentration of antibody estimated to confer protection in an immunized population. In other words, individual children whose antibody level is above 0.35 mcg/mL do not necessarily have protection from disease. When a population immunized with a novel PCV results in a proportion of individuals with antibody concentrations above 0.35 mcg/mL that is non-inferior to the proportion above 0.35 among a population immunized with a licensed PCV, then it is inferred that the new PCV would have shown similar efficacy against disease to that of the licensed PCV. Of note, this correlate of protection is not serotype specific but was instead inferred based on overall efficacy against all serotypes together [38]. For some serotypes, the correlate of protection is likely lower and for others higher than 0.35 mcg/mL[39]. Based on immunogenicity bridging studies, when IgG is measured using the GSK assay the equivalent correlate of protection has been established as 0.20 mcg/mL.

This immunogenicity-based licensure process has been accepted worldwide, and was used to license PCV10 and PCV13 without efficacy trials against a disease outcome. Such trials would have been close to impossible to conduct in a head-to-head fashion given the availability of licensed PCV7 and therefore only a limited incidence of disease in populations using PCV7.
Because PCV10 and PCV13 RCT immunogenicity data resulted in product licensure, by definition the immunogenicity results showed non-inferiority to PCV7. Here our focus is on not only the RCT data but also updated immunological data generated in post-licensure immunogenicity studies spanning both vaccine products, different regions of the world and differing immunization schedules. The purpose of the immunogenicity section is to link the immunogenicity data to disease impact and effectiveness data and to focus on any serotype-specific nuances or product nuances that might inform product choice.

3.1.2 IMMUNOGENICITY FINDINGS:

3.1.2.1 EVIDENCE FROM HEAD TO HEAD RANDOMIZED CONTROLLED TRIALS:

Ten RCTs provide head to head evidence for the comparison between 2+1 and 3+0 schedules at the post-primary time point, three studies provide pre-booster data (not shown) and five studies provide post-dose 3 data (e.g. after the primary series for a 3+0 vs. after the booster dose for a 2+1 schedule). A random effects meta-analysis was done on the difference in antibody concentration

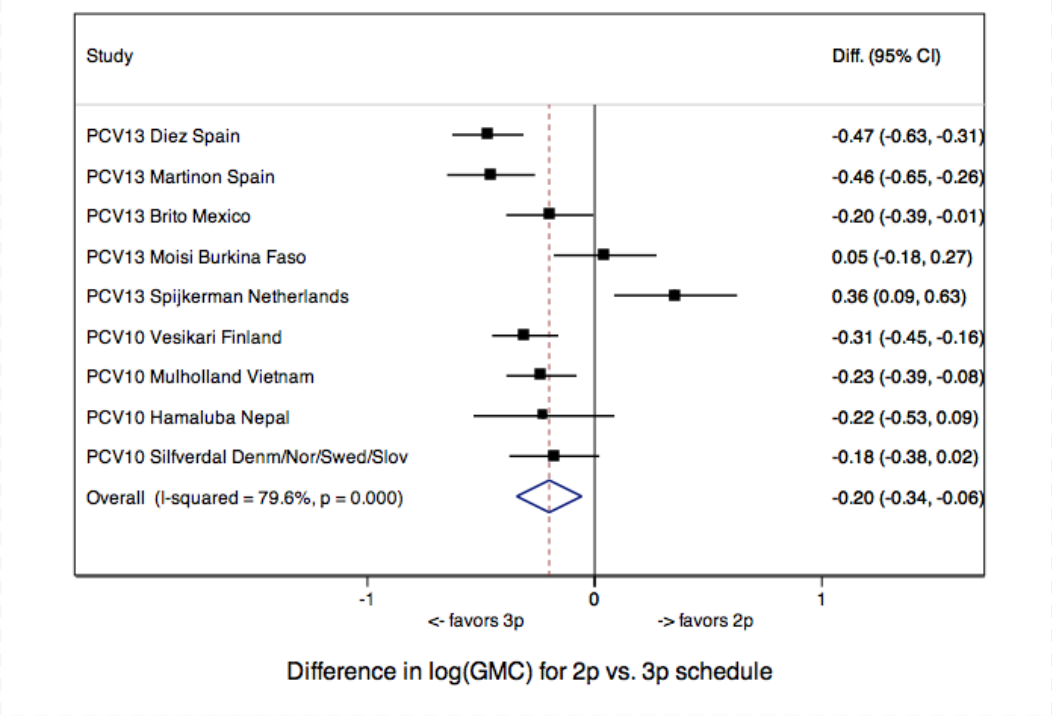
(log(GMC)) and the ratio of percent responders above the correlate of protection to compare the RCT data for the two schedules.

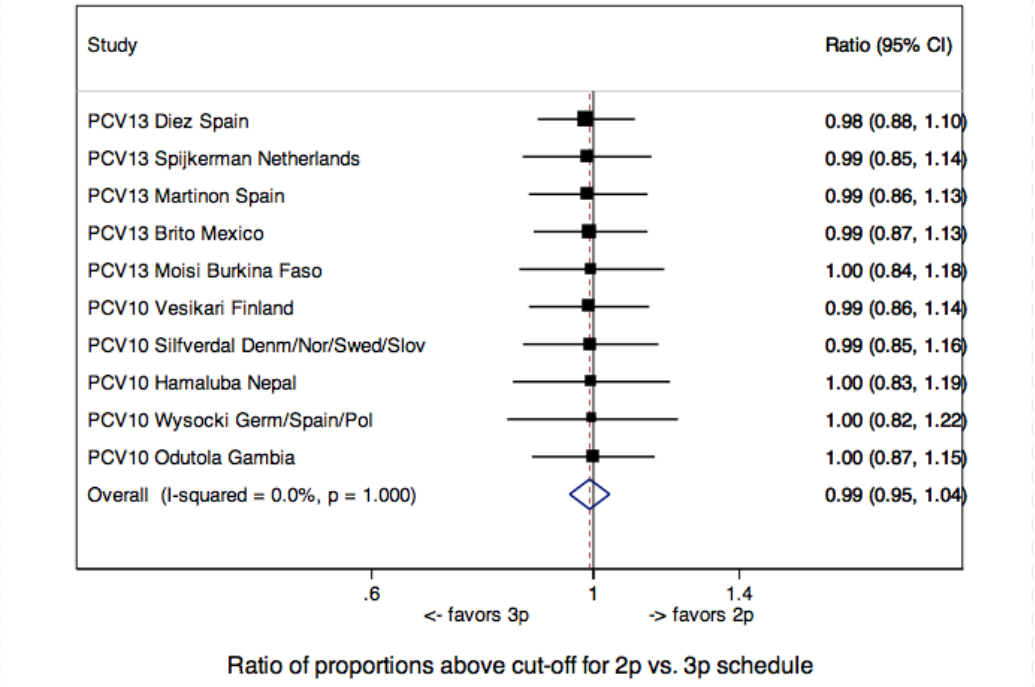
Figure 1shows the Forest plots of the head to head evidence comparing log(GMC) and percent responders at the post-primary time point for STs 1, 6B, 19F and 23F. As summarized in Table 1, log(GMC) and percent responders were similar following either a 3-dose or 2-dose primary series for STs 3 and 19F. For STs 1, 5, 7F, 14, 19A and 23F, the log(GMC) favored the three-dose primary schedule, but percent responders were similar for the 3p and 2p schedules. STs 6A and 6B demonstrated more favorable results for a 3p schedule for both log(GMC) and percent responders at the post-primary time point.

When looking at the post-dose 3 evidence, there is a switch to favoring a 2+1 schedule over a 3+0 schedule for 7 serotypes, for the log(GMC) endpoint. **Figure 2** shows the Forest plots of the head to head evidence for STs 1, 6B, 19F and 23F by both difference in log(GMC) and ratio of percent responders. **Table 2** summarizes the evidence for the post-dose 3-time point. For STs 3 and 19A, both GMC and percent responder data are similar for both schedules. For seven serotypes (STs 1, 5, 6A, 7F, 14, 19F and 23F), the log(GMC) data suggest that the 2+1 schedule is preferable, but the percent responders is similar for both schedules. For ST 6B, the two outcomes favor a 2+1 schedule.

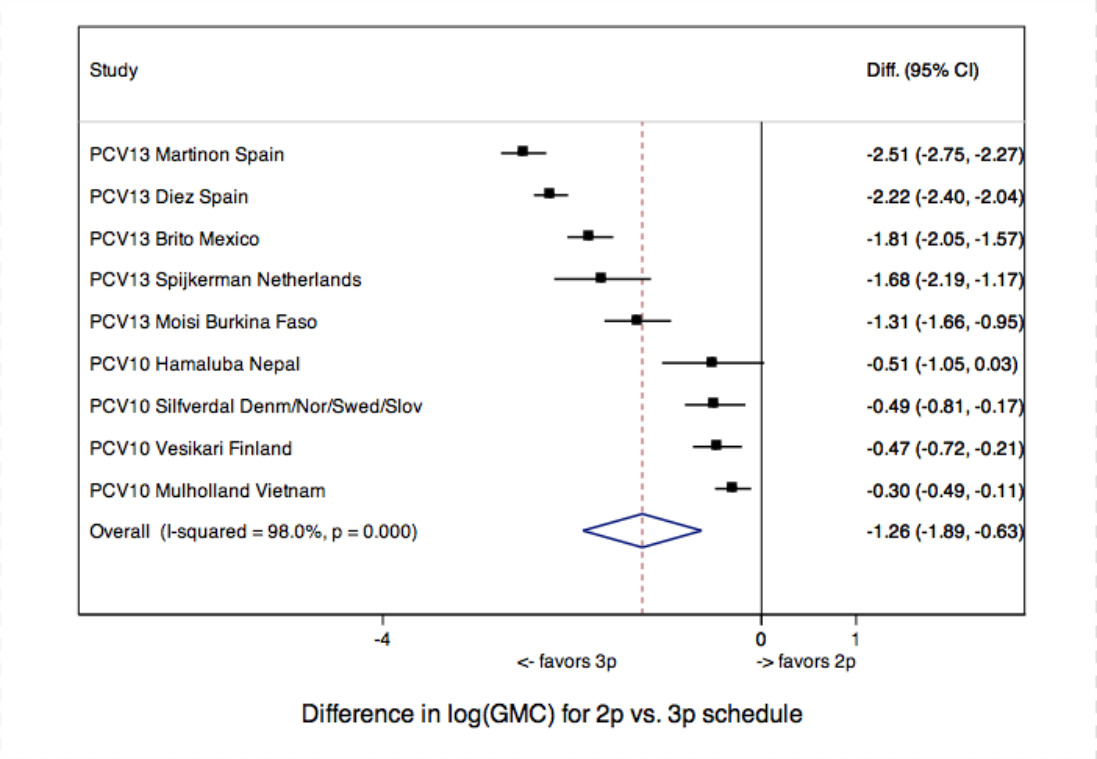
Figure 1: Evidence from RCTs on the difference in log(GMC) and ratio of percent responders for a 2 primary dose (2p) vs. 3 primary dose (3p) schedule at the post-primary blood draw: STs 1, 6B, 19F and 23F

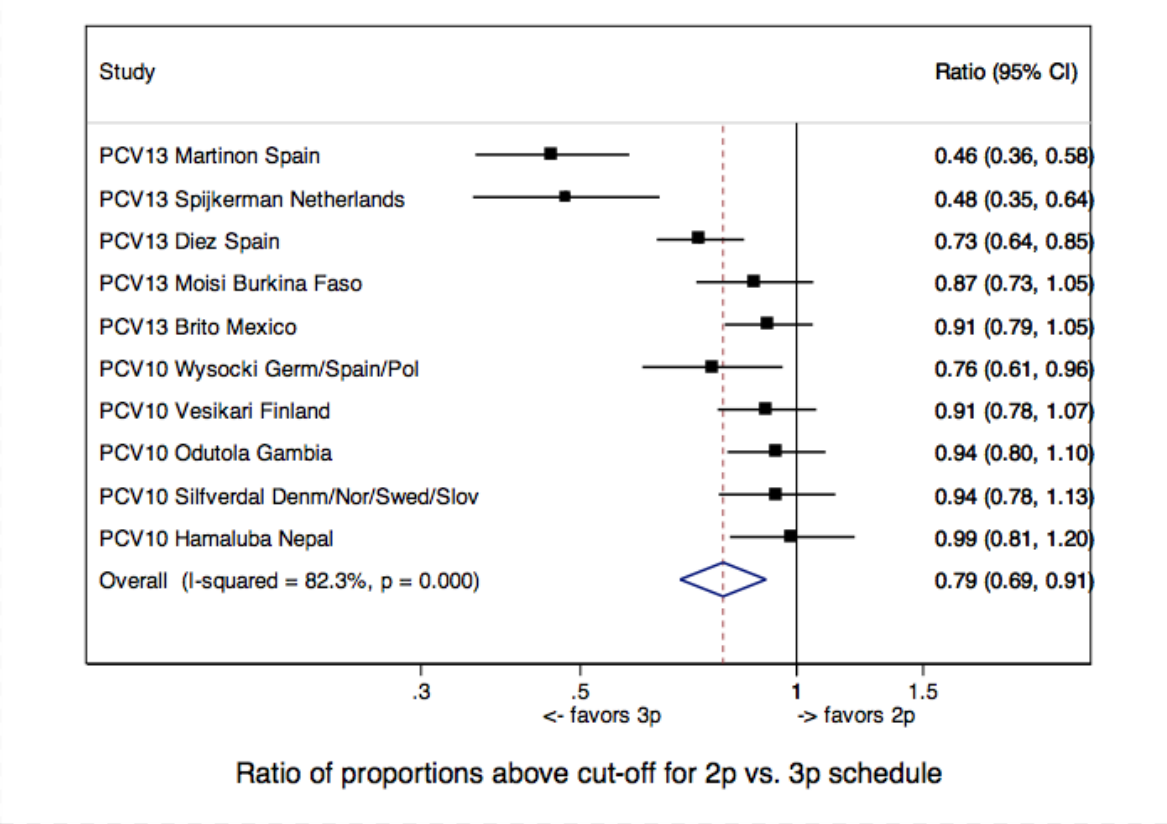
SEROTYPE 1:



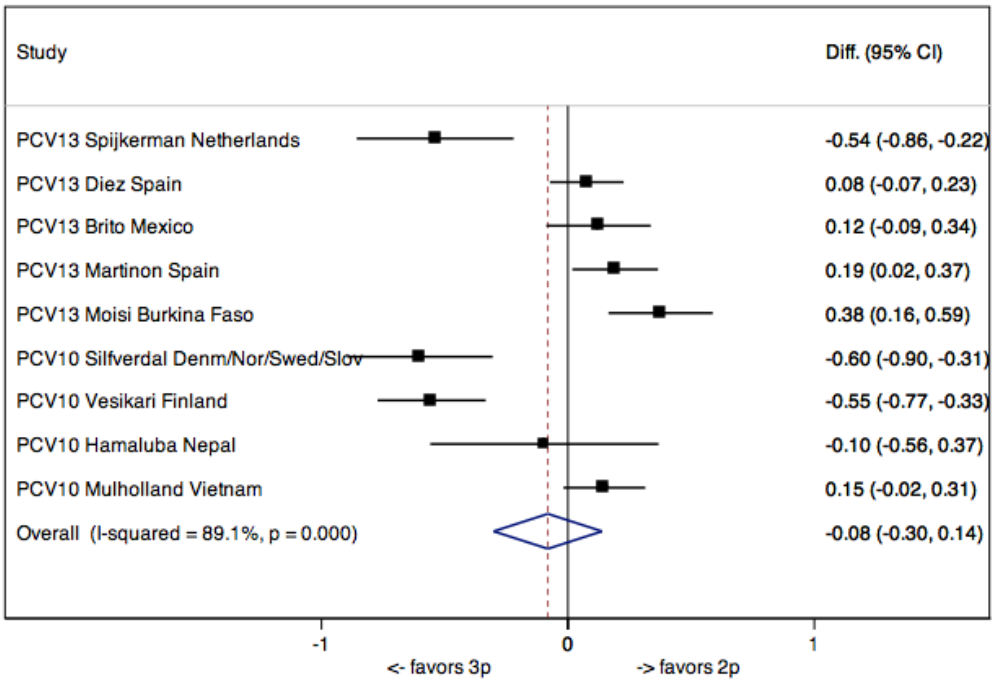


SEROTYPE 6B:

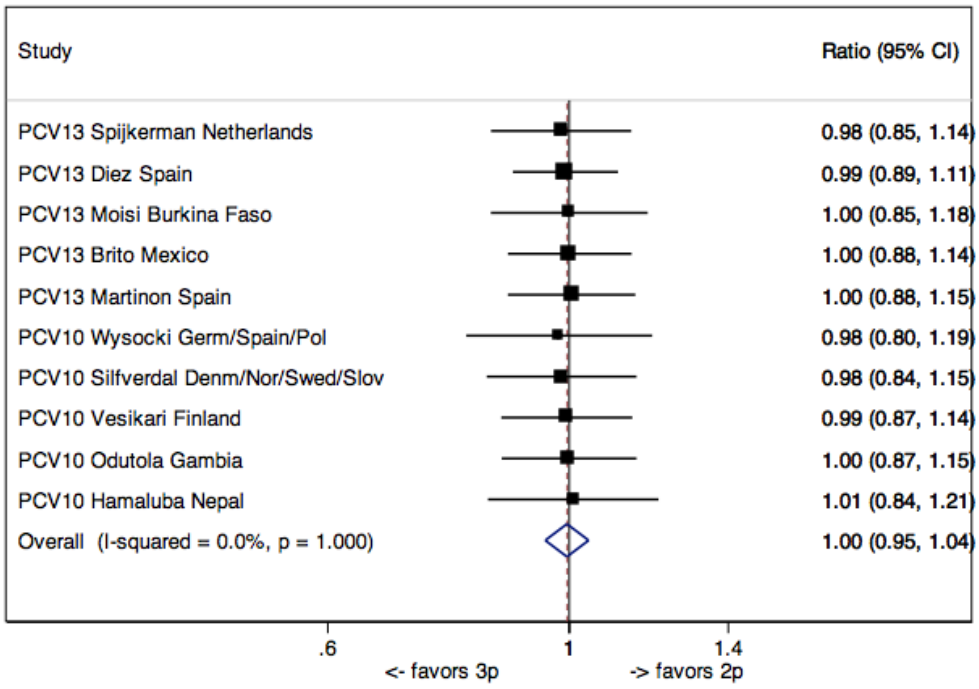

Study
Diff. (95% CI)
PCV13 Martinon Spain
-2.51 (-2.75, -2.27)
PCV13 Diez Spain
-2.22 (-2.40, -2.04)
PCV13 Brito Mexico
-1.81 (-2.05, -1.57)
PCV13 Spijkerman Netherlands
-1.68 (-2.19, -1.17)
PCV13 Moisi Burkina Faso
-1.31 (-1.66, -0.95)
PCV10 Hamaluba Nepal
-0.51 (-1.05, 0.03)
PCV10 Silfverdal Denm/Nor/Swed/Slov
-0.49 (-0.81, -0.17)
PCV10 Vesikari Finland
-0.47 (-0.72, -0.21)
PCV10 Mulholland Vietnam
-0.30 (-0.49, -0.11)
Overall (I-squared = 98.0%, p = 0.000)
-1.26 (-1.89, -0.63)
-4
0
1
<- favors 3p
-> favors 2p
Difference in log(GMC) for 2p vs. 3p schedule


Study
Ratio (95% CI)
PCV13 Martinon Spain
0.46 (0.36, 0.58)
PCV13 Spijkerman Netherlands
0.48 (0.35, 0.64)
PCV13 Diez Spain
0.73 (0.64, 0.85)
PCV13 Moisi Burkina Faso
0.87 (0.73, 1.05)
PCV13 Brito Mexico
0.91 (0.79, 1.05)
PCV10 Wysocki Germ/Spain/Pol
0.76 (0.61, 0.96)
PCV10 Vesikari Finland
0.91 (0.78, 1.07)
PCV10 Odutola Gambia
0.94 (0.80, 1.10)
PCV10 Silfverdal Denm/Nor/Swed/Slov
0.94 (0.78, 1.13)
PCV10 Hamaluba Nepal
0.99 (0.81, 1.20)
Overall (I-squared = 82.3%, p = 0.000)
0.79 (0.69, 0.91)
.3
.5
1
1.5
<- favors 3p
-> favors 2p
Ratio of proportions above cut-off for 2p vs. 3p schedule

SEROTYPE 19F:

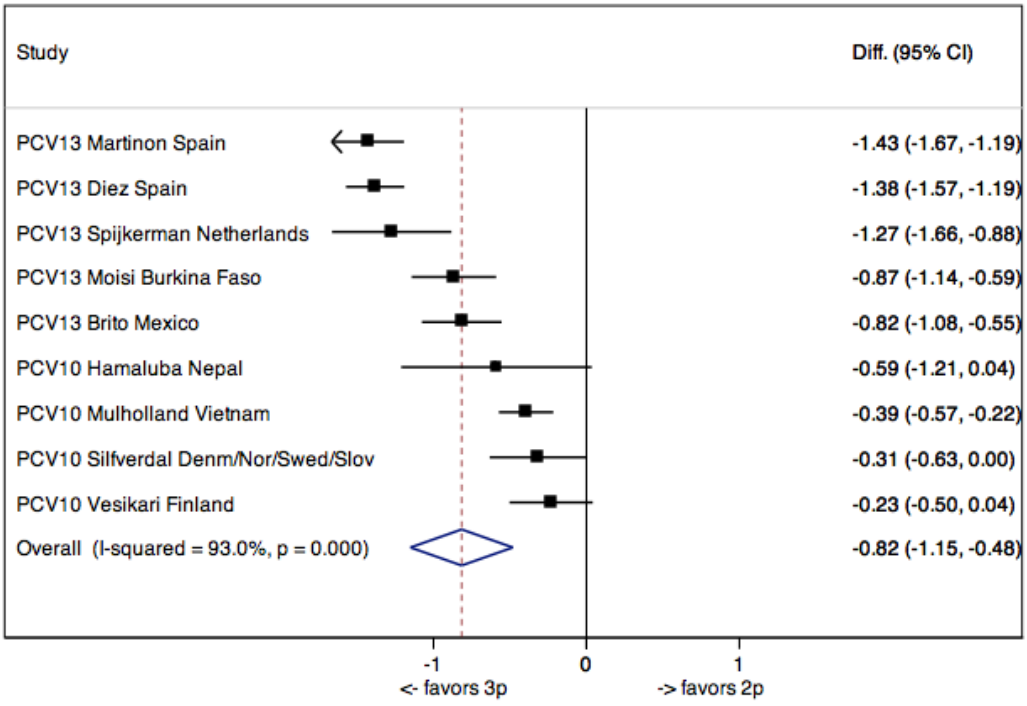


Difference in log(GMC) for 2p vs. 3p schedule

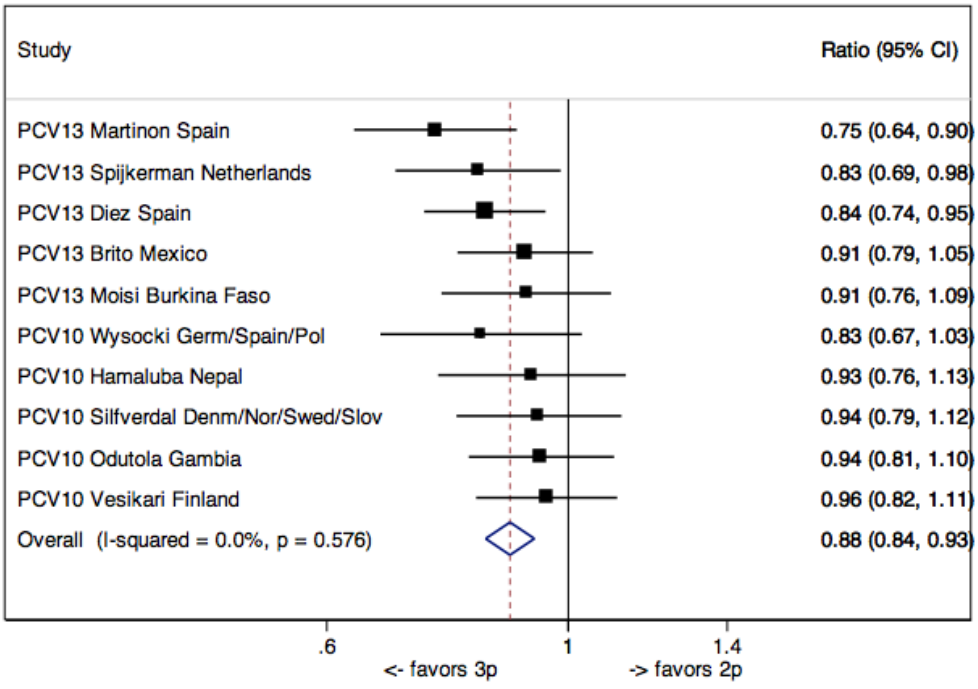


Ratio of proportions above cut-off for 2p vs. 3p schedule

SEROTYPE 23F:



Difference in log(GMC) for 2p vs. 3p schedule



Ratio of proportions above cut-off for 2p vs. 3p schedule

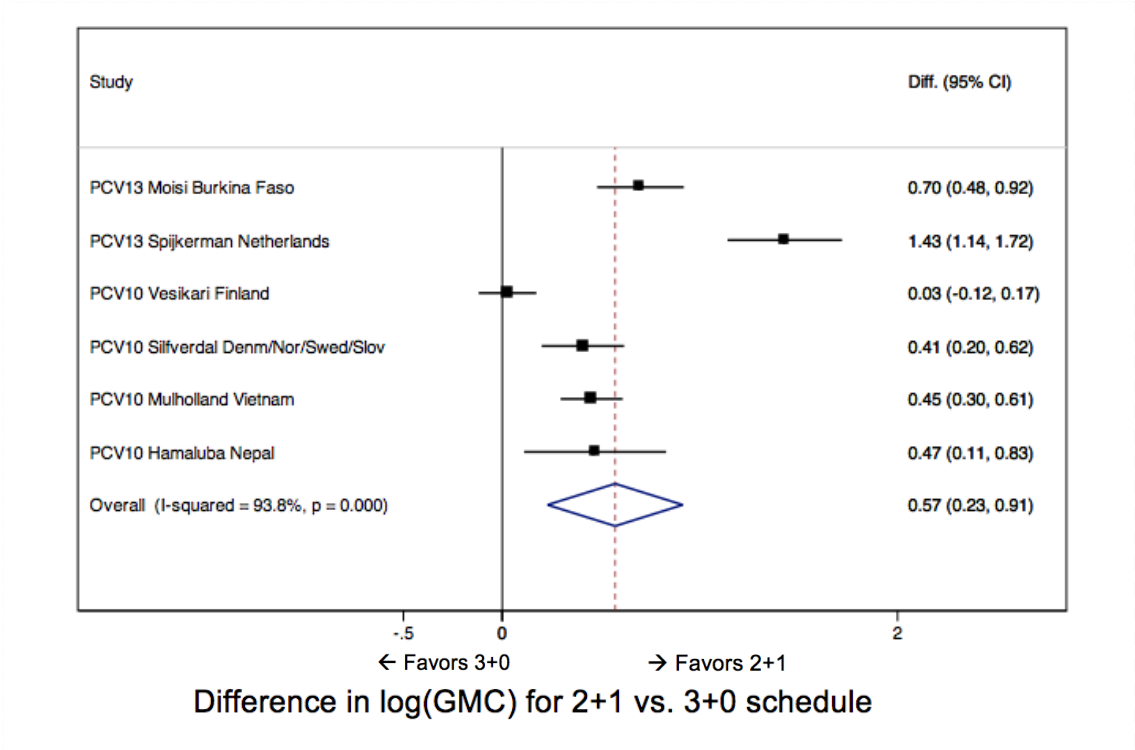
Table 1: Summary of evidence from head to head comparisons at the post-primary time point

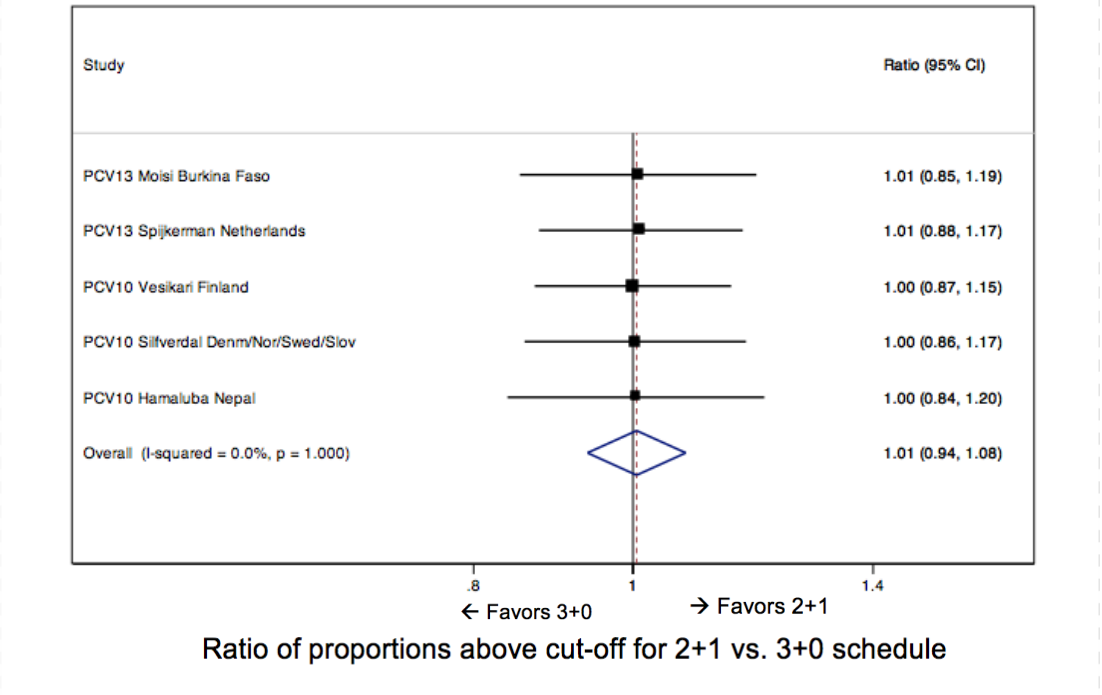
Result	GMC: Similar %Response: Similar	GMC: Favors 3p %Response: Similar	GMC: Favors 3p %Response: Favors 3p
Serotypes	3 19F	1 5 7F 14 19A 23F	6A* 6B*

*Prevalence Ratio (PR) For % response 2p vs 3p =0.93 for 6A and 0.77 for 6B

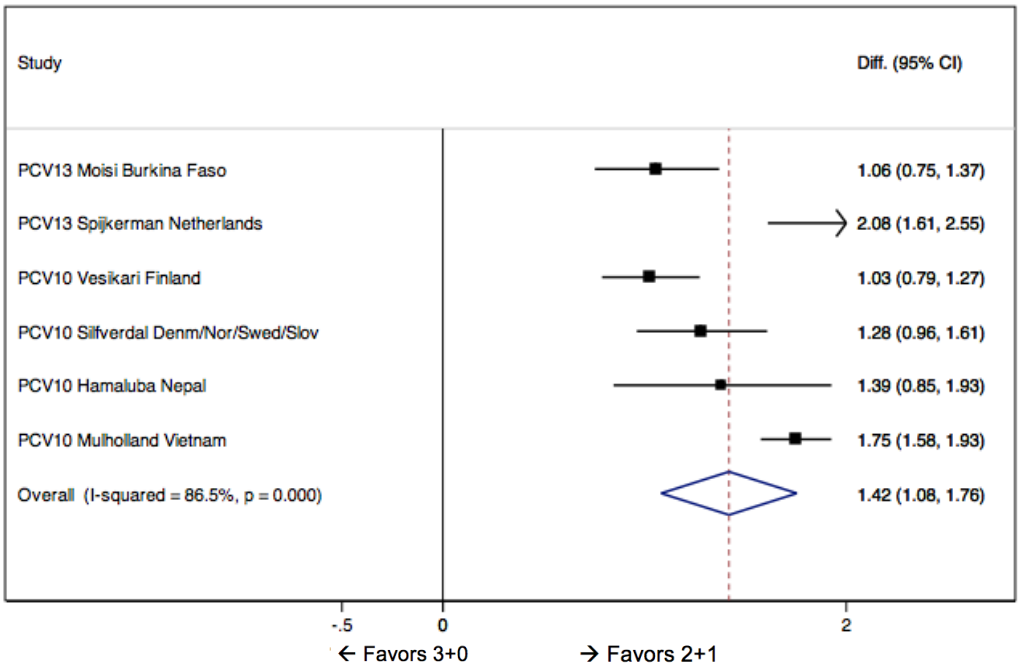
Figure 2 : Evidence from RCTs on the difference in log(GMC) and ratio of percent responders for a 2+1 vs. 3+0 schedule at the post-dose 3 blood draw: STs 1, 6B, 19F and 23F

SEROTYPE 1:

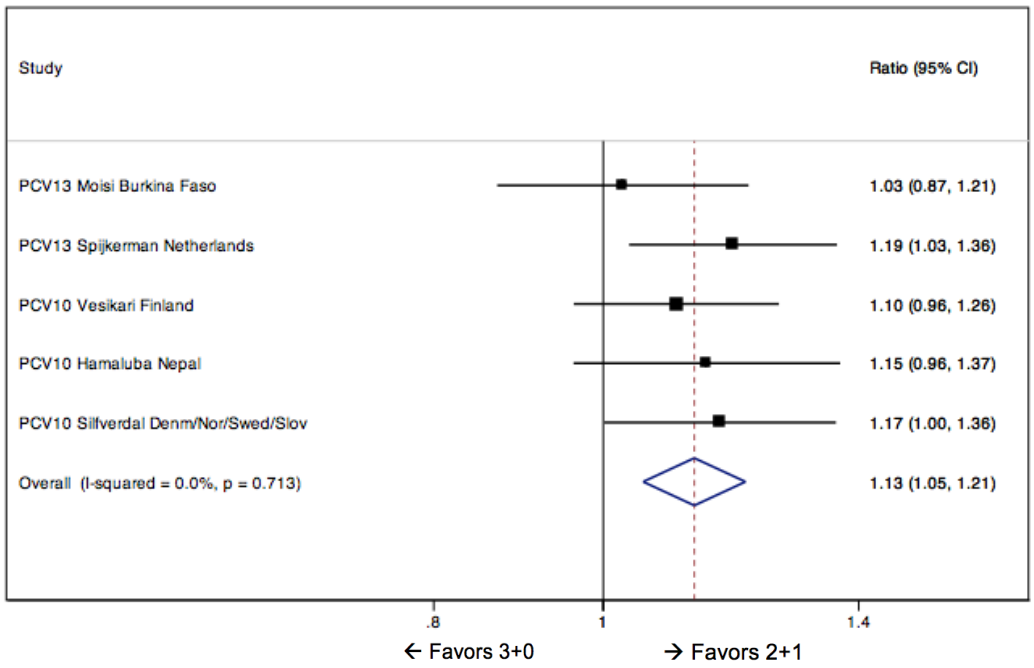




SEROTYPE 6B:

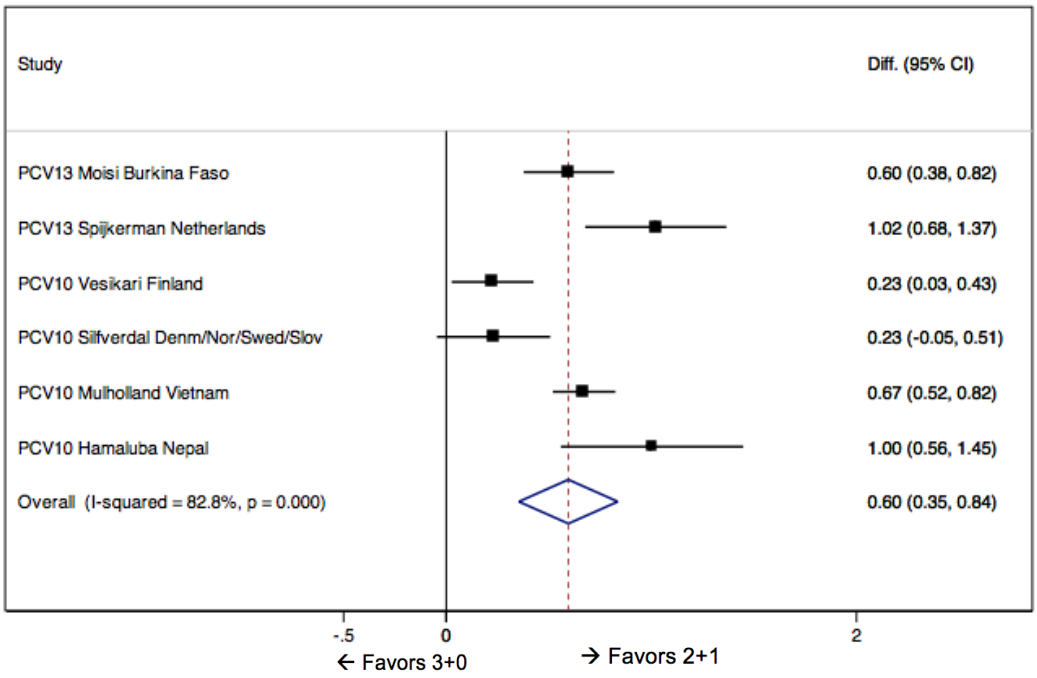


Difference in log(GMC) for 2+1 vs. 3+0 schedule

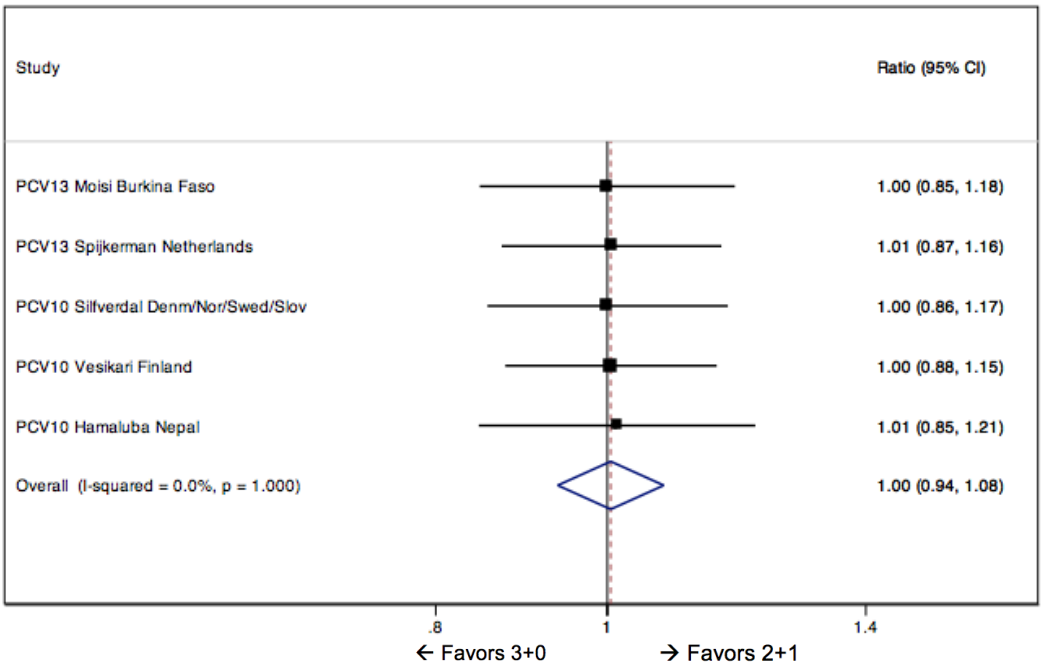


Ratio of proportions above cut-off for 2+1 vs. 3+0 schedule

SEROTYPE 19F:

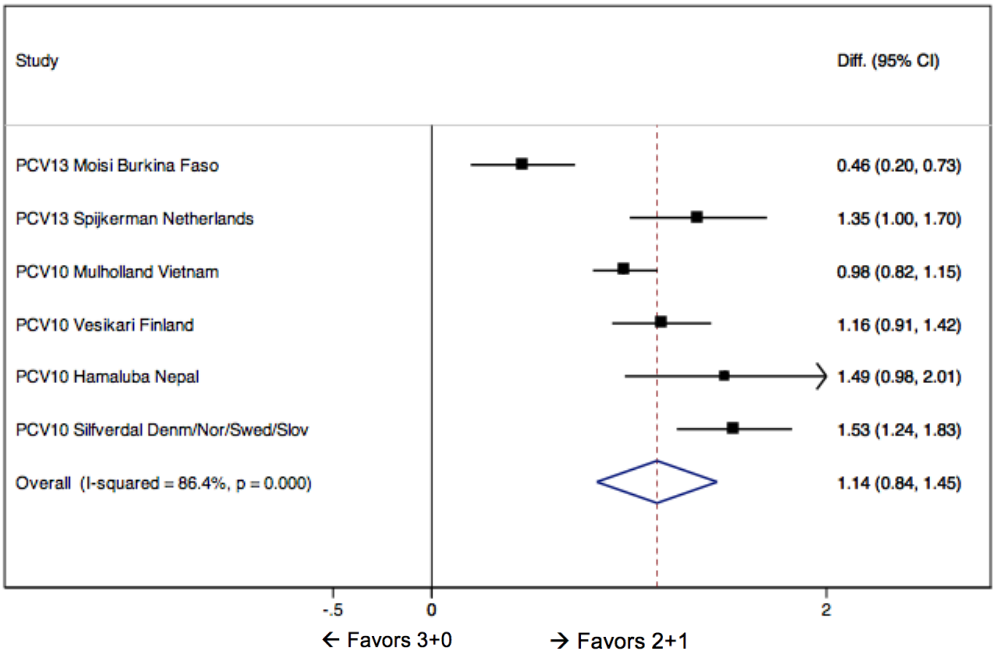


Difference in log(GMC) for 2+1 vs. 3+0 schedule

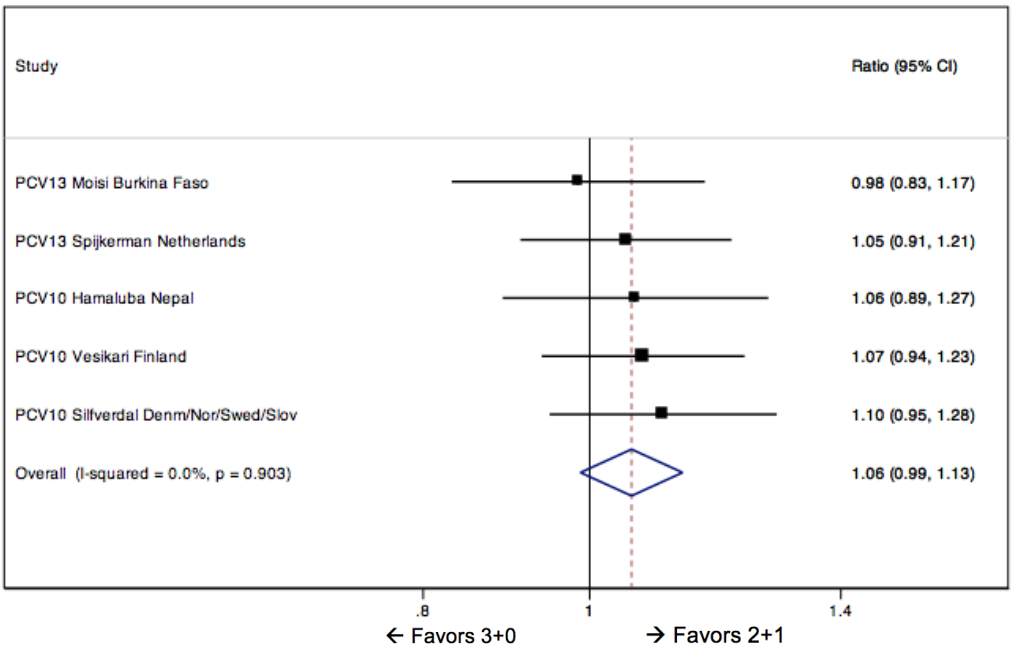


Ratio of proportions above cut-off for 2+1 vs. 3+0 schedule

SEROTYPE 23F:



Difference in log(GMC) for 2+1 vs. 3+0 schedule



Ratio of proportions above cut-off for 2+1 vs. 3+0 schedule

Table 2 : Summary of evidence from head to head comparisons at the post-dose 3 time point

Result	GMC: Similar %Response: Similar	GMC: Favors 2+1 %Response: Similar	GMC: Favors 2+1 %Response: Favors 2+1
Serotypes	3* 19A	1 5 6A 7F 14 19F 23F	6B**

*2 studies, 1 with GMC 2+1<<<GMC 3+0, 1 with GMCs equal

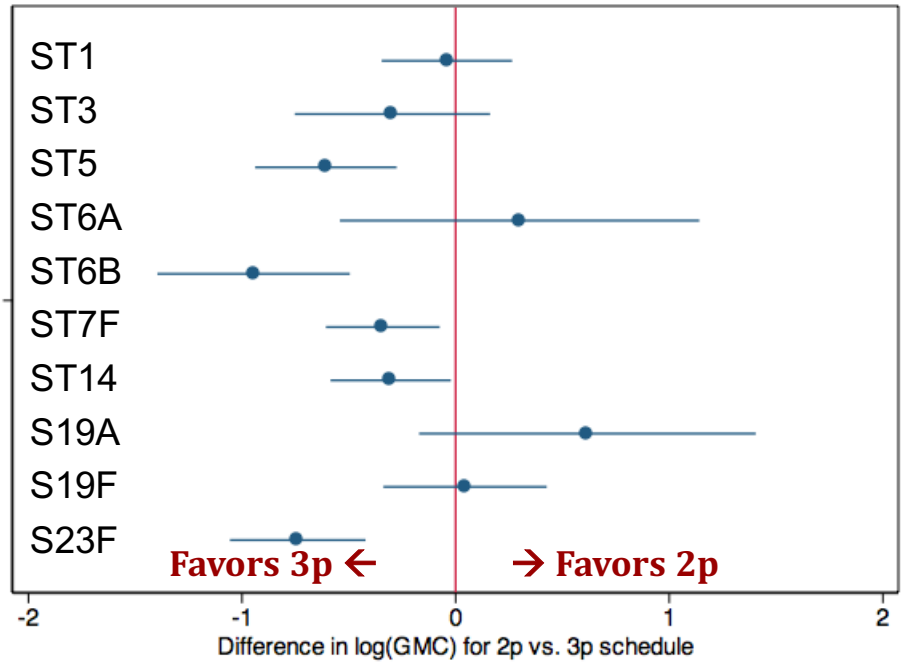
**Prevalence Ratio (PR) for % response 2+1 vs 3+0 = 1.13

3.1.2.2 Evidence from Other Trials (Single arm and non-randomized):

Evidence from head to head studies was combined with evidence from single arm studies to evaluate the 2+1 and 3+0 schedules at three time points: post-primary, pre-boost and post-dose 3, with n=67, n=49 and n=67 study arms reporting data on these respective time points. There was more evidence for antibody concentrations (GMC) than for proportion of subjects above the response threshold. Log(GMC) and percent responders were compared across schedules in a descriptive analysis. In addition, a multivariate meta-analysis model was built to investigate the effect of schedule on log(GMC), adjusting for several confounders including product, region, country income level, DTaP co-administration, age at first dose and allowing for interaction with dosing interval (e.g. interval between primary doses <8 or ≥8 weeks).

At the post-primary time point, the univariate analysis showed significantly higher GMCs for serotypes 5, 6B, 7F, 14, and 23F for the 3-dose compared with the 2-dose schedule (**Figure 3**). In the multivariate analysis, differences in GMCs were also significant for serotype 6A (when the dosing interval was >=8 weeks) but were no longer significant for serotype 14. When focusing on percent responders, differences between schedules were most marked for serotypes 6B and 23F for both products as well as 6A and 19A in PCV10 studies. The statistical significance of these differences could not be evaluated.

Figure 3 : Between-study comparisons of schedule at the post-primary time point for vaccine serotypes, meta-analysis of log(GMC) and percent of subjects achieving titers over the threshold of protection



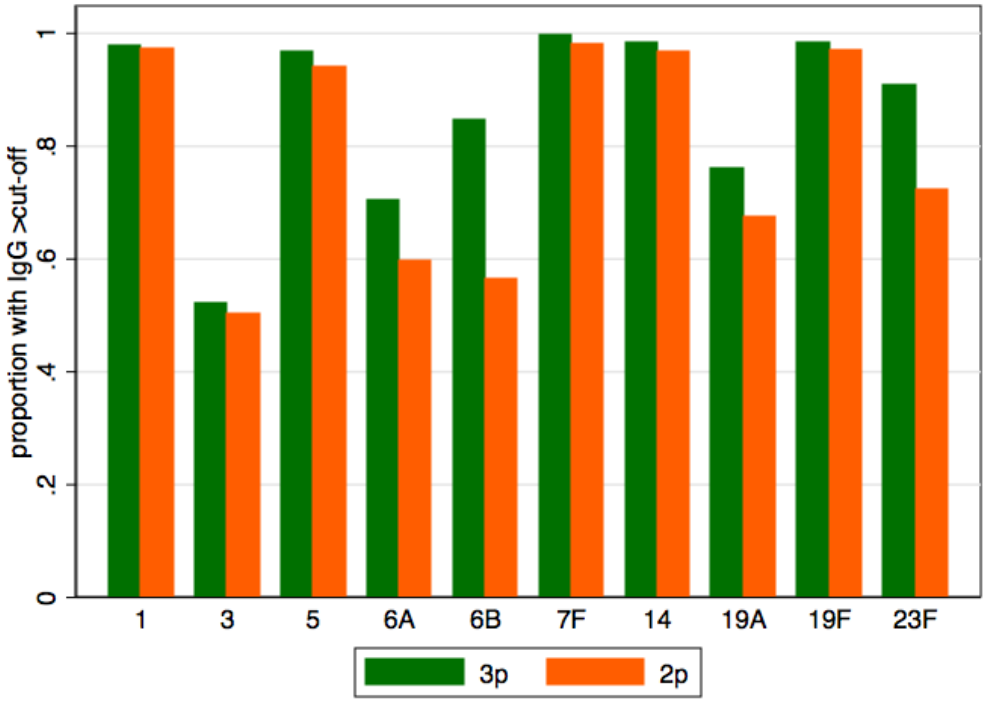
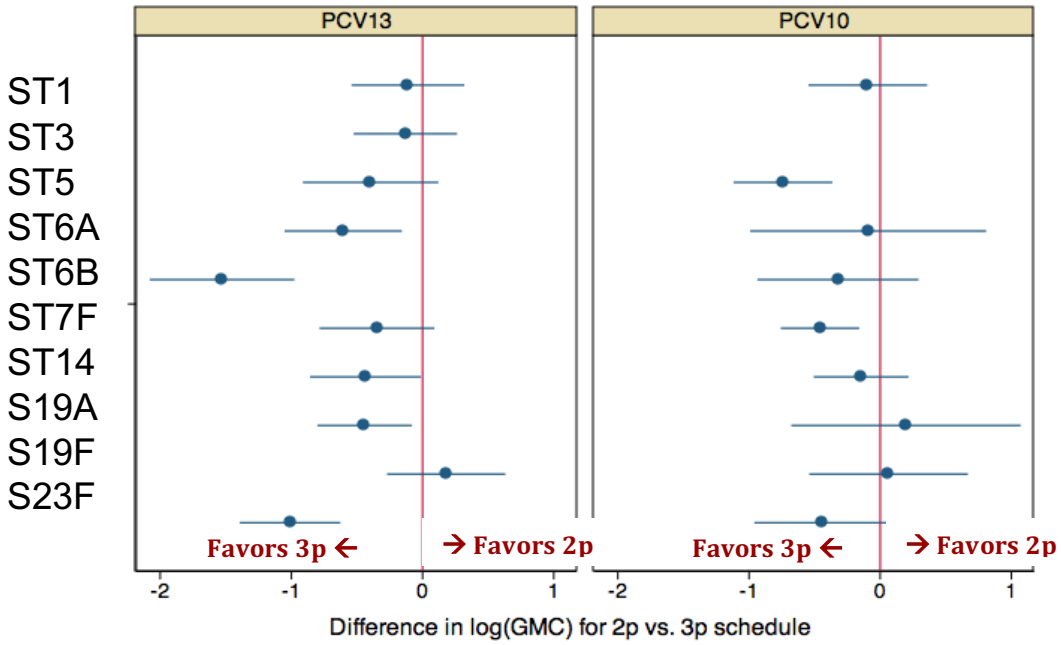
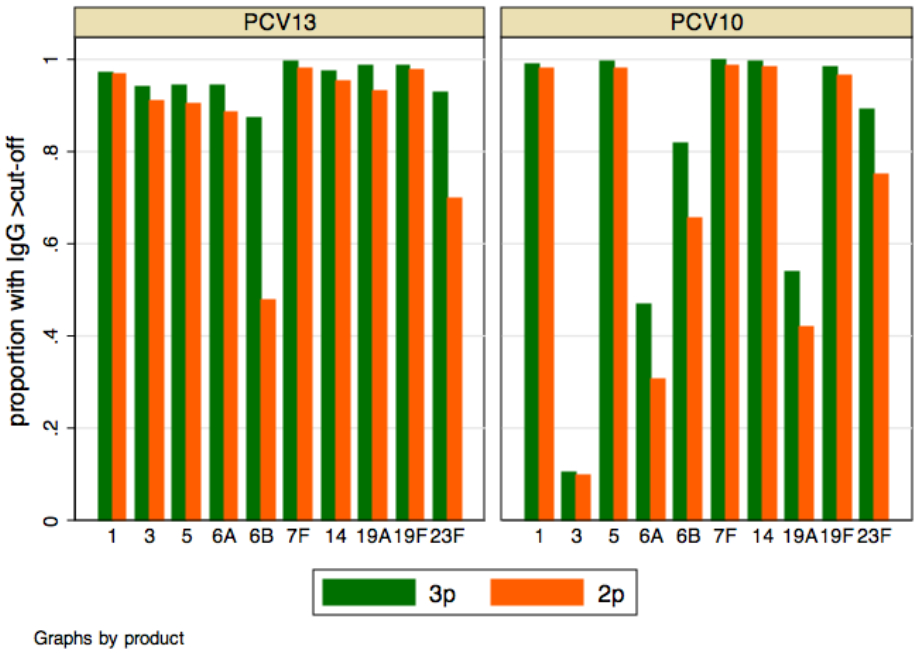


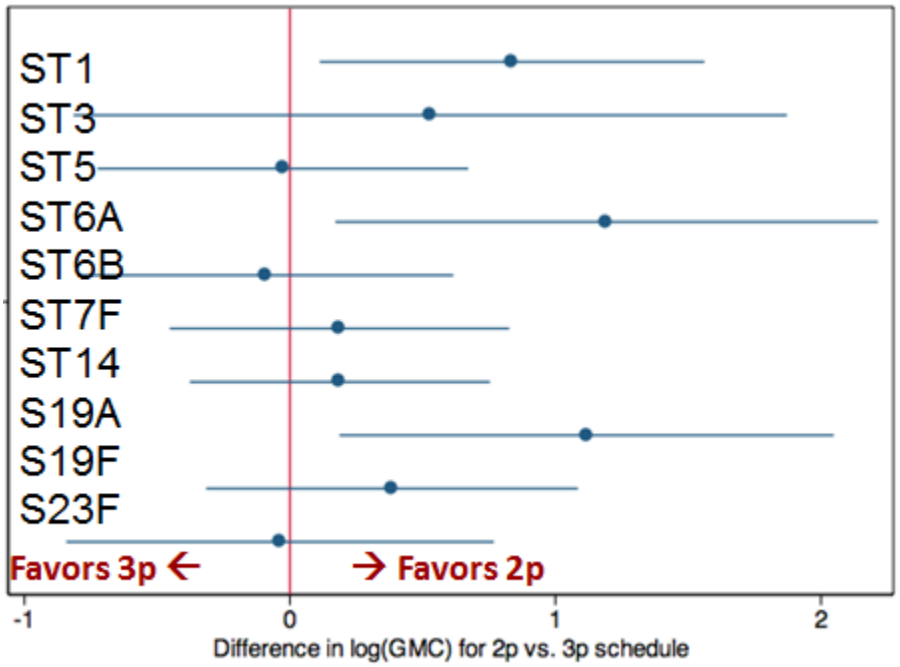
Figure 4: Between-study comparisons of schedule by PCV product at the post-primary time point for vaccine serotypes, meta-analysis of log(GMC) and percent of subjects achieving titres over the threshold of protection





At the pre-boost time point, most differences between the three-dose and two-dose primary series became indistinguishable for the vaccine serotypes (**Figure 5**). This was also true when results were separated out by product (**Figure 6**). No multivariate analyses were done for GMCs at this time point. There were no data on the percent responders at the pre-boost time point for a 2+1 schedule using PCV10.

Figure 5: Between-study comparisons of schedule at the pre-boost time point for vaccine serotypes, meta-analysis of log(GMC) and percent of subjects achieving titres over the threshold of



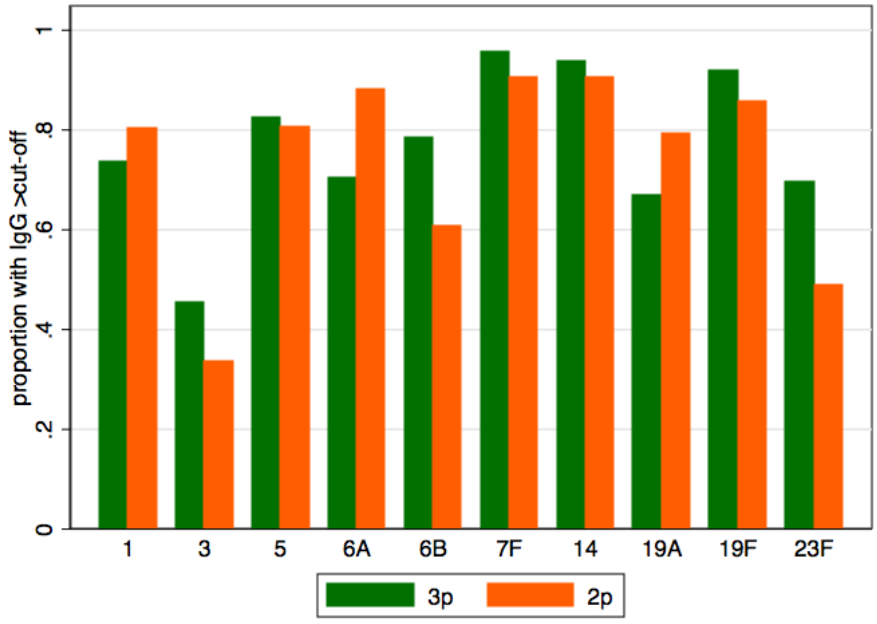
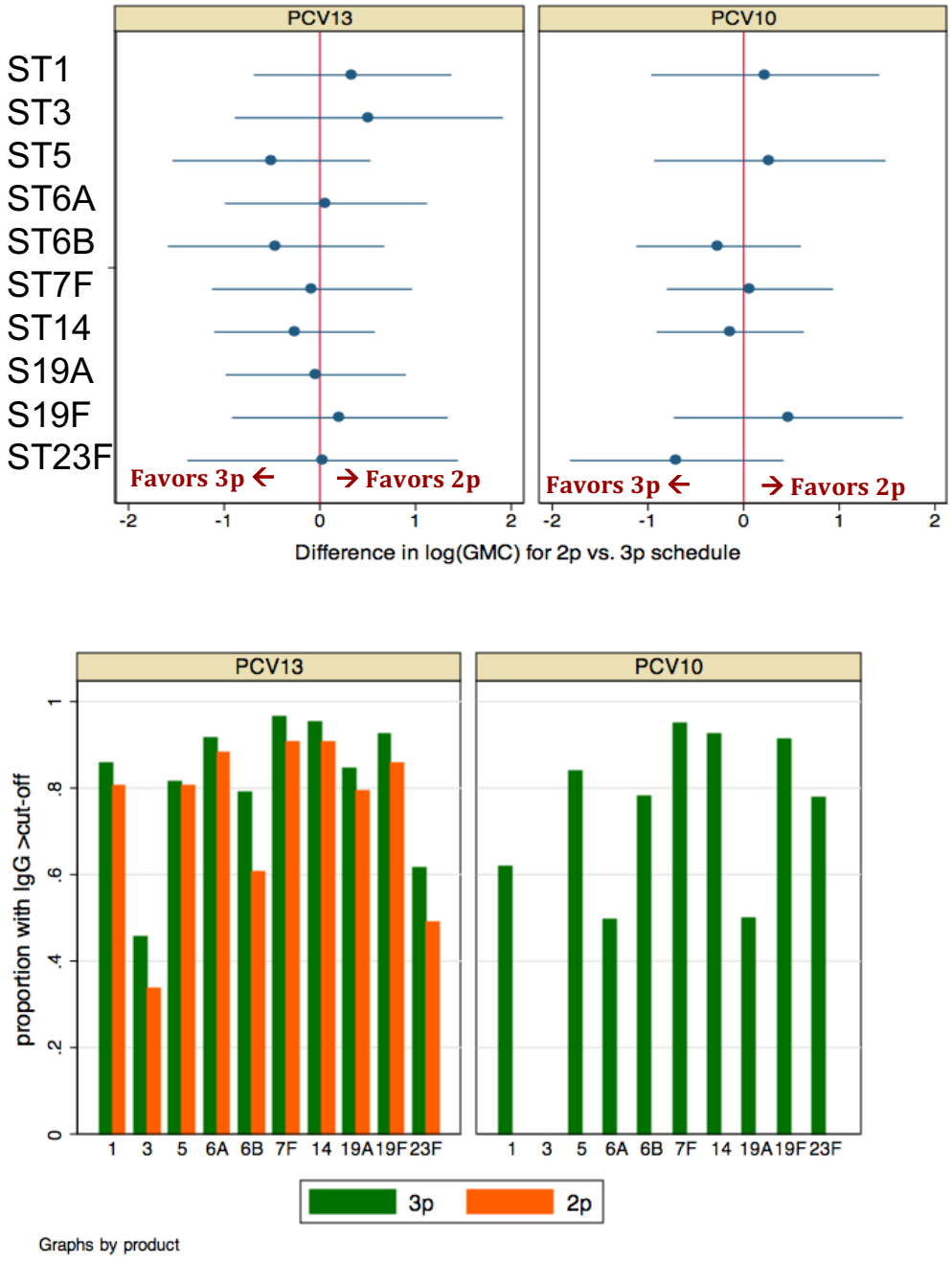


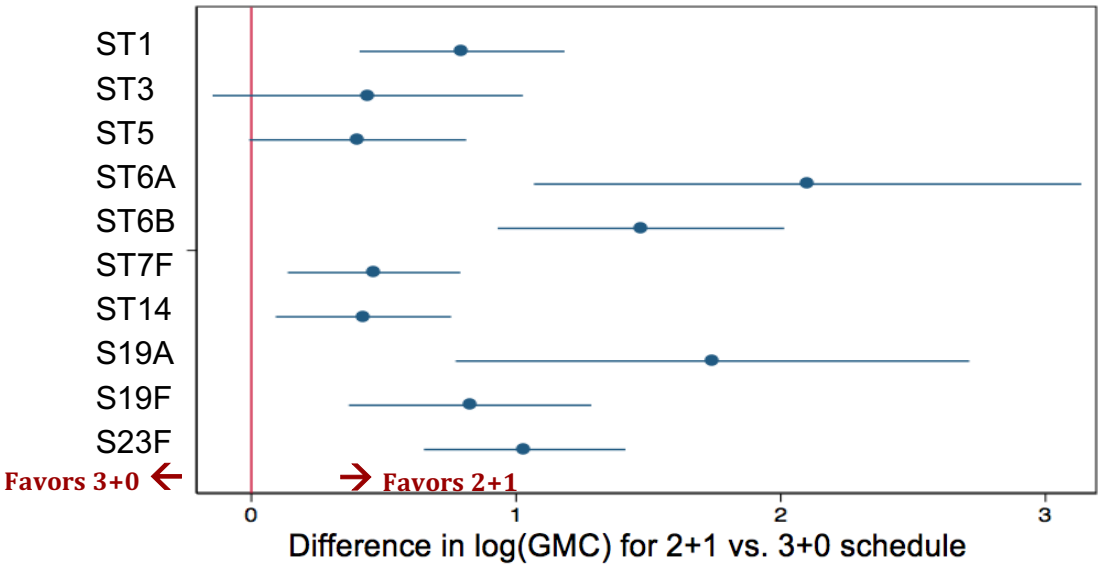
Figure 6: Between-study comparisons of schedule by PCV product at the pre-boost time point for vaccine serotypes, meta-analysis of log(GMC) and percent of subjects achieving titres over the threshold of protection



At the post-dose-3 time point, the univariate analysis of antibody GMCs favors the 2+1 schedule over the 3+0 for all serotypes except STs 3 and 5 (**Figure 7**). In the multivariate analysis, GMCs are higher after a 2+1 schedule for all serotypes but serotype 14. However, the differences in antibody concentration seen in these models do not translate into substantial differences in percent responders except for STs 6A and 19A (**Figure 8**). For these two serotypes, the proportion of responders is

significantly higher after a 2+1 schedule of PCV10 than a 3+0 schedule; however, this observation may be due to the differential age at which the "post dose 3" immune response is measured, as natural boosting can occur between the end of the primary series and the time of the booster dose and lead to higher antibody concentrations.

Figure 7: Between-study comparisons of schedule at the post-dose-3 time point for vaccine serotypes, meta-analysis of log(GMC) and percent of subjects achieving titres over the threshold of



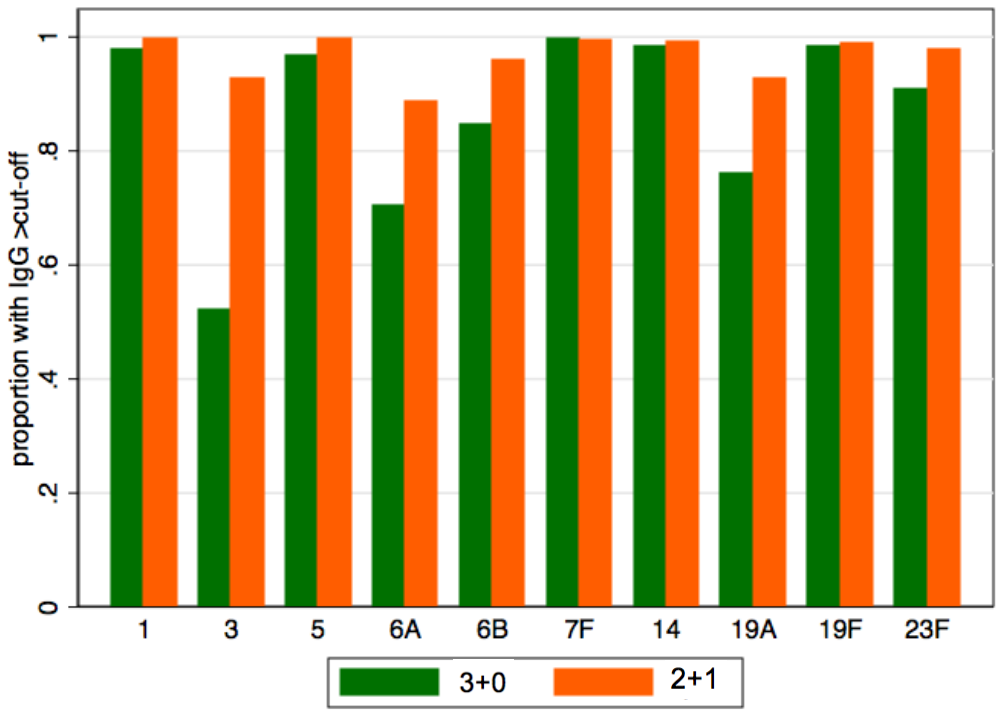
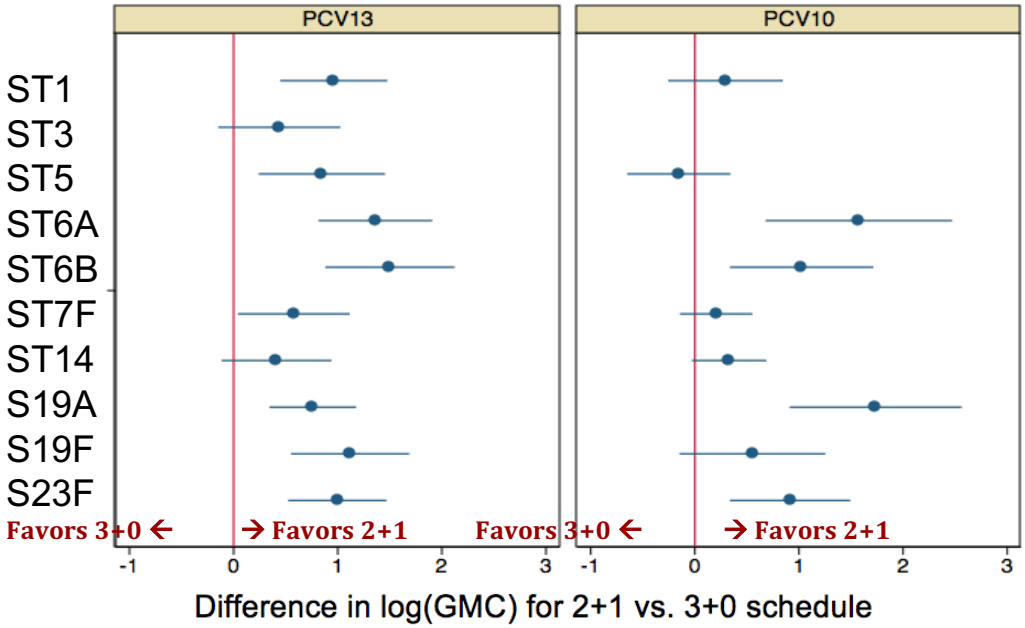
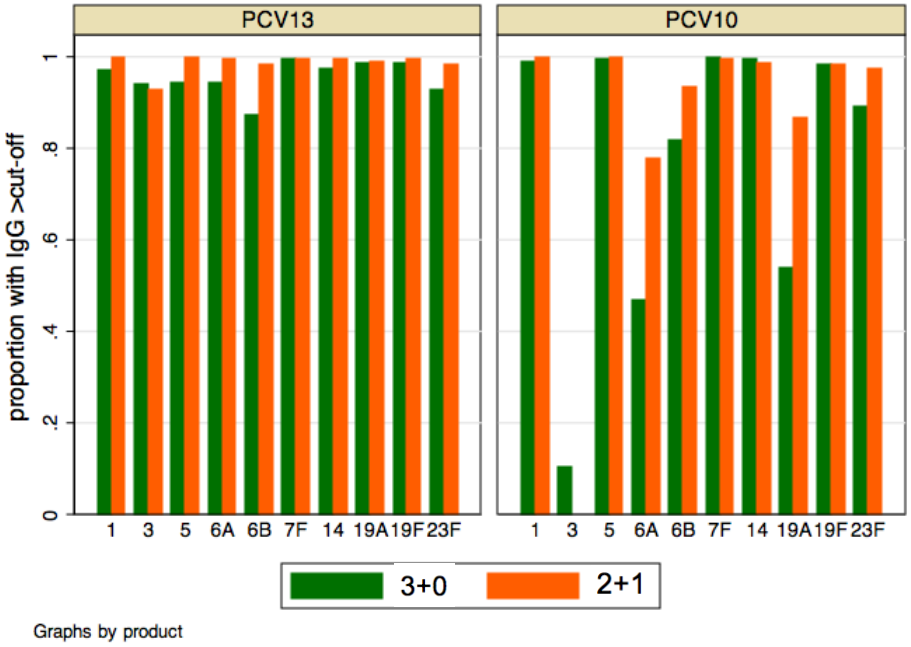


Figure 8: Between-study comparisons of schedule by PCV product at the post-dose-3 time point for vaccine serotypes, meta-analysis of log(GMC) and percent of subjects achieving titres over the threshold of protection





3.2 Nasopharyngeal Carriage Direct Effects and Dosing Schedule:

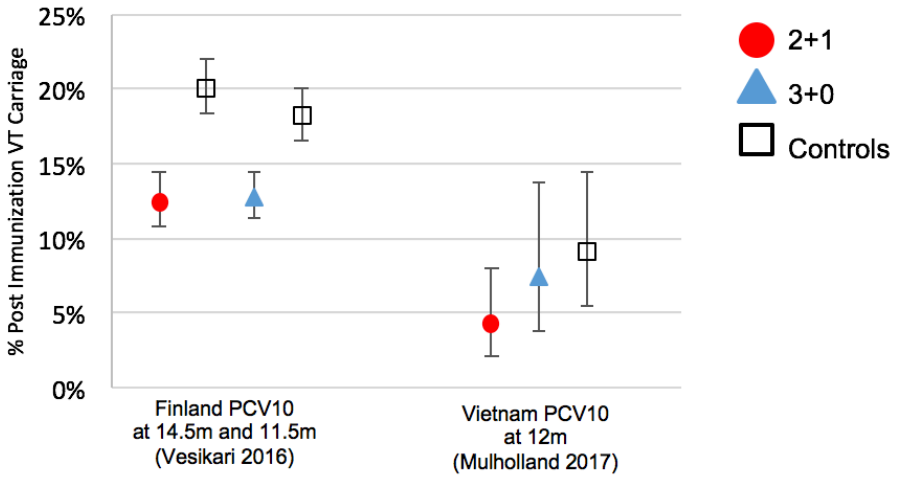
3.2.1 Direct Effects on Vaccine-Type NP Carriage:

We identified 22 studies with 29 arms that provided evidence on 2+1 vs 3+0 schedules for PCV10/13: 2 were head-to-head trials directly comparing schedules, 9 were arms of only one schedule (n=5 3+0, n=4 2+1), and 17 were observational studies (18 arms) in the context of routine PCV10/13 use (n=9 3+0, n=9 2+1).

Head to Head Studies:

Two head-to-head trials (**Figure 9**) were conducted comparing vaccine-type NP carriage (defined as the proportion of children carrying vaccine serotypes, as opposed to the proportion of isolates that were vaccine serotypes) among children who received 3+0 vs. 2+1[40]. Both trials evaluated PCV10, included an additional non-PCV control group and were conducted in low carriage settings (9-20% NP carriage at age 12-15 months in controls). In the Vietnam trial (Mulholland, personal communication, 2017; [41, 42]), post-vaccination PCV10-type carriage at age 12 months for both schedules were lower than that in controls (VT=9.1%, n=187) but was not statistically significant as the sample size was small and carriage in the population was so low. The 2+1 schedule (4.3%, n=231) was lower than the 3+0 schedule (7.5%, n=134) but was also not statistically different. The trial in Finland, which did have a large sample size, observed very similar PCV10-type carriage between the 2+1 schedule (12.5%, n=1289) and 3+0 (12.8%, n=1803) [40]. However, the 2+1 swabs were taken at an age 3 months older (14.5 months) than the 3+0 swabs (11.5 months) and carriage in controls increased slightly during this period from 18.2% to 20.1% (n=1987). When differences between vaccinated and controls at comparable ages are considered, the 2+1 schedule may have had a slightly larger effect: i.e., 20.1% in placebo arm vs. 12.5% in 2+1 arm is a 37.8% relative reduction while 18.2% in placebo arm vs. 12.8% in 3+0 arm is a 29.7% relative reduction, but this difference was not statistically significant.

Figure 9: Head-to-head trials comparing PCV10-type carriage in children who received 3+0 vs 2+1 schedules



Footnote: In the Finland trial, the 3+0 arm was assessed at 11.5m of age while the 2+1 arm was assessed 3 months later at 14.5m of age where carriage was higher in the control arm (carriage increased with age in this trial, shown here for both ages in

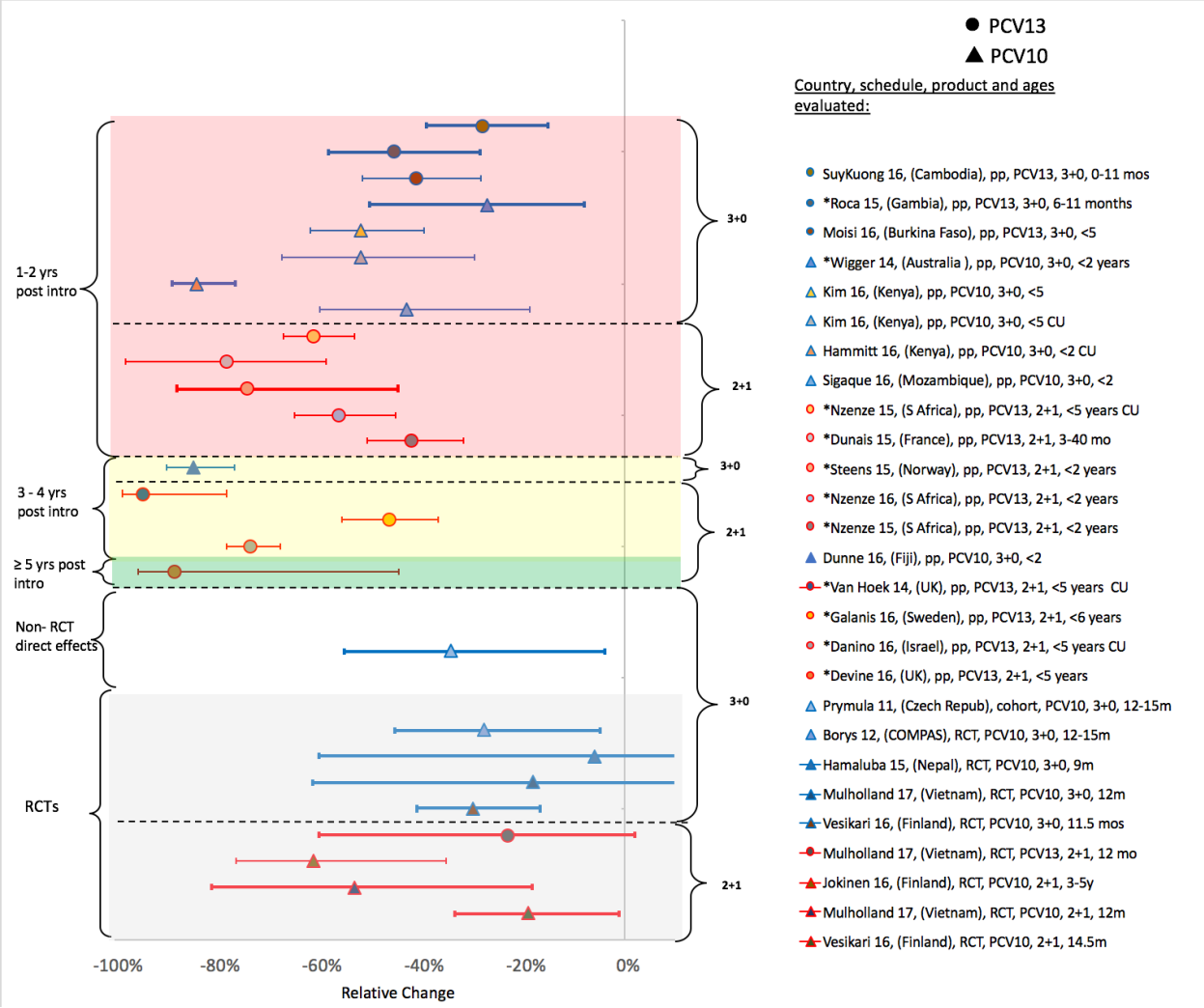
controls), implying that the 2+1 arm may have had a greater impact on reducing carriage but because carriage was low were not statistically significant.

OTHER TRIALS (SINGLE ARM AND NON-RANDOMIZED):

Figure 10 shows effectiveness against vaccine-type carriage from eight trial arms (grey section) and one non-randomized comparisons (white section) of a single schedule (i.e., did not directly compare schedules): four 2+1 arms [one PCV13 and three PCV10] and five 3+0 arms (PCV10). (Note: the red, yellow and green portions of the figure present data from observational studies which are described in the next section below.) The results from four arms in the two head-to-head trials above compared to their respective controls are also plotted [40, 41, 43]. Percent change relative to controls (i.e., vaccine effectiveness) was calculated as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Effectiveness in reducing VT carriage varied widely among trials for both schedules (2+1 studies range in vaccine effectiveness was 19%-88% compared to 6%-84% for 3+0 studies) but the vaccine effectiveness of 2+1 trials had a greater reduction in VT carriage (2+1 meta-estimate =41% reduction, 95%CI: 28-59%) than 3+0 trials (meta-estimate = 24% reduction, 95%CI: 17-35%; p=0.09). Conclusions were similar when considering the five trial arms from low income countries only (**Figure 12**).

There were only 4 arms that looked at 3+0 dosing schedule, of which all but one (COMPAS) used schedules with 1-month intervals [44]. Due to the lack of data, an assessment of the impact of a 2-month interval vs a 1-month interval on declines in carriage could not be performed.

Figure 10: Clinical trials and observational studies evaluating impact on vaccine-type carriage in children who received 3+0 (blue points/lines) vs 2+1 schedules (red points/lines)



Footnote: 'Vaccine-type carriage' is defined as the proportion of children carrying vaccine serotypes, as opposed to the proportion of isolates that were vaccine serotypes. Points and 95% confidence intervals (whiskers) denote the relative change in VT carriage, defined for observational studies of routine use (red, yellow, green sections) as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials (bottom grey section) and non-randomized comparisons (white) as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies are grouped by years of PCV10/13 use: green background = impact after 5+ years of PCV use in the population, yellow background = 3-4 years of PCV use, and red background = 1-2 years of PCV use. Within color group, studies are ordered by schedule (3+0 = blue markers/lines and 2+1= red markers/lines) and within each schedule by product (PCV13=circles and PCV10=triangles).

*Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

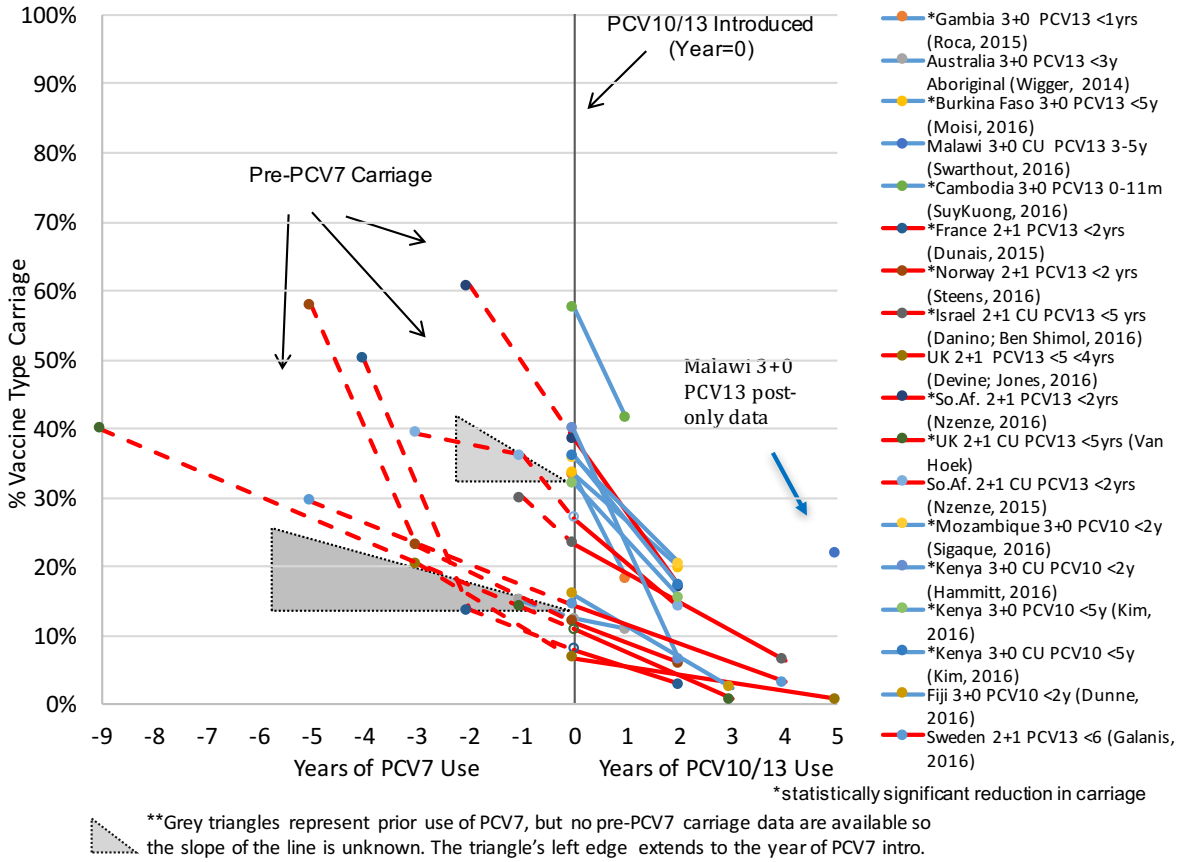
OBSERVATIONAL STUDIES POST INTRODUCTION NATIONAL IMMUNIZATION PROGRAMS:

We identified 18 studies with 19 arms evaluating the impact on vaccine-type NP carriage of PCV10/13 introduction into routine national programs, 9 arms with a 2+1 schedule and 9 with a 3+0 (green, yellow and red sections of **Figure 10** and **Figure 11**). Only 2 represented data from a mature program of 5+ years of use (a 2+1 pre/post study in the UK and a 3+0 post-only study in Malawi), both used PCV13 [45, 46]. The UK study was in the context of low pre-PCV carriage (no pre-PCV7 data were available but 1 year post-PCV7 introduction carriage was 15%) and showed VT-carriage at 1% in year 5 post-PCV13[45]. However, in Malawi after ~5 years of use there was still 22% VT-carriage (no pre-PCV data were available)[46].

Percent relative change in **Figure 10** was calculated as (pre% - post%)/pre% where 'pre' is carriage prior to or at the time of PCV10/13 introduction. Of 18 arms evaluating the percent relative change in vaccine-type NP carriage before vs. after PCV10/13 introduction, 9 were from programs using 2+1 and 9 were 3+0 (**Figure 10**). Of these, 11 (n=9 2+1 and n=2 3+0) were conducted in countries with preceding use of PCV7 (indicated by '*' in **Figure 10** and dashed lines in **Figure 11**).

Figure 11 depicts the percent of children who carried vaccine-serotypes over time for 18 study arms that provided data before and after PCV10/13 introduction. One study, in Malawi, had post-PCV13 data only (i.e., % change data) but was included because it was conducted in the setting of a mature PCV program after ~5 years of PCV13 use [46].

Figure 11: Vaccine-type NP carriage before and after PCV10/13 introduction in countries using 3+0 (blue lines) vs 2+1 schedules (red lines), for all studies



Footnote: 'Vaccine-type carriage' is defined as the proportion of children carrying vaccine serotypes, defined as 10-VT for the PCV10 trials and 13-VT for the PCV13 trials. Solid lines depict post-PCV10/13 carriage while dotted lines depict post-PCV7 carriage prior to PCV10/13 introduction for countries with prior use of PCV7. Studies are colored by schedule: blue lines = 3+0 and red lines = 2+1. Grey shaded triangles point to studies where pre-PCV7 carriage is unknown but assumes some decline; the triangle extends left to the year PCV7 was introduced to indicate how much PCV7 use there was prior to PCV10/13 introduction.

Several issues hamper determining which schedule is better at reducing vaccine-type NP carriage. First, among the observational studies there was complete confounding by product in that all 2+1 arms used PCV13 while 6 of the 9 3+0 arms used PCV10. Second, all of the 2+1 studies were in the context of preceding use of PCV7 prior use while only one of the 3+0 studies had previously used PCV7. If these factors can be ignored, there was no difference in the percent relative change between 2+1 schedules (meta-average=50%, 95%CI: 38-64%) and 3+0 schedules (meta-average =49%, 95%CI: 39-63%) across all studies after adjusting for years of use. However, in the 13 studies of short term use (1-2 years of PCV10/13 use), impact was generally higher among 2+1 studies (meta-estimate of percent reductions = 49% (CI 37-65%) and ranged from 42%-78%) than among 3+0 studies (meta-estimate of percent reductions = 43% (CI 34- 55%) and ranged from 27-52%, with the exception of an 84% reduction in one study in Kilifi, Kenya that had high immunization rates and used a catch-up campaign in all children <5y) [47]. Only 1 study represented data from a mature program of 5+ years of use (2+1 in the UK described above)[45]. Only four had data after 3 or more years of use, one with 3+0 and 3 with 2+1; the impact of the 3+0 schedule is within the range of those of the 2+1 schedules so we did not identify any evidence of a difference by schedule in the limited number of settings with long-term use. The magnitude of this

long-term impact was larger than that observed in the clinical trials, ranging in observational settings from 46% to 94% reductions in VT carriage for the 2+1 studies and an 84% reduction for the 3+0 study, while for RCTs reductions in VT carriage ranged from 6-49% for 2+1 trials and 19-61% for 3+0 trials.

Figure 10 shows that, regardless of schedule, post-PCV10/13 carriage prevalence is lower when there have been more years of PCV use and when pre-PCV carriage prevalence is lower to start with. For any given year post PCV10/13 introduction, the percent of children with VT carriage by schedule overlaps; no schedule is clearly higher or lower. It is difficult to discern any schedule-specific effects because the data are confounded by prior experience with PCV7; all 9 2+1 studies were in the context of preceding use of PCV7 while for 3+0 study arms only 2 of 9 were in the context of previous PCV7 use. The persistent carriage of PCV13-types in Malawi ~5 years after 3+0 PCV13 introduction, a setting with high PCV coverage, does suggest that in high burden areas a 3+0 schedule may not eliminate vaccine-type carriage (the persistence in carriage applied to all vaccine types, not just one or two serotypes); there was no such long-term data in high burden settings for 2+1 [46].

Other observational data include a study in a low carriage (28% all serotype carriage) setting in Poland that observed 1.4% VT carriage in vaccinated children in a city that introduced PCV13 with a 2+1 schedule (years of use not known) vs. 16% VT carriage in children in a city that did not introduce PCV13, a 91% relative difference[48].

Of the 3+0 pre-post observational studies, all but one (Australia) used schedules with 1-month intervals between dosing, and that study had 4 years of prior PCV7 use so was not comparable to the others which did not [49]. Therefore, assessment of the impact of a 2-month interval vs a 1-month interval on declines in carriage could not be performed.

The observational data were stratified by income status of the countries conducting the studies: 'High Income' countries included upper middle-income countries and 'Low Income' countries included lower middle-income countries, as per 2016 World Bank status (**Figure 11** and **Figure 13**). All 8 arms conducted in low income settings evaluated 3+0 schedules (**Figure 13b**). Among studies conducted in high-income settings, 8 evaluated 2+1, all with previous use of PCV7, compared to 2 that evaluated 3+0 schedules, only one of which previously used PCV7. This highlights a gap in the available evidence in low income settings on the impact of 2+1 schedules on vaccine-type NP carriage.

When considering observational studies conducted in routine use in low-income countries only, there were no 2+1 arms; the 7 3+0 arms only had short-term (i.e., 1-2 years post-introduction) impact data (**Figure 13**).

Figure 12: Clinical trials and observational studies evaluating impact on vaccine-type carriage in children who received 3+0 (blue points/lines) vs 2+1 schedules (red points/lines), subset for low-income countries

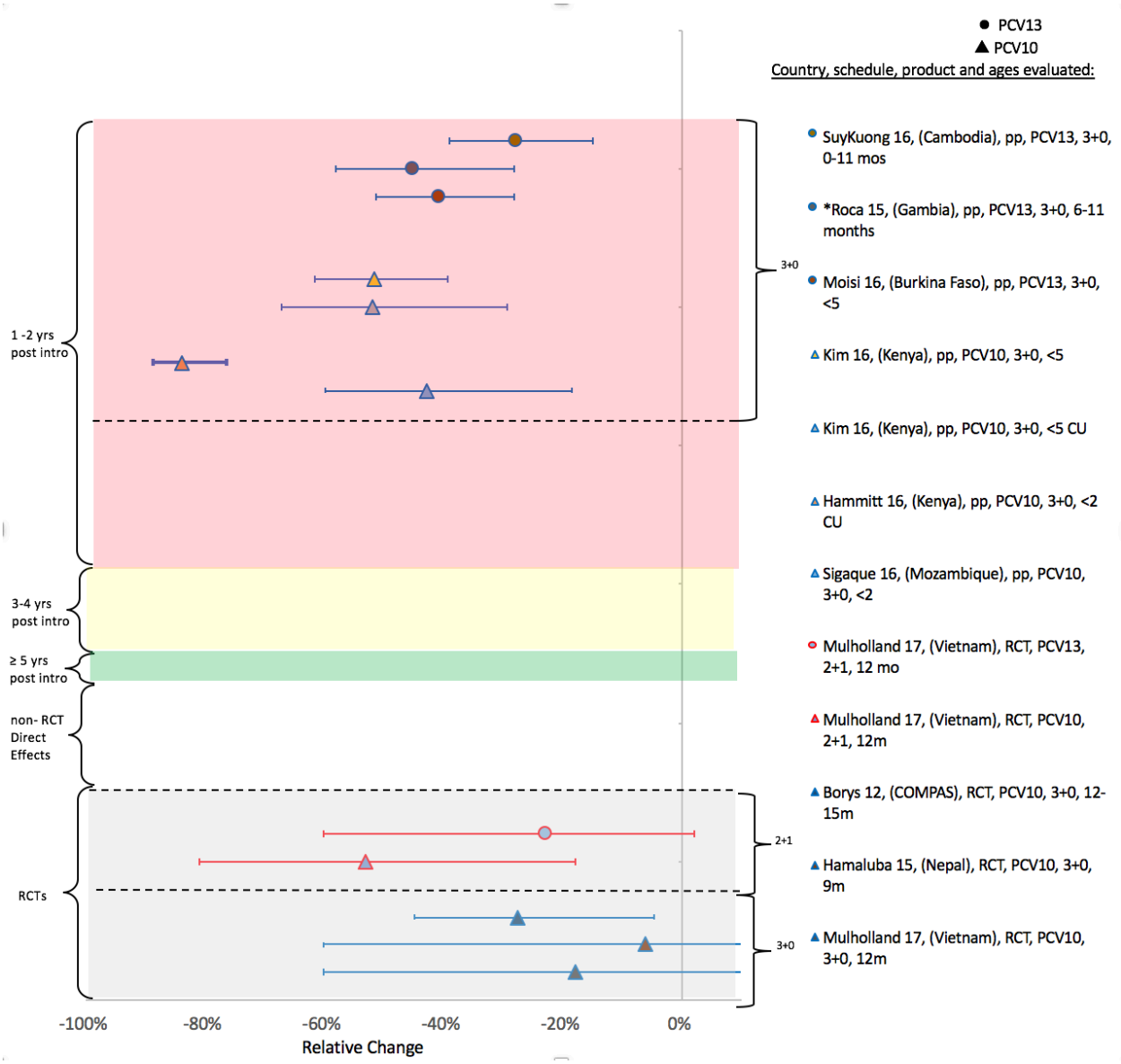
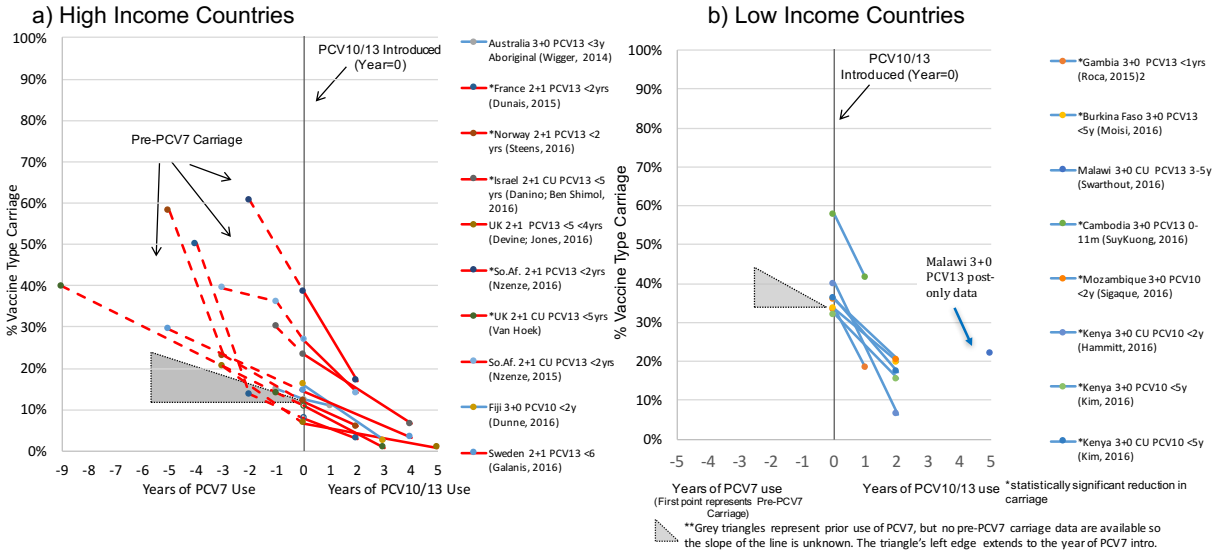


Figure 13: Vaccine-type NP carriage before and after PCV10/13 introduction in countries using 3+0 (blue lines) vs 2+1 schedules (red lines), stratified by income status of country



Footnote: Solid lines depict post-PCV10/13 carriage while dotted lines depict post-PCV7 carriage prior to PCV10/13 introduction for countries with prior use of PCV7. Studies are colored by schedule: blue lines = 3+0 and red lines = 2+1. Grey shaded triangles point to studies where pre-PCV7 carriage is unknown but assumes some decline; the triangle extends left to the year PCV7 was introduced to indicate how much PCV7 use there was prior to PCV10/13 introduction.

3.2.2 Direct Effects on Serotype Specific NP Carriage:

3.2.2.1 Serotype 1 NP Carriage:

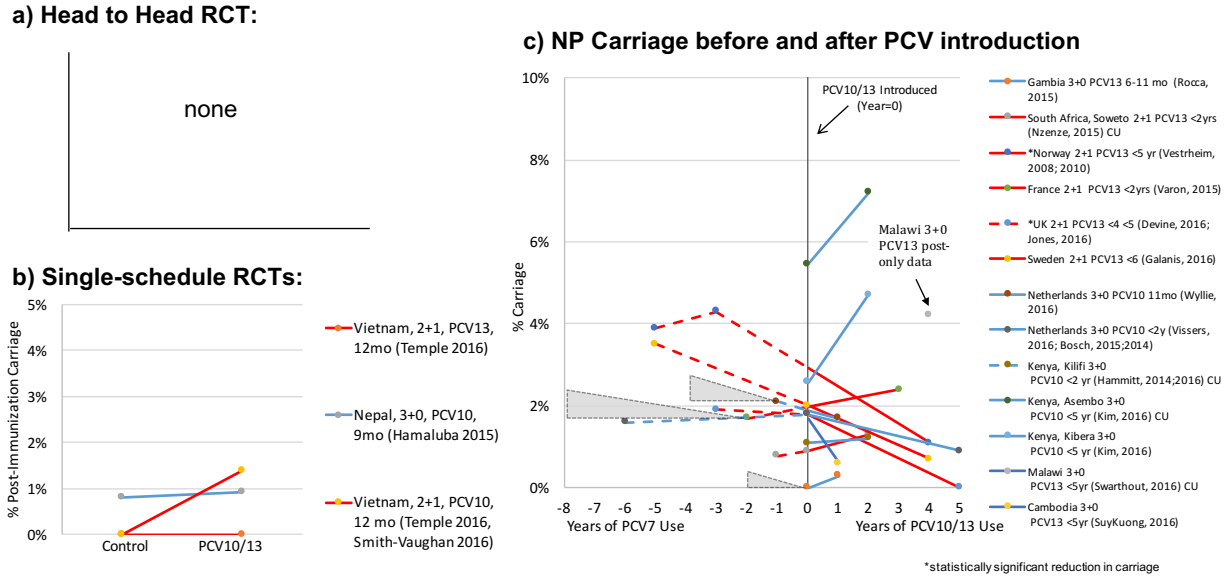
The impact of schedule on serotype 1 carriage was not assessed because it rarely carried and therefore any data would be unstable due to very low sample size.

3.2.2.2 Serotype 3 NP Carriage:

We identified 14 studies evaluating 16 arms: n=9 3+0 study arms evaluating impact on ST3 (1 clinical trial and 8 pre-post introduction observational study arms, 1 of which observed 0% ST3 carriage pre-PCV13, and 1 post-only study with 5 years of PCV13 use) and n=7 2+1 study arms (two from a clinical trial that had 0% ST3 carriage in controls, and N=5 observational pre-post introduction studies, all of PCV13; **Figure 14**).

There was no evidence to suggest that either schedule impacted ST3 carriage as more studies had increases in ST3 carriage than decreases, for both schedules, and regardless of product used. No decreases were seen in any clinical trial either; however, ST3 carriage was low so were not powered to detect reductions.

Figure 14: Serotype 3 NP carriage in observational studies before and after PCV10/13 introduction and clinical trials in countries using 3+0 (blue lines) vs 2+1 schedules (red lines)



3.2.2.3 Serotype 6A NP Carriage:

We identified two head-to-head trials (Finland, Vietnam) that compared 3+0 to 2+1 impact on ST6A carriage, but both evaluated PCV10 which does not contain 6A antigen (Mulholland, personal communication, 2017) [40]. The Vietnam trial observed higher ST6A carriage at 12m of age in the 2+1 arm (4.8%) compared to the 3+0 arm (0.7%), but was not statistically significant; Both schedules had lower ST6A carriage compared to controls (9.9%) (Mulholland, personal communication, 2017). Carriage of ST6A was low (<2.5%) in the Finnish trial, and no reductions in either PCV schedule arm was observed compared to controls [40].

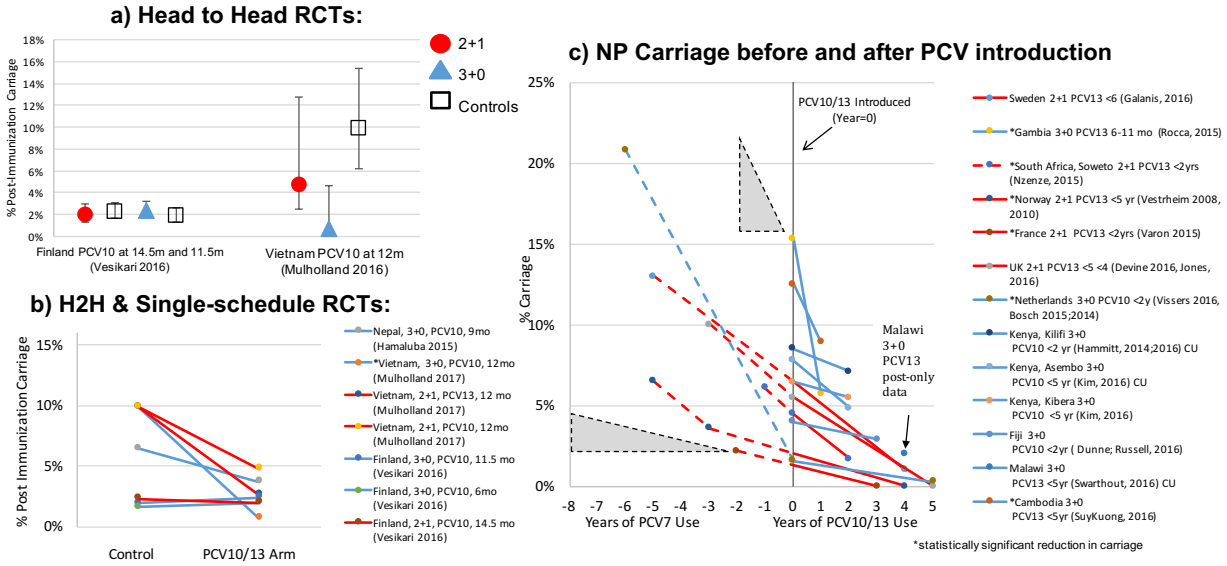
For indirect comparisons between products, we identified 20 additional single-schedule evaluations (**Figure 15**). There were 12 3+0 schedule study arms of PCV10/13 impact on ST6A: n=4 clinical trials, n=8 pre-post introduction observational studies, 1 of which had preceding PCV7 use, and 1 post-only study with 4.5 years post-introduction data. For 2+1, there were 8 study arms: 3 from a clinical trial and 5 observational studies. All 5 pre-post studies of 2+1 use had preceding PCV7 use compared to 1 of the 12 3+0 studies.

In clinical trials evaluating only a single-schedule, no differences in impact were seen by schedule after controlling for carriage in the population; i.e., when carriage in controls was greater than 5%, percent reduction was 32% and 59% for 2+1 trials vs. 43% and 89% for 3+0 trials (the two remaining 3+0 and 2+1 trials had less than 3% carriage in controls and saw no impact). In studies of routine use, reductions were seen for both schedules, and the heterogeneity in %reduction was greater within schedule than between schedules so there is no evidence that one schedule performed better than another in routine use.

But several issues hamper comparison of the schedules. First, among the observational studies there was complete confounding by product in that all 2+1 studies used PCV13 while 10 of the 12 3+0 arms

used PCV10. Second, while most 3+0 studies were conducted in settings with greater than 6% pre-PCV10/13 ST6A carriage, 2+1 studies were conducted in lower carriage settings which were not powered to detect reductions. Third, 2+1 schedules were disproportionately evaluated in the context of prior PCV7 use (all 2+1 studies), compared to only 2 of 8 3+0 studies; in addition, for all studies with preceding use of PCV7, none assessed carriage at the time of the switch from PCV7 to PCV10/13 so pre-PCV10/13 carriage can only be inferred from a carriage survey conducted mid PCV7-use. However, despite these factors, the heterogeneity of responses was greater within schedule than between schedules so it is likely that schedules produced similar declines in ST6A carriage in routine use.

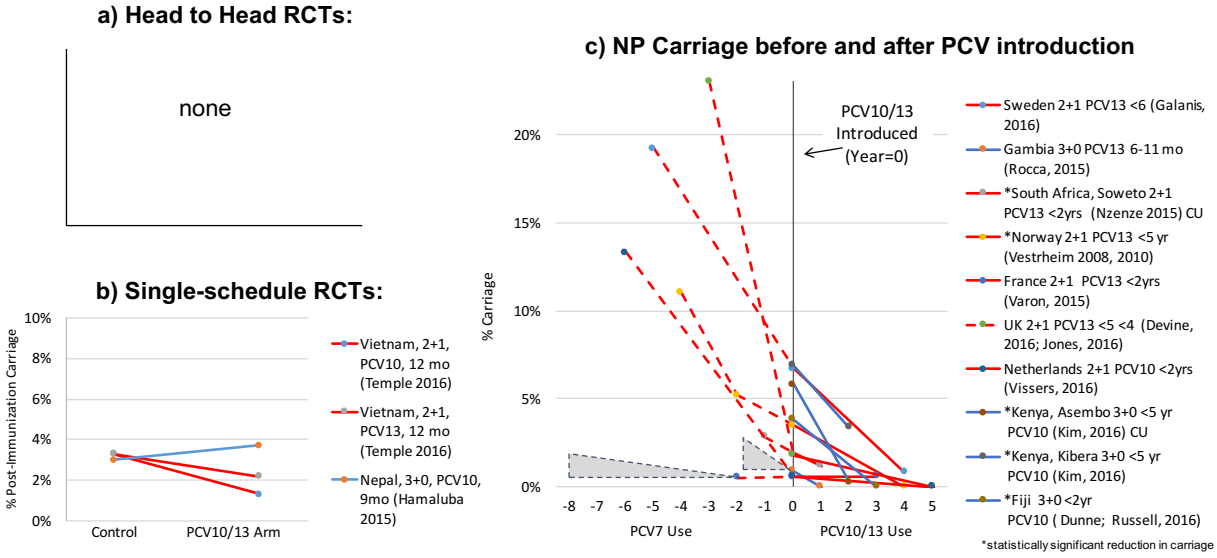
Figure 15: Serotype 6A NP carriage in observational studies before and after PCV10/13 introduction and clinical trials in countries using 3+0 (blue lines) vs 2+1 schedules (red lines)



3.2.2.4 SEROTYPE 6B NP CARRIAGE:

No head to head data were found. In the three single-schedule trial arms (1 of 3+0 and 2 of 2+1) evaluating impact on ST6B carriage found, ST6B carriage in PCV10- and in PCV13-vaccinated children using a 2+1 schedule was lower than in controls (Vietnam, non-significant), while carriage was higher (not significant) in the 3+0 trial (Nepal) (Mulholland, personal communication, 2017)[50]. In the 10 observational studies found (4 of 3+0 and 6 of 2+1), declines were seen for both schedules in all studies. Although all observational studies of 2+1 were in the context of previous PCV7 use which protects against ST6B, declines were seen during the PCV7 period with a 2+1 schedule and further declines were seen after switch to PCV13 in studies (Israel and Norway) that still had over 3% carriage at PCV13 introduction (**Figure 16**) [51, 52].

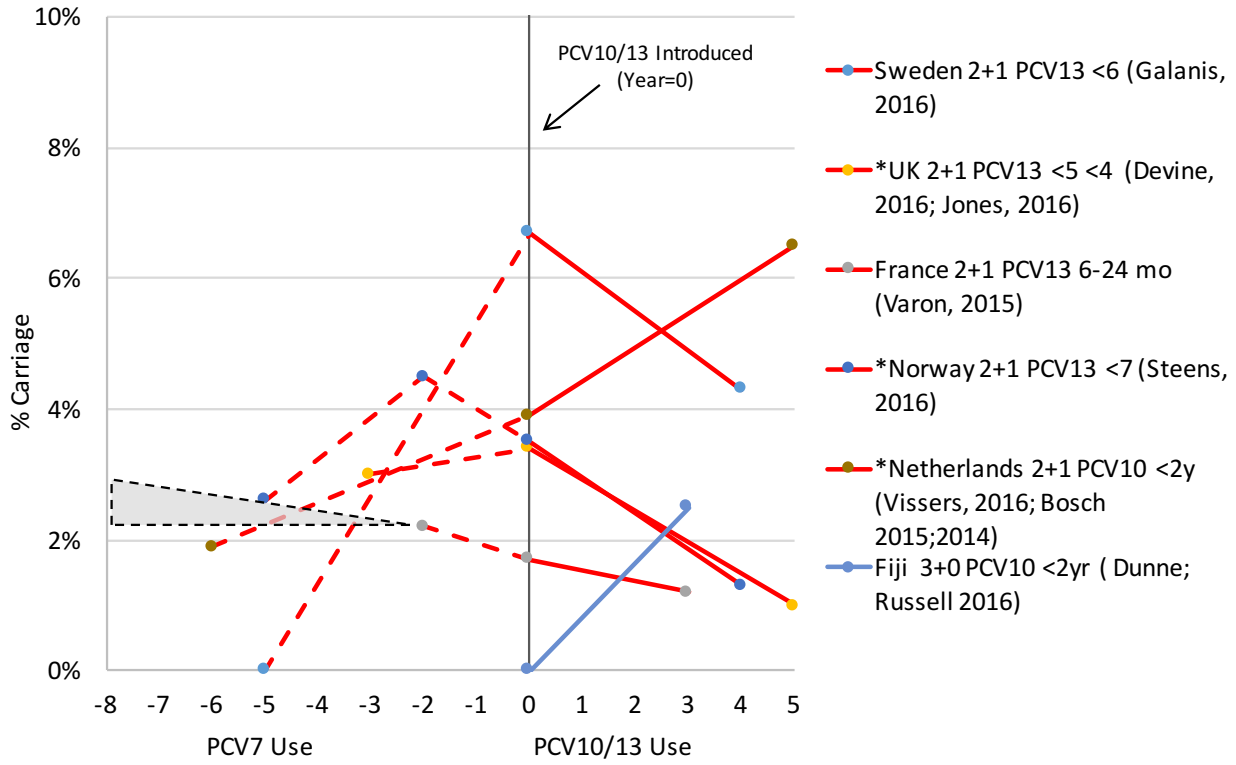
Figure 16: Serotype 6B NP carriage in observational studies before and after PCV10/13 introduction and clinical trials in countries using 3+0 (blue lines) vs 2+1 schedules (red lines)



3.2.2.5 Serotype 6C NP Carriage:

No head-to-head trials directly comparing schedules or any single-schedule trials were identified for ST6C. In the 6 observational studies of routine use that were identified (1 of 3+0 and 5 of 2+1; **Figure 17**), ST6C carriage was low (0%-4.5%) pre-PCV10/13 so studies were not powered to detect reductions. There was insufficient data to compare schedules as the single 3+0 study used PCV10 which is unlikely to have an impact on ST6C. We found no evidence to suggest that 2+1 schedule impacted ST6C carriage as results were inconsistent: one observed an increase in ST6C carriage 3 years after PCV10 introduction and, two had no change and two had decreases (not significant). All 2+1 studies also previously used PCV7.

Figure 17: Serotype 6C NP carriage in observational studies before and after PCV10/13 introduction in countries using 3+0 (blue lines) vs 2+1 schedules (red lines)



3.2.2.6 Serotype 19A NP Carriage:

We identified two head-to-head trials (Finland, Vietnam) that compared 3+0 to 2+1 impact on ST19A carriage, but both used PCV10 which does not contain ST19A and results were inconsistent [40](Mulholland, personal communication, 2017). In the Vietnam trial, neither schedule reduced ST19A carriage relative to controls at 12m of age: 2+1 = 3.0%, 3+0 = 4.5%, controls =1.6% (no statistically significant differences). In the Finnish trial, carriage was lower for 3+0 (0.5%) than for 2+1 (1.1%), but carriage in controls was very low (1.2% and 1.0%) and no differences were statistically significant.

For indirect comparisons between schedules, we identified 23 additional study arms that evaluated a single schedule: 13 evaluated 3+0 (6 single-schedule trial arms and 7 observational study arms of routine use that included one post-only long-term study) and 10 study arms evaluated 2+1 (3 single-schedule trial arms and 7 observational studies of routine use; **Figure 18**). Among pre-post studies, all 2+1 studies had preceding PCV7 use compared to only 1 of 6 3+0 studies.

In the single-schedule trials we also found no evidence that either schedule had an impact, but ST19A carriage was low and only one trial (2+1) was in the context of PCV13 use which did not see lower carriage at 12 months compared to controls. Only one trial (3+0) had a decline relative to controls (not statistically significant).

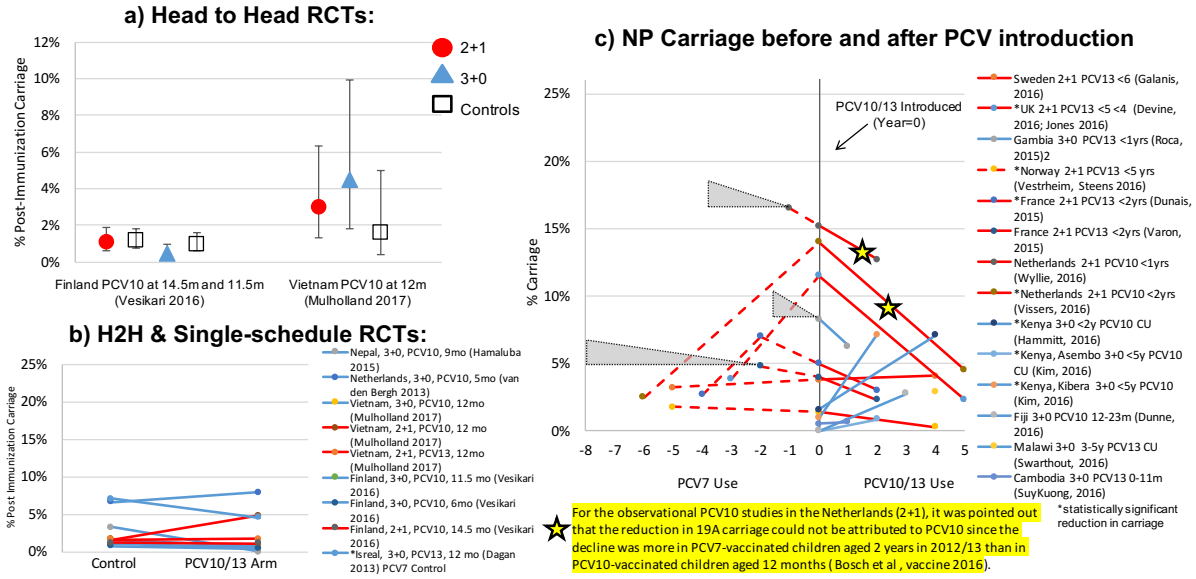
Because product confounds the analysis (i.e., PCV13 contains ST19A while PCV10 does not), results from observational studies of routine use are shown separately by product:

PCV13: There were 3 3+0 and 5 2+1 observational studies that used PCV13. Declines were similar between schedules but of the 3 3+0 studies, only one had that was sufficient to assess impact (one was post-only and one had pre-PCV carriage that was too low to assess a decline).

PCV10: Of PCV10 observational studies, 4 evaluated 3+0 and 2 evaluated 2+1. Carriage in all 3+0 studies increased and the 2 2+1 studies were both conducted in The Netherlands where the observed reductions could not be attributed to PCV10 (greater declines were observed in PCV7-vaccinated children than in PCV10-vaccinated children).

There were other challenges other than product that made it difficult to assess effect of schedule on 19A carriage. In general, 2+1 studies were conducted in settings of high ST19A carriage while 3+0 studies were generally conducted in the context of low (less than 2%) carriage (i.e., the effect could simply be 'regression to the mean'). The one 3+0 study (The Gambia; Roca 2015) with higher carriage did see a small decline with PCV13 (from 8% to 6% after 1 year of use) [53]. Also, all 2+1 studies had preceding use of PCV7 compared to one among 3+0 studies and there was an increase in ST19A prior to PCV10/13 introduction in 3 of these; declines were seen in all 2+1 studies after the switch from PCV7 to PCV10/13. The only 3+0 study that had prior PCV7 use was The Gambian study but carriage was not monitored pre-PCV7 . The one other 3+0 study that used PCV13 (Cambodia, SuyKuong 2016) had no change after 1 year (0.6% to 0.7%) [54].

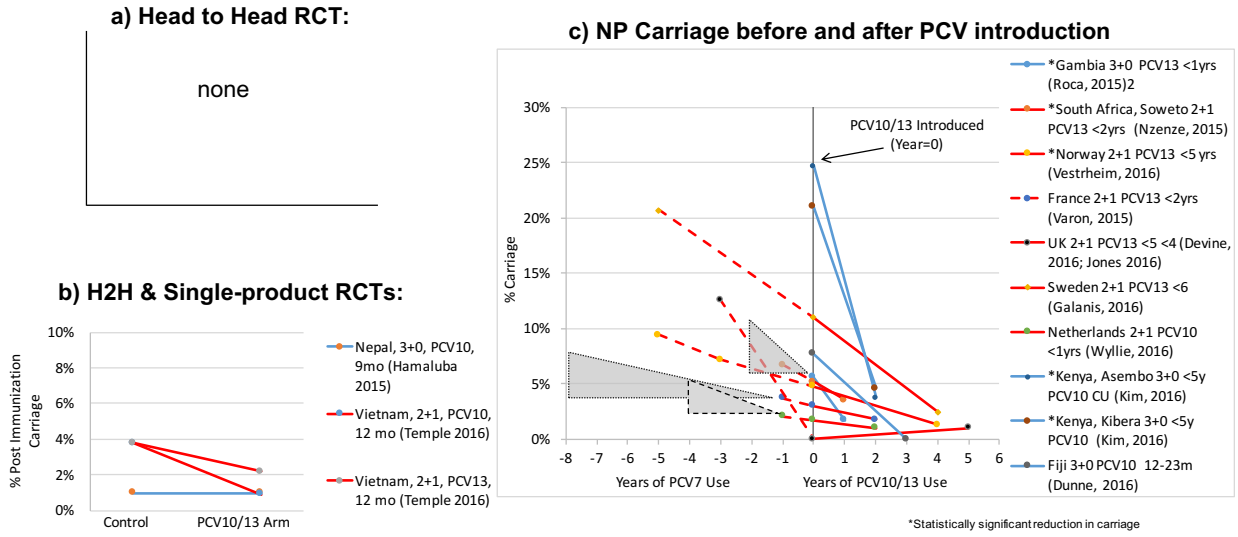
Figure 18: Serotype 19A NP carriage in observational studies before and after PCV10/13 introduction and clinical trials in countries using 3+0 (blue lines) vs 2+1 schedules (red lines)



3.2.2.7 Serotype 19F NP Carriage:

No head to head data were found. In the three single-schedule trials found (1 of 3+0 and 2 of 2+1) that evaluated impact on ST19F carriage, ST19F carriage was lower in vaccinated children using a 2+1 schedule (one each PCV10 and PCV13) than in controls (Vietnam, non-significant), while carriage was similar (but very low) in the 3+0 trial compared to controls (Nepal). In the 10 observational studies found (4 of 3+0 and 6 of 2+1), declines were seen for both schedules in all studies (except one 2+1 (UK) that had a small (<2%) increase from 0% carriage in year of switch from PCV7 and could be due to natural fluctuation). Although all observational studies of 2+1 were in the context of previous PCV7 use which protects against ST19F, declines were seen during the PCV7 period with a 2+1 schedule and further declines were seen after switch to PCV13 in studies that still had documented carriage at PCV13 introduction (**Figure 19**).

Figure 19: Serotype 19F NP carriage in observational studies before and after PCV10/13 introduction and clinical trials in countries using 3+0 (blue lines) vs 2+1 schedules (red lines)



3.3 Nasopharyngeal Carriage Indirect Effects and Dosing Schedule:

3.3.1 Indirect Effects on Vaccine-type NPC: RCTs:

One study done as a follow up to the FinIP trial assessed NPC in older siblings of children who had received PCV10 (either 2+1 or 3+1 schedule) compared to older siblings of children who had received placebo. One to two years after the FinIP trial, the vaccine effectiveness of the 2+1 schedule for reducing PCV10 VT carriage was 31% (95% CI 3%, 50%) and the effectiveness of the 3+1 schedule was 28% (95% CI -1%, 49%)[55]. These vaccine effectiveness estimates are very close, and with the limited

data from a single study, no discernible difference between schedules can be detected based on clinical trial data.

3.3.2 Indirect Effects on Vaccine-Type Carriage: 2+1 Dosing Schedule:

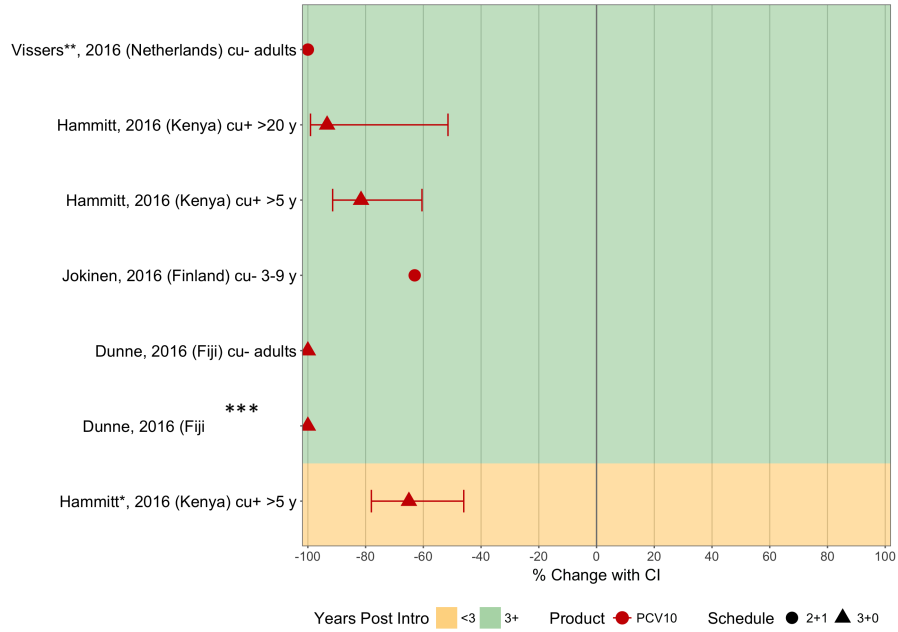
Two studies provide data on the indirect impact of a 2+1 schedule and PCV10. One study from the Netherlands reports data on VT carriage following transition from PCV7 to PCV10 using a 2+1 schedule. In this study, there was 100% elimination of PCV10 VT carriage after 3 years of PCV7 and 4.5 years of PCV10 use compared to the pre PCV era. (Figure 20)[56] Plotting prevalence of PCV10 carriage over time among adults in the Netherlands shows that carriage was decreasing in the PCV7 era as well. (Figure 21) The other study is a follow up to the FinIP clinical trial, but because the later time point is 3 years after PCV10 introduction in the NIP, older siblings from both the control and PCV10 recipient groups meet inclusion criteria for being defined as an indirect group for the purposes of our review. Among older siblings of children who were originally controls in the FinIP study, there was a 63% decrease in PCV10 carriage between the third and first year following PCV10 national implementation. Among older siblings of PCV10 recipients in the original FinIP study, there was a 57% reduction in PCV10 carriage over that same time frame. [55] Of note, this Finnish study is a post-only study as the baseline survey was at one year post-PCV10 introduction and is compared to three years post-PCV10.

Only one unpublished study from the UK has data on 5 years post-PCV13 introduction among persons over 5. This study did find a significant reduction in the odds of carriage of the six additional serotypes in PCV13 in the PCV13 era compared to the pre-PCV era. (E Miller 2017, unpublished manuscript)

3.3.3 Indirect Effects on Vaccine-Type Carriage: 3+0 Dosing Schedule:

Two studies report on the *de novo* introduction of PCV10 using a 3+0 schedule, one from a HIC/UMIC country (Fiji) and one from a LIC/LMIC country (Kenya). There was 100% elimination of VT carriage in adults and infants too young to be immunized after 3 years of PCV10 use in the Fiji study. [57] In Kilifi, Kenya there was a significant reduction (65%, 95% CI: 46, 78) in VT carriage among persons over 5 after an average of 2 years post-introduction.[58] VT carriage was also reduced 65% to 100% in all age groups surveyed after 4 years of PCV10 use.(Figure 20) Prevalence of PCV10 carriage among adults in Kilifi was decreasing in the two years pre-PCV10 as well. (Figure 21)

Figure 20: Percent change in prevalence of PCV10 VT carriage compared to the pre PCV period by schedule

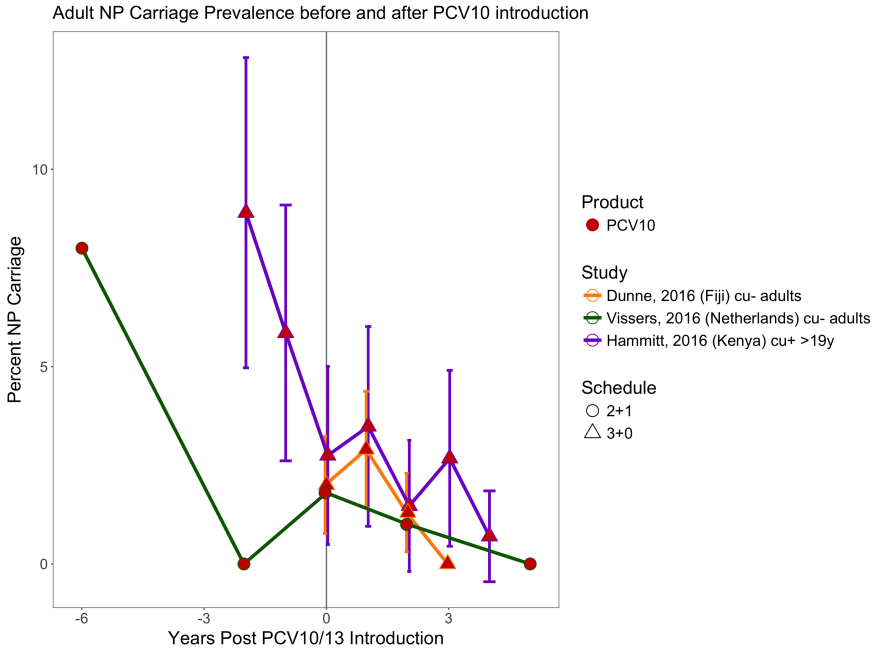


*Median of 2 year post-PCV10, years 2011-2015

**Prior use of PCV7

*** Jokinen 2016: comparison is between 3 years post-PCV10 and 1 year post-PCV10 among siblings of controls

Figure 21: Carriage prevalence of PCV10 serotypes over time among adults in pre-post survey studies by schedule



3.4 Invasive Pneumococcal Disease Direct Effects and Dosing Schedule:

Data summarized in this section can be found in **Annex B under TABLE IPD 1 – 22** (some unpublished data not included). Study and serotype specific findings are reported in separate tables according to whether an impact was documented. The findings are stratified by type of study (pre/post, or case-control effectiveness study), product, schedule and prior PCV7 use. The tables are color coded as: green for those studies with a statistically significant finding; yellow for those with a point estimate showing no impact or an impact that is not statistically significant; and red for those where the outcome of interest increased significantly. Figures with multiple studies are not considered to be adequate summary graphics for these highly heterogeneous data and, therefore, were not included for this outcome.

3.4.1 Direct Effects on Vaccine-Type IPD:

Head to Head Studies:

No head to head studies comparing the two schedules were available.

Observational Studies:

Statistically significant reductions in IPD caused by serotypes within each vaccine were observed for both schedules across both products. Comparison of impact of PCV10 or PCV13 using either schedule on PCV10-type and PCV13-type IPD, respectively, observed across studies should be done with caution due to differences in duration of PCV7/PCV10/PCV13 use, age groups studied, vaccine coverage, serotype distribution, and analytic methods used. Both schedules elicited reductions in IPD caused by serotypes within each vaccine; however, quantitative comparisons in disease reduction across studies should not be made due to confounders related to a study setting.

3.4.2 Direct Effects on Serotype Specific IPD:

3.4.2.1 Serotype 1 Invasive Disease:

Studies assessing PCV13 impact on ST 1 are predominantly from 2+1 schedule settings. Studies from France, England/Wales, Israel, South Africa, Morocco, Norway, and Sweden all demonstrated significant reductions in the rate of ST 1 IPD among children under 5. In Kilifi, Kenya (PCV13, 3+0 schedule) there was a significant reduction in the ST 1 IPD rate among children under 5 years of age following PCV10 introduction and routine use for 5 years (Scott, personal communication, 2017). In Australia (PCV10, 3+0 schedule), a non-significant reduction in ST 1 IPD rate was observed in children at 3.5 years of PCV13 routine use.

3.4.2.2 Serotype 3 Invasive Disease:

PCV10 demonstrated no reduction in in ST 3 IPD regardless of the schedule used. Studies assessing PCV13 impact on ST 3 IPD in a setting of a 2+1 schedule showed mixed results; most studies showed no effect while two studies (England & Wales, 68% reduction (95%CI: 6,89%) and France, 85% reductions (95%CI 36,96%))showed statistically significant reductions 1-4 years after introduction[59, 60]. A study from Australia (3+0 schedule) showed non-significant increases in ST3 disease following 3 years of PCV13 use[61]. There is

limited evidence for 3+0 schedule, and inconsistent evidence for 2+1 schedule, with the majority of studies showing no impact on ST3 IPD in vaccine age-eligible cohorts or in indirect age strata.

3.4.2.3 Serotype 6A Invasive Disease:

Studies from Israel, and South Africa measuring impact of PCV13 introduction using a 2+1 schedule on ST 6A IPD showed no significant reductions[62-64] ; while two reports from Finland (2+1 schedule) reported significant reductions in ST 6A IPD rates, 4 and 5 years post PCV10 introduction[65, 66]. A study from Sweden (2+1 schedule) showed non-significant reduction in ST 6A IPD in counties using PCV10 and significant reductions in counties using PCV13[67].A PCV13 impact study from Australia (3+0 schedule) showed no significant impact on type 6A [61]. However, all these studies were conducted in countries with previous PCV7 use where reductions post-PCV7 in ST 6A IPD were already observed and little disease remained for prevention. Data from Kilifi, Kenya suggest no impact on ST 6A IPD among children <5 years old 5 years post-PCV10 introduction using 3+0 schedule (Scott, personal communication, 2017).

3.4.2.4 Serotype 19A Invasive Disease:

Significant reduction in ST19A IPD following PCV13 introduction were reported in studies from countries using a 2+1 schedule (England and Wales, France, Denmark, Israel, and South Africa)[59, 60, 62, 63, 68], as well as Australia (3+0 schedule)[69]. A study from Sweden (2+1) reported non-significant increases in ST 19A IPD in counties using PCV10, while significant reductions were reported in counties using PCV13[67]. Two studies from Finland (2+1 schedule) measured impact of PCV10 on ST 19A IPD and found significant reductions[66, 70]. However, the impact in Finland was no longer significant when the follow up analysis adjusted for pre-vaccine introduction decreases in ST 19A disease (Nuorti, personal communication, 2017)[71]. A study from Kenya (3+0 schedule) found no reductions in ST19A IPD following PCV10 use for 5 years after introduction (Scott, personal communication, 2017).

Reductions in ST19A IPD were observed with PCV13 use for both 2+1 and 3+0 schedules in all but one study. No distinction could be made in the magnitude of the ST19A impact by schedule. For indirect impact on ST19A IPD, no conclusions can be drawn on distinctions by schedule because of data limitations.

3.4.2.5 Serotype 19F Invasive Disease:

A study from Kenya (3+0 schedule) found non-significant reductions in ST 19F IPD following PCV10 introduction (Scott, personal communication, 2017). Reductions in ST 19F IPD were observed in countries using 2+1 schedule; however, studies were conducted in countries with previous PCV7 use where reductions post-PCV7 in ST 19F IPD were already observed and little disease remained for prevention.

3.4.2.6 Serotypes 6B and 23F Invasive Disease:

A study from Kenya (3+0 schedule) found reductions in ST 6B and 23F IPD following PCV10 introduction (Scott, personal communication, 2017). In countries using 2+1 schedule, all with prior PCV7 use, reductions post-PCV7 were already observed and little disease remained to measure PCV13 impact.

3.4.2.7 Serotype 6C Invasive Disease:

There were no studies evaluating the effects of PCV10 on ST 6C IPD. Studies from PCV13 countries using a 2+1 schedule (Sweden, England and Wales, Israel)[51, 59, 72], and one study from Australia (3+0 schedule) found no impact on ST 6C IPD 3-4 years post-introduction[61].

Data are not sufficient to conclude that either schedule with either PCV10 or PCV13 has an impact on ST 6C disease. Therefore, no assessment can be done of PCV schedules on the 6C IPD outcome.

3.5 Invasive Pneumococcal Disease Indirect Effects and Dosing Schedule:

IPD studies represent the bulk of the information that is available on the indirect effects of PCV10 and PCV13. Eighteen studies were included, most representing European countries using PCV13 in a 2+1 schedule. Fifteen studies are from countries using PCV13—two with a 3+0 schedule—and 3 studies are from PCV10 countries—all using a 2+1 schedule.

3.5.1 Indirect Effects on Vaccine-Type IPD: 2+1 Dosing Schedule:

Sixteen studies reported data on VT IPD from countries using a 2+1 schedule, from Europe (n=13 studies), North America (n=2 studies from Canada) and Africa (n=1 study from South Africa). VT IPD decreased 41% to 80% compared to the pre PCV period (Figure 22 and Figure 23). IPD due to the 3 or 6 additional serotypes in PCV10 or PCV13, respectively, decreased 18% to 100% in all countries compared to the PCV7 period except for 1 study that reported a 15% increase in PCV13-nonPCV7 IPD among elderly >64 years old [73] (Figure 26).

3.5.2 Indirect Effects on Vaccine-Type IPD: 3+0 Dosing Schedule:

Data are limited from countries using a 3+0 schedule and are available only from Australia and the Gambia, both PCV13 countries [69, 74]. Figure 23 depicts the relative change in PCV13 IPD ranging from a decrease of 78% to an increase of 5% (not significant) compared to the pre PCV period. IPD due to the 6 additional serotypes in PCV13 decreased 17% to 77% in the PCV13 period compared to the PCV7 period in these two country settings (Figure 26).

3.5.3 Indirect Effects on Serotype specific IPD:

3.5.3.1 Indirect Effects on Serotype 3 Invasive Disease

For indirect effects, only two of five PCV13 2+1 studies reported a significant decrease in serotype 3 IPD. One PCV13 3+0 study evaluated ST 3 and found no significant change.[69] Results are likely confounded by PCV product use and prior rates of ST 3 disease, and so differences in indirect impact by schedule are difficult to evaluate if present.

3.5.3.2 Indirect Effects on Serotype 6A Invasive Disease

All three 2+1 studies from PCV13 countries reported a reduction in ST 6A IPD, and results were mixed from three studies reporting on 2+1 in PCV10 countries. Only one study reported on a 3+0 schedule with PCV13 use, where no change was found in 6A IPD among unvaccinated age groups when compared to a PCV7 era baseline.[69] The comparison of PCV impact by schedules on ST 6A IPD is difficult to discern since most studies were conducted in countries with previous PCV7 use and therefore little ST 6A disease left to prevent.

3.5.3.3 Indirect Effects on Serotype 19A Invasive Disease

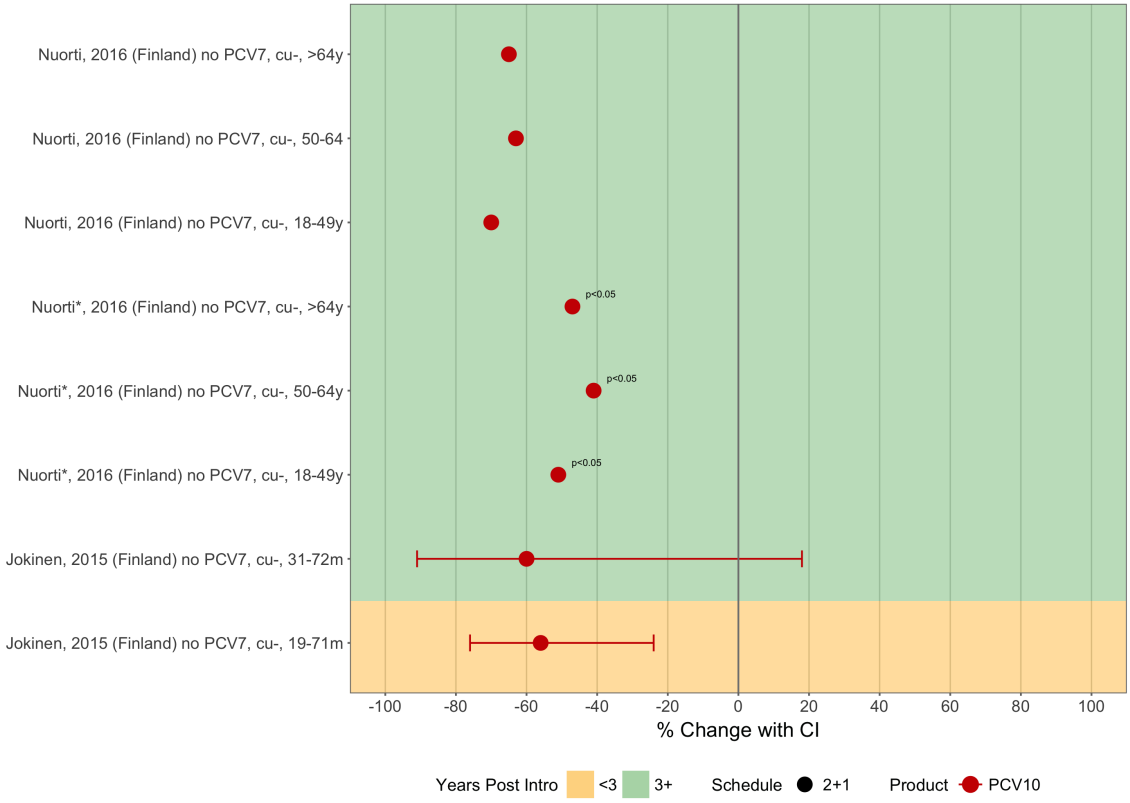
PICO I: Schedule

All PCV10 countries reporting indirect effects on serotype 19A IPD used a 2+1 schedule, and all found an increase in disease that was non-significant or of unknown significance. In contrast, 2+1 countries using PCV13 had impact in reducing ST19A disease in most countries after introduction, with the exception of one study from Ireland.[75] Data is limited to one study from a 3+0 country using PCV13 where significant reductions are reported.[69] It is hard to distinguish between the effect of PCV product choice and schedule on 19A disease.

3.5.3.4 Indirect Effects on Serotype 6C Disease

Indirect impact of PCV use on 6C IPD is limited to data from four countries, three using a 2+1 schedule and one using a 3+0 schedule. Data from 2+1 countries is mixed and not significant or of unknown significance. In the 3+0 PCV13 setting, there was a significant decrease in 6C disease compared to the PCV7 era only for elderly >65 years (Australia, Jayasinghe 2017).

Figure 22: Impact on PCV10 IPD types vs pre PCV period, 2+1 schedule



* Post PCV10 data are an average rate combining all PCV10 years

Figure 23: Impact on PCV13 IPD types vs pre PCV period by schedule

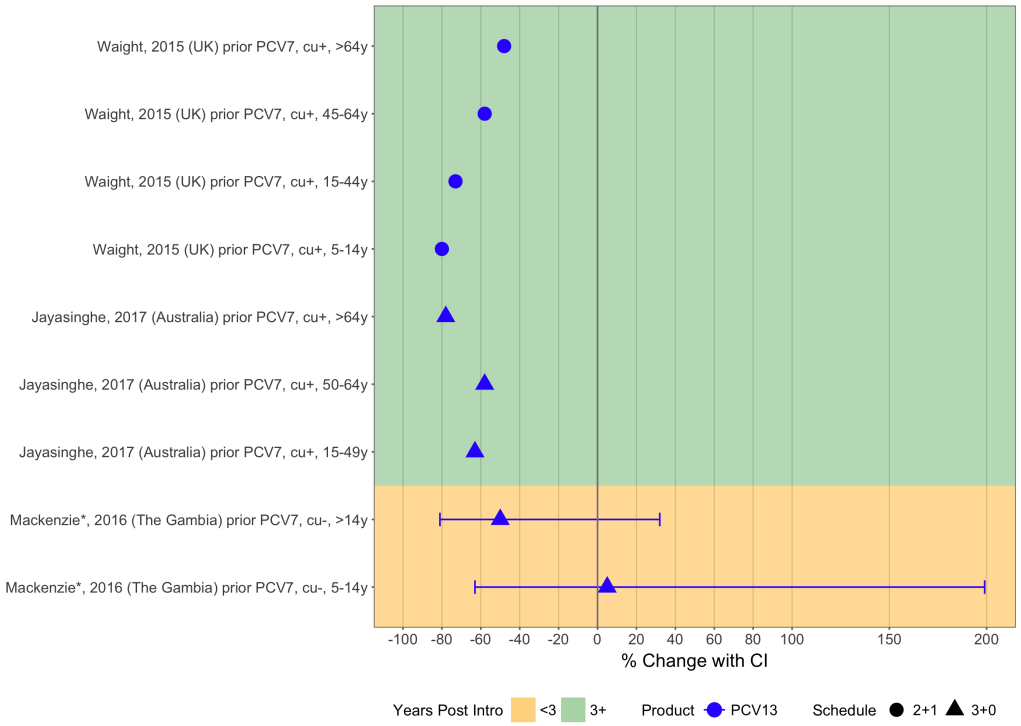
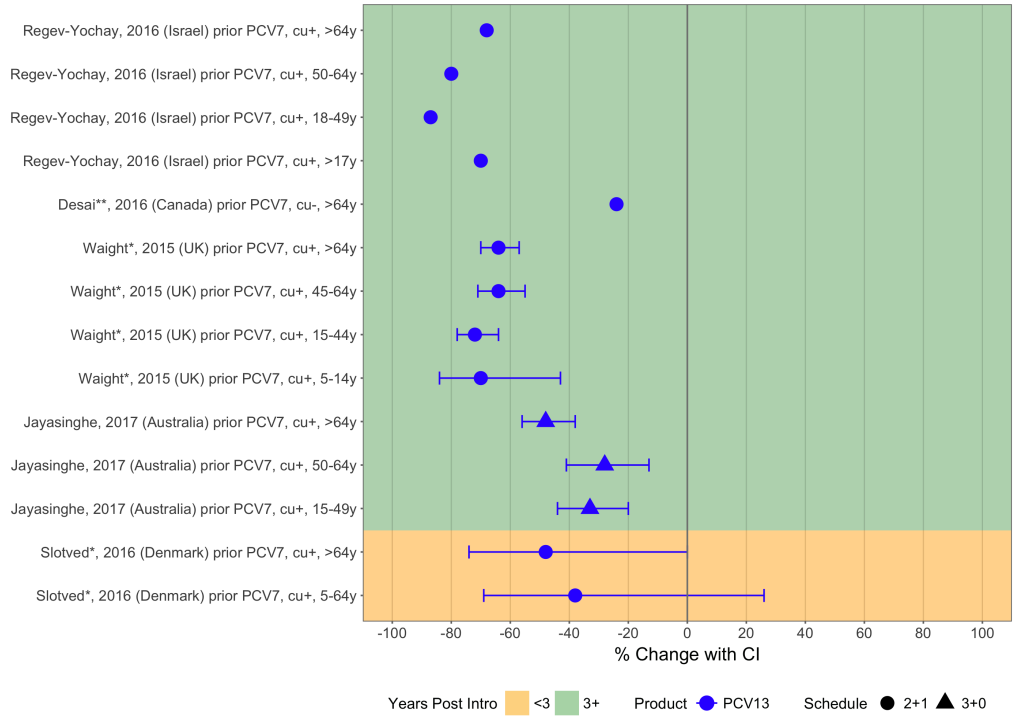
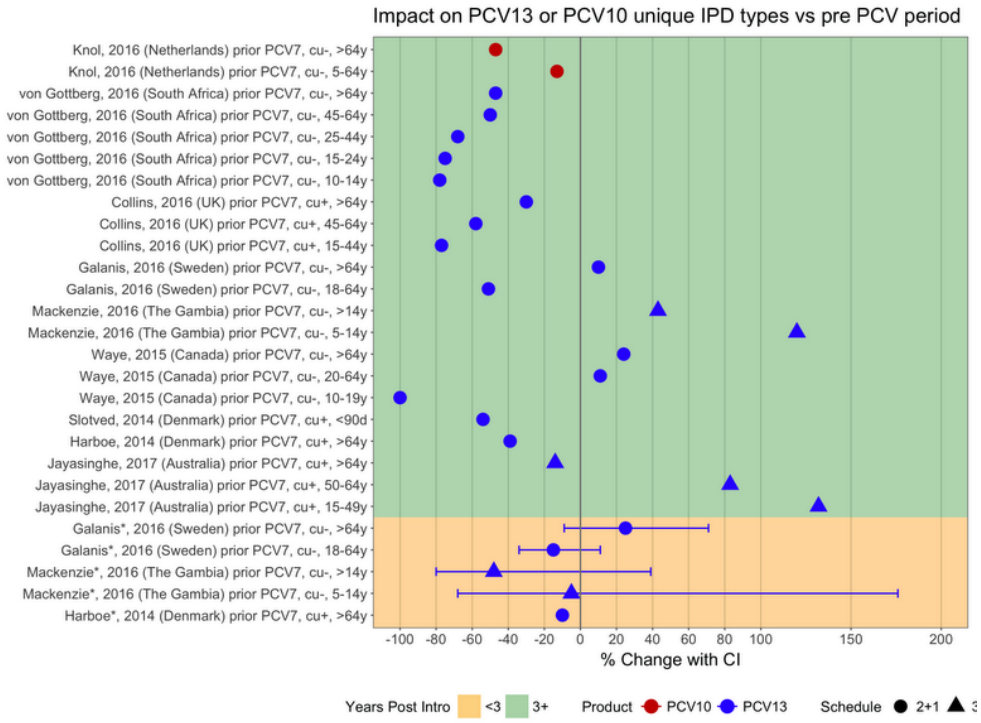


Figure 24: Impact on PCV13-type IPD vs PCV7 period by schedule



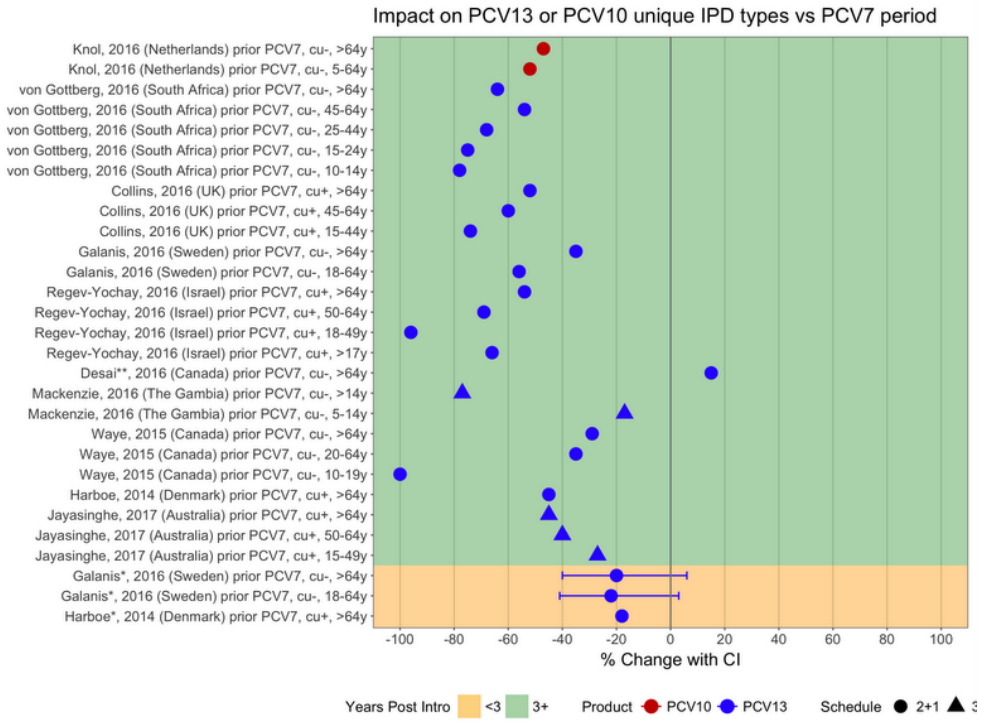
*Post PCV13 data are an average rate combining all PCV13 years
**Country with PCV13 use following interim period of PCV10 use

Figure 25: Impact on PCV13 or PCV10 unique IPD types vs pre PCV period by schedule



*Post PCV13 data are an average rate combining all PCV13 years

Figure 26: Impact on PCV13 or PCV10 unique IPD types vs PCV7 period by schedule



*Post PCV13 data are an average rate combining all PCV13 years
**Country with PCV13 use following interim period of PCV10 use

3.6 Pneumonia Direct Effects and Dosing Schedule:

3.6.1 Direct Effects on Pneumonia: RCTs:

There was one randomized controlled trial evaluating PCV against pneumonia (**Annex B: TABLE Pneumo 2**) [3]. This Finnish study evaluated PCV10 using a 2+1 schedule and showed 28% (6% - 45%) efficacy against clinical pneumonia and 43% (19% - 61%) efficacy against consolidated pneumonia. There were no clinical trials that evaluated either a 3+0 schedule or PCV13.

3.6.2 Direct Effects on Pneumonia: Case-Control Studies:

All five case-control studies evaluated PCV13[5, 6, 8, 74, 76]; there were no studies that evaluated PCV10. Three of five studies were from Africa (**Annex B: TABLE Pneumo 3**). Three studies evaluated 2+1 schedules and vaccine effectiveness ranged from 20.1% to 40.6% for ≥ 2 doses against radiologically-confirmed pneumonia and 68% against bacteremic pneumonia; all measures were statistically significant[6, 8, 76]. Two studies evaluated 3+0 schedules, both from Africa [74, 77]. Vaccine effectiveness for a 3+0 schedule ranged from 58% to 63% against radiologically-confirmed pneumonia, but none were significant. The study in Togo found an 80% effectiveness for a 3+0 schedule against severe pneumonia, but this was not statistically significant[77].

3.6.3 Direct Effects on Pneumonia: Pre/Post Observational Studies using a 2+1 Dosing Schedule:

There were 5 studies[78-82] that evaluated a 2+1 schedule against clinical pneumonia using PCV10 and 12 studies [10, 17, 78, 83-91] using PCV13; one study evaluated PCV10 and PCV13 use [78]. For PCV10 studies, in children <2 years, significant reductions ranged from 13% to 36% compared to the pre-PCV period. Compared to the PCV7 period, one study found a 3% increase, although this was not significant. For PCV13 studies, significant reductions ranging from 7% to 58% in children <2 years were observed.

Eight studies [9, 84, 90, 92-96] evaluated a 2+1 schedule against radiologically-confirmed pneumonia and all used PCV13. Compared to the pre-PCV period, there were significant reductions observed ranging from 33% to 66.2% for children <5 years. Compared to the PCV7 period, reductions ranged from 37.8% to 48%.

Four studies[10, 79, 88, 97] evaluated pneumococcal pneumonia; three using PCV13 one using PCV10. The PCV10 study from Finland observed a 70% significant reduction in children 3-42 months of age[79]. Of the three PCV13 studies, the studies from Argentina and Italy found 70% reductions in disease in children <5 years (72.1% v. baseline [9] and 70% v. PCV7 period [97]). The study from the UK found a 75.1% reduction in disease in children <2 years compared to baseline and a 24.5% reduction compared to the PCV7 period [88].

Five studies[79, 89, 91, 92, 98] evaluated 2+1 schedules against empyema; one study using PCV10 and four using PCV13. The PCV10 study found a non-significant 3% reduction in children 3-42 months [79]. For the PCV13 studies effectiveness estimates and significance varied.

3.6.4 Direct Effects on Pneumonia: Pre/Post Observational Studies using a 3+0 Dosing Schedule:

Five studies evaluated a 3+0 schedule against clinical or radiologically-confirmed pneumonia; three using PCV10 [99-101] and two using PCV13[102, 103]. For PCV10 use, significant reductions in clinical pneumonia among children <2 years ranged from 13.3% to 35% compared to the pre-PCV period. One study evaluated PCV13 on a 3+0 schedule and found a 46.9% non-significant reduction in children <5 years. For radiologically-confirmed pneumonia, reductions from 15% to 48% were observed in children <1 year with PCV10 use. A study from Nicaragua using PCV13 found a 33% significant reduction in children <1 year.

No studies evaluated a 3+0 schedule against pneumococcal pneumonia or empyema.

3.7 Pneumonia Indirect Effects and Dosing Schedule:

Indirect effect data on pneumonia are still limited and results are more variable than for IPD and NP carriage, in part due to the variability in clinical pneumonia outcomes assessed. Many studies were excluded based on having fewer than three years of post PCV10/13 use or because they presented data on age groups that included both direct and indirect effects mixed together (Annex B). The longest time period after PCV10/13 introduction reported on was 4 years. One Finnish study with less than 3 years of data (median range of 2.5 years) post PCV10 was kept in the analysis as it demonstrated differences in the first year post-PCV10 compared to years 2 and 3, which were analyzed separately, and because it looked at children just ahead of the vaccinated birth cohort in a setting without use of catch up [79].

3.7.1 Indirect Effects on Pneumonia: 2+1 Dosing Schedule:

Eight studies reported on pneumonia outcomes in countries using a 2+1 schedule: 3 studies from PCV10 countries (including one study where PCV13 was used briefly before PCV10) and 5 studies from PCV13 countries. For clinical pneumonia, compared to a pre PCV period, the findings for relative reduction in the

PCV10/13 period were very heterogeneous, ranging from a 59% decrease to a 16% increase (**Figure 27** and

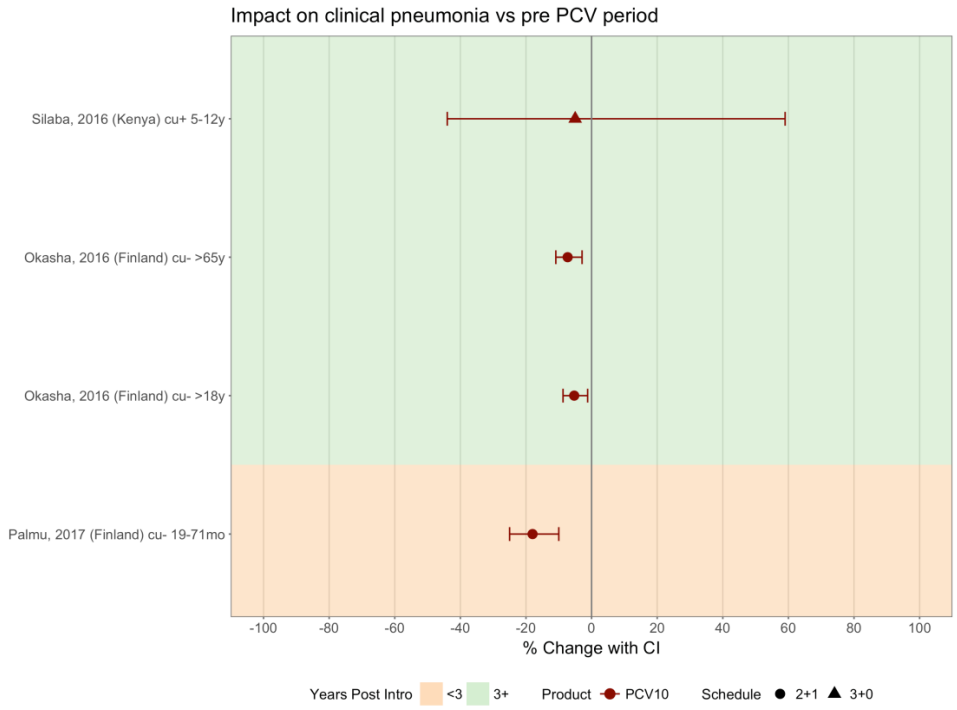


Figure 28 below). Prior PCV7 use did not account for these differences as even in the PCV7 to PCV13 period, 2+1 countries had very inconsistent changes in rates of clinical pneumonia, ranging from a 67% decrease to a 57% increase reported within the same study for two different age groups [104](**Figure 29**).

Three studies reporting on pneumococcal pneumonia found reductions ranging from 39% to 70% in the context of a 2+1 schedule and PCV10 (n=1 study) or PCV13 (n=2 studies) use (**Figure 30** and **Figure 31**).

3.7.2 Indirect Effects on Pneumonia: 3+0 Dosing Schedule:

Only two studies from Kenya had data on pneumonia using a 3+0 schedule. In Kenya, after 4 years of PCV10 use, there was a non-significant reduction of 5% in severe or very severe clinical pneumonia hospitalizations among 5-12 year olds [101] (**Figure 27**). The same study reported a non-significant reduction of 11% in radiologically confirmed pneumonia admissions in this same age group.

Another Kenyan study reported on pneumococcal pneumonia in adults and found a significant reduction of 94% after 3 years of PCV10 use (**Figure 30**). Among only HIV uninfected adults, there was 100% elimination of pneumococcal pneumonia [105].

Figure 27 Impact on clinical pneumonia in countries without prior PCV7 use

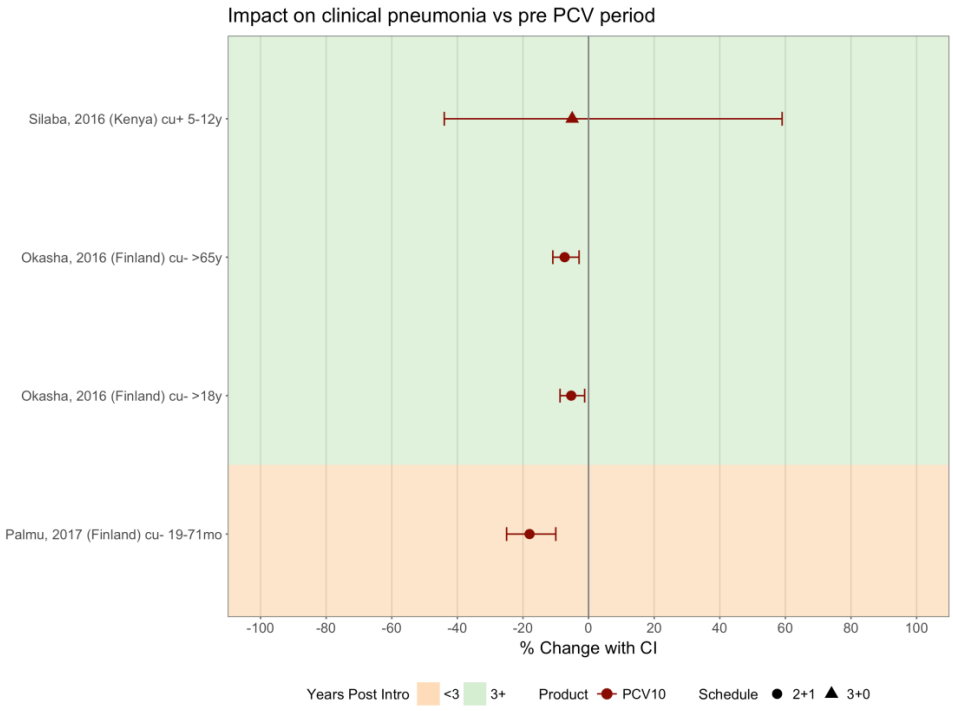
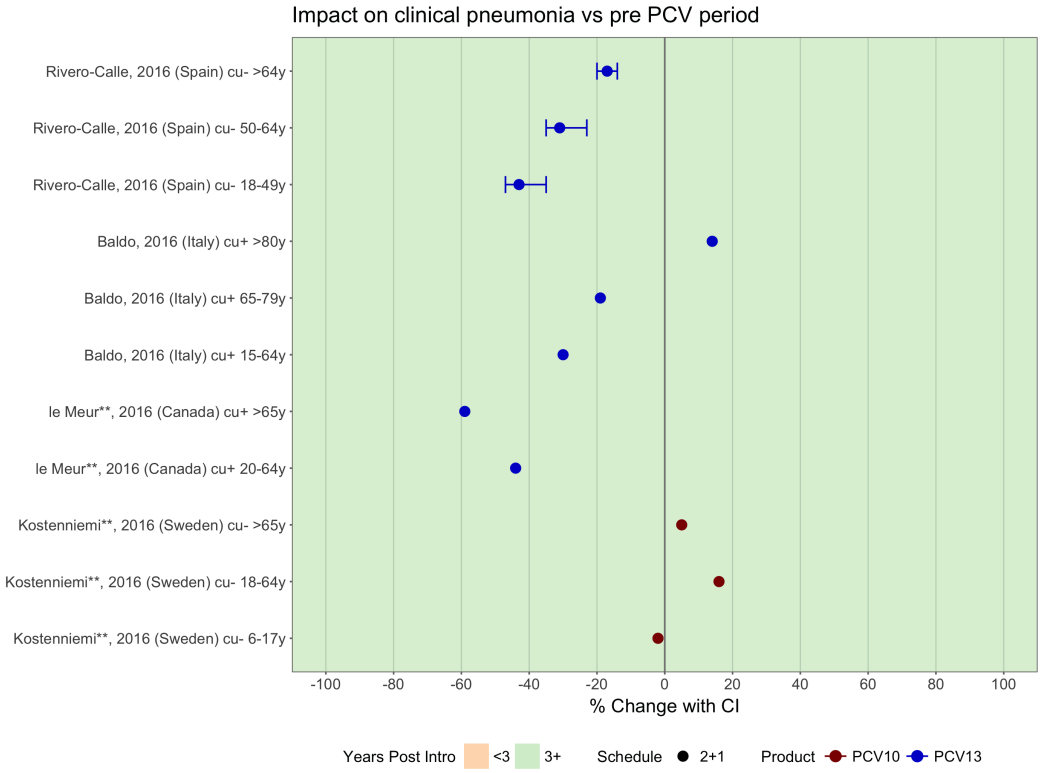
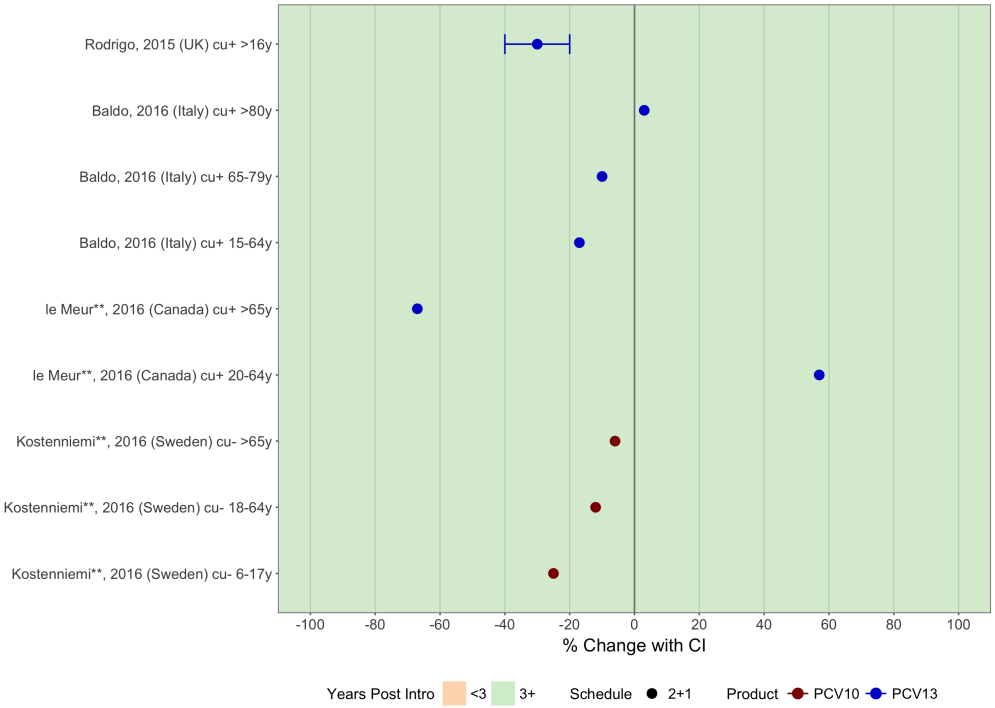


Figure 28: Impact on clinical pneumonia in countries with prior PCV7 use, 2+1 schedule



**le Meur (Canada): switched from PCV7 to PCV10 and then PCV13
**Kostenniemi (Sweden): switched from PCV7 to PCV13 and then PCV10

Figure 29: Impact on clinical pneumonia vs PCV7 period, 2+1 schedule



**le Meur (Canada): switched from PCV7 to PCV10 and then PCV13
**Kostenniemi (Sweden): switched from PCV7 to PCV13 and then PCV10

Figure 30: Impact on clinical pneumonia in countries without prior PCV7 use

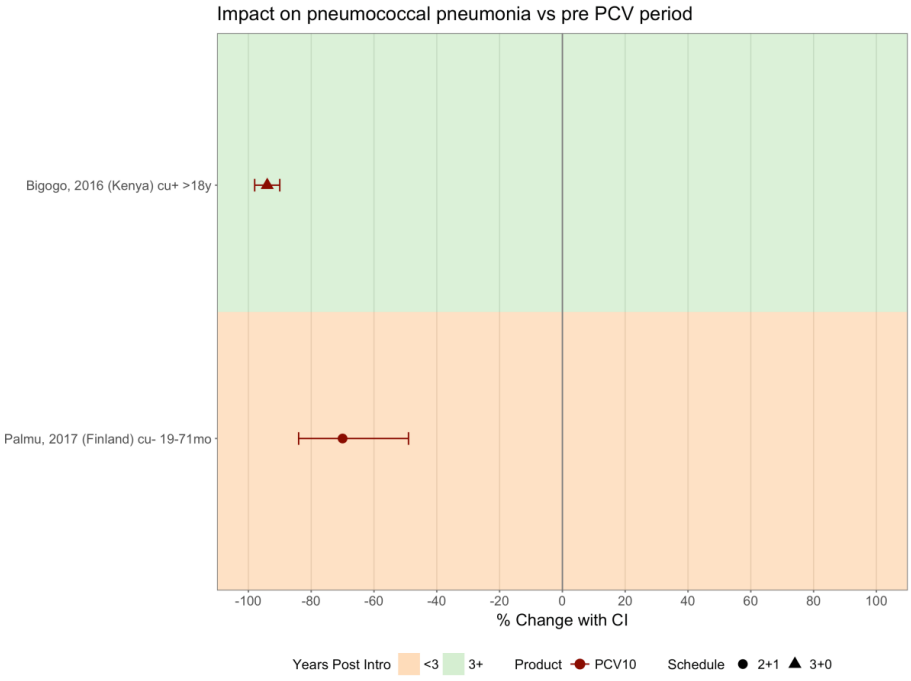
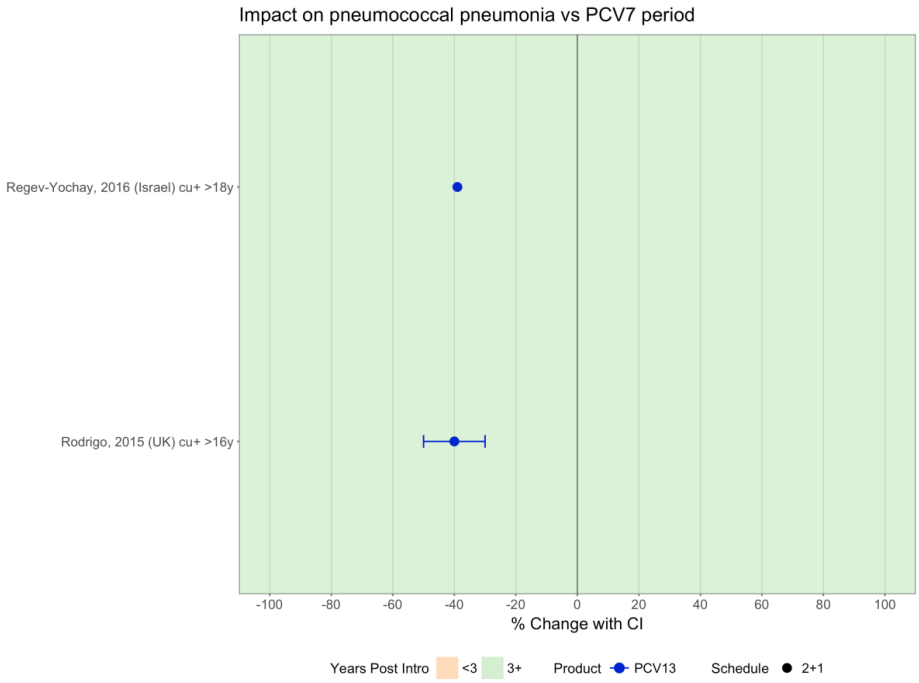


Figure 31: Impact on pneumococcal pneumonia vs PCV7 period, 2+1 schedule



4.0. PICO II: PCV10 vs. PCV13 Effectiveness and Impact On Currently Recommended Dosing Schedules:

Executive Summary:

I. Immunogenicity by product:

Serotypes common to PCV10 and PCV13:

- PCV10 and PCV13 are both highly immunogenic in infants for the 10 serotypes they have in common, for all dosing schedules evaluated, and with or without concomitant DTaP administration.
- At least one immunogenicity study is available from every WHO region. This evidence includes 5 head-to-head studies.

Serotypes 3, 6A and 19A:

- PCV13 is immunogenic (i.e. induces high concentrations of antibody) against serotypes 3, 6A and 19A, the three serotypes included in that vaccine but not in PCV10.
- PCV10 induces increases in antibody against serotypes 6A and 19A following the primary series, although the proportion of children achieving the correlate of protection is lower with a 2-dose than a 3-dose priming schedule and, regardless of schedule, is lower than that observed in infants receiving PCV13 [38]. After a booster dose, >80% of PCV10 vaccinated infants have antibody concentrations above the correlate of protection for both serotypes but the absolute concentrations remain lower than in PCV13-vaccinated infants.
- There is very limited evidence to evaluate the immunogenicity of PCV10 against serotype 3, a serotype not included in the vaccine.

II. NP Carriage:

Vaccine-type NP carriage:

- **Availability of data**: We identified 23 studies that provided evidence of PCV10 vs. PCV13 products on NP carriage in the context of 2+1 vs 3+0 schedules: 2 head-to-head trials directly compared products, 9 single-product arms (8 PCV10, 1 PCV13), and 18 observational arms of routine use (13 PCV13 and 5 PCV10). Of these, 8 studies (4 PCV13 and 4 PCV10) were from low income settings.
- **Results**: Declines were seen for both products. No differences were seen between PCV10 and PCV13 in the head-to-head, single product studies, or observational studies. But there was considerable confounding by schedule and previous use of PCV7 (i.e., PCV13 studies predominantly measure the impact only on the additional 6 serotypes that are not in PCV7).

Serotype 3:

- **Availability of data:** We identified 1 head-to-head trial directly comparing products and 16 single-product study arms, n=9 of PCV13 (one trial and 7 observational studies plus one post-only study evaluating carriage ~5 years after PCV13 introduction with a 3+0 schedule) and n=7 of PCV10 (two trial arms and 5 observational studies).

- **Results**: There is no evidence to suggest that either product impacted ST3 carriage. An equal number of studies of both products showed increases and decreases in ST3 carriage following introduction for both products and carriage was not lower than controls in any clinical trial.

Serotype 6A:

- **Availability of data:** We identified 1 head-to-head trial directly comparing products and 20 additional single-product evaluations: 9 of PCV13 (one from a trial and 8 from observational studies) and 11 of PCV10 (6 single-product arms and 5 observational studies of routine use). There was 1 post-only study (3+0) evaluating carriage ~5 years after PCV13 introduction.
- **Results**: Reductions were seen for both products in all studies except in a PCV10 trial in Finland that had very low (<2.5%) carriage in controls where no difference in 6A carriage was found between PCV10-vaccinated children and controls. In the head-to-head trial, impact was slightly greater with PCV13 but was not statistically significant. In studies of routine use, declines in 6A were generally more pronounced for countries that used PCV13.

Serotype 6C:

- **Availability of data:** No head-to-head trials directly comparing products or any trial data were identified for ST6C. We identified 6 observational studies of routine use (4 PCV13 and 2 PCV10).
- **Results**: PCV13 may have more impact on ST6C carriage than PCV10 as 2/4 PCV13 studies observed declines in ST6C carriage (one statistically significant) while both PCV10 studies observed increases (one statistically significant).

Serotype 19A:

- **Availability of data**: We identified 1 head-to-head trial directly comparing products and 23 single-product studies: 10 PCV13 (2 single-product trial and 7 observational studies of routine use, plus one post-only study evaluating carriage ~5 years after PCV13 introduction with a 3+0 schedule) and 13 PCV10 (7 single-product trials and 6 observational studies of routine use).
- **Results**: Generally, results favored PCV13 over PCV10 as no increased in 19A carriage were observed for any PCV13 trial or study while increases were observed for PCV10 in both observation studies (two were statistically significant) and in trials compared to controls (none significant).

III. NP Carriage Indirect Effects:

VT Carriage:

- Published data are only available on the indirect effects of PCV10 with respect to NP carriage at least 3 years after introduction (n=3 studies). One unpublished report has data from a PCV13 country. Based on the limited data, both products have demonstrated impact in lowering VT carriage in vaccine non-eligible age groups. There are insufficient data to discern any differential impact between products.

Serotype-specific findings:

- Limited data are available on the indirect impact of PCV10 on the carriage of serotypes 3, 6A and 19A, three serotypes contained in PCV13 but not in PCV10. There was no significant change in these three non-PCV10 serotypes in Kilifi, Kenya among persons over 5 years after PCV10 introduction. In Finland, significance was not reported for changes in these individual serotypes in unvaccinated children after PCV10 introduction. There are no comparison data on PCV13 from which to make any product comparisons.

IV. IPD Direct Effects by Product:

Vaccine-type IPD:

- Available evidence indicates both products are effective in reducing the serotypes common to vaccines in both vaccinated and unvaccinated populations.

Serotype 3:

- As expected, PCV10 (which does not contain a serotype 3 antigen) induced no reduction on ST 3 IPD in vaccine-eligible age groups. Evidence for direct reduction in ST 3 IPD following PCV13 was inconclusive. Evidence for or against increases in ST 3 IPD following PCV10 and PCV13 use are also inconclusive.

Serotype 6A:

- PCV10 data are very limited and the benefit of including ST6A in PCV13 is difficult to determine. The low baseline rate of ST6A IPD, due to prior PCV7 use, makes interpreting PCV13 effect on ST6A difficult.

Serotype 6C:

- There are very limited data on PCV10 effects against type 6C IPD. Most studies show either significant or non-significant positive impact of PCV13 on ST6C IPD.

Serotype 19A:

- Effectiveness and impact against 19A IPD in vaccine age eligible children were demonstrated for PCV13. Effectiveness studies showed non-significant moderate to high effectiveness against ST19A IPD from PCV10 use; however, these studies were not powered to test significance. Impact studies did not indicate an impact from PCV10.

V. IPD Indirect Effects:

Vaccine-type IPD:

- There are more data on PCV13 (n=15 studies) than on PCV10 (n=3 studies.)
- Both PCV10 and PCV13 are effective in reducing IPD due to the serotypes contained in the vaccines in indirect populations. For serotypes that are in PCV13 but not in PCV10, there are some limited data that suggests PCV13 may be more effective in reducing serotype 3, 6A and 19A IPD, but PCV13 impact varied by setting for these serotypes. More years of surveillance will be needed to discern evolving changes in serotype replacement.

Serotype 3:

- PCV10 induced no reduction in ST 3 IPD in vaccine non-eligible age groups based on data from 3 studies conducted in 2 countries.
- PCV13 impact on ST 3 disease varied and no conclusions can be drawn.

Serotype 6A:

- PCV10 was found to have no significant indirect impact on ST 6A IPD, whereas PCV13 was associated with consistent indirect effects in unvaccinated populations though significance was not always reported.

Serotype 19A:

- Among vaccine non-age eligible cohorts (i.e. indirect effects), evidence on PCV10 using communities shows an increase or no change in serotype 19A IPD rates, whereas the impact of PCV13 use on 19A IPD rates generally shows benefit.

VI. Pneumonia Direct Effects:

- This review identified 35 studies evaluating 3-dose schedules (2+1 or 3+0) using PCV10 or PCV13: one clinical trial [3], five case-control studies [4-8], and 29 pre/post observational studies [9-37] (Table 1). The majority of studies were from Europe (n=17) [3, 6, 8, 12, 13, 15, 16, 20, 23, 27-30, 32-34, 36] or the Americas region (n=11) [9-11, 14, 17, 21, 22, 24, 26, 31, 35]; 5 studies were from Africa [4, 5, 7, 25, 37] and two studies from Oceania, both from Fiji [18, 19]. There were no studies identified from Asia or the North America; however, the review was limited to 3-dose schedules and therefore excluded many countries using a 3+1 schedule including the U.S.
- The review found evidence of impact from both products (PCV10 and PCV13) for clinical and chest X-ray confirmed (CXR) pneumonia. Evidence of impact for pneumococcal pneumonia was found with PCV10 and PCV13 use. The evidence regarding empyema using PCV10 or PCV13 was mixed. There is no systematic evidence that one product is better than another.

VII. Pneumonia Indirect Effects:

- Heterogeneity in case definitions for clinical pneumonia and serotype distribution may in part contribute to the wide variability in results. Both products had large impact on pneumococcal pneumonia, though the number of studies reporting on this outcome is limited (n=4 studies). Overall, there is no clear evidence suggesting a differential effect by PCV product on the incidence of pneumonia in older children and adults.

FINDINGS:

4.1 IMMUNOGENICITY AND PRODUCT CHOICE:

4.1.1 IMMUNOGENICITY HEAD TO HEAD EVIDENCE:

There are five head to head trials that provide evidence for a direct comparison between PCV10 and PCV13. These RCTs vary on the time points and serotypes studied and immunological endpoints reported. Table 3 details the type of evaluation done in the five RCTs included. In these studies, PCV13 induced higher antibody than PCV10 after a 2 or 3-dose primary series for some serotypes common to both products (1, 5, 7F, 23F) but evidence was mixed for other serotypes (6B, 14, 19F) [41, 106] . **Figure 32** shows the head to head comparison between PCV10 and PCV13 at the post-primary blood draw for the Vietnam and Papua New Guinea trials. Differences in antibody responses were also seen before and after the booster dose: before the booster dose, PCV13 vaccinees had higher antibody to some serotypes (14, 19F), PCV10 vaccines had higher antibody to other serotypes (1, 6B, 23F) and evidence was mixed for the remaining serotypes (5, 7F) [107, 108]. After the third dose, PCV13 induced higher antibody levels for serotypes 3, 6A and 19A as well as 1, 5, 6B, 7F and 23F (slightly better); results were mixed for the remaining two serotypes (14, 19F) [107-109] [41]. There were no direct comparisons between products for the percent responder endpoint, post-primary series.

Table 3 : Immunogenicity evidence available from head to head studies of PCV13 vs. PCV10

Study	Dosing schedule	Post-Primary			Post-dose 3		
		GMC	**SE(GMC)**	**% >cutoff**	**GMC**	**SE(GMC)**	**% >cutoff**
Prymula Spain/Cz.	3+1	✓ Different serotypes for PCV10/13		✓ PCV10 only	✓ Different serotypes for PCV10/13		✓ PCV10 only
Wijmenga Netherlands	3+1	Pre- and post-booster data only					
Mulholland Vietnam	2+1	✓	✓		✓	✓	
Pomat Papua NG	3+0	✓			✓		
Van Westen Netherlands	3+1	Pre- and post-booster data only					

Figure 32: Head to head comparisons between PCV10 and PCV13 at the post-primary blood draw

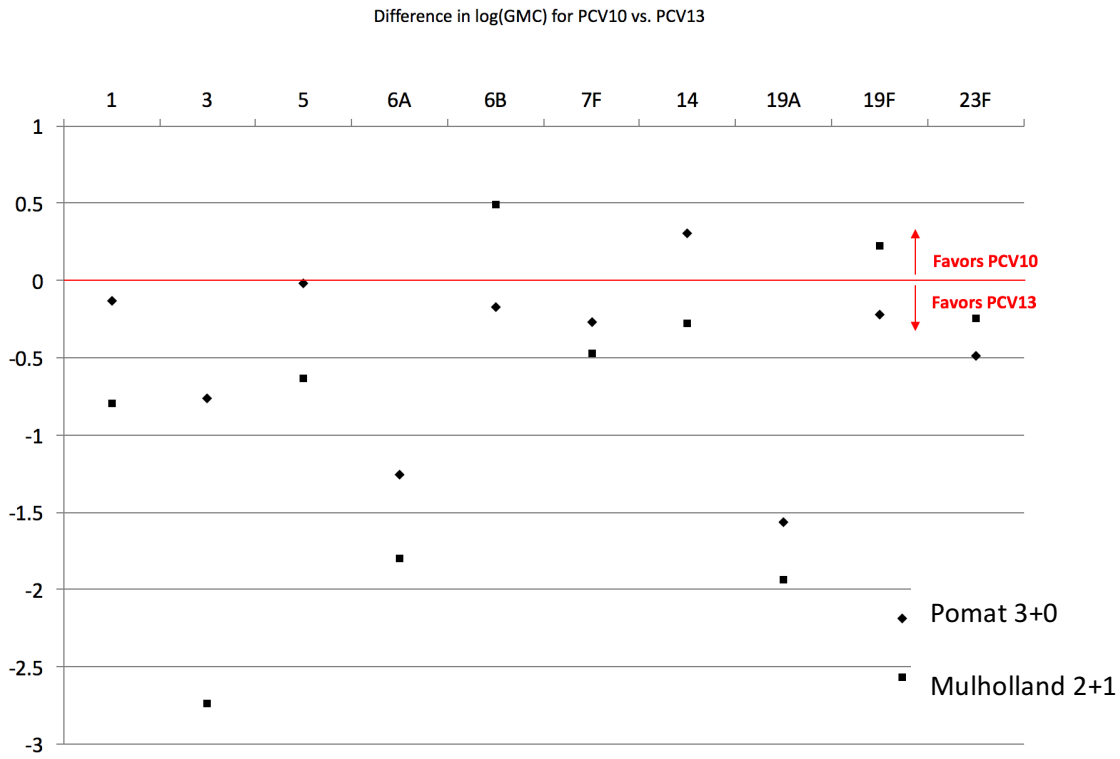
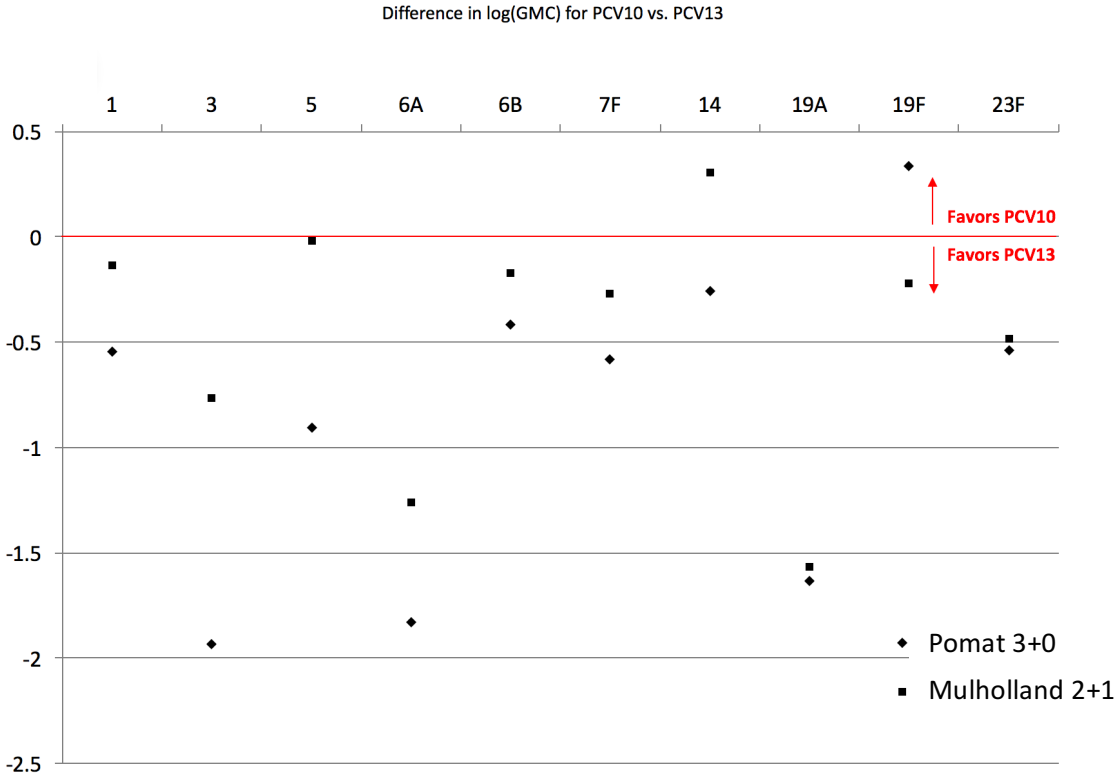


Figure 33: Head to head comparisons between PCV10 and PCV13 at the post-dose 3 blood draw



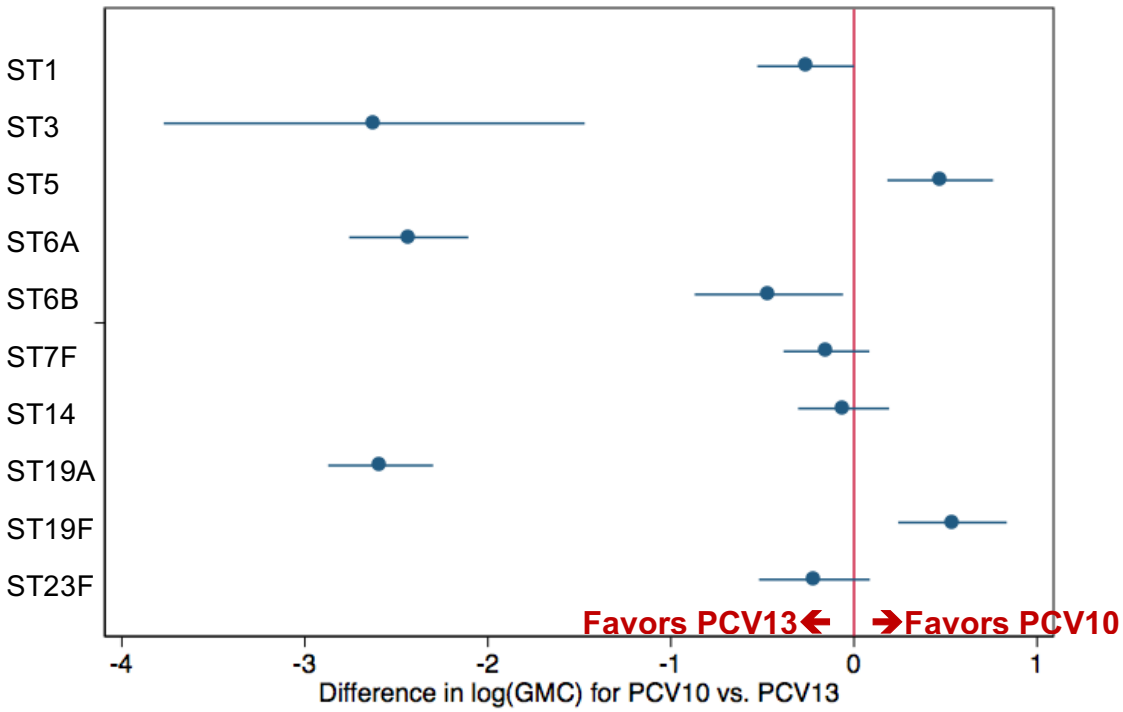
4.1.2 IMMUNOGENICITY SINGLE ARM AND NON-RANDOMIZED EVIDENCE:

Combining head to head studies with single arm studies, there were 63 studies with data on PCV10 and 56 studies on PCV13. There was more evidence for GMC antibody concentrations than proportion of subjects above the correlate of protection. The geographic distribution of studies by product and schedule is shown in **Annex B: Table Imm 1 and 2**. A total of 119 study arms were included. Inclusion criteria were applied to individual study arms, so, for example, a 2+0 schedule could contribute data on the post-two dose primary time point and a 3+1 schedule could contribute data to the post-three dose primary time point.

In order to evaluate the effects of PCV product on immunogenicity, univariate and multivariate meta-analyses were done for antibody concentrations and direct comparisons for percent responders. At the post-primary time point, both PCV10 and PCV13 induced strong immunological responses for the 10 shared vaccine serotypes and a high proportion of infants achieved the correlate of protection, regardless of the number of primary doses (Figure 34 and Figure 35). However, multivariate models showed that PCV13 elicited significantly higher GMCs than PCV10 for serotypes 1, 6B, 7F and 23F whereas PCV10 elicited higher GMCs for serotypes 5 and 19F and the two products were not significantly different for serotype 14.

For STs 3, 6A, and 19A, which are included in PCV13 but not in the PCV10 formulation, PCV13 was highly immunogenic based on percent of subjects responding. For PCV10, there was insufficient evidence to evaluate immunogenicity for ST 3, since response to ST 3 was almost never tested in PCV10 studies. After primary vaccination with PCV10, >45% of subjects had antibody concentrations to 6A and 19A that were above the correlate of protection (range 22-79% for 6A and 22-89% for 19A, based on 27 study arms) (Figure 34).

Figure 34: Between-study comparisons of PCV product at the post-primary time point



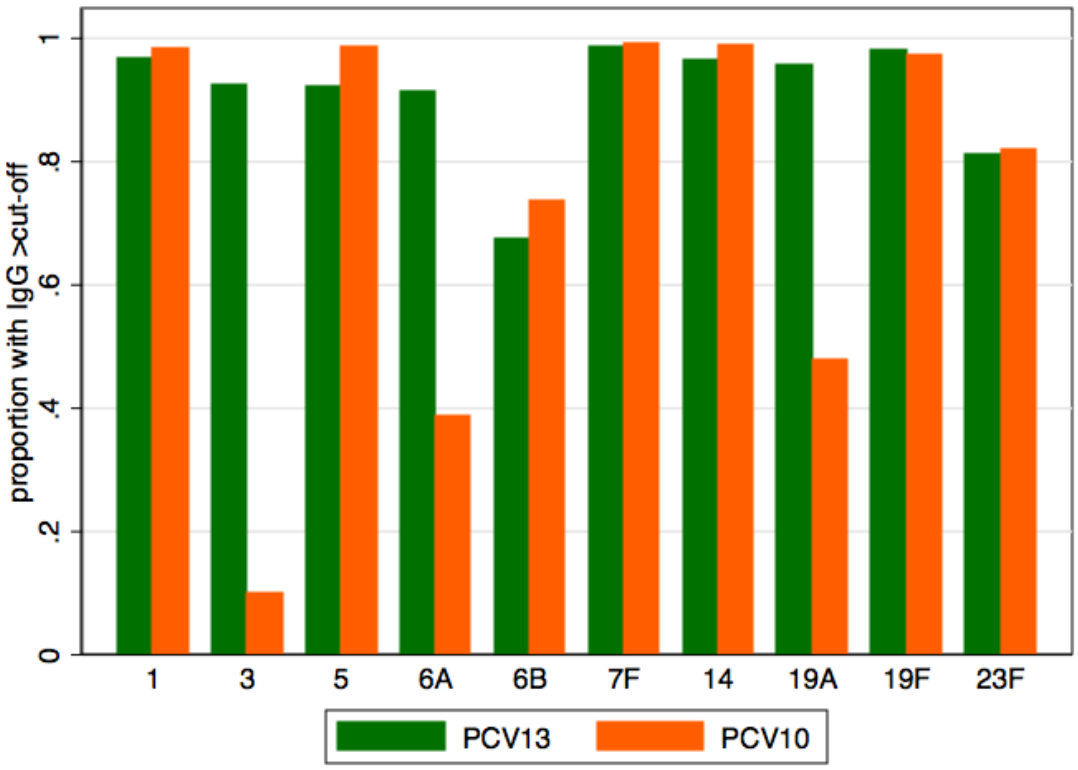
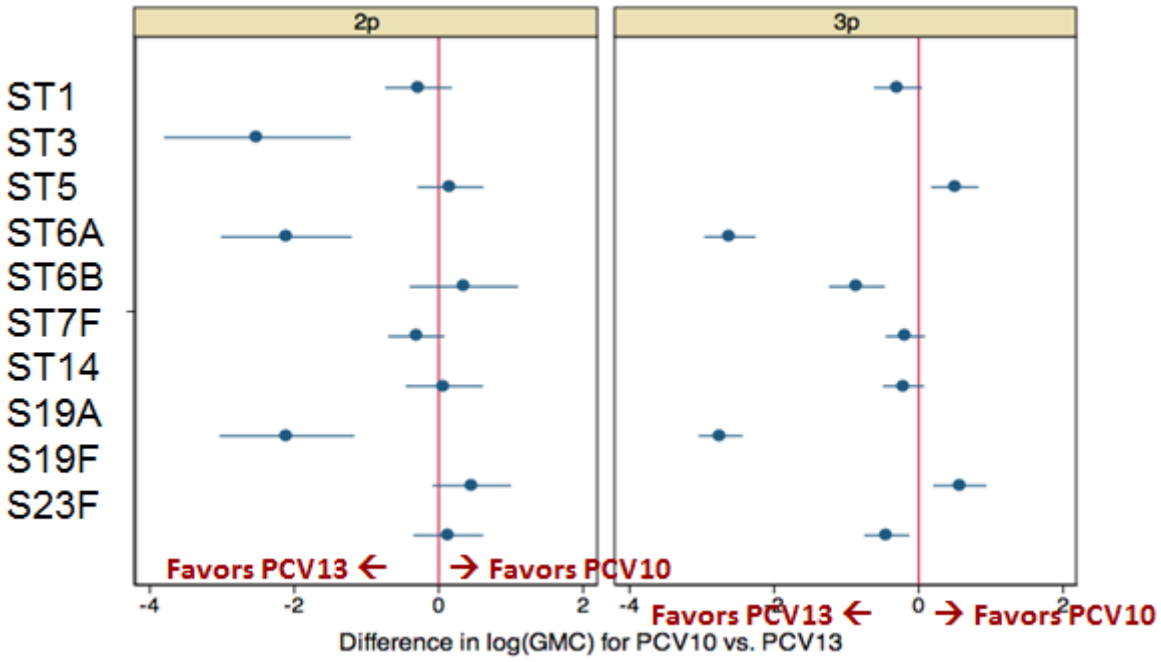
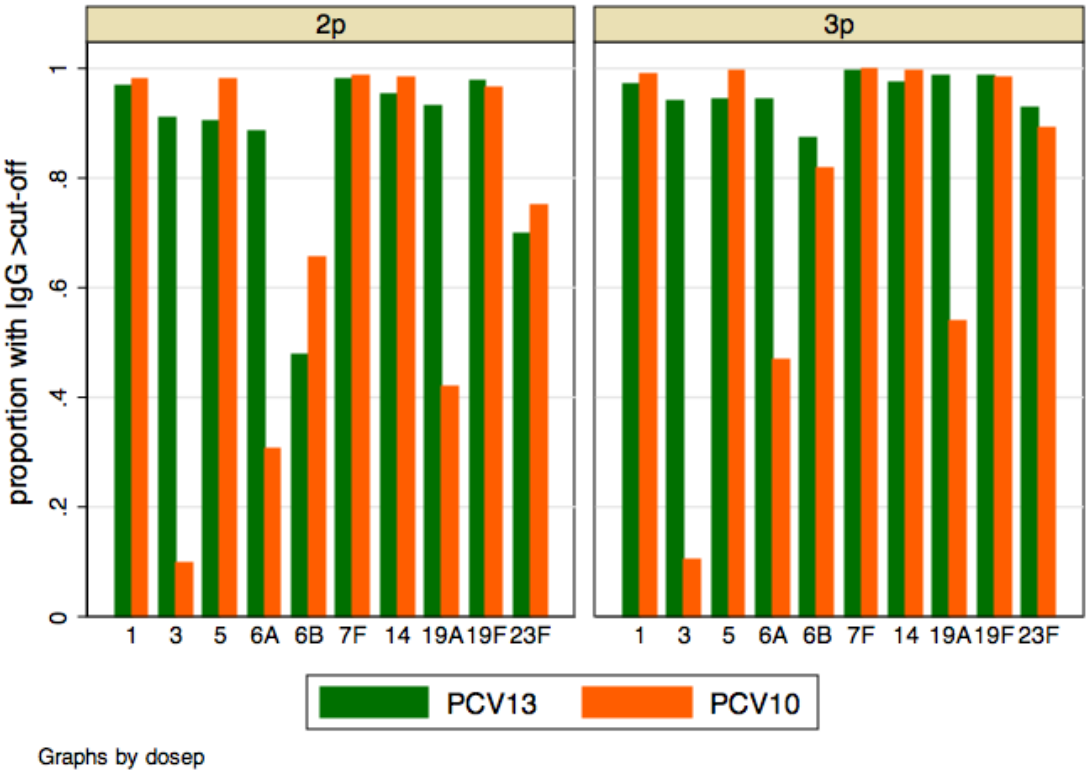


Figure 35: Between-study comparisons of PCV product by schedule at the post-primary time point

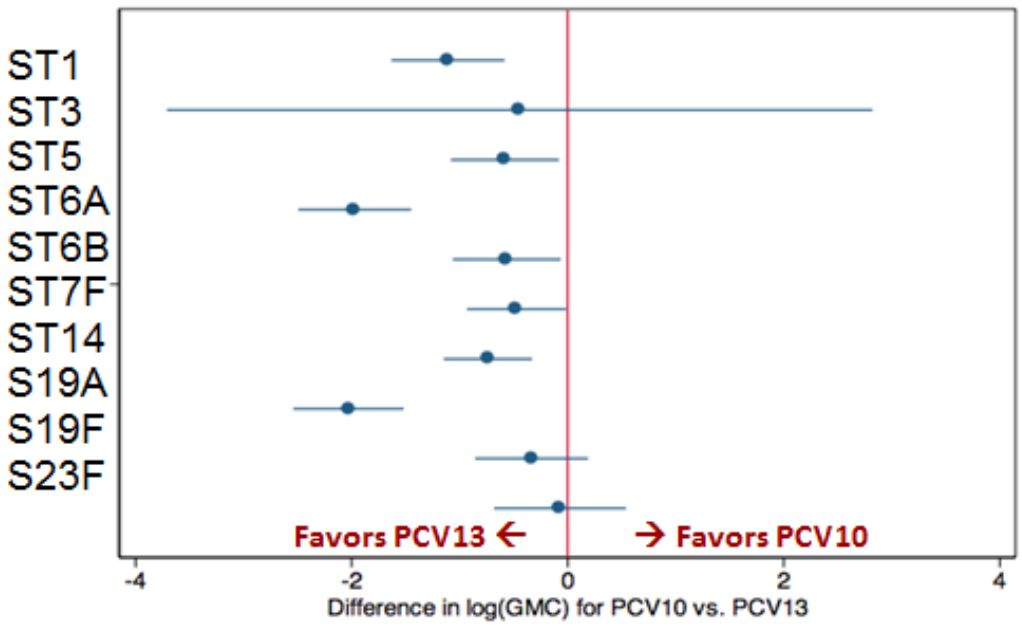


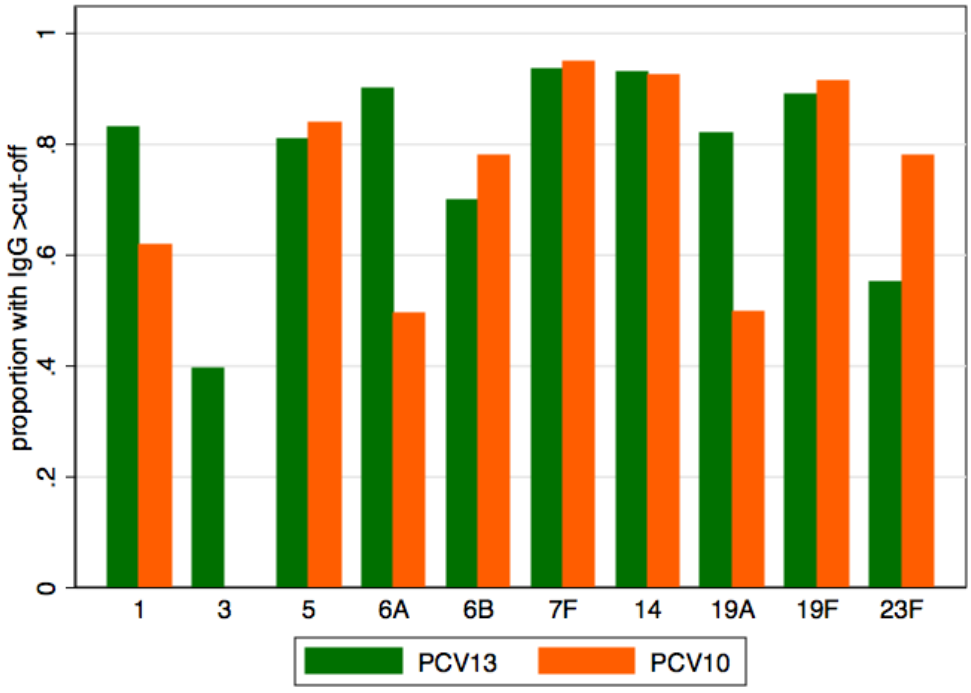


PICO II: Product

At the pre-booster time point, there are some serotype-specific differences following immunization with either PCV10 or PCV13. PCV13 is more immunogenic for STs 6A and 19A by both antibody concentration and percent responders. PCV10 has a higher percent response rate for ST 23F, however the GMC concentrations do not differ significantly from PCV13 vaccinees (**Figure 36**). PCV13 has a moderately better response to ST 1 by both GMC and percent responders. Antibody response to other STs (5, 6B, 7F, 14 and 19F) are not clearly distinguishable by PCV product, mostly due to similar proportion of infants reaching a response threshold.

Figure 36: Between-study comparisons of PCV product at the pre-booster time point



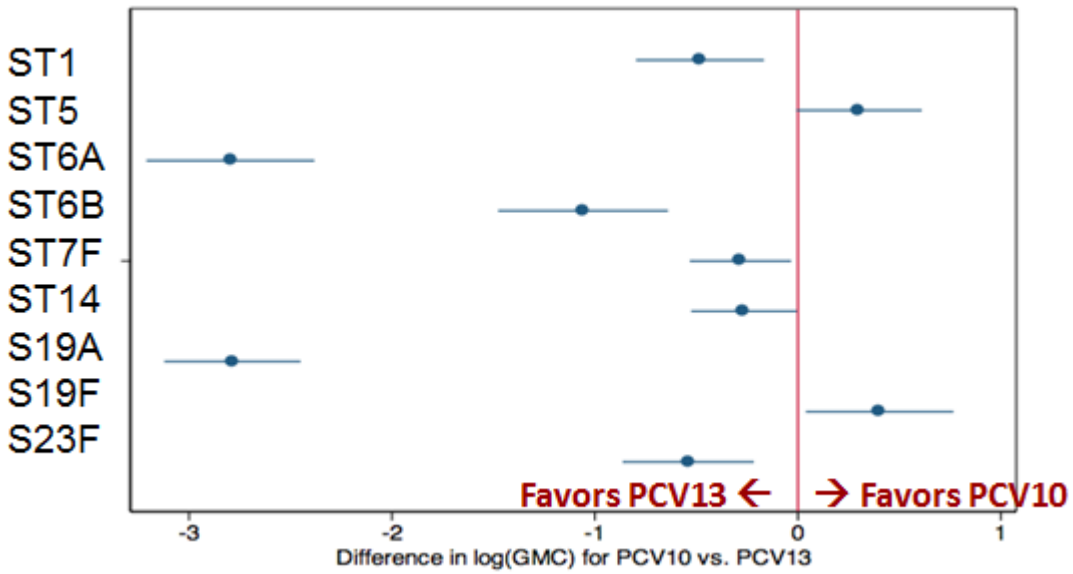


PICO II: Product

After the full three-dose series, immune response to STs 6A and 19A remain lower for PCV10 recipients compared to PCV13 (**Figure 37**). However, the percent responders (using the post-primary correlate of protection) improved to >80% after the booster dose (range 37-99% and 45-96%, respectively). Evidence of boosting by PCV10 of antibodies to STs 6A and 19A was also reflected in antibody concentrations, which increased 5-6 fold for each of the two serotypes compared to post-primary levels (based on evidence from 24 studies). These immunogenicity data raise the possibility that PCV10 may demonstrate cross-protection to ST 6A and 19A disease or colonization which is discussed further in sections three (NP colonization), four (IPD) and nine (3, 6A and 19A). There are limited opsonophagocytic data on the functional activity of the cross-reacting antibodies following PCV10 primary or booster immunization, but of those published, post-booster OPA responses for 6A and 19A after PCV10 are significantly lower than those following PCV13 boost.

Post-dose 3 evidence indicates that immunological response to the other vaccine STs common to PCV10 and PCV13 are comparable (**Figure 37**). Although antibody concentrations were significantly higher for STs 1, 6B, 7F, 14 and 23F following PCV13 and for serotypes 5 and 19F following PCV10 in both univariate and multivariate analyses, the percent of children responding did not differ substantially between products. Serotype-specific findings were similar for the products when stratified by schedule (**Figure 38**).

Figure 37: Between-study comparisons of PCV product at the post-dose 3 time point



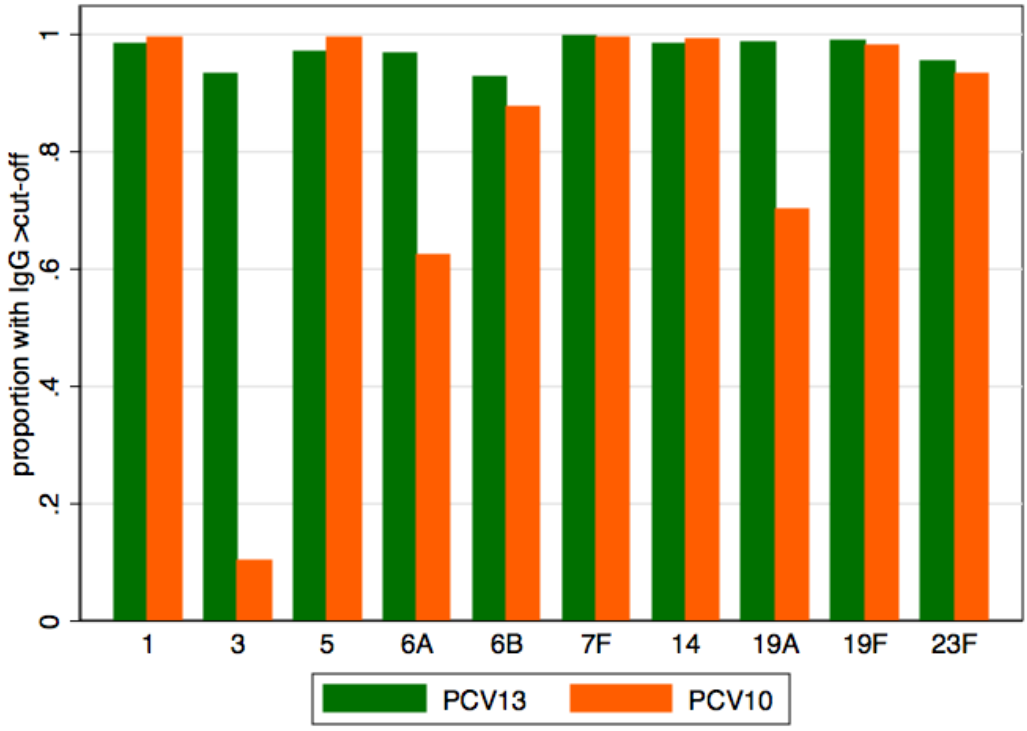
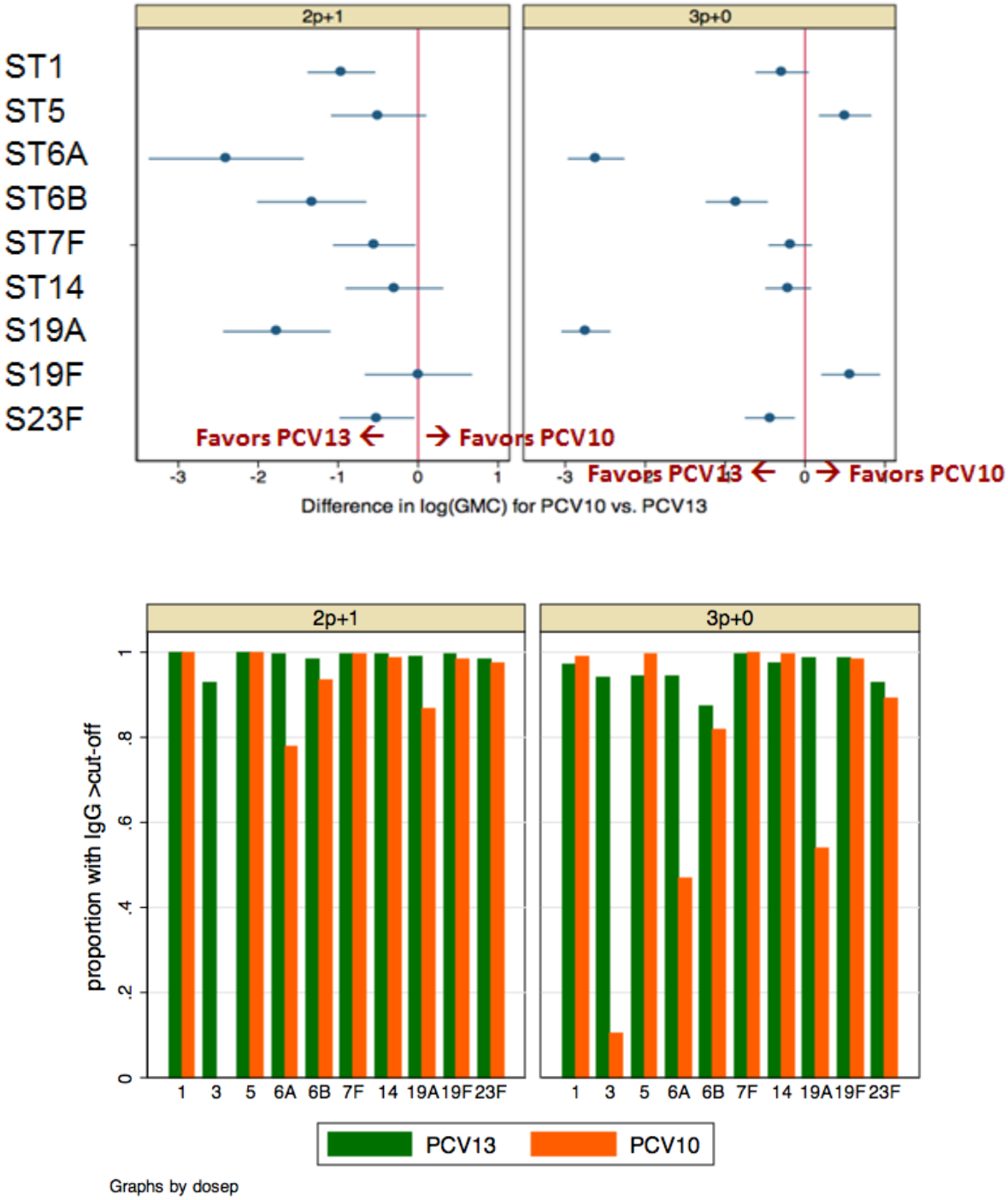


Figure 38: Between-study comparisons of PCV product by schedule at the post-dose 3 time point



Other variables that may affect the immune response were studied, including geographic region, age at first dose, interval between doses, and age at last dose. Post-primary antibody levels were generally higher in Africa and Asia for PCV10, but not for PCV13. However, proportions of children achieving the correlate of protection following the priming series are similar across regions for PCV10 and lower in Africa and Asia than in other regions for PCV13. Together, these data suggest that both PCVs elicit a wide range of immune response but poor immune responses in a subset of children may explain similar proportions above the correlate of

protection compared with other regions. This finding may be confounded by the fact that children in Africa and Asia receive whole-cell rather than acellular pertussis vaccine concomitantly with PCV, the acellular vaccine lacking the adjuvant effect associated with receipt of concomitant whole-cell pertussis vaccine. For PCV13, antibody responses to most serotypes increase with age at first dose, producing differences in antibody concentrations and proportions above the correlate of protection both post-primary series and post-dose 3. The effects of the age of immunization appear to be less marked for PCV10, with variations according to serotype, outcome and endpoint.

4.1.3 IMMUNOGENICITY META-REGRESSION ON PCV PRODUCT:

As described above, the number of primary doses, age at first dose, geographic region of the study population, and DTaP co-administration when considered one at a time (i.e. in univariate analyses) all influence PCV immunogenicity. Since these variables interact with each other, additional multivariable analyses were done to understand the independent effects of each variable on the immune response.

4.1.4 PCV PRODUCT INTERCHANGEABILITY:

The current WHO position paper on pneumococcal vaccines provides the following statement regarding the use of both PCV10 and PCV13 to immunize an individual (i.e. a mixed product regimen):

When primary immunization is initiated with one of these vaccines, it is recommended that remaining doses are administered with the same product. Interchangeability between PCV10 and PCV13 has not yet been documented. However, if it is not possible to complete the series with the same type of vaccine, the other PCV product should be used[110].

Since that 2012 WHO position statement three reports, from two studies, have been presented in published or abstract form on the use of PCV10 and PCV13 mixed product regimens. An immunogenicity study of PCV10 booster following PCV13 priming found lower antibody concentrations and opsonic activity as well as lack of memory B-cell induction than among those who received PCV13 booster [111, 112]. The other study assessed PCV13 booster following PCV10 or PCV13 priming and found no differences in immunogenicity of the booster dose for serotype 19A, by the product used for priming [113]. The clinical significance of these findings is not clear, reinforcing the WHO 2012 policy statement

4.2 Nasopharyngeal Carriage Direct Effects and Product Choice:

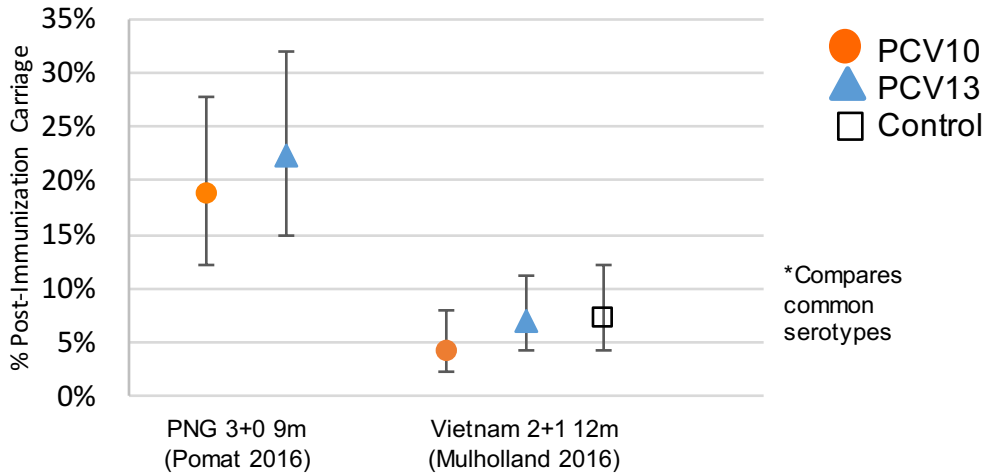
4.2.1 Direct Effects on Vaccine-Type NP Carriage:

We identified 22 studies with 29 arms that provided evidence on PCV13 vs. PCV10 products for 2+1 or 3+0 schedules: 2 head-to-head trials directly comparing products, 9 single product arms (8 PCV10, 1 PCV13), 1 non-randomized (cohort) study (PCV10) and 17 observational studies with 18 arms in the context of routine use (13 using PCV13 and 5 using PCV10).

Head to Head Evidence:

Two trials (**Figure 39**) directly compared PCV13-type NP carriage (defined as the proportion of children carrying PCV13-type serotypes) among children who received PCV13 vs. PCV10. One trial was conducted in a high burden country (PNG) and had high PCV13-type carriage (>80% by age 4 months)[106, 114]. This trial found similar PCV13-type carriage between PCV13 (30%) and PCV10 (32%) at 9 months of age following a 3+0 schedule; however, there was no unvaccinated control group to demonstrate whether both schedules reduced VT carriage relative to no vaccination. In the Vietnam trial (Mulholland, personal communication, 2017; [41, 42]), post-vaccination PCV10-type carriage at age 12 months was lower than that in controls (VT=9.1%, n=187) but was not statistically significant as the sample size was small and carriage in the population was so low. The PCV10 vaccinated group had lower VT colonization (4.3%, n=231) than the PCV13 vaccinated group (7.0%, n=203) but was also not statistically significant.

Figure 39: Head-to-head trials comparing PCV13-type carriage in children who received PCV10 vs. PCV13

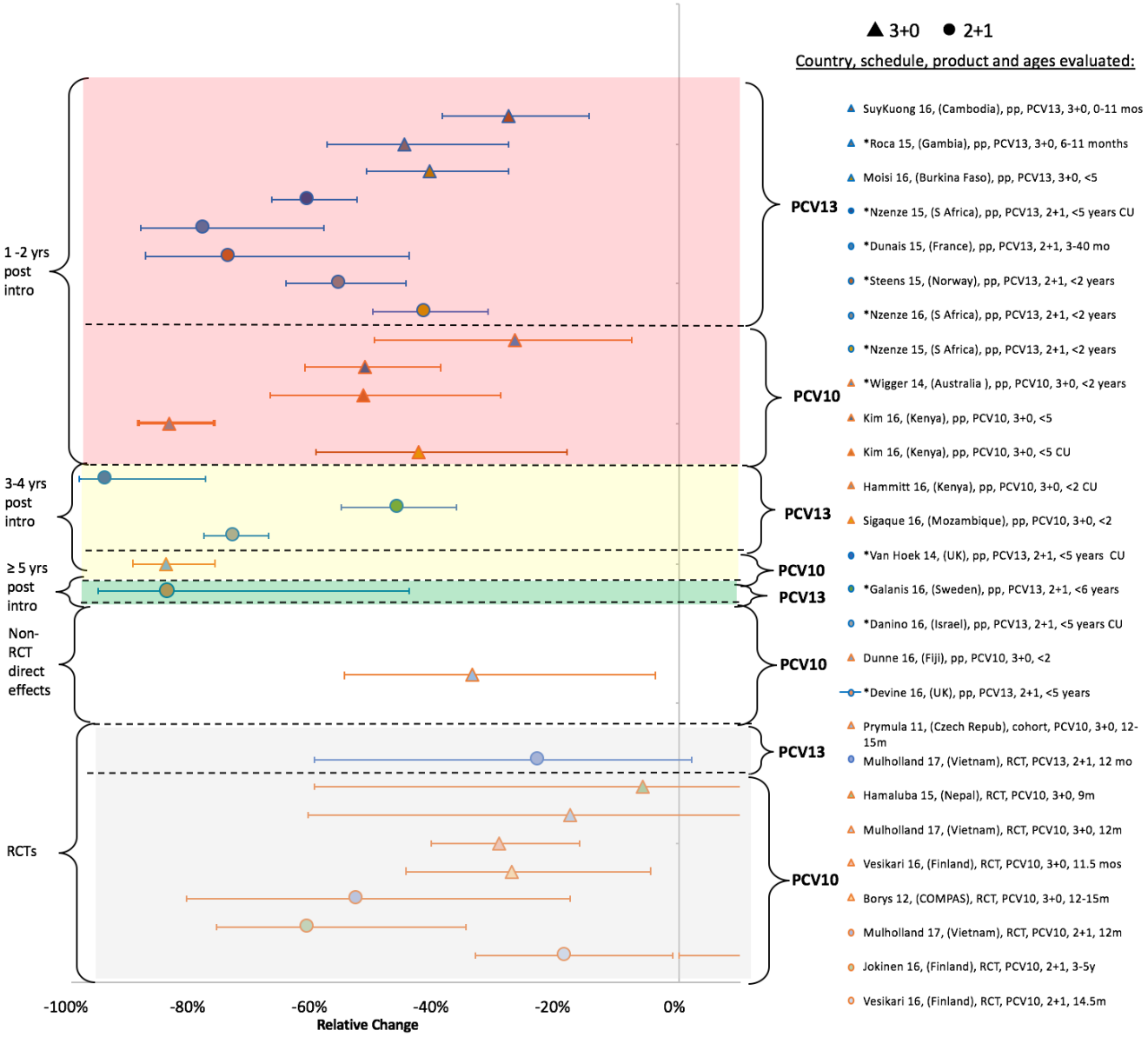


Single Product Clinical Trials and Non-Randomized Trials:

Figure 40 shows effectiveness against vaccine-type carriage (defined as PCV10-type impact for the PCV10 trials and PCV13-type impact for the PCV13 trials) for 8 single-product arms and 1 non-randomized (cohort) study that did not directly compare products: one of which evaluated PCV13 (2+1) and 8 PCV10 (n=6 3+0 and n=2 2+1). Also plotted in the figure is the relative change in the PCV10/13 vaccinated children when compared to

controls for the Vietnam head-to-head trial (Mulholland, personal communication, 2017). Percent change relative to controls (i.e., vaccine effectiveness) was calculated as (unvaccinated% - vaccinated%) / unvaccinated% where 'unvaccinated' is a non-PCV control group. Although the head-to-head trial is the only trial of PCV13, its 23% percent reduction in VT carriage was in range of that of the PCV10 trials which had wide heterogeneity (range 6% to 61% reduction in VT carriage; meta-average=29%, 95%CI: 22-40%) which was not fully explained by the age at assessment or amount of carriage in controls. Conclusions were similar when considering the 5 trials (1 PCV13 and 4 PCV10) from low income countries only (**Figure 41**).

Figure 40: Clinical trials and observational studies evaluating impact on product-specific vaccine-type carriage in children who received PCV13 (blue points/lines) vs PCV10 schedules (orange points/lines)



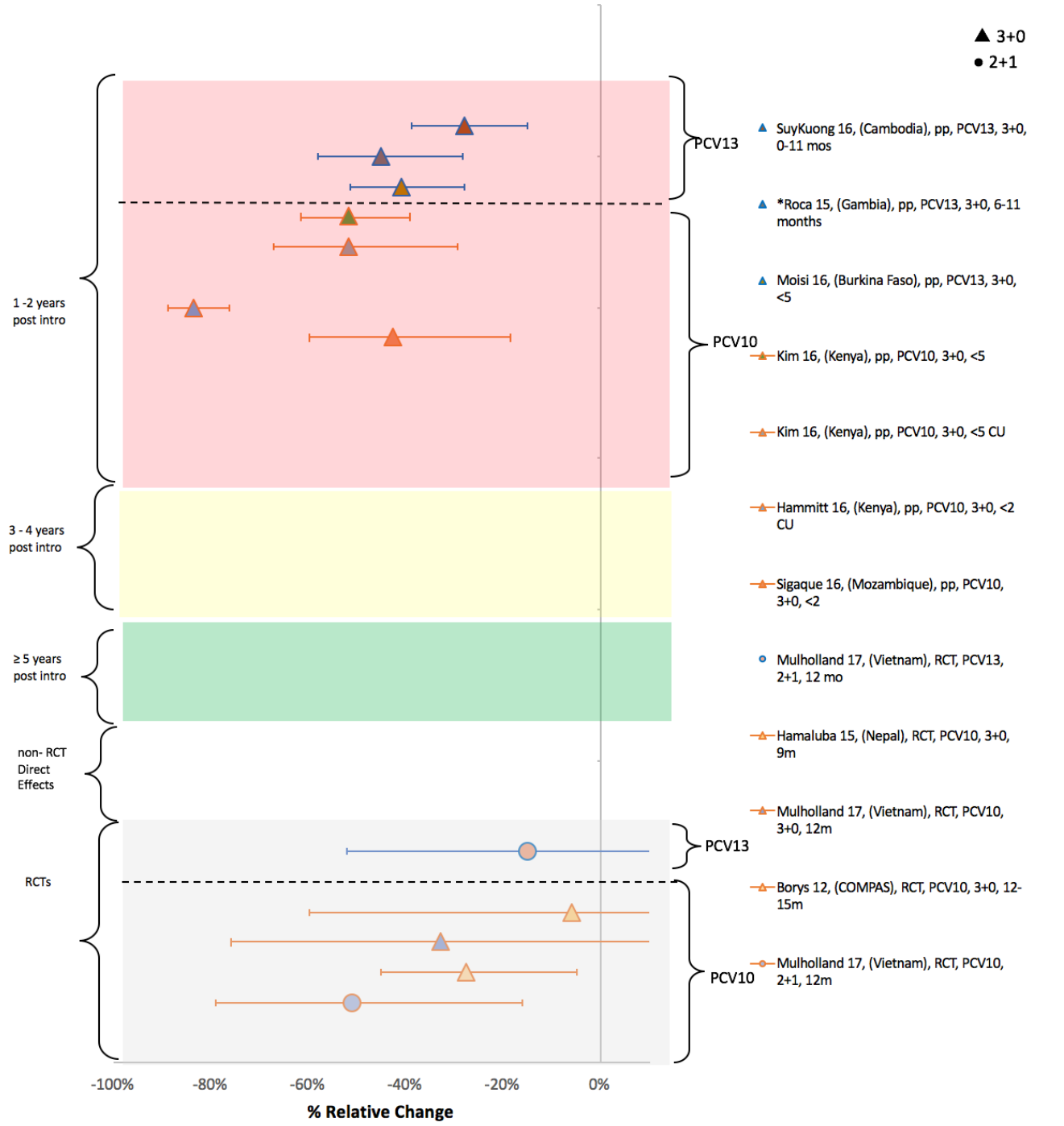
Footnote: 'Vaccine-type carriage' is defined as the proportion of children carrying vaccine serotypes, as opposed to the proportion of isolates that were vaccine serotypes. Points and 95% confidence intervals (whiskers) denote the relative change in VT carriage defined for observational studies in routine use settings (red, yellow, green sections) as (pre% - post%)/pre% and for clinical trials (bottom grey section) and non-randomized comparisons (white) as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies are grouped by years of

PICO II: Product

PCV10/13 use: green background = impact after 5+ years of PCV use in the population, yellow background = 3-4 years of PCV use, and red background = 1-2 years of PCV use. Within color group, studies are ordered by product (PCV13 = blue markers/lines and PCV10= orange markers/lines) and within each product by schedule (3+0=circles and 2+1=triangles).

*Observational studies include countries with preceding use of PCV7; only those that had carriage prevalence data at the time PCV10/13 was introduced were analysed.

Figure 41: Clinical trials and observational studies evaluating impact on vaccine-type carriage in children who received PCV13 (blue points/lines) vs PCV10 (orange points/lines), restricted to low-income countries



OBSERVATIONAL STUDIES POST INTRODUCTION NATIONAL IMMUNIZATION PROGRAM:

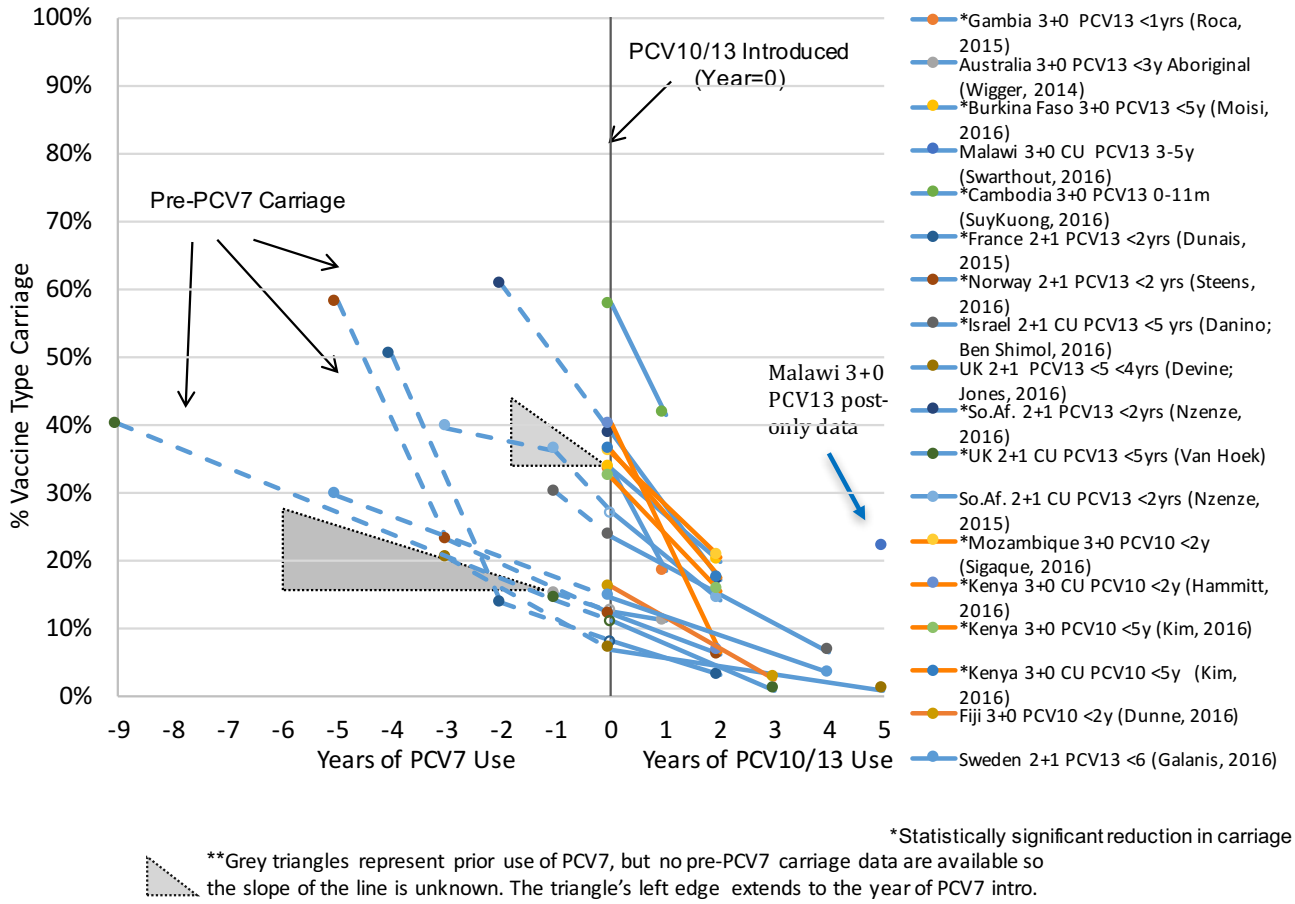
We identified 18 arms evaluating the impact of PCV10/13 introduction into routine national programs on vaccine-type NP carriage (defined as PCV10-type impact for the PCV10 trials and PCV13-type impact for the PCV13 trials): 13 using PCV13 and 5 using PCV10 (**Figure 40 and Figure 42**). Only two (both PCV13) represented data from a mature program with at least 5 years of use (2+1 in the UK and 3+0 post-only data in Malawi). The UK study was in the context of low pre-PCV carriage (no pre-PCV7 data were available but 1 year post-PCV7 introduction VT carriage was 15%) and showed VT-carriage at 1% in year 5 post-PCV13. However, in Malawi after ~5 years of PCV13 use there was still 22% VT-carriage (no pre-PCV data were available but this is likely a high carriage setting).

Declines were seen for both products and were of similar magnitude for their respective vaccine-type carriage. Of 18 arms evaluating the percent relative change in VT NP carriage before vs. after PCV10/13 introduction (regardless if there was preceding use of PCV7 or not), n=12 evaluated PCV13 and n=6 PCV10 (**Figure 40**). Only one reported data from a mature program of 5+ years of use (PCV13 2+1 in the UK) and only 5 had data after 3 or more years of use, 4 with PCV13 and 1 with PCV10. Results of the PCV10 study were within the range of the PCV13 studies, so we found no evidence of a difference by product against VT carriage with long-term use. The magnitude of this long-term impact observed in conditions of widespread use was larger than that observed in the clinical trials, ranging in observational settings from 46%-94% compared to a range of 6%-61% in clinical trial conditions. Among the remaining 13 studies that reported on NP carriage after only 1-2 years of PCV10/13 use, impact on VT carriage varied more widely than with longer term use because of heterogeneity in use of catch-up programs, age range swabbed and perhaps coverage, and was similar across products: sort-term reductions (i.e., 1-2 year post-introduction) ranged from 28%-78% among PCV13 studies compared to 27%-84% reductions among PCV10 studies.

Several issues hamper determining which product is better at reducing vaccine-type NP carriage among the observational studies. First, there was complete confounding by product in that all PCV10 studies evaluated 3+0 schedules while only 3 of 12 studies of PCV13 evaluated 3+0 schedules. Second, 11 of the 12 studies of PCV13 were with preceding use of PCV7 while only one PCV10 study had previously used PCV7. Therefore, the PCV13 studies predominantly measure the impact only on the additional 6 serotypes that are in PCV13 but not PCV7. If these factors can be ignored, reductions in the relevant VT-type carriage was similar between products: meta-average=48% reduction (95%CI 40-58%) for PCV13 studies compared to meta-average=50% reduction (95%CI 36-70%) for PCV10 studies.

Regardless of product, **Figure 42** shows that post-PCV10/13 VT carriage is lower when there have been more years of PCV use and when pre-PCV carriage prevalence is lower to start with (note that some studies from **Figure 40** are not included here because they provided percent change but not carriage prevalence and vice versa). For any given year post PCV10/13 introduction, when there are data for both products, the rate of decline is similar and percent carriage prevalence for the two products overlaps without one being clearly higher or lower. As above for studies in the percent change analysis, it is difficult to discern any product-specific effects because these data are confounded by prior experience with PCV7 (n=1 PCV10 studies vs. 11 of 12 PCV13 studies were in the context of previous PCV7 use) so PCV13 studies predominantly measure the impact only on the additional 6 serotypes that are in PCV13 but not PCV7. One study (Malawi) had data post-PCV13 data only (i.e., no line drawn showing decline in carriage) but was conducted in a mature PCV program after ~5 years of PCV13 use [46]. The persistent carriage of PCV13-types in Malawi after long-term use of PCV13 with high immunization rates does suggest that in high burden areas a 3+0 schedule may not eliminate vaccine-type carriage; there was no such long-term data in high burden settings for PCV10. One additional study (not plotted) in a low carriage (28% all type) setting in Poland observed 1.4% VT carriage in vaccinated children in a city that introduced PCV13 with a 2+1 schedule (years of use not known) vs. 16% VT carriage in children in a city that did not introduce PCV13, a 91% relative difference.

Figure 42: Vaccine-type NP carriage before and after PCV10/13 introduction in countries using PCV13 (blue lines) vs. PCV10 (orange lines)



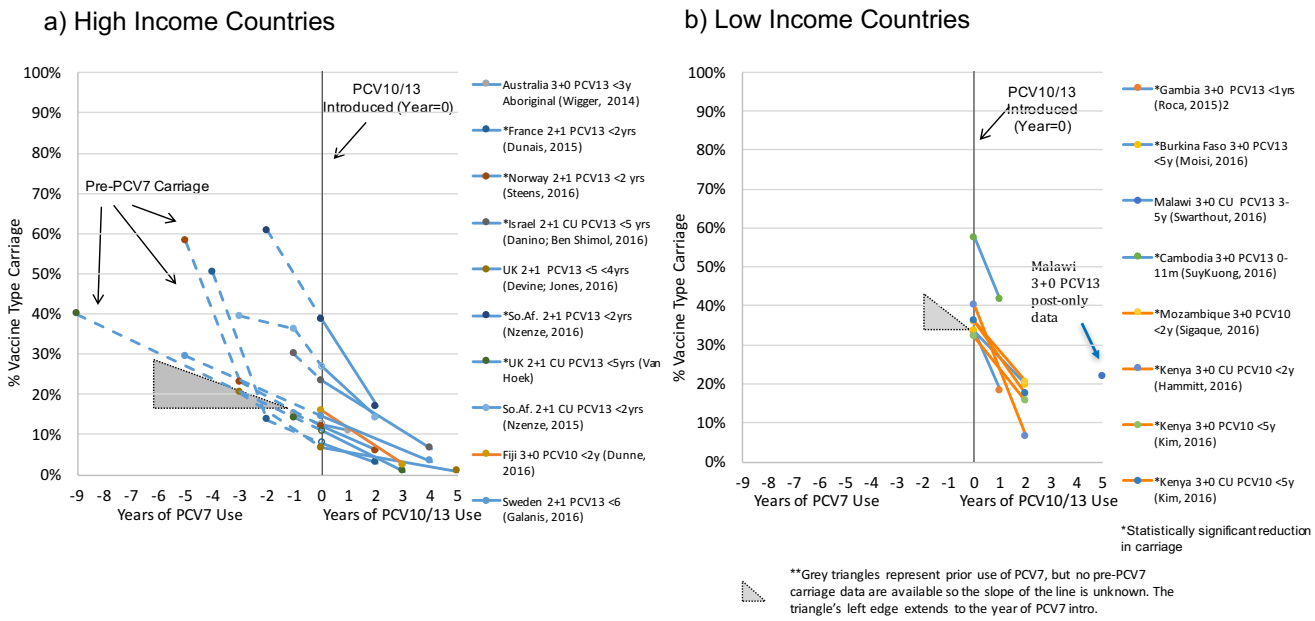
*Statistically significant reduction in carriage

**Grey triangles represent prior use of PCV7, but no pre-PCV7 carriage data are available so the slope of the line is unknown. The triangle's left edge extends to the year of PCV7 intro.

Footnote: 'Vaccine-type carriage' is defined as the proportion of children carrying vaccine serotypes, defined as 10-VT for the PCV10 trials and 13-VT for the PCV13 trials). Solid lines depict post-PCV10/13 carriage while dotted lines depict post-PCV7 carriage prior to PCV10/13 introduction for countries that had preceding use with PCV7. Studies are colored by product: blue lines = PCV13 and orange lines = PCV10. Grey shaded triangles point to studies where pre-PCV7 carriage is unknown but assumes some decline; the triangle extends left to the year PCV7 was introduced to indicate how much PCV7 use there was prior to PCV10/13 introduction.

The observational vaccine-type data were stratified by income status of the countries conducting the studies (**Figure 43 a and b**). Conclusions were similar when considering just the 8 studies conducted in low income settings, 4 of PCV13 and 4 of PCV10 (**Figure 43 b**).

Figure 43: Vaccine-type NP carriage before and after PCV10/13 introduction in countries using PCV13 (blue lines) vs PCV10 (orange lines), by income status of the country



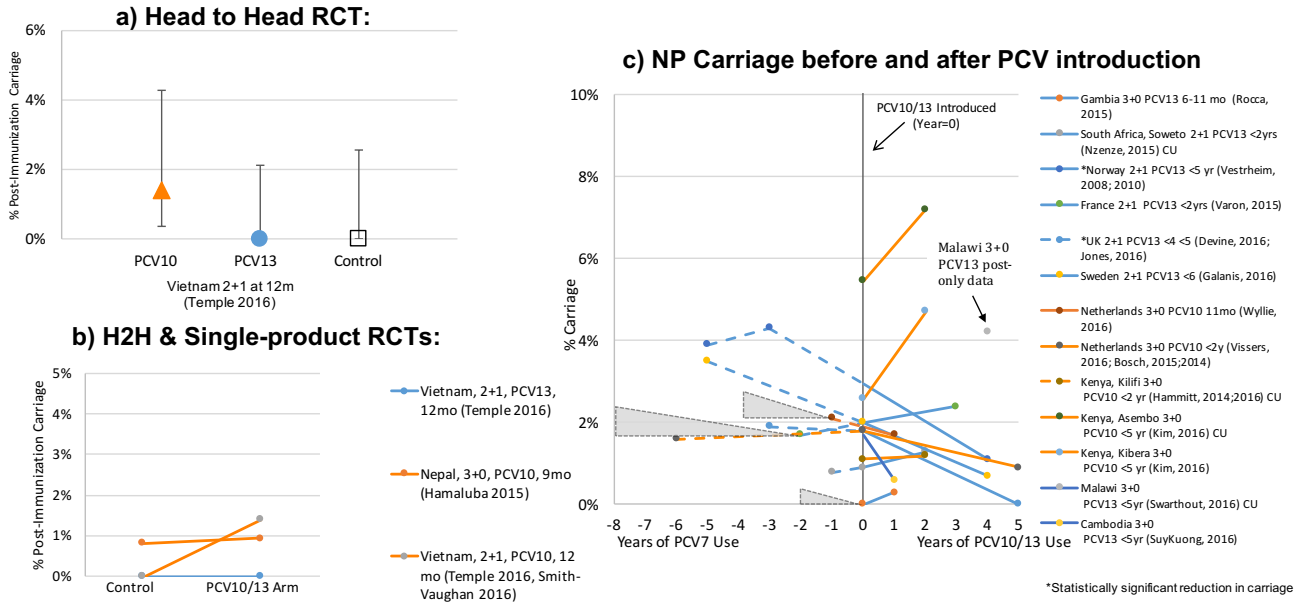
4.2.2 Direct Effects on Serotype Specific NPC:

4.2.2.1 Serotype 3 NPC:

We identified one head-to-head trial (Vietnam, Mulholland, personal communication, 2017) that compared PCV10 to PCV13 impact on ST3, which observed 0% carriage in the PCV13 group compared to 1.4% in the PCV10 group, but was not statistically significant, and carriage in controls was low (3.3%)[41].

For indirect comparisons between products, there were 16 arms evaluating impact on ST3, 9 of PCV13 (1 clinical trial, which observed 0% ST3 carriage in the control group, 7 pre-post introduction observational studies, 1 of which observed 0% ST3 carriage pre-PCV13, and 1 post-only study with 5 years of PCV13 use) and 7 of PCV10 (2 clinical trial arms, one with 0% ST3 carriage in controls, and 5 observational studies) (**Figure 44**). ST3 carriage was low (less than 3%) in all but one study. There is no evidence that to suggest that either product impacted ST3 carriage. Percent carriage of ST3 increased in 2 or more studies for both PCV10 and PCV13. And the one PCV10 (Nepal, Hamaluba 2015) clinical trial that had non-zero ST3 carriage in controls found no difference in %ST3 carriage between controls and vaccinated children (**Figure 44**) [50].

Figure 44: Serotype 3 NP carriage observational studies of before and after PCV10/13 introduction and clinical trials in countries using PCV13 (blue lines) vs PCV10 (orange lines)



4.2.2.2 SEROTYPE 6A NPC:

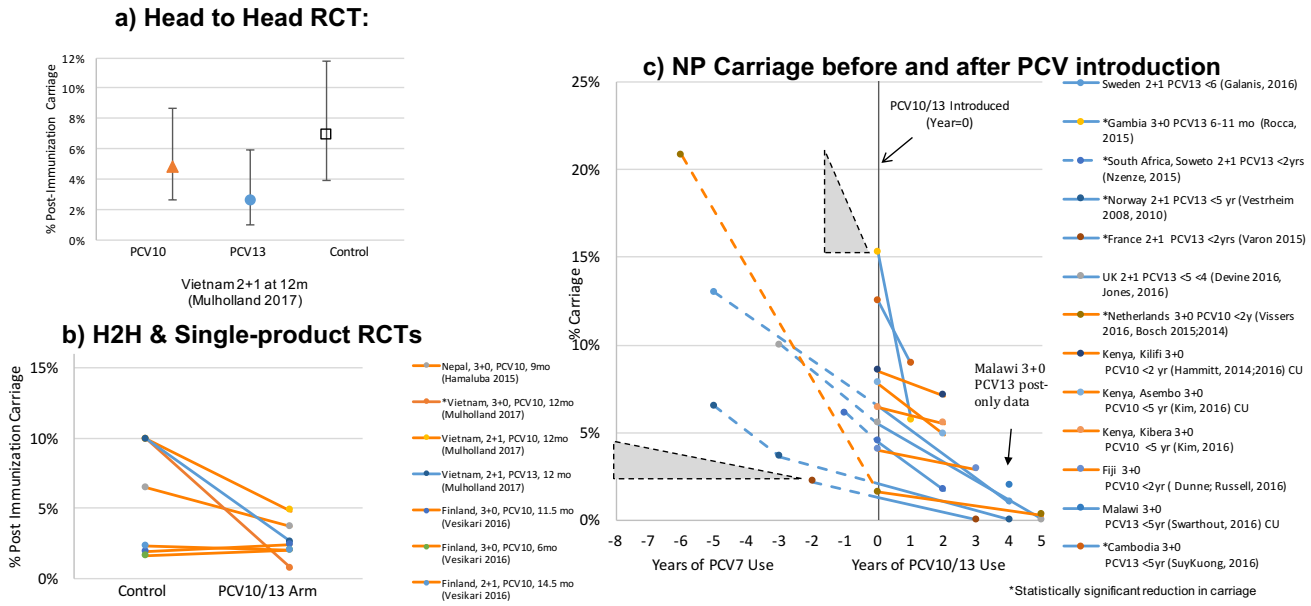
We identified one head-to-head trial (Mulholland, personal communication, 2017) that compared PCV10 to PCV13 impact on ST6A using a 2+1 schedule, which observed 2.6% carriage in the PCV13 group compared to 4.8% in the PCV10 group, but was not statistically significant; both had lower carriage than controls (6.9%) [41].

For indirect comparisons, there were n=9 additional studies of PCV13 impact on ST6A (one from a trial and 7 pre-post introduction observational studies, 6 of which had preceding PCV7 use, and 1 post-only study 5 years after introduction), and 11 additional evaluations of PCV10 (6 single arm trials and 5 observational studies, one of which had preceding PCV7 use) (**Figure 45**). Several issues hamper determining which product is better. First, all PCV10 were in the context of 3+0 schedules (except for two 2+1 PCV10 trials). Second, for all studies with preceding use of PCV7, none assessed carriage at the time of the switch. And third, the years of PCV7 use prior to PCV10/13 introduction differed by study. If these factors can be ignored, then there is no evidence that one product had a bigger impact than the other when used in routine use.

Of the six PCV10 single product trials evaluating impact on ST6A carriage (**Figure 45**), reductions were observed in the three that had over 5% carriage in controls; the remaining three PCV10 trials had less than 3% ST6A carriage in controls and no impact was observed.

An additional study in Brazil (Brandileone, 2016) assessed impact of PCV10 on ST6A, but it was not with a 3-dose schedule; this study evaluated impact of a 3+1 schedule with catch-up in children <23m of age [115]. We describe it here because it shows the potential (or lack thereof) for PCV10 to impact on vaccine-related serotypes under conditions of maximized use (i.e., 4 doses plus catch-up) after 3 years of use. Although a decline in ST6A carriage was not found (carriage pre-PCV10 was 4.2% vs. 4.0% after PCV10), this may not mean that there was no effect of PCV10 on ST6A since there was an increase other non-VT STs, especially ST6C which increased from 1.8% to 11.2% post-PCV10 (p<.0001).

Figure 45: Serotype 6A NP carriage observational studies of before and after PCV10/13 introduction and clinical trials in countries using PCV13 (blue lines) vs PCV10 (orange lines)



*Note: Figure (b) includes all trial data, i.e., PCV10 and PCV13 arms relative to non-PCV control arms in head-to-head to trials as well as single-product trials.

4.2.2.3 SEROTYPE 6B NPC:

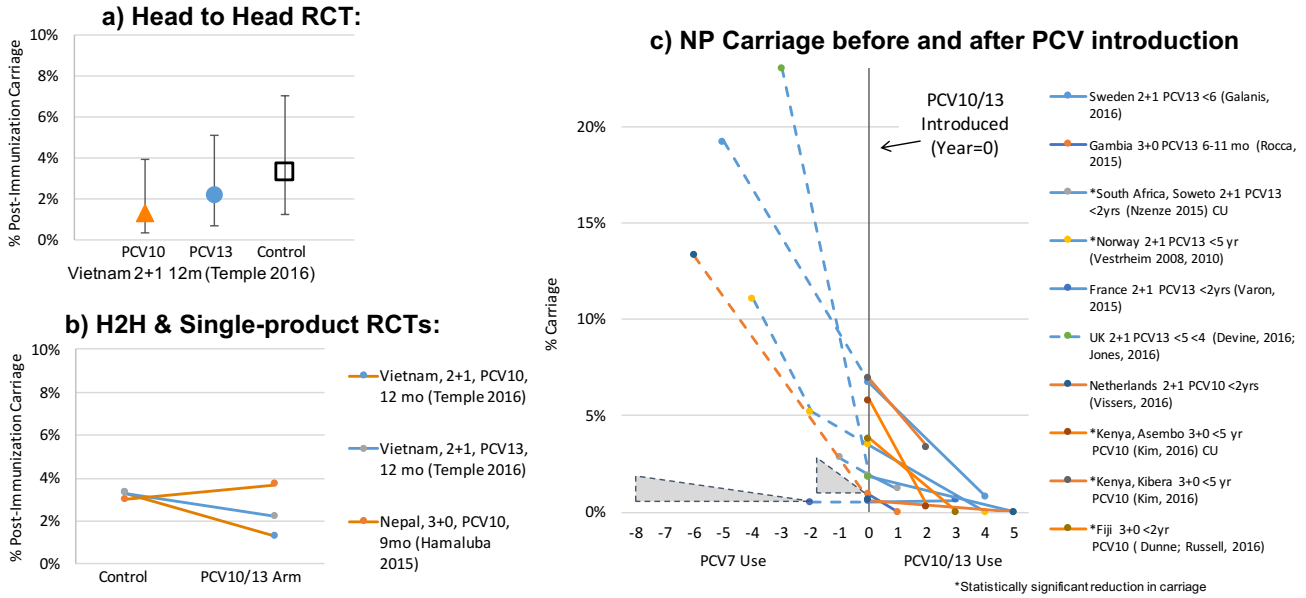
Because impact of PCV10 on ST6A is predicated on the assumption that this is the result of cross-protection from ST6B, results for ST6B were also compared between products.

We identified one head-to-head trial (Vietnam, Temple, 2016) that compared PCV10 to PCV13 impact on ST6B, which observed 2.2% carriage in the PCV13 group compared to 1.3% in the PCV10 group, but was not statistically significant, and both were lower than the carriage in controls (3.3%; not significant) [41].

For indirect comparisons, there were n=7 indirect studies of PCV13 impact on ST6B (1 from a single arm trial and 6 from pre-post comparisons with preceding PCV7 use), and 6 PCV10 studies (2 single arm trials and 4 observational studies, one of which had prior PCV7 use) (**Figure 46**). All observational studies were conducted in settings with <10% ST6B carriage at the time of PCV10/13 introduction. Similar declines were observed for both products when considering pre-PCV10/13 carriage rates.

Of the two single-product PCV10 trials that evaluated impact on ST6B carriage, one elicited lower (non-significant) carriage in the PCV10 vaccinated children compared to controls (2+1; Hamaluba, 2015) and one did not (3+0; Temple, 2016) (**Figure 46**).

Figure 46: Serotype 6B NP carriage observational studies of before and after PCV10/13 introduction and clinical trials in countries using PCV13 (blue lines) vs PCV10 (orange lines)



*Note: RCT figure includes all trial data, i.e., PCV10 and PCV13 arms relative to non-PCV control arms in head-to-head to trials as well as single-product trials.

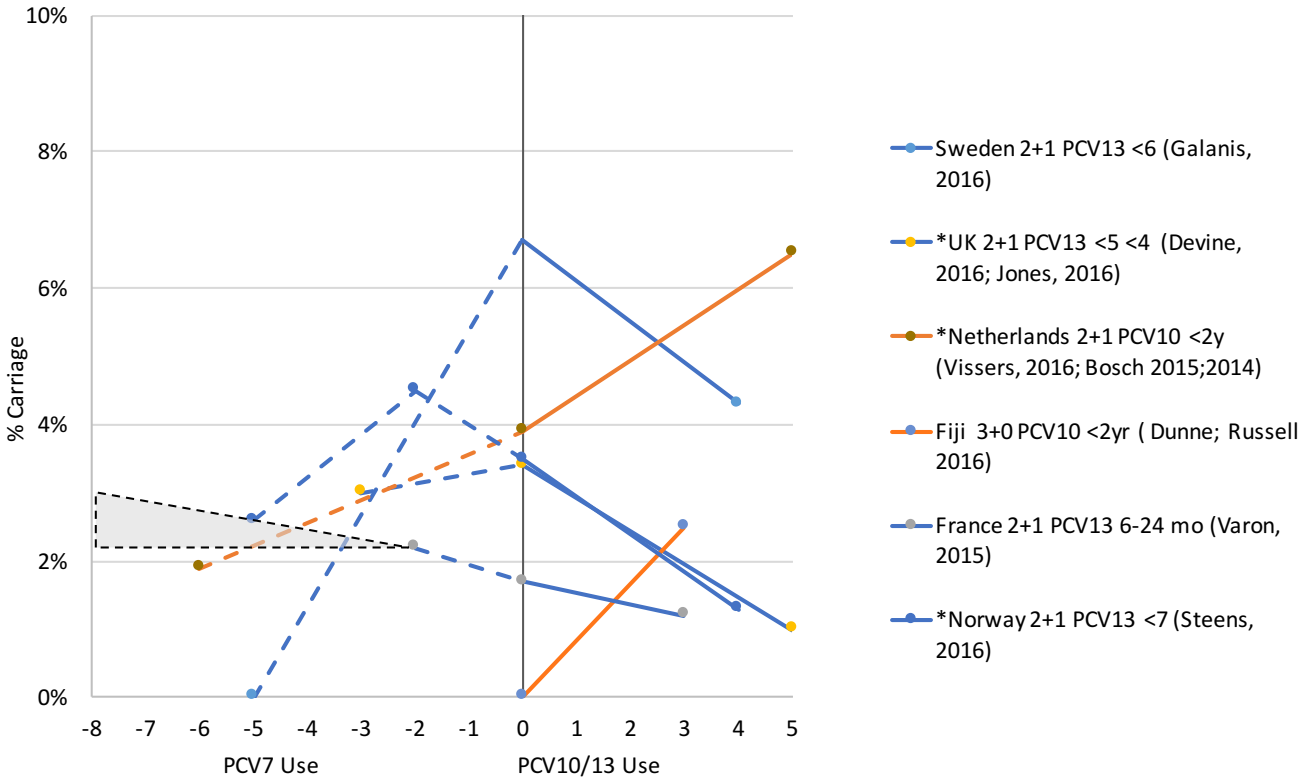
4.2.2.4 SEROTYPE 6C NPC:

No head-to-head trials directly comparing products or any trial data were identified for ST6C. We identified 6 observational studies of routine use (4 of PCV13 and 2 of PCV10; **Figure 47**).

ST6C carriage was low (0%-5%) pre-PCV10/13 so studies were not powered to detect reductions, but PCV13 may have more impact on ST6C carriage than PCV10 as 2/4 PCV13 studies observed declines in ST6C carriage (one statistically significant) while both PCV10 studies observed increases (one statistically significant).

All but one study (PCV10) had previously used PCV7 and increases were observed in four of these studies prior to switch to PCV10/13.

Figure 47: Serotype 6C NP carriage observational studies of before and after PCV10/13 introduction in countries using PCV13 (blue lines) vs PCV10 (orange lines)



4.2.2.5 Serotype 19A NPC:

We identified one head-to-head trial (Mulholland, personal communication, 2017) that compared PCV10 to PCV13 impact on ST19A, which observed 1.7% carriage in the PCV13 group compared to 3.0% in the PCV10 group, but was not statistically significant (carriage in controls was 1.6%).

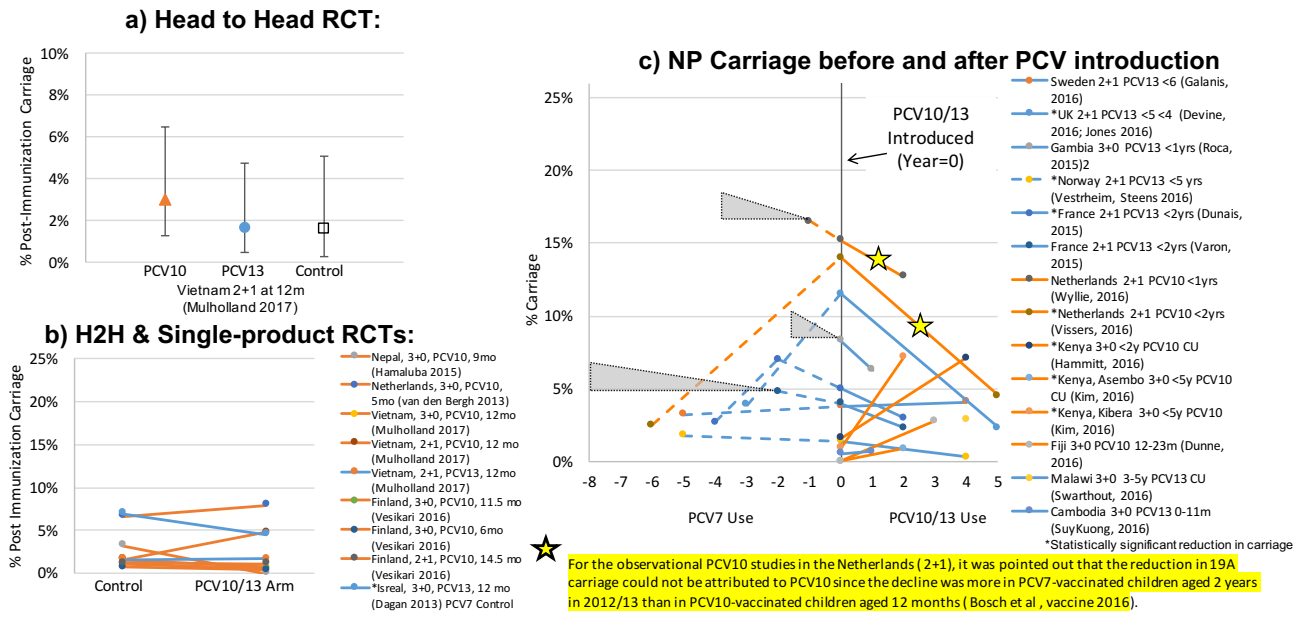
For indirect comparisons, there were n=10 arms of PCV13 impact on ST19A (1 single-product controlled trial and 8 pre-post introduction observational studies, plus one post-only study evaluating carriage ~5 years after PCV13 introduction with a 3+0 schedule), and 13 PCV10 studies (7 single arm trials and 6 observational studies) (**Figure 48**).

Generally, results favored PCV13 over PCV10 as no meaningful increases in 19A carriage were observed for any PCV13 trial or study while large (over 4%) increases were observed for PCV10 in observational studies (two were statistically significant) and in trials compared to controls (none significant). All but one (very low carriage and no change) PCV13 observational study had declines in 19A carriage compared to only 2 of 13 PCV10 studies (both from The Netherlands), and investigators of these studies did not attribute decline to PCV10 since greater declines were seen in PCV7-vaccinated children than in PCV10-vaccinated children.

The one PCV13 single product trial evaluating impact on ST19A carriage observed significantly lower carriage compared to PCV7-vaccinated controls (Israel), whereas only one of 6 PCV10 trials had lower carriage relative to controls (not significant) (**Figure 48**). However, ST19A carriage in controls was low (less than 3% at 9m of age) in all but two trials.

An additional study in Brazil (Brandileone, 2016) assessed impact of PCV10 on ST19A, but it was not with a 3-dose schedule; this study evaluated impact of a 3+1 schedule with catch-up in children <23m of age [115]. We describe it here because it shows the potential (or lack thereof) for PCV10 to impact on vaccine-related serotypes under conditions of maximized use (i.e., 4 doses plus catch-up) after 3 years of use. Although a decline in ST19A carriage was not found (1.8% pre-PCV10 vs. 2.5% after PCV10), this may not mean that there was no effect of PCV10 on ST19A. Many studies have found increases in ST19A carriage following PCV7 introduction resulting from serotype replacement, and in this study, there was an increase in non-VT, non-related STs (from 8.2% to 23.5%; p<.0001), especially ST6C which increased from 1.8% to 11.2% post-PCV10 (p<.0001), and an increase in all Spn carriage (from 40.3% at baseline to 48.8% post-PCV10, p=.01).

Figure 48: Serotype 19A NP carriage observational studies of before and after PCV10/13 introduction and clinical trials in countries using PCV13 (blue lines) vs PCV10 (orange lines)



*Note: RCT figure includes all trial data, i.e., PCV10 and PCV13 arms relative to non-PCV control arms in head-to-head to trials as well as single-product trials.

4.2.2.6 Serotype 19F NPC:

Because impact of PCV10 on ST19A is predicated on the assumption that this is the result of cross-protection from ST19F, results for ST19F were also compared between products.

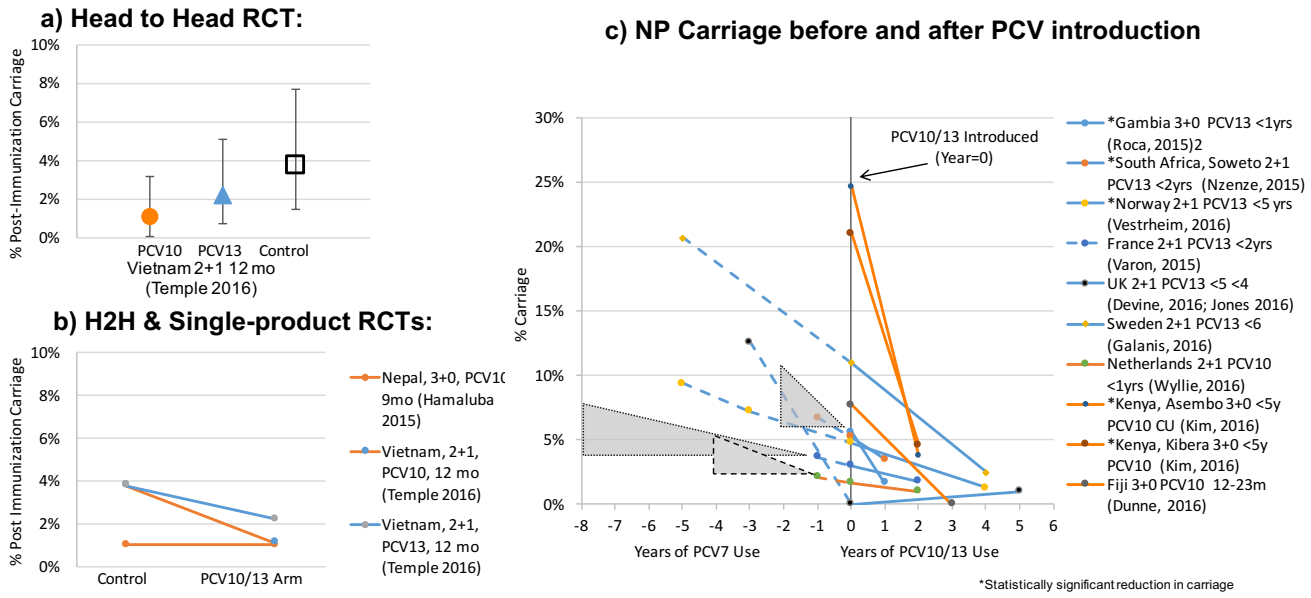
We identified one head-to-head trial (Vietnam, Temple 2016) that compared PCV10 to PCV13 impact on ST19F, which observed 2.2% carriage in the PCV13 group compared to 1.1% in the PCV10 group, but was not statistically significant; both had lower carriage than controls (3.8%) [41].

For indirect comparisons, there were n=7 PCV13 studies (one single arm trial and 6 pre-post introduction observational studies with prior PCV7 use), and 6 PCV10 studies (2 single arm trials and 4 observational studies, one with prior PCV7 use) (**Figure 49**). For both products, there were declines in all studies except one PCV13 study that had 0% carriage at time of switch from PCV7 to PCV13. All PCV13 observational studies were

conducted in settings with less than 5% 19F carriage prior to PCV introduction, compared to only 1 of the PCV10 studies, which had a similar rate of decline as the PCV13 studies. The 2 high-carriage (20-25%) PCV10 studies had higher rates of decline in that they reached the same level of 19F carriage after 2 years of use (post-PCV10 carriage <5%) as for low carriage settings.

The only single-product trial, a PCV10 trial with 3+0, that evaluated impact on ST19F carriage was conducted in a setting with low carriage in the control group (1% at age 9 months) so impact was not able to be measured (the PCV10-vaccinated group also had 1% 19F carriage).

Figure 49: Serotype 19F NP carriage observational studies of before and after PCV10/13 introduction and clinical trials in countries using PCV13 (blue lines) vs PCV10 (orange lines)



*Note: RCT figure includes all trial data, i.e., PCV10 and PCV13 arms relative to non-PCV control arms in head-to-head to trials as well as single-product trials.

4.3 Nasopharyngeal Carriage Indirect Effects and Product Choice:

4.3.1 Indirect Effects on NPC: RCTs:

One study conducted as a follow up to the FinIP trial assessed NPC in older siblings of children who had received PCV10 (either a 2+1 or 3+1 schedule) compared to older siblings of children who had received placebo. One to two years after the FinIP trial, the vaccine effectiveness of PCV10 (2+1 or 3+1 schedule) for

reducing VT carriage was significant at 29% (95% CI 6%, 47%).[55] There are no comparable data on the indirect effect of PCV13 on NP carriage from clinical studies to make a comparison.

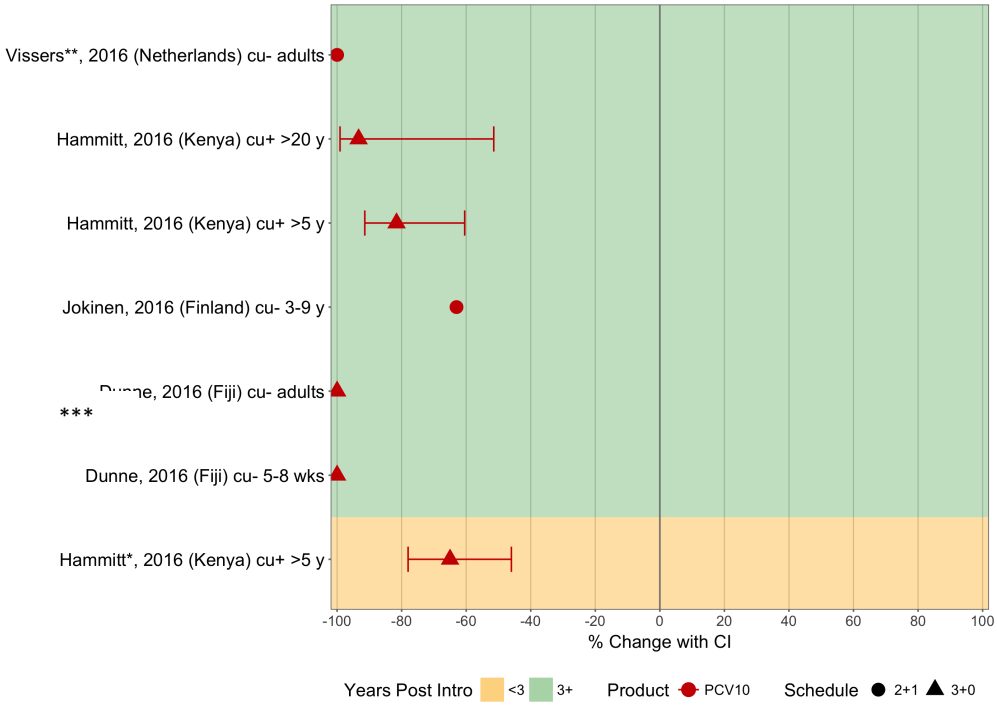
4.3.2 Indirect Effects on Vaccine-Type NP Carriage using PCV10:

There are limited but consistent data on the indirect effects of PCV10 introduction on VT NP carriage in older children and adults. Data are limited mainly because most NP carriage studies did not have at least three years of post-introduction data. Four NP carriage studies were included: three studies on the *de novo* use of PCV10 using a 2+1 (Finland) or 3+0 (Fiji and Kenya) schedule, and one study from the Netherlands where PCV7 preceded PCV10 based on a 3+1 schedule that was subsequently reduced to a 2+1 schedule.[55-58] All four studies report reduction of PCV10 VT carriage in various age groups not directly vaccinated—including among infants too young to vaccinate--with a relative reduction in VT carriage ranging from 52% to 100% **(Figure 50**). In Kilifi, Kenya, where a catch up campaign targeting all children under 5 years was used to introduce PCV10, there was a 65% reduction (95% CI: 46%, 78%) in PCV10 VT carriage among all persons over 5 years of age achieved in a period that averaged just two years post PCV10.[58] When looking at prevalence of VT NP carriage over time in adults, the three studies with this data all show appreciable reductions (**Figure 51**).

4.3.3 Indirect Effects on Vaccine-Type NP Carriage using PCV13:

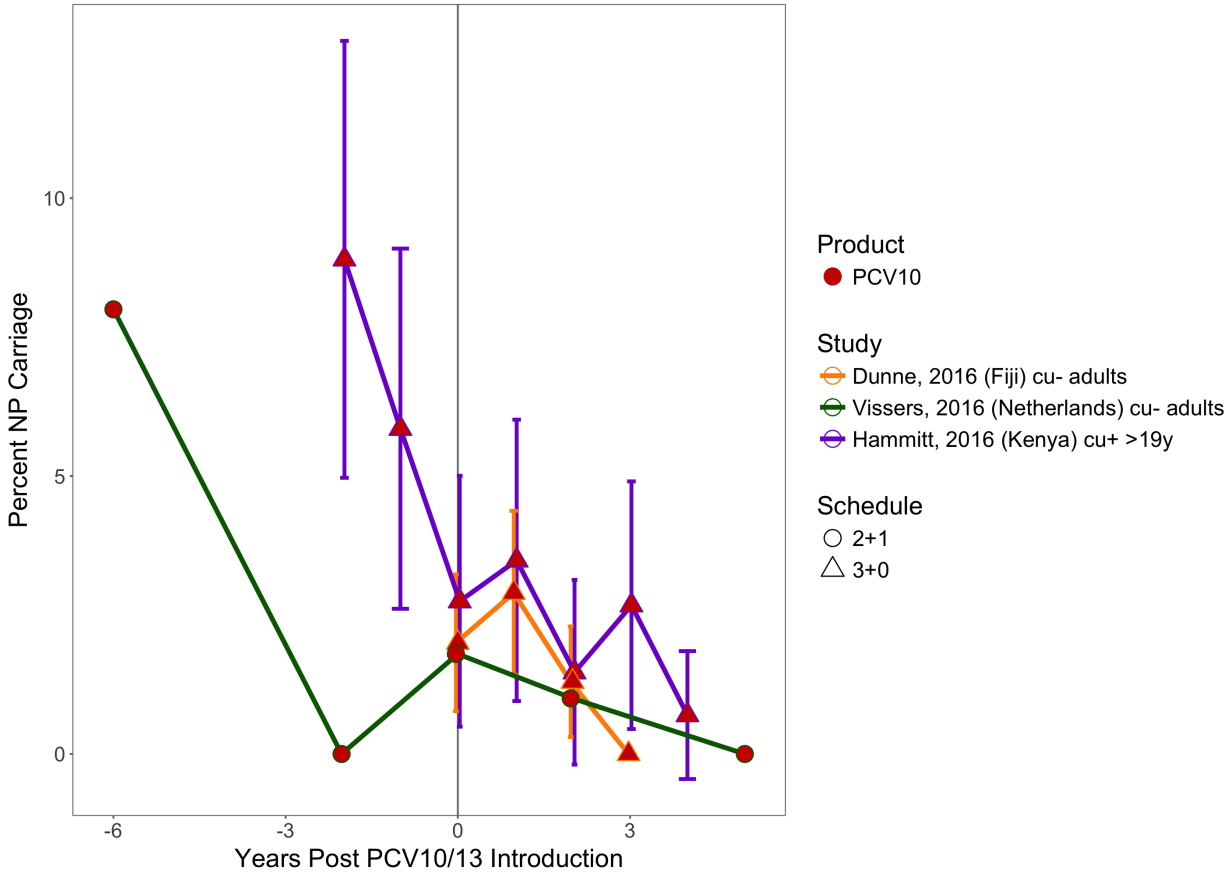
Only one unpublished study from the UK has data on VT carriage among persons over 5 after 5 years of PCV13 use. This study did find a significant reduction in the odds of carriage of the six additional serotypes in PCV13 in the PCV13 era compared to the pre PCV era. (Miller, personal communication, 2017)

Figure 50: Percent change in prevalence of PCV10 VT carriage compared to the pre PCV period by product



*Hammitt: years 0-4 post PCV10 averaged
**Vissers: prior use of PCV7
***Jokinen: control siblings, post year 3 vs. post year 1 for comparison

Figure 51: Carriage prevalence of PCV10 serotypes among adults in pre-post survey studies



4.3.4 Indirect Effects on Serotype 3, 6A, 6C and 19A NP Carriage using PCV10:

Two studies report on individual serotype carriage from PCV10 countries using a 2+1 schedule. In Finland, serotype 3, 6C and 19A have increased and 6A has decreased following PCV10 introduction, though the significance of these changes are not reported (**Figure 51 Figure 52, Figure 53** and **Figure 54**)[55]. In the Netherlands, there was a slight increase in serotypes 3, 6A and 19A combined during the PCV7 period, but these serotypes were not detected in parents sampled after 4.5 years of PCV10 use (**Figure 52**). [56]

Kilifi, Kenya is the only site with serotype-specific data on 3, 6A and 19A following PCV10 use with a 3+0 schedule. Individual serotype changes over time have not been found to be statistically significant among persons over 5 years of age (Scott, personal communication Dec 13, 2016). No serotype 6C has been detected in the Kilifi study (Scott, personal communication July 28, 2017).

4.3.5 Indirect Effects on Serotype 3, 6A, 6C and 19A NP Carriage using PCV13:

There are no studies with indirect effects data on NP carriage of serotypes 3, 6A, 6C and 19A following regular implementation of PCV13. Thus, no comparisons can be made with PCV10.

Figure 52: Carriage prevalence of individual serotypes before and after PCV10 introduction

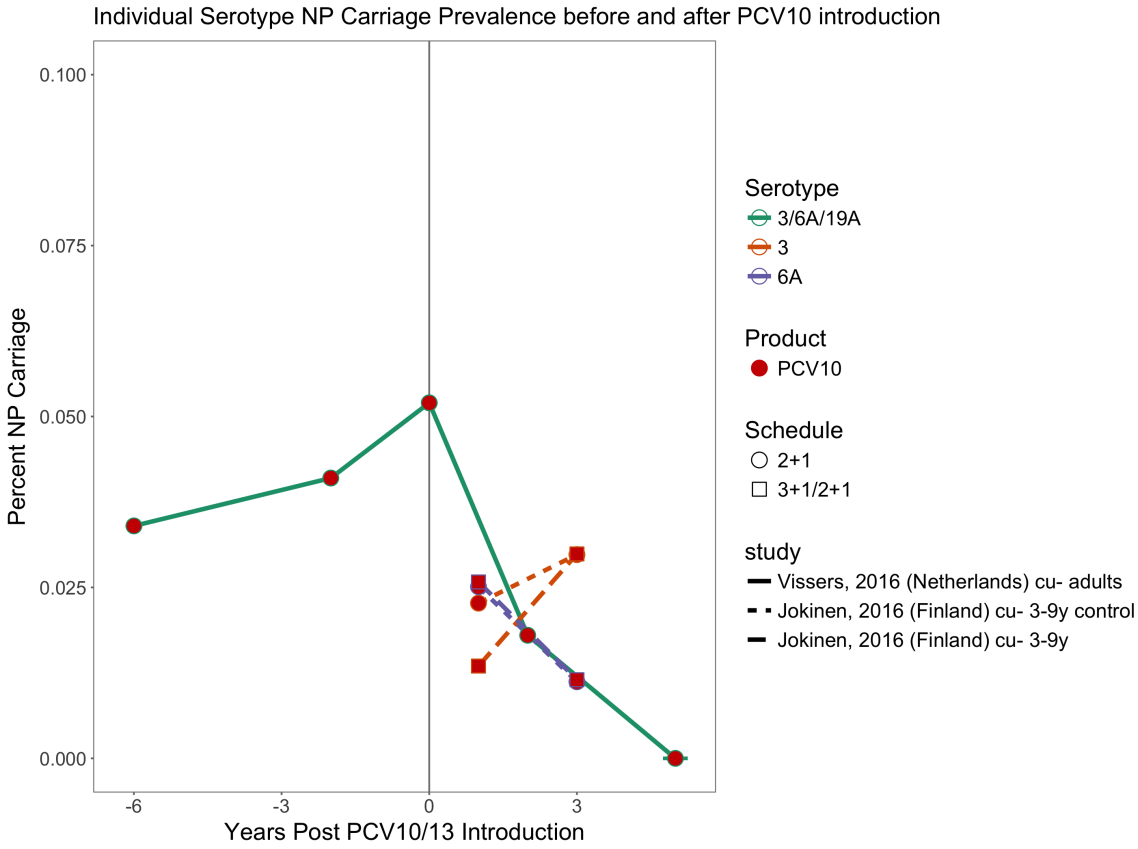


Figure 53: 19A carriage prevalence 1 to 3 years after PCV10 introduction

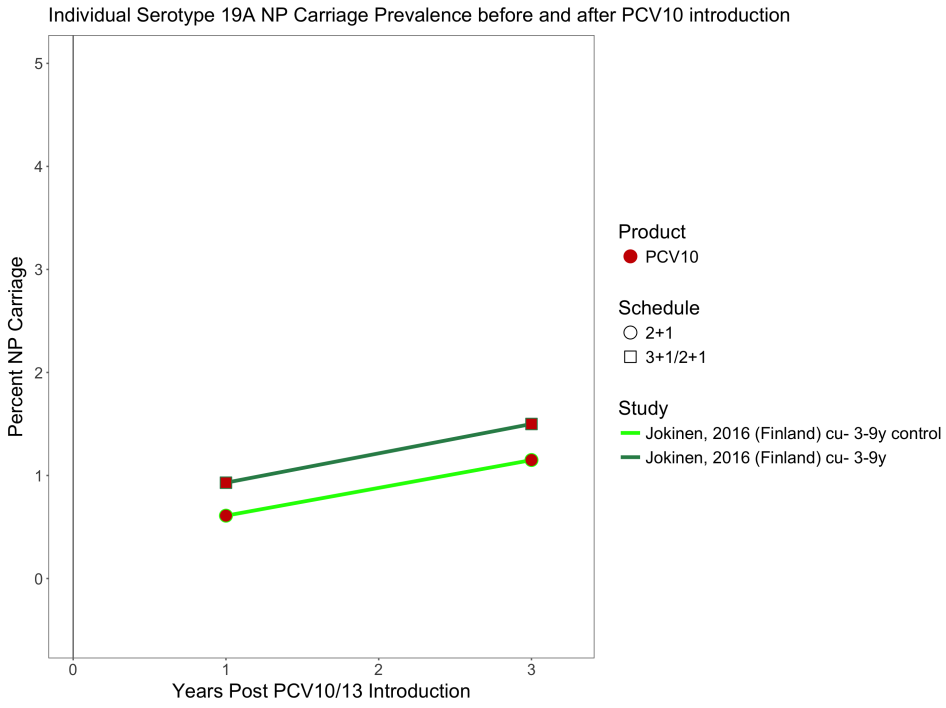
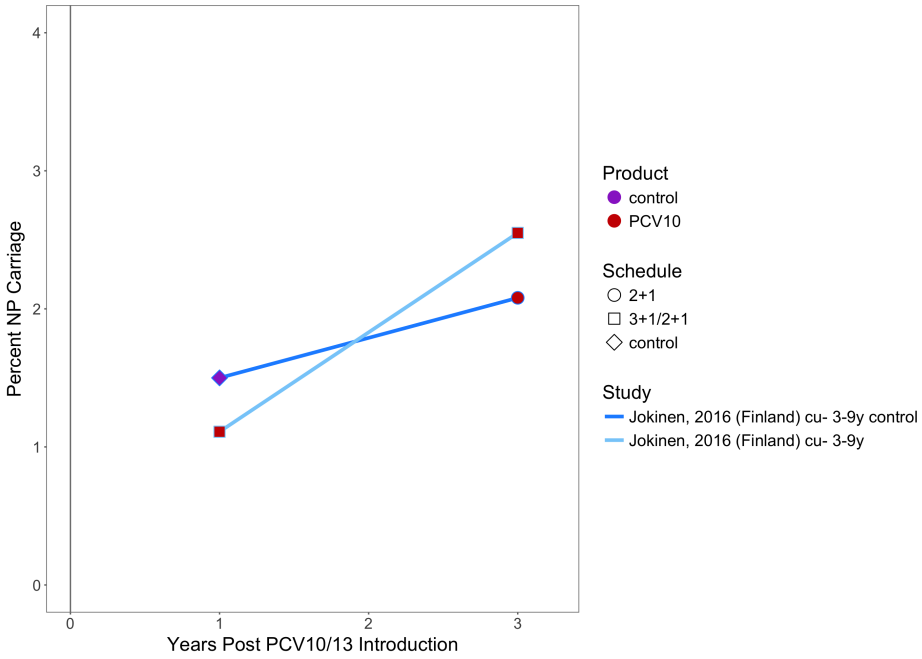


Figure 54: 6C carriage prevalence 1 to 3 years after PCV10 introduction



4.4 Invasive Pneumococcal Disease Direct Effects and Product Choice:

Study and serotype specific findings in this section can be found in **Annex B under TABLE IPD 1 – 22**. Results are reported in separate tables according to whether an impact was documents. The tables are color coded as: green for those studies with a statistically significant finding; yellow for those with a point estimate showing no impact or an impact that is not statistically significant; and red for those where the outcome of interest increased significantly. The findings are stratified by type of study (pre/post, or case-control effectiveness study), product, schedule and prior PCV7 use. Single product studies were assessed. No head to head studies were available comparing the two products.

4.4.1 Direct Effects on Vaccine-Type IPD:

Significant reductions in IPD caused by the ten shared serotypes included in each respective vaccine were observed following introduction of both products. The context of PCV10 and PCV13 introduction differ, limiting the ability to make quantitative impact comparisons across studies. Specifically, most PCV10 impact data are in countries which had not previously used PCV7, whereas only a very small proportion of PCV13 impact data are from non-PCV7 using countries. Available evidence indicates that both products induce statistically significant reductions in disease caused by most of the serotypes that are in PCV10/13 but not PCV7. For settings where PCV10 or PCV13 were used de novo, the evidence also demonstrated significant overall reductions in the vaccine serotypes.

Studies also indicate that both products reduce VT IPD in unvaccinated age cohorts. Available evidence indicates both products are effective in reducing the serotypes common to vaccines in both vaccinated and unvaccinated populations.

4.4.2 Direct Effects on Serotype Specific IPD:

4.4.2.1 Serotype 3 IPD:

Data on effectiveness of either product against ST3 IPD were limited.

Two impact studies (both from Finland)[116] [66]and one case-control effectiveness study (Brazil)[117] showed no impact of PCV10 on ST3 IPD, as expected since the vaccine does not contain ST3.

Studies assessing PCV13 impact on ST3 IPD showed mixed results, where the majority of the studies indicated no effect whereas two studies (England & Wales, 68% reduction (95%CI: 6,89%)[59] and France, 85% reductions (95%CI 36,96%)) [60] showed statistically significant reductions among the vaccinated age cohort, 2-4 years after introduction.

As expected there was no effect of PCV10 on ST 3 IPD in vaccine-eligible age groups. Evidence for direct reduction in ST 3 IPD following PCV13 was inconclusive. Evidence for or against increases in ST 3 IPD following PCV10 and PCV13 use are inconclusive

4.4.2.2 Serotype 6A IPD:

Limited data are available measuring impact or effectiveness of either product on ST 6A IPD in vaccine age eligible cohorts.

Effectiveness of PCV10 against type 6A IPD was not statistically significant in the single case-control study reported (Brazil)[117], while two reports from Finland reported significant reductions in ST 6A IPD rates, 4 and 5 years post PCV10 introduction[66, 70]. Data from Kilifi, Kenya suggest no impact on ST 6A IPD among children <5 years old 5 years post-PCV10 introduction (Scott, personal communication, 2017).

PCV13 was found to be effective against ST 6A IPD in the only reported case-control study (UK)[39]. Most studies measuring impact of PCV13 introduction on ST 6A IPD rate showed no significant reduction; however, all these studies were conducted in countries with previous PCV7 use where the ST 6A IPD rate had already been substantially reduced. There are no studies reporting ST 6A IPD rate changes following PCV13 without preceding PCV7 use.

PCV10 data are very limited and the benefit of including ST6A in PCV13 is difficult to determine. The low baseline rates due to prior PCV7 use make interpreting PCV13 data difficult because resulting impact should be attributed to PCV7.

4.4.2.3 Serotype 19A IPD:

Results of PCV10 effectiveness studies against ST 19A disease were mixed: while significant effectiveness was demonstrated in case control studies from Canada and Brazil[117, 118], no significant effectiveness was demonstrated in case control studies from Finland [119] and the Netherlands[120], or from an indirect cohort study from Brazil[121]. Two reports from Finland [66, 116] measured impact of PCV10 on ST 19A IPD rates 4

and 5 years post-PCV10 introduction and found significant reductions. However, this impact was no longer significant when a follow up analysis adjusted for pre-vaccine introduction decreases in ST 19A disease (Nuorti, personal communication, 2017)[71]. A study from Kilifi, Kenya found no reductions in 19A IPD disease rates in vaccine age eligible cohorts following PCV10 introduction (Scott, personal communication, 2017).

Significant reduction in type 19A IPD in vaccine age eligible cohorts following PCV13 introduction was reported in studies from England/Wales, France, Denmark, Israel, South Africa, and Australia [59, 60, 62, 63, 68], while non-significant reductions were reported from Sweden[72]. In addition, case control studies from UK, Canada, South Africa, Germany, and Taiwan reported significant effectiveness against type 19A IPD in vaccine age eligible children [112 39][122-125].

Effectiveness and impact against 19A IPD in vaccine age eligible children were demonstrated for PCV13. Effectiveness studies showed non-significant moderate to high reductions in ST19A IPD from PCV10 use; however, these studies were not powered to test significance. Impact studies did not indicate an impact from PCV10.

4.4.2.4 Serotype 6C IPD:

There were no studies available evaluating the effects of PCV10 on ST6C IPD

Studies from Sweden, England and Wales, Israel, and Australia found no impact of PCV13 on type 6C IPD, 3-4 years post-introduction[51, 59, 61, 72].

There is very limited data on PCV10 effects against type 6C IPD. Most studies show either significant or non-significant positive impact of PCV13 on ST6C IPD.

4.5 Invasive Pneumococcal Disease Indirect Effects:

IPD studies represent the bulk of the information that is available on the indirect effects of PCV10 and PCV13. Eighteen studies were included, most representing European countries using PCV13 in a 2+1 schedule. Fifteen studies are from countries using PCV13—two with a 3+0 schedule—and 3 studies are from PCV10 countries—all using a 2+1 schedule.

4.5.1 Indirect Effects on IPD Using PCV10:

Three studies from two European countries (the Netherlands and Finland) report on the indirect impact on PCV10 type IPD. While both these countries use a 2+1 schedule, the Netherlands had a period of PCV7 use and a prior period using a 3+1 schedule. In Finland, PCV10 was introduced *de novo* and the reduction in PCV10 type IPD has ranged between 41% and 70% in older children and adults after 2.5 to 5 years of PCV10 use [66, 126] (**Figure 55**). In the Netherlands, PCV7 type IPD decreased 78% to 89% overall in the PCV10 period compared to the pre PCV period, and IPD due to the additional 3 serotypes in PCV10 decreased 47% to 52% compared to the PCV7 period [127] **(Figure 59**).

4.5.2 Indirect Effects on Serotype Specific IPD:

There is no evidence of significant change in serotypes 3, 6A or 19A disease after PCV10 introduction in Finland and the Netherlands (**Figure 60 and Figure 61**) [66, 127]. Serotype 6A disease did not change significantly in children too old to be vaccinated in Finland and decreased slightly in the elderly in Finland and persons over 5 years of age in the Netherlands but significance was not reported [59, 61][128]. Only one study from the Netherlands reported on serotype 6C and the significance of the increase there in elderly >65 years is not reported (Annex B) (**Figure 63 and Figure 64**).

4.5.3 Indirect Effects on IPD Using PCV13:

The data on PCV13 IPD reduction is more robust, with data from different regions and schedule. Fifteen studies report on VT IPD in PCV13 countries, including 2 studies from countries using a 3+0 schedule (Australia and the Gambia). One study is from a region of Canada that switched from PCV7, to PCV10 and then PCV13 sequentially [73]. Compared to the pre PCV period, PCV13 IPD has decreased 48% to 80% in these countries, the exception being one study from the Gambia that found a 5% increase (not significant) in PCV13 disease 2.5 years after the transition to PCV13 among 5-14 year olds [74] (**Figure 56**). In countries that switched from PCV7 to PCV13, this reduction in VT IPD continued the trend from the PCV7 period, with continued reductions in PCV13 IPD ranging from 24% to 87% compared to the PCV7 period (**Figure 57**).

Serotypes unique to PCV13 decreased after transition to the higher valency PCV compared to the PCV7 period (**Figure 59**). The magnitude of these reductions ranged between 17% and 100%, with the exception of one study from Canada that reported a 15% increase in PCV13-nonPCV7 disease in the elderly >64 years [73]. The reduction in the 6 additional serotypes in PCV13 reversed increases in these serotypes that were found in some countries during the era of PCV7 use, so the overall change in additional VT serotype disease has been variable compared to the pre PCV era **(Figure 58**).

4.5.4 Indirect Effects on Serotype Specific IPD:

Serotype-specific findings were also assessed following PCV13 introduction with data from ten studies representing seven countries.

4.5.4.1 Serotype 3 IPD

Indirect effects of PCV13 on serotype 3 IPD were varied, with two studies recording statistically significant decreases and other studies reporting no significant change (**Annex B TABLE IPD Ind Eff 2**). [59, 73, 129]

4.5.4.2 Serotype 6A IPD

Reduction in 6A IPD after PCV13 introduction is more consistently reported compared to the PCV7 period. Following PCV13 use, UK, Denmark, South Africa and Australia all reported reduction in 6A IPD, with UK and Australia reporting statistical significance in >5 year olds and ≥50 year olds, respectively. [59, 68, 69, 130]

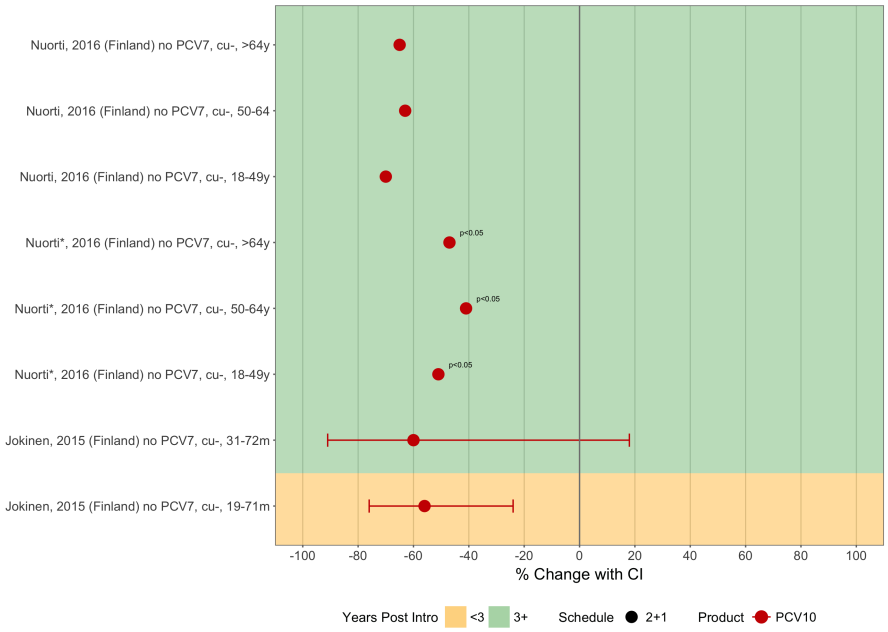
4.5.4.3 Serotype 19A IPD

Results from studies assessing PCV13 indirect effects mostly showed reductions in 19A IPD , with significant decreases reported in the UK, Australia and Canada in the PCV13 era compared to the PCV7 era [59, 69, 73]. In Denmark, a decrease in 19A has also been documented, but significance was not reported [68]. In contrast to the aforementioned studies, an Irish study reported an increase in 19A most abruptly in 2015 but the significance of this finding and the completeness of case ascertainment are not reported (**Figure 60 and Figure 62**) (**Annex B TABLE IPD Ind Eff 2**) [75].

4.5.4.4 *Serotype 6C IPD*

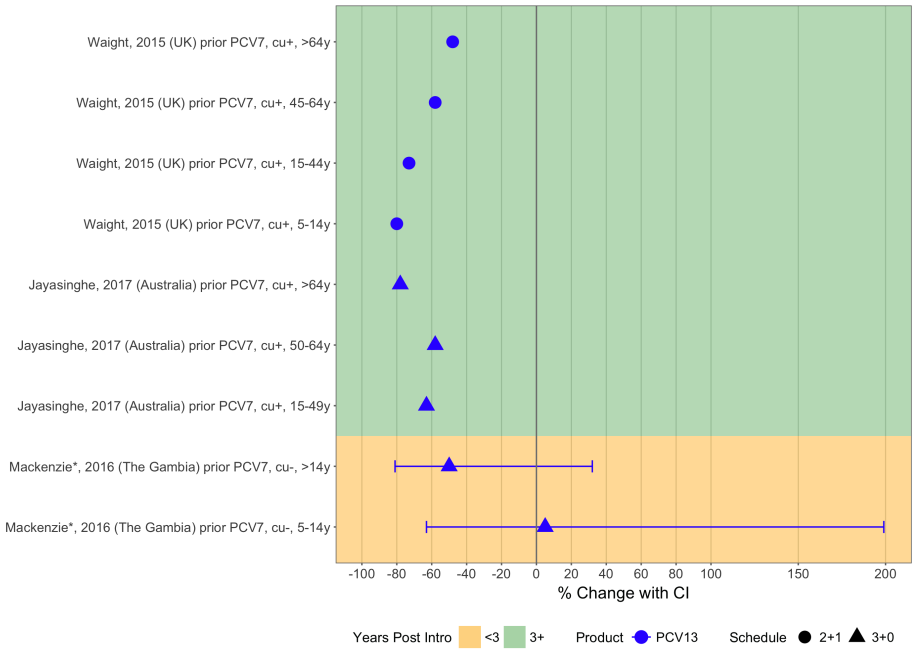
No significant impact on 6C disease has been reported compared to the PCV7 era in three PCV13 studies from the UK, Israel and Australia with the exception of a 34% decrease in 6C disease (95% CI 7%, 56%) among Australians over 65 years (**Figure 63 and Figure 65**)[59, 69, 131].

Figure 55: Impact on PCV10 IPD types vs pre PCV period



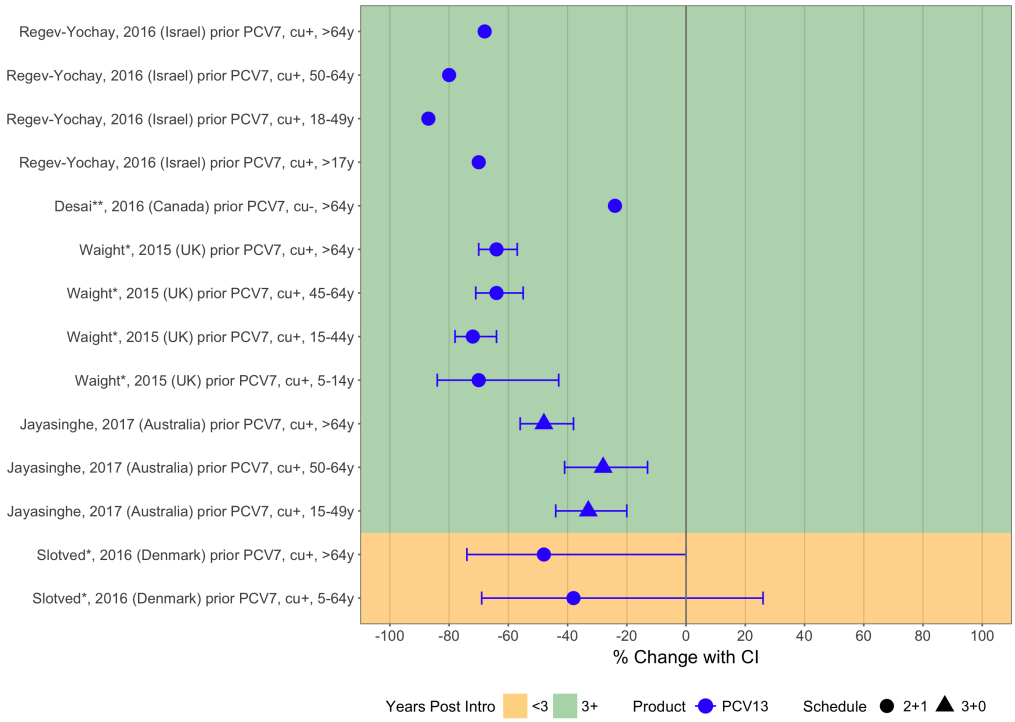
* Post PCV10 data are an average rate combining all PCV10 years

Figure 56: Impact on PCV13 IPD types vs pre PCV period



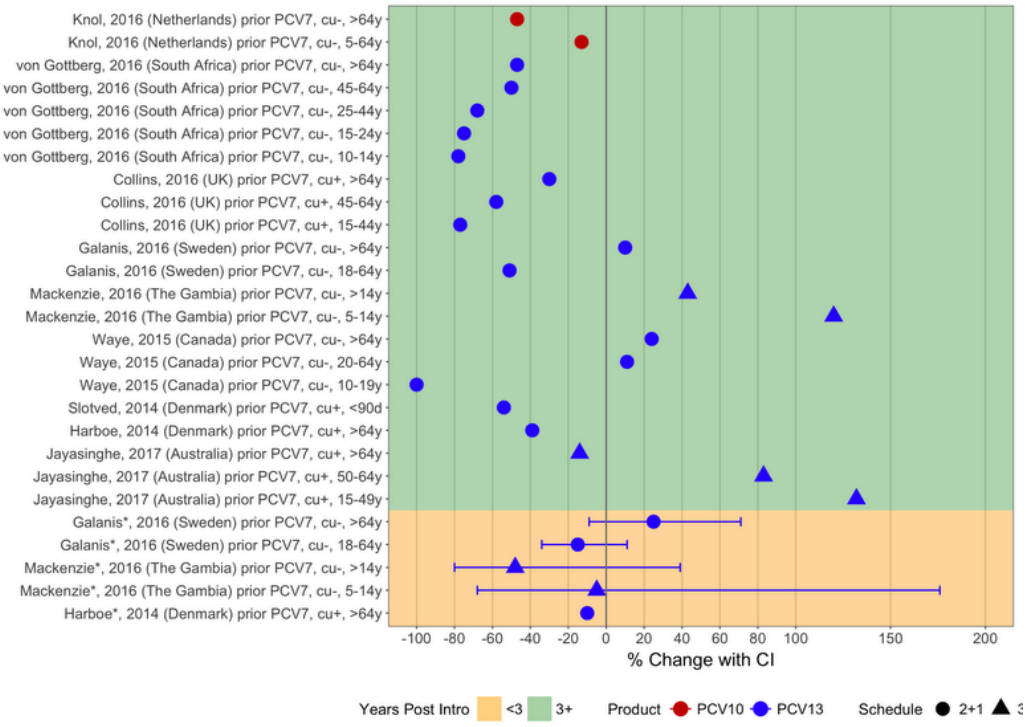
* Post PCV10 data are an average rate combining all PCV10 years

Figure 57: Impact on PCV13-type IPD vs PCV7 period



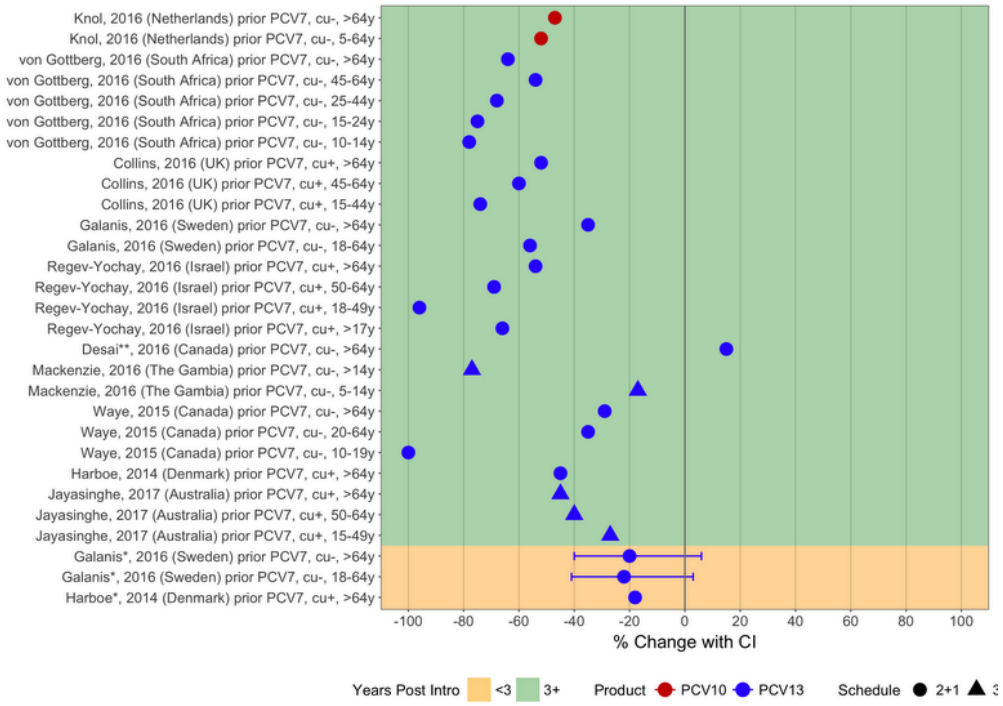
*Post PCV13 data are an average rate combining all PCV13 years
**Country with PCV13 use following interim period of PCV10 use

Figure 58: Impact on PCV13 or PCV10 unique IPD types vs pre PCV period



*Post PCV13 data are an average rate combining all PCV13 years

Figure 59: Impact on PCV13 or PCV10 unique IPD types vs PCV7 period



*Post PCV13 data are an average rate combining all PCV13 years
**Country with PCV13 use following interim period of PCV10 use

Figure 60: Impact on serotype 19A IPD vs PCV7 period

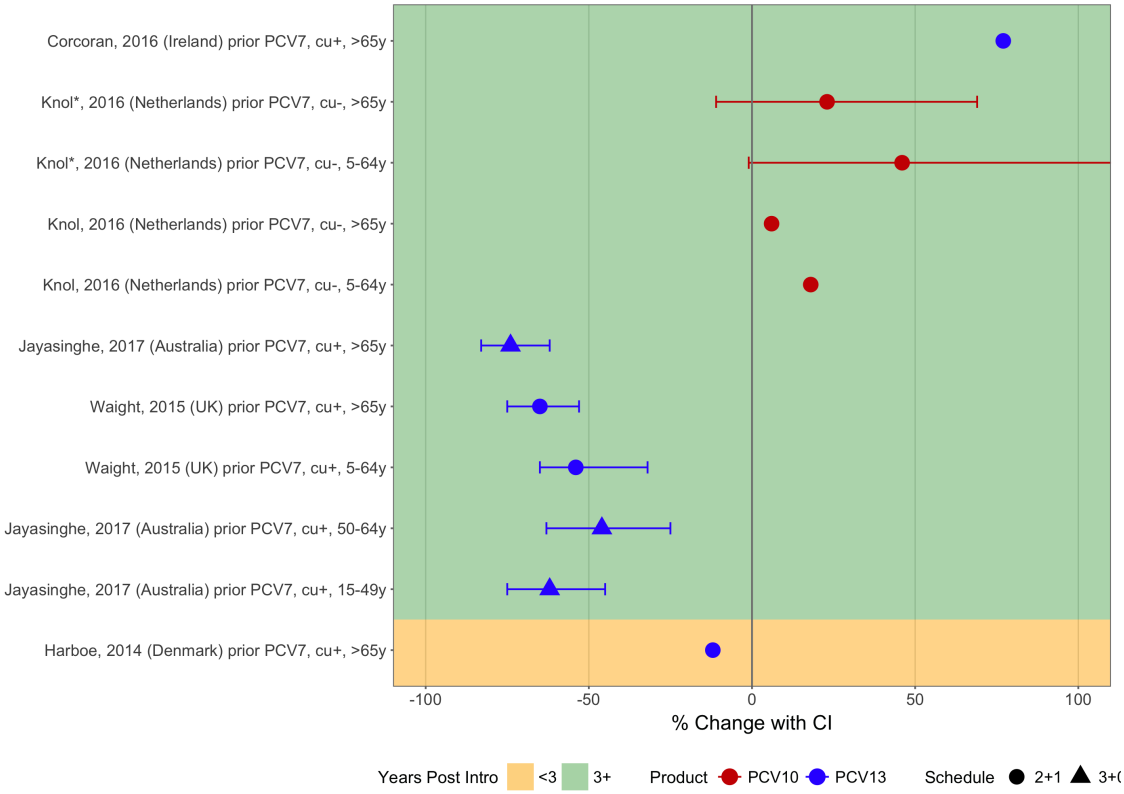


Figure 61: Serotype 19A IPD incidence before and after PCV10 introduction

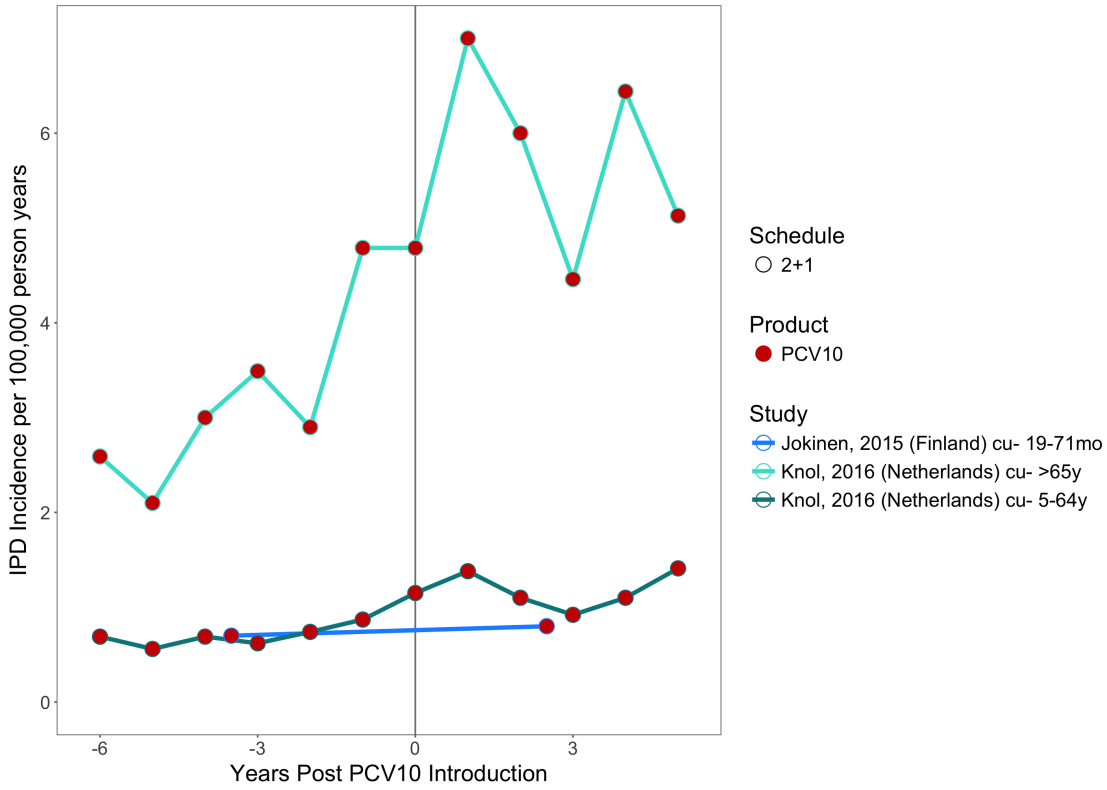


Figure 62: Serotype 19A IPD incidence before and after PCV13 introduction

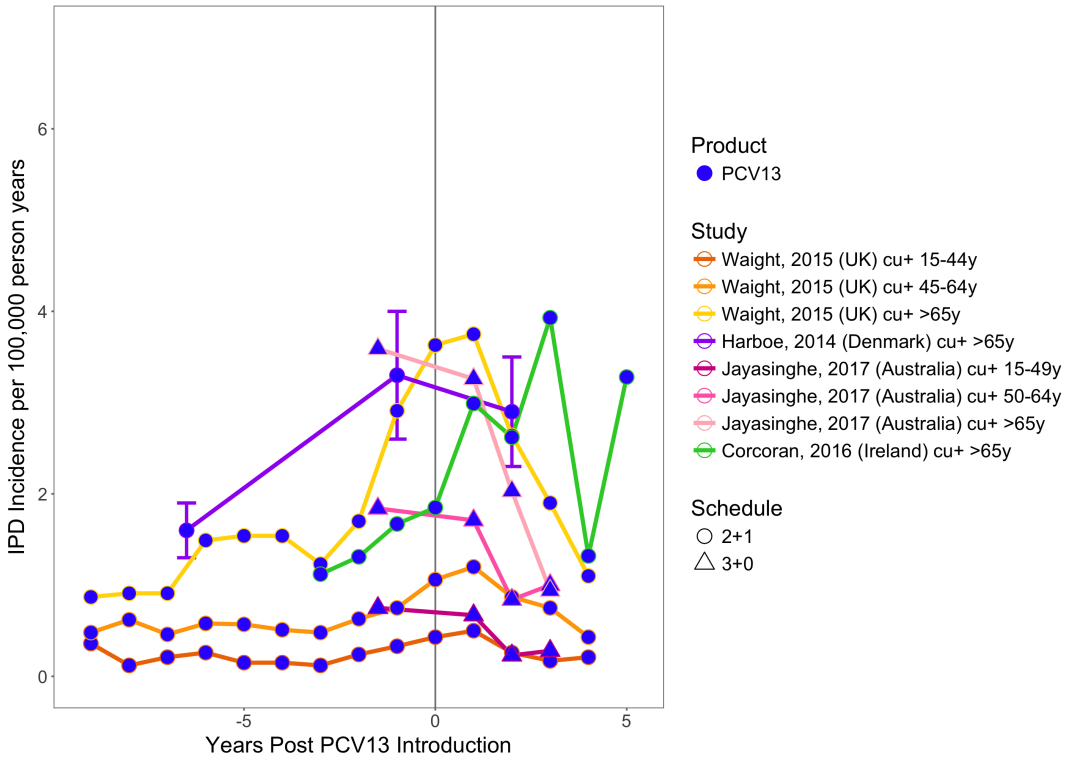


Figure 63: Impact on serotype 6C IPD vs PCV7 period

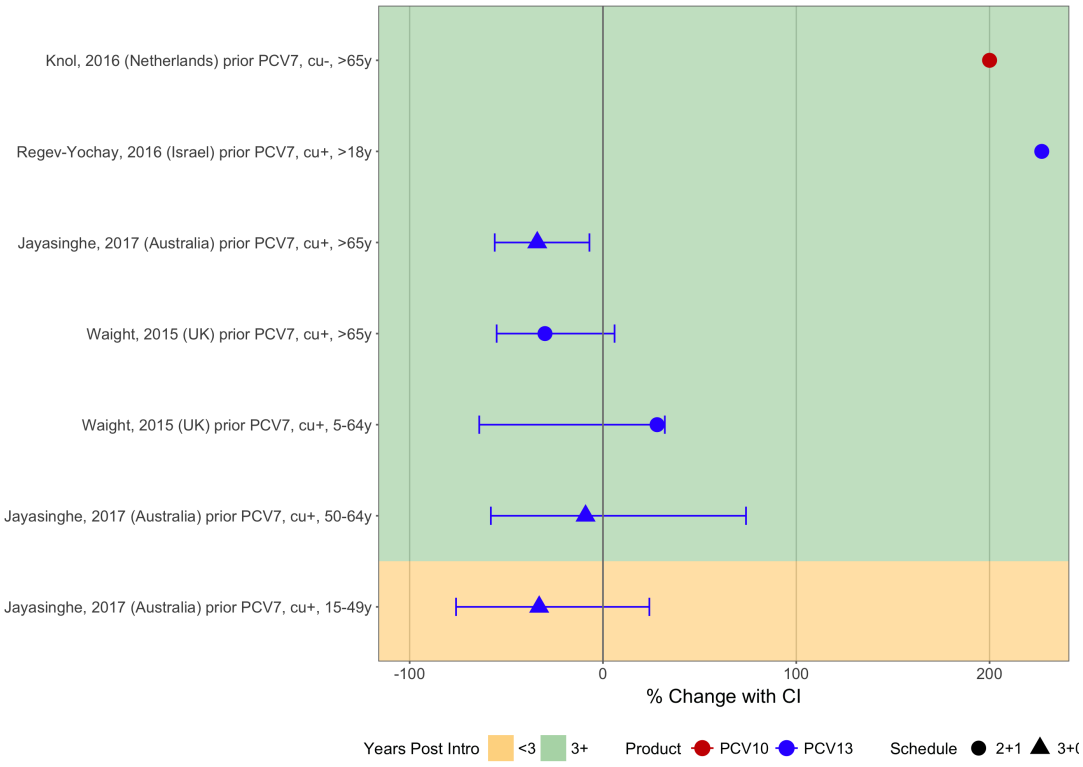


Figure 64: Serotype 6C IPD incidence before and after PCV10 introduction

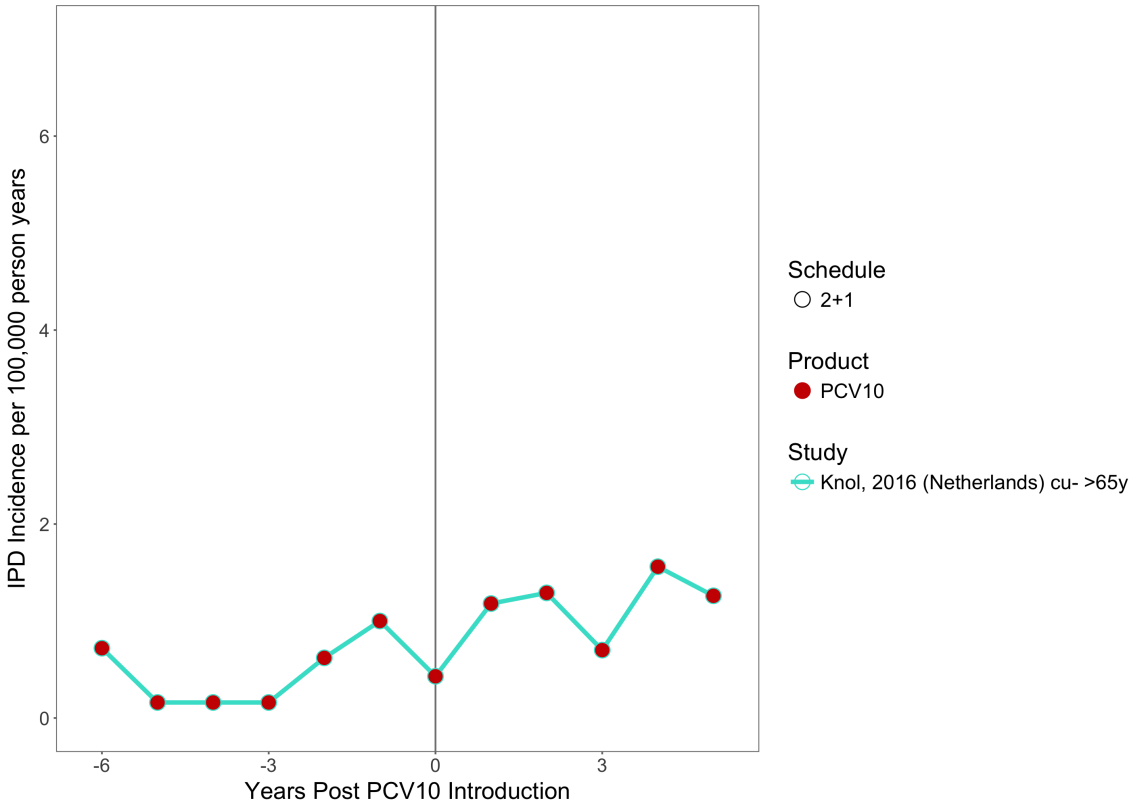
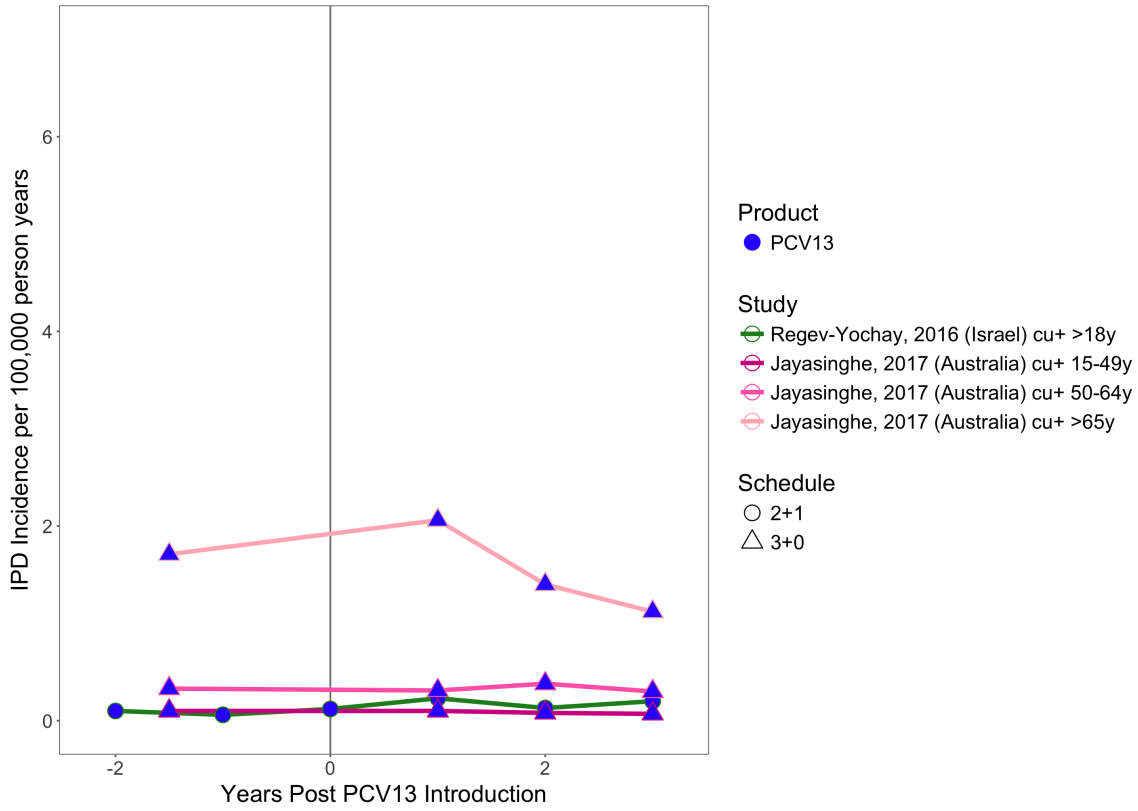


Figure 65: Serotype 6C IPD incidence before and after PCV13 introduction



4.6 Pneumonia Direct Effects and Product Choice:

4.6.1 Direct Effects on Pneumonia: RCTs:

There was one randomized controlled trial evaluating PCV against pneumonia [3]. The Finnish study evaluated PCV10 using a 2+1 schedule and showed 28% (6% - 45%) efficacy against clinical pneumonia and 43% (19% - 61%) efficacy against consolidated pneumonia.

There were no clinical trials that evaluated either a 3+0 schedule or PCV13.

4.6.2 Direct Effects on Pneumonia: Case Control Studies:

All five case-control studies evaluated PCV13 [5, 6, 8, 74, 76]; there were no studies that evaluated PCV10. Three of five studies were from Africa (**Annex B TABLE Pneumo 1**). Three studies evaluated 2+1 schedules and vaccine effectiveness ranged from 20.1% to 40.6% for ≥ 2 doses against radiologically-confirmed pneumonia and 68% against bacteremic pneumonia; all measures were statistically significant [6, 8, 76]. Two studies evaluated 3+0 schedules, both from Africa [5, 74]. Vaccine effectiveness for a 3+0 schedule ranged from 58% to 63% against radiologically-confirmed pneumonia, but none were significant. The study in Togo found an 80% effectiveness for a 3+0 schedule against severe pneumonia, but this was not statistically significant [5].

4.6.3 Direct Effects on Pneumonia: Pre/Post Observational Studies using PCV10:

There were five studies that evaluated 2+1 schedules against clinical pneumonia in children <2 years with reductions ranging from 13% to 36% compared to the pre-PCV period[78-81]. Three studies evaluated 3+0 schedules with changes in clinical pneumonia incidence ranging from reductions of 13.3% to 35% compared to the pre-PCV period; all reductions were statistically significant[18, 19, 25]. There were two studies using a 3+0 schedule that showed reductions of 15% and 48% in radiologically-confirmed pneumonia[18, 25]. One study evaluated PCV10 against pneumococcal pneumonia or empyema and found 77% and 3% reductions, respectively, although the reduction in empyema was non-significant [79].

4.6.4 Direct Effects on Pneumonia: Pre/Post Observational Studies using PCV13:

There were 12 studies using a 2+1 schedule that evaluated a clinical pneumonia endpoint[10, 17, 23, 24, 31, 78, 83, 84, 87-89, 91]. For children <2 years, reductions ranged from 7% to 58% compared to a pre-PCV baseline period and all reductions were statistically significant. Compared to the PCV7 period, changes in incidence ranged from +8% to -60.5%, with statistical significance varying. One study evaluated a 3+0 schedule against clinical pneumonia + hypoxemia in children <5 years and found a non-significant 47% reduction. [103]

There were 8 studies using a 2+1 schedule [9, 84, 90, 92-96] and one study [102] using a 3+0 schedule that evaluated a radiologically-confirmed pneumonia endpoint. For 2+1 schedules, in children <2 years, reductions ranged from 34% to 66.2% and all reductions were significant. Compared to the PCV7 period, reductions ranged from 38% to 48% and significance varied. In children <5 years, reductions ranged from 33% to 53% compared to pre-PCV era; all reductions were significant. For the study that evaluated a 3+0 schedule, significant reductions (range: 26% to 33%) were seen in all age groups.

Three studies evaluated pneumococcal pneumonia; the studies from Argentina and Italy evaluated a 2+1 schedule and found 70% reductions in disease in children <5 years (72.1% v. baseline [10] and 70% v. PCV7 period, respectively[97]. The study from the UK found a 75.1% reduction in disease in children <2 years compared to baseline and a 24.5% reduction compared to the PCV7 period [88].

Four studies evaluated 2+1 schedules against empyema; effectiveness estimates and significance varied [89, 91, 92, 98]. No studies evaluated 3+0 schedules against empyema.

4.6.5 Direct Effects on Serotype Specific Empyema:

This review identified one study [98] that reported serotype-specific results for the impact of PCV13 on empyema. The study found non-significant reductions in empyema caused by serotypes 1 and 3 and a non-significant increase in empyema caused by serotype 19F compared with the PCV7 era.

4.7 Pneumonia Indirect Effects and Product Choice:

Indirect effect data on pneumonia are still limited and results are more variable than for IPD and NP carriage, in part due to the variability in clinical pneumonia outcomes assessed. Many studies were excluded based on having fewer than three years of post PCV10/13 use or because they presented data on age groups that included both direct and indirect effects mixed together. The longest time period after PCV10/13 introduction reported on was 4 years. One Finnish study with less than 3 years of data (median range of 2.5 years) post PCV10 was kept in the analysis as it demonstrated differences in the first year post-PCV10 compared to years 2

and 3, which were analyzed separately, and because it looked at children just ahead of the vaccinated birth cohort in a setting without use of catch up[79].

4.7.1 Indirect Effects on Pneumonia Using PCV10:

Five studies from PCV10 countries were included in this analysis: two countries where PCV10 was introduced *de novo* (Finland [79, 132] and Kenya [101, 105]) and one Swedish study where PCV7, PCV13 and PCV10 were used sequentially [133]. In Finland and Sweden (n=3 studies), PCV10 is used in a 2+1 schedule; and in Kenya (n=2 studies), a 3+0 schedule is used. Clinical pneumonia decreased 5-18% compared to the pre PCV period in 3 studies with *de novo* PCV10 use, and two of these studies report the decrease to be significant (**Figure 66**). In Sweden, where there was an interim period of PCV7 and PCV13 use, the relative reduction in clinical pneumonia after 3 years of PCV10 use compared to the PCV7 period ranged between 6% and 25% (**Figure 68**).

Only one study reported on radiographically confirmed pneumonia from Kenya and found a non-significant reduction of 11% in children 5-12 years old after 4 years of PCV10 use [101].

Two studies reported on pneumococcal pneumonia after 2.5 to 3 years of PCV10 use and found significant reductions of 70% to 94% [79, 105](**Figure 69**).

4.7.2 Indirect Effects on Pneumonia Using PCV13:

Data from five PCV13 countries all using a 2+1 schedule was available, reporting on clinical pneumonia (n=4 studies) and pneumococcal pneumonia (n=2 studies). One of these countries (Canada [104]) switched from PCV7 to PCV10 and then PCV13, all other countries switched only from PCV7 to PCV13. Compared to the pre PCV period, clinical pneumonia decreased 17% to 59% in all settings but one (Italy) where it increased 14% in adults over 80 years [83](**Figure 67**). Compared to the PCV7 period, clinical pneumonia changes ranged between a 67% decrease and a 57% increase, thus findings were very inconsistent between and even within studies (**Figure 68**).

Findings on pneumococcal pneumonia were more consistent, though very limited in number of studies reporting. Reductions in pneumococcal pneumonia due to all serotypes was reported ranging from 39% to 40% in two PCV13 studies compared to the PCV7 period [131, 134] (**Figure 70**). One study also reported separately on PCV7 VT pneumococcal pneumonia and pneumonia due to the six additional PCV13-nonPCV7 serotypes, both of which decreased in incidence by 79% and 41%, respectively, compared to the PCV7 period [134].

Figure 66: Countries without prior PCV7 use, PCV10

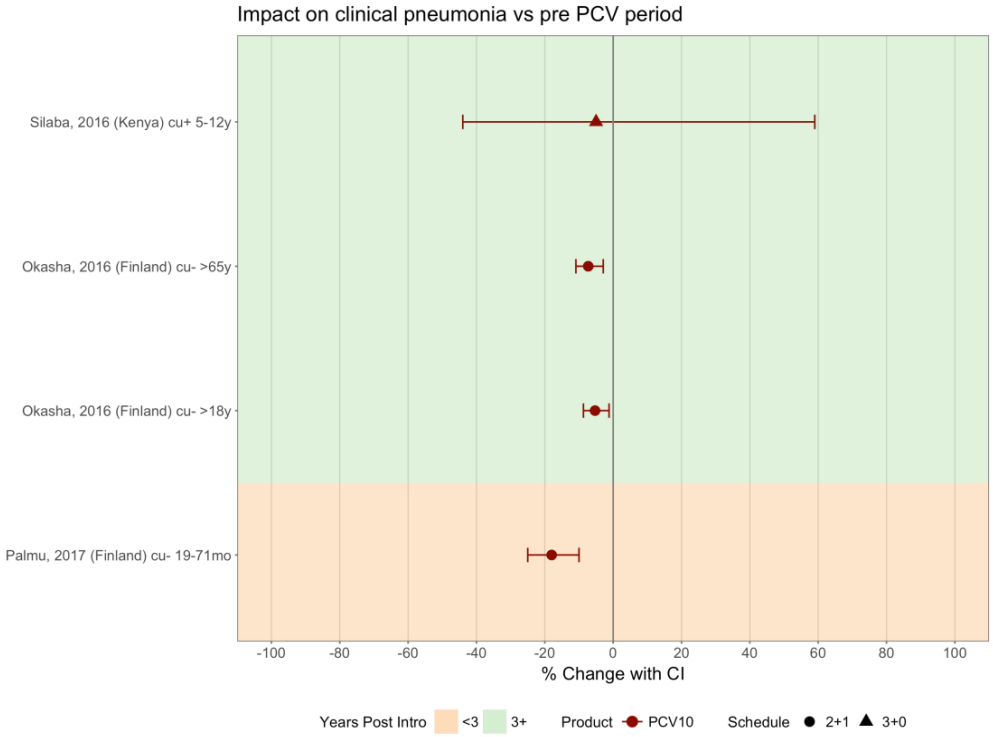
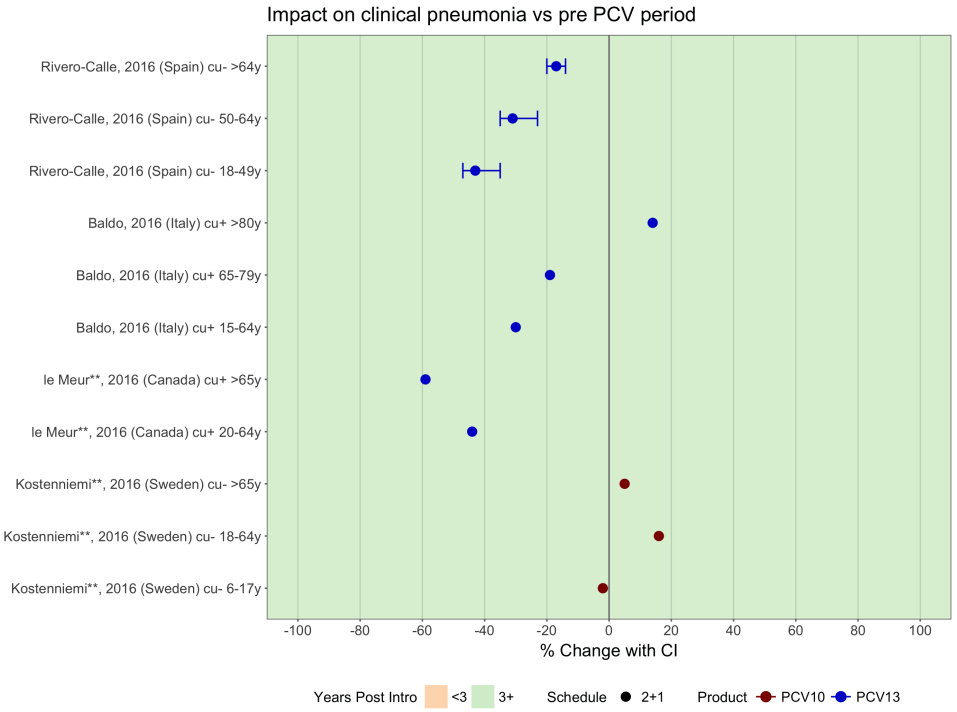
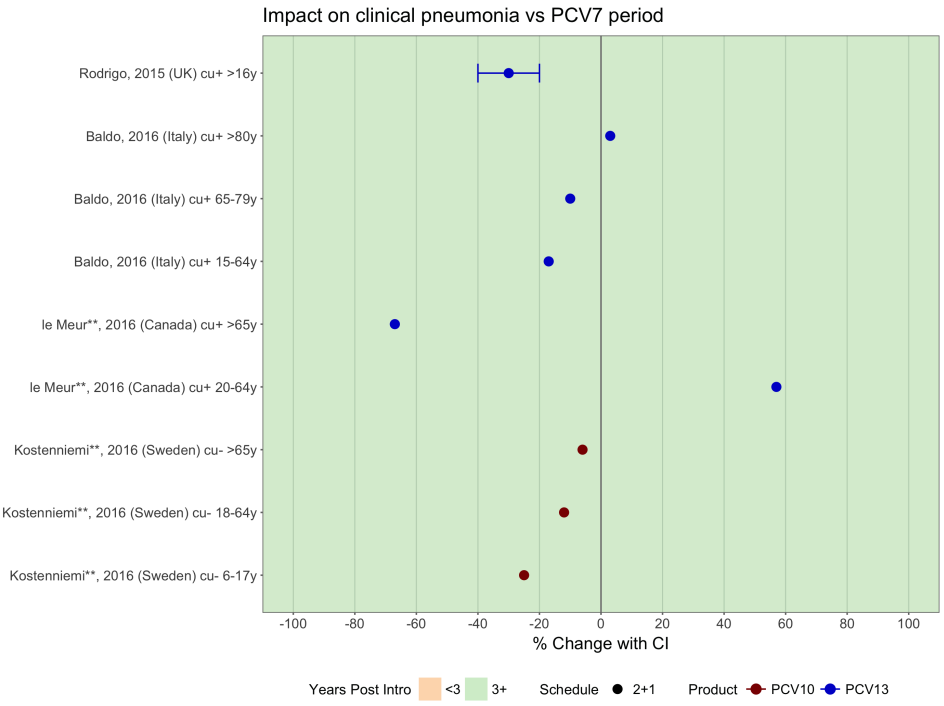


Figure 67: Countries with prior PCV7 use, PCV10 vs. PCV13



**le Meur (Canada): switched from PCV7 to PCV10 and then PCV13
**Kostenniemi (Sweden): switched from PCV7 to PCV13 and then PCV10

Figure 68: Impact on clinical pneumonia vs PCV7 period, PCV10 vs. PCV13



**le Meur (Canada): switched from PCV7 to PCV10 and then PCV13
**Kostenniemi (Sweden): switched from PCV7 to PCV13 and then PCV10

Figure 69: Countries without prior PCV7 use, PCV10

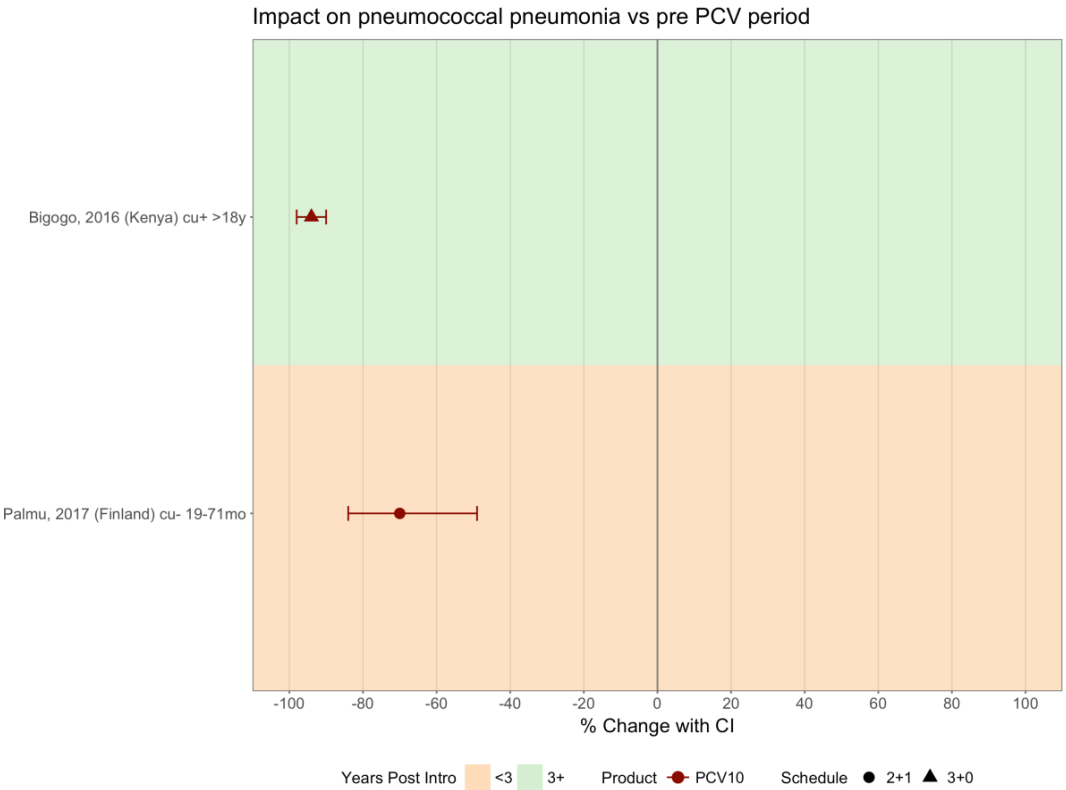
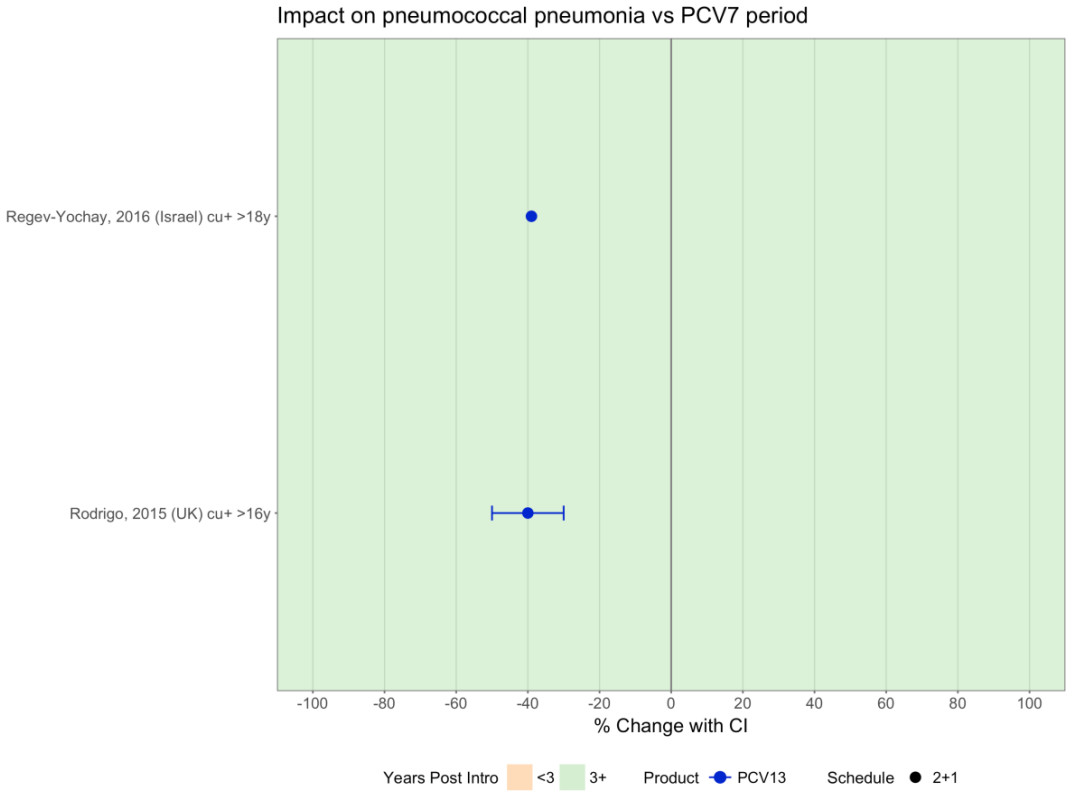


Figure 70: Impact on pneumococcal pneumonia vs PCV7 period, PCV13



5.0. PICO 3: VALUE OF CATCH-UP VACCINATION IN VACCINE NAÏVE CHILDREN IN ADDITION TO THE BIRTH COHORT:

EXECUTIVE SUMMARY:

I. Immunogenicity:

Schedule:

- Head-to-head evidence suggests 2 doses are more immunogenic than 1 dose in children 12-24 months of age (there was no head-to-head in older age groups). While one dose was immunogenic, in recipients of 2 doses, a greater proportion achieved the correlate of protection for a broader range of serotypes. In single-schedule trials, there was high %response for both schedules for most serotypes, but 2-doses may produce higher response than 1-dose for STs 6B and 23F and for 19A when using PCV10.

Product:

- In the head-to-head trial that directly compared immunogenicity of PCV10 to PCV13 in children 12-48 months of age with a one dose catch-up schedule, higher responses were observed in PCV13 recipients than in PCV10 recipients for most serotypes in common and for the serotypes in PCV13 but not in PCV10, and four serotypes (3, 6A, 6B, 23F) had <90% of subjects above the correlate of protection for PCV10 while no serotypes had <90% for PCV13. In single-product trials, higher responses were observed in PCV13 trials than in PCV10 trials for most serotypes in common and for the serotypes in PCV13 but not in PCV10, but the differences were not large.

II. NP Carriage Direct Effects:

- Four studies (n=1 head-to-head randomized controlled trial, n=1 single-arm trial, n=1 'head-to-head' observational study that compared communities with and without catch-up, and n=1 observational pre-post study) provided data on NP colonization prevalence in directly immunized children outside the vaccine-targeted age range of NIP schedules.
- The clinical trials provide some evidence that vaccination may produce a reduced prevalence of VT carriage in the age strata vaccinated. This may be a combination of direct effect from the single PCV dose plus any indirect effects from immunizing the birth cohort in the community, if the direction of transmission is from younger infants to older siblings or contacts. The large observational study (Kilifi, Kenya) observed rapid declines in VT carriage the first year of PCV10 use but in the same country the observational head-to-head study comparing two communities (Kibera and Asembo, Kenya), one with catch-up and one without, did not observe meaningful differences in VT carriage (although there was potentially some confounding due to differences in the communities).

III. NP Carriage Indirect Effects:

- With limited data from different regions, income strata and years after introduction, no conclusions can be drawn on the indirect impact of catch up vaccination programs on VT carriage. The Kenya data suggests that, in the setting of catch up, significant reductions can be seen in VT carriage by year 2.

IV. IPD Indirect Effects

- A number of factors, including variability in the number of years post PCV10/13 introduction as well as regional differences in serotype distribution and disease epidemiology, make it difficult to draw any conclusions about the indirect impact of catch up campaigns on the incidence of VT IPD.

V. Pneumonia Indirect Effects:

- No firm conclusions can be drawn on the impact of catch up campaigns on the incidence of pneumonia in vaccine non-eligible age groups.

FINDINGS:

5.1 IMMUNOGENICITY AND CATCH-UP:

5.1.1 BACKGROUND:

The 2012 Pneumococcal Vaccine position paper recommends 2 catch up doses at an interval of at least 2 months to unvaccinated children 12-24 months and children 2-5 years who are at high risk of pneumococcal infection. No recommendation statement was made regarding non-high-risk children 2-5 years of age. The purpose of this analysis was to assess the optimal catch up schedule for children not considered high-risk between the ages of 12 and 59 months of age.

Table 4: Inclusion and Exclusion Criteria for studies assessing the Immunogenicity of 1 or 2 Dose Catch-Up

Inclusion Criteria	Exclusion Criteria
IgG or % responder (% above the cut-off of 0.35 [or 0.20 if a GSK lab]) data available after 1 or more doses received in children 12-59 months of age, inclusive (i.e., 0+1, 0+2 or 0+3).	High risk population
If the trial did not have a non-PCV comparison group, then must have pre/post results or fold-change reported	Prior vaccination with any pneumococcal vaccine
Received PCV10 or PCV13	

5.1.2 Findings:

There were 11 studies included in the analysis. Only 0+1 and 0+2 catch up schedules were found that assessed PCV10/13 in children >12 months of age (**Annex B: TABLE Imm 3**). This landscape analysis was limited to serotypes: 1, 3, 5, 6A, 6B, 7F, 14, 19A, 19F, and 23F. In order to analyze impact on immunogenicity in the 2-5-year-old cohort, previous exposure to pneumococcus was considered by calculating fold-rise in GMC as: postdose1 GMC/predose1 GMC or postdose2 GMC/predose1 GMC. In addition, the proportion of subjects above the correlate of protection after vaccination (0.35 mcg/mL, or 0.2 mcg/mL if GSK lab analysed the samples) was compared to the proportion of subjects above the correlate of protection at baseline. Ten studies with 28 PCV10/13 arms provided pre- and post-vaccination data for these comparisons.

Overall general findings: Compared to pre-vaccine levels, antibody concentrations (GMC) increased following immunization with either PCV10 or PCV13, using either a 1-dose or a 2-dose catch-up regimen. The immunogenicity response was almost always greater with 2 doses than with 1 dose, with magnitude varying by product and serotype. However, this dose-effect analysis is confounded by age in that children who received a 0+1 catch-up dose were older at vaccination (87.5% were over 2 years) than children who received a 0+2 catch-up (7% were over 2 years). A 1-dose schedule in children 12-24 months of age may not produce the

same level of immune response as 1 dose in older children. Studies were also confounded by product as there were no PCV10 1-dose arms evaluating STs 6A, 6B, 14, 19F or 23F.

Details on the impact of schedule (0+1 vs 0+2) and product are described in the sections below.

5.1.2.1Schedule (0+1 VS 0+2 Catch-Up Doses):

HEAD TO HEAD TRIALS:

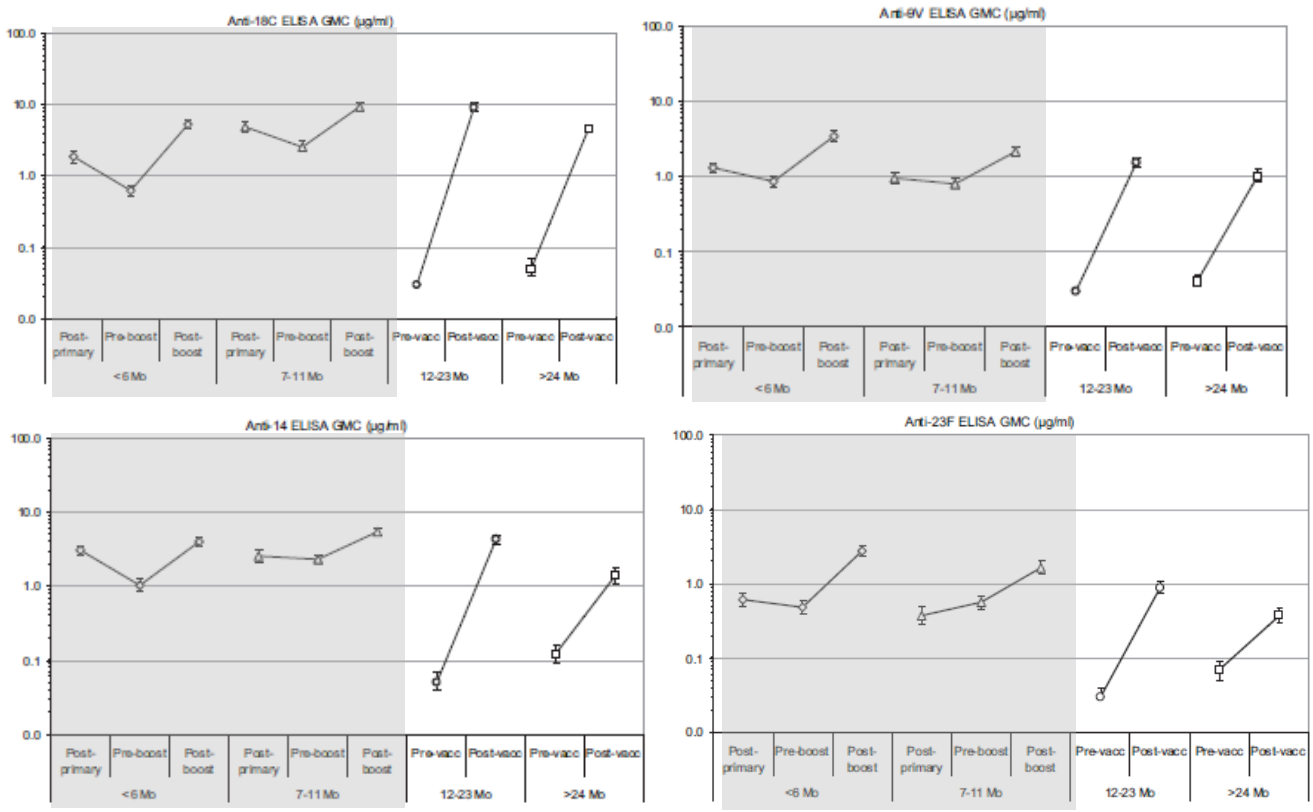
Fold-rise in GMC:

Two studies evaluated both a 0+1 and a 0+2 schedule: one study evaluated similarly aged children (PCV13 in children 12-15 months of age, Burkina Faso; Moisi, Personal Communication, 2017) and the other evaluated 2 doses in children 12-23 months vs 1 dose in children 24-59 months (PCV10, Finland; Vesikari 2011)[135].

In the Burkina Faso trial that evaluated numbers of doses in similarly aged children, fold-change in serotype specific antibody concentration was at least 2 times higher following 2 doses as compared to 1 dose for all evaluated serotypes, but the 1-dose schedule produced at least a 4-fold rise for all evaluated serotypes, with the exception of a 3.6 fold-rise for serotype 5 (**Figure 72**). Note, however, that antibody was measured 3 months after immunization in the 1-dose arm compared to 1 month after in the 2-dose arm, which may underestimate a comparable antibody level in the 1-dose arm. A third arm in the Burkina Faso study evaluated fold-rise amongst children 2-4 years old that received a single dose; their pre-vaccination antibody levels were higher than those in the younger (12-15 months) children, especially for serotypes 5, 6A, 6B and 19A. The vaccine elicited less than a 4-fold rise (1.7-3.9 fold) for these four serotypes (>4-fold rise was observed for all other serotypes evaluated) while only ST5 did not have a 4-fold rise in the younger children. This illustrates the impact of age at dosing on antibody response, which is relevant in interpreting results of studies in which the number of doses administered differed by age of the child, as in the Finnish study.

In the Finnish trial (Vesikari 2011), toddlers (12-23 months) received 2 doses of PCV10, while children aged 2-5 years of age received one dose of PCV10. A significant rise in GMC was observed for all VT serotypes as well as 6A and 19A for both doses, but GMC was significantly higher with 2 doses (12-23 mo.) than with 1 dose (>24 mo) for serotypes 9V, 14, 18C and 23F (**Figure 71**, Vesikari 2011)[135].

Figure 71: Vesikari 2011 "Figure 2": Pre-vaccination and post-vaccination 22F-ELISA GMCs (log scale) 1-Dose (>24 mo) and 2-Dose (12-23 mo) Catch-up



Proportion Above Correlate of Protection:

In the Burkina Faso trial (Moisi, Personal Communication, 2017), more serotypes had >90% of subjects above the correlate of protection (IgG>0.35 ug/mL) after 2 doses than after 1 dose; the actual proportion above the correlate of protection was also generally higher following two, rather than one dose. In the 0+1 arm, assessed 3 months after vaccination, the proportion of children with serotype specific antibody concentrations above the correlate of protection increased for all serotypes, from a range across STs of 1-68% pre-PCV to 67-100% post-PCV. For all serotypes >90% of children had an antibody concentration above the correlate of protection except 3 (67%), 6B (81%) and 23F (77%). By comparison, in the 0+2 arm for all serotypes except serotype 3 (80%) more than 90% of children had antibodies above the correlate of protection, as measured 1 month after the second dose. For all serotypes, the proportion above the correlate of protection was at least 5% greater after 2 doses than after 1 dose for all but five serotypes (5, 7F, 14, 18C, and 19A) which all had 98-99% above the correlate of protection in the 1-dose arm. Over 95% of participants had IgG>0.35 ug/mL for all serotypes except serotype 3 (83% above the correlate of protection) after vaccination.

In the Finnish trial (Vesikari, 2011), although none of the differences between 1 and 2 doses are likely significant for any serotype, there is a pattern across serotypes of higher response with 2 doses compared to 1 dose: 6 of 10 serotypes evaluated had a greater proportion above the correlate of protection, 3 serotypes observed 100% for both doses, and 19F was higher for 1 dose (100% 1 dose vs 98.5% 2 doses)[135]. However,

there is correlation across serotypes that could account for some of this consistency of direction in that a child with a low concentration for one serotype is more likely to be low for all serotypes. But there was heterogeneity across serotypes in the magnitude of the difference suggesting it goes beyond the influence of autocorrelation and the additional dose may increase IgG for some serotypes, specifically 23F and 6B, two serotypes where the 2nd dose consistently makes a difference; the proportion above the correlate of protection for serotype 23F was: 12–23 mo pre-vaccination=4.5% (1.7–9.6%) and post-dose-2=91.7% (85.7–95.8%) compared to 24-59 mo pre-vaccination=22.9% (16.2–30.7%) and post-dose-1=66.9% (58.4 –74.6%); for serotype 6B it was: 12–23 mo pre-vaccination=3.0% (0.8 –7.5%) and post-dose-2=81.2% (73.5– 87.5%) compared to 24-59 mo pre-vaccination=26.3% (19.1–34.5%) and post-dose-1=68.6% (60.2–76.1%)[135].

SINGLE SCHEDULE TRIALS

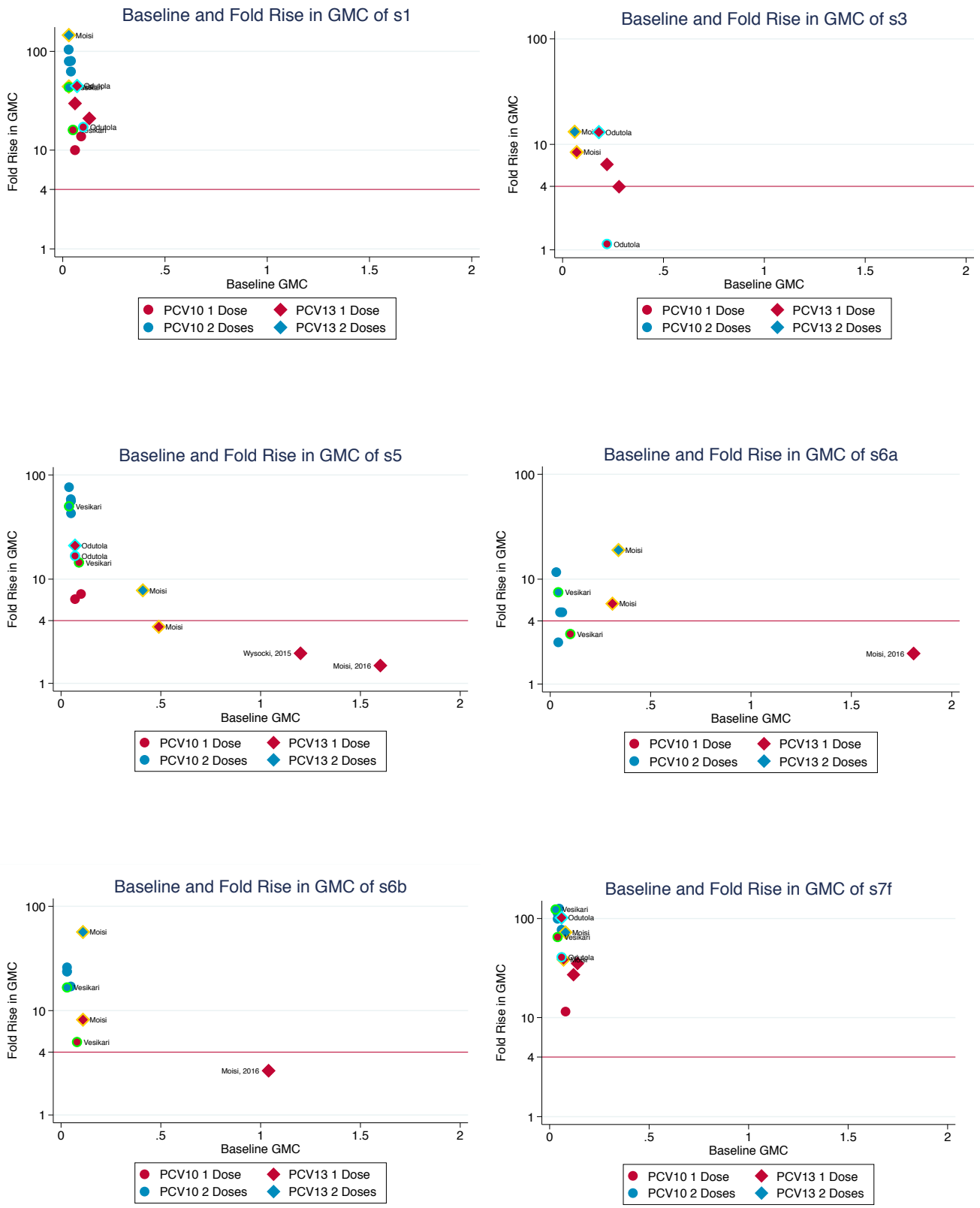
Nine single-schedule trials were found. Eight trials with 9 PCV10/13 arms provided baseline and post vaccination data to evaluate either a 0+1 (3 PCV10 and 2 PCV13) or a 0+2 (4 PCV10) catch-up schedule. Results from single-schedule trials are shown combined with results from the head-to-head trials in **Figure 72**.

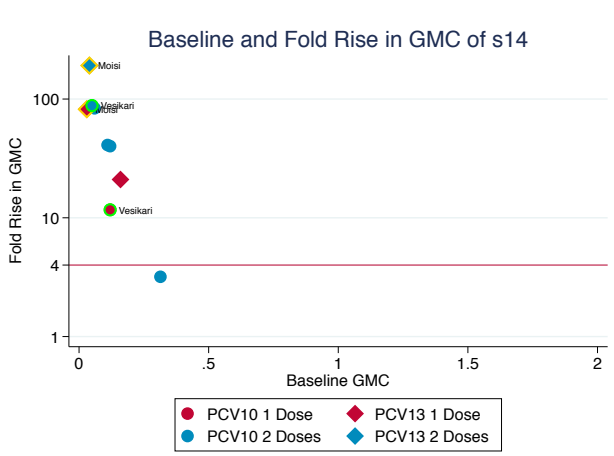
Fold-rise in GMC:

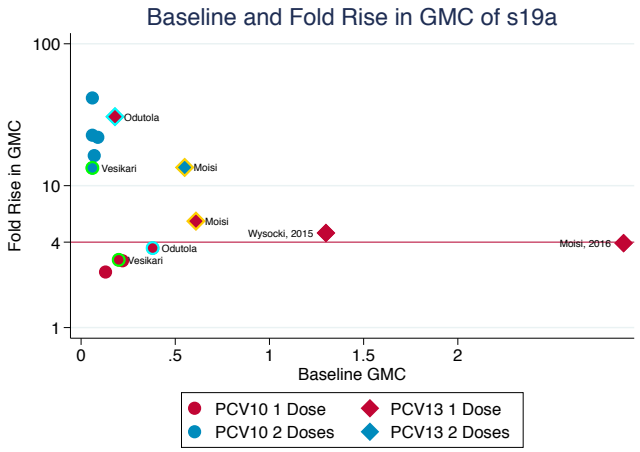
While most 1-dose schedules (red points) produced increases in GMC of at least 4-fold for all serotypes contained in the product evaluated, in general fold-change was greater for 2-dose schedules (blue points) than for 1-dose schedules after accounting for pre-dose1 GMC (**Figure 72**). Fold change in 0+2 arms exceeded 4-fold for all arms for all STs except one study for ST14 (PCV10). In 0+1 arms, serotypes 3, 6A, 6B, 19A, and 23F all had at least one study with less than a 4-fold change. When fold-change did not exceed 4-fold, either the pre-dose1 GMC was already higher than the threshold (0.35 or 0.2 for GSK labs) or the serotype was not covered by the vaccine (e.g., ST6A for PCV10). ST3 was difficult to assess as there was only one 2-dose arm (from the head-to-head trial) but it did have higher fold-change than 4 of 5 1-dose arms. ST6A, ST6B and 23F were also difficult to assess as only 1 single-schedule trial evaluated a 1-dose schedule (in children 2-4y) and they had unusually high pre-PCV titres (third arm in Moisi 2016 head-to-head trial described above). One study in Venezuela, which is not included in the figures (no pre-PCV13 data provided), reported ≥7-fold-rises for all PCV13 serotypes for children 24-59 months who received 1-dose and ≥16-fold-rises for all PCV13 serotypes for children 7-23 months who received 2-doses [136].

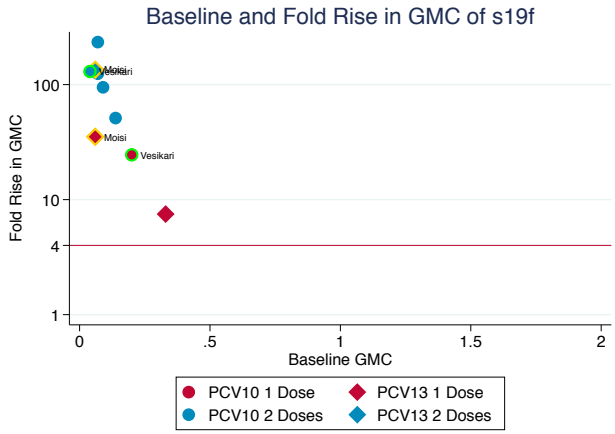
Caveats: This dose-effect analysis is confounded by age in that children who received a 0+1 catch-up dose were older at vaccination (87.5% were over 2 years) than children who received a 0+2 catch-up (7% were over 2 years). A 1-dose schedule in children 12-24 months of age may not produce the same level of immune response as 1 dose in older children. Studies were also confounded by product as there were no PCV10 1-dose arms evaluating STs 6A, 6B, 14, 19F or 23F. Lower GMCs pre-dose1 were also associated with higher fold changes for both products and schedules. Two PCV13 studies (both 1-dose schedules) had high pre-dose1 GMC values resulting in lower fold changes. Serotypes 1, 5, 7F, 14 and 19F generally had higher fold change values than serotypes 3, 6A, 6B, 19A, 23F.

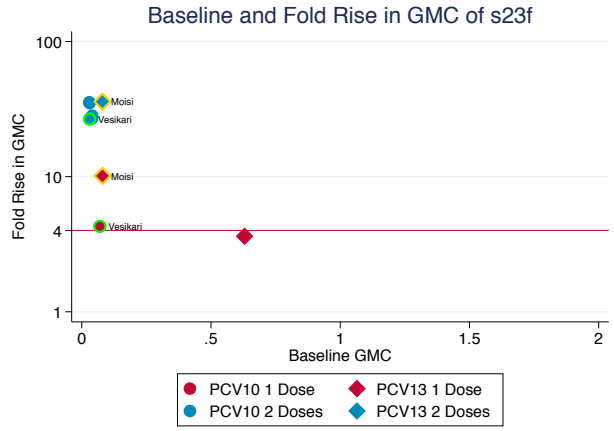
Figure 72: Pre-vaccination ('Baseline') vs Fold Rise of 1-Dose and 2-Dose Catch-up











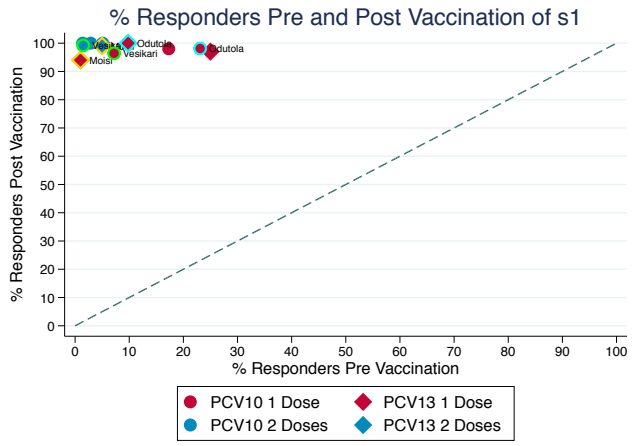
Footnote: Red points denote a 1-dose schedule and blue denotes a 2-dose schedule. PCV10 studies are coded as a circle and PCV13 studies are coded as a diamond. Red line represents 4-fold increase in GMC. Outline colour denotes head to head studies: Gold – Moisi, 2017; Green – Vesikari 2011; Blue – Odutola, 2014.

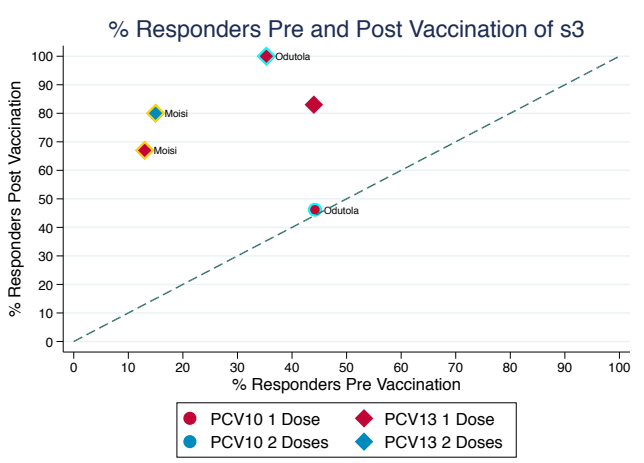
Proportion Above the Correlate of Protection:

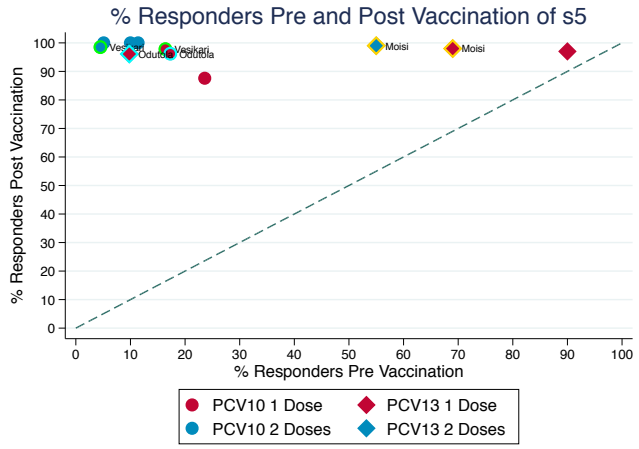
The change in the proportion of subjects with antibody concentrations above the correlate of protection comparing the pre-PCV to post-PCV values, varied by serotype and schedule (**Figure 73**). Generally, there were no differences between a 1 or 2 dose catch up schedule for serotypes 1, 3, 5, 6A, 7F or 19F although data were limited. A larger proportion of subjects reached the correlate of protection with a 2-dose schedule for serotypes 6B and 23F. For 19A, all 1-dose PCV13 arms had very high (>99%) response and for PCV10 arms the response to 19A appeared equivalent between the two schedules. For serotype 14, 1-dose arms of PCV13 had a very high response while for PCV10 2-doses (>99% response) appeared better than 1-dose (90%), but there was only one 1-dose PCV10 trial.

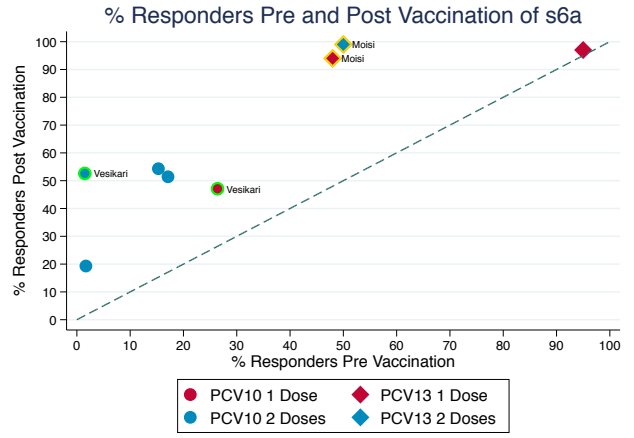
For all study arms evaluated, serotypes 1, 5, 7F, 14, and 19F all had a high proportion (>90%) of subjects with antibodies above the correlate of protection compared to serotypes 3, 6A, 6B, 19A and 23F where there were multiple study arms with <90% of subjects above the correlate of protection.

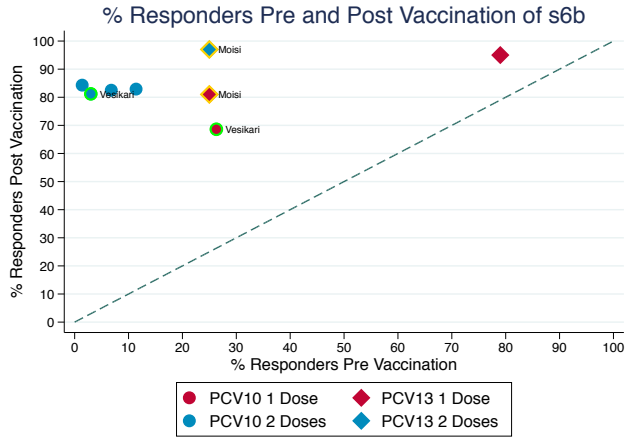
Figure 73: Percent of subjects above the correlate of protection Pre and Post Vaccination

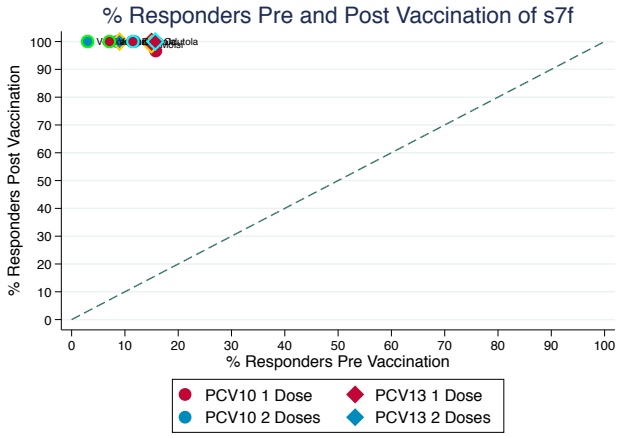


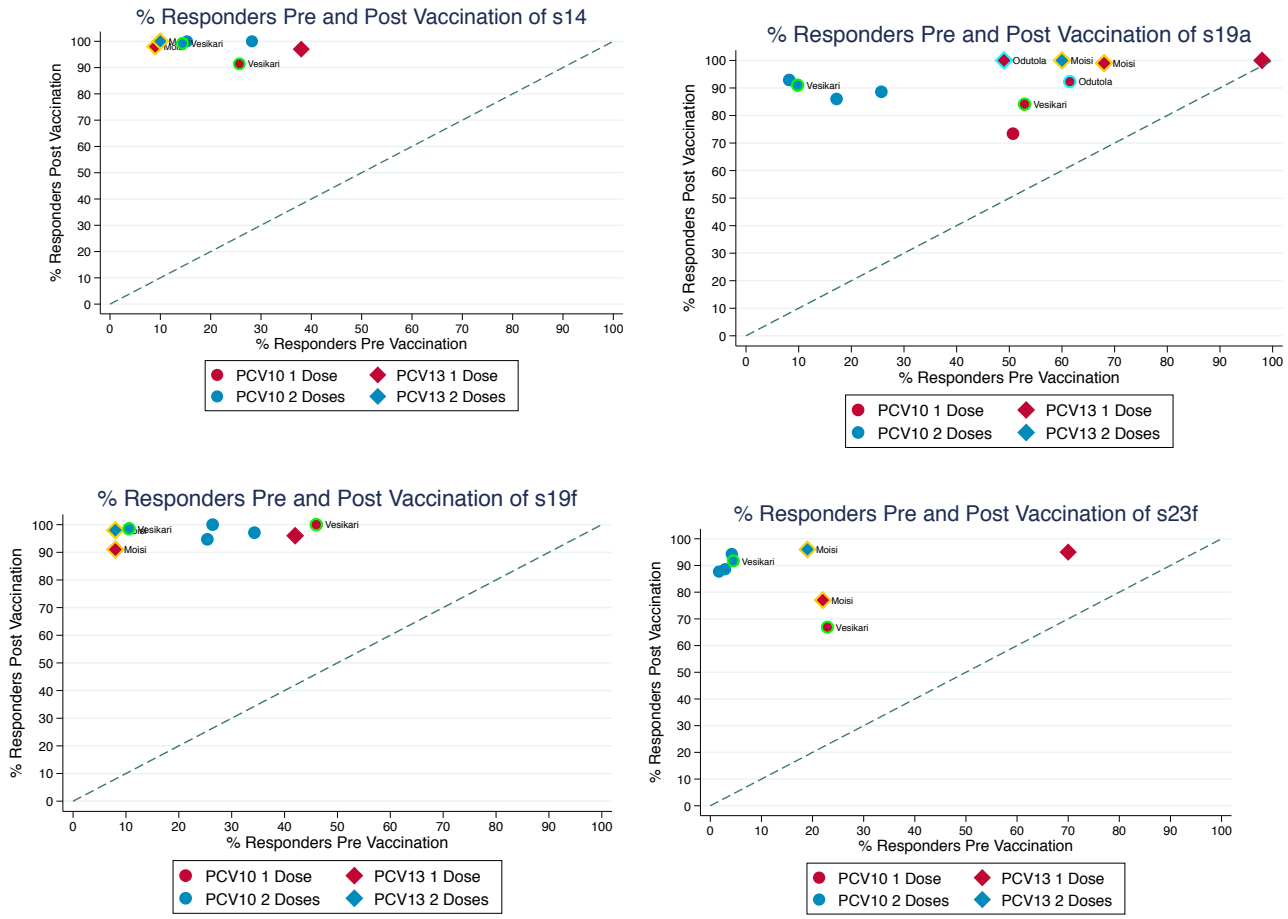












Footnote: Red points denote a 1-dose schedule and blue denotes a 2-dose schedule. PCV10 studies are coded as a circle and PCV13 studies are coded as a diamond. Blue dashed line represents no change in % of subjects above the correlate of protection pre/post. Outline colour denotes head to head studies: Gold – Moisi, 2017; Green – Vesikari 2011; Blue – Odutola, 2014.

5.1.2.2 Product:

Head to Head Trials:

There was one study that directly compared immunogenicity of 1 dose of PCV10 to PCV13 in children 12-48 months of age (The Gambia; Odutola, 2015)[137].

Fold-rise in GMC:

GMCs increased significantly for all serotypes contained in each vaccine for both products. GMCs were higher for PCV13 recipients than PCV10 recipients for serotypes 1, 6B, 7F, 9V, 14, and 23F, while PCV10 had higher GMCs for serotypes 18C and 19F. PCV13 recipients had increases for all serotypes 3, 6A and 19A that are in PCV13 but not included in PCV10, while PCV10 recipients had a significant increase only for serotype 19A which was lower than that for PCV13.

Proportion Above the Correlate of Protection:

The proportion of subjects above the correlate of protection increased from pre-PCV to post-PCV and was >90% for all serotypes contained in each vaccine following vaccination with 1 dose for both products, except serotypes 6B (80.8) and 23F (65.4%) in PCV10-vaccinated children. The proportion above the correlate of protection was higher for PCV13 than for PCV10 for serotypes 6B and 23F, two serotypes where a 2nd dose consistently makes a difference, and for serotypes 3, 6A and 19A which are not included in PCV10.

SINGLE SCHEDULE TRIALS:

Fold-rise in GMC:

After considering effects of schedule and pre-dose1 GMC across the STs evaluated in common (1, 5, 6B, 7F, 14, 19F and 23F), PCV13 had higher fold-change responses than PCV10 for most studies; exceptions were serotypes 5 (insufficient data), 7F (equivalent), 19F (insufficient data) and 23F (equivalent) (**Figure 72**). For serotypes 6B and 14, data were very limited (i.e., based on comparison to just one study). However, the differences were not large (a 2-dose schedule of PCV10 had a stronger immune response than a 1-dose schedule of PCV13). Serotypes 5, and 19F had insufficient data for evaluation due to confounding by schedule and pre-dose1 GMC. Serotypes 6A and 19A that are in PCV13 but not PCV10 had insufficient data to evaluate. There were no data on 1-dose schedules of PCV10 for STs 6A, 6B, 14, 19F and 23F so for these serotypes conclusions are based on comparing 2-dose schedules. The Venezuela study (not shown in figures because no pre-PCV13 data provided) reported ≥7-fold-rises for all PCV13 serotypes for children 24-59 months who received 1-dose and ≥16-fold-rises for all PCV13 serotypes for children 7-23 months who received 2-doses [136].

Proportion Above The Correlate of Protection:

The change in the proportion of subjects above the correlate of protection from pre-PCV to post-PCV varied by serotype and product (**Figure 73**). Generally, no differences by product were seen for serotypes 1, 5, 7F, 14, 19F or 23F; by contract, for PCV13, 1 dose resulted in a higher response for serotypes 14 and 23F. A greater proportion of subjects who were vaccinated with PCV13 reached the correlate of protection than for PCV10 for serotypes 3 (albeit only 1 PCV10 study), 6A, 6B and 19A.

5.2 NASOPHARYNGEAL CARRIAGE DIRECT EFFECTS AND CATCH-UP:

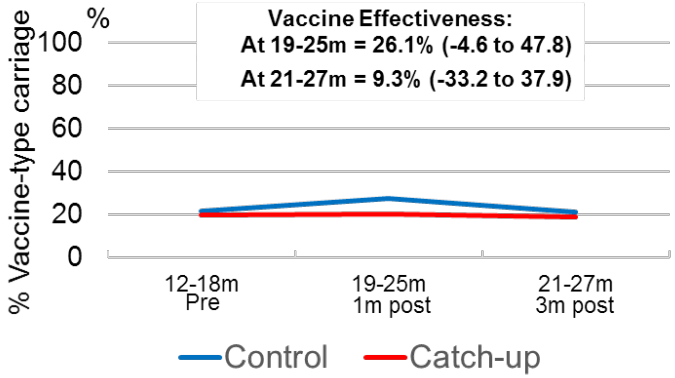
A limited number of PCV10/13 studies, using 2+1 or 3+0 schedules, directly addressed the questions of whether immunization of older children (I.e. catch-up) (1) protects those children from new acquisitions of VT carriage after they are vaccinated (i.e., they only evaluate prevalence), (2) protects younger or older unvaccinated kids and parents from VT colonization through indirect protection, or (3) improves the impact (i.e. program effectiveness of direct and indirect effects is greater than vaccine efficacy of direct effects only) in vaccinated children (both infants who received 2+1 or 3+0 and older children).

Four studies were found that assessed prevalence of carriage in the context of catch-up with 1 or 2 doses in children 12-59m of age. Three studies evaluated impact compared to no catch-up (n=1 head-to-head randomized clinical trial (Finland), n=1 observational study with comparator to other areas (Kenya) and n=1 'head-to-head' observational study that compared communities with and without catch-up (Kibera and Asembo, Kenya)) provided NP colonization prevalence data in immunized children outside the National Immunization Program vaccine-targeted age range. One additional study (Venezuela) assessed carriage in

children 24-59 months provided PCV catch-up without comparison to a PCV naïve group. Details of each study are below.

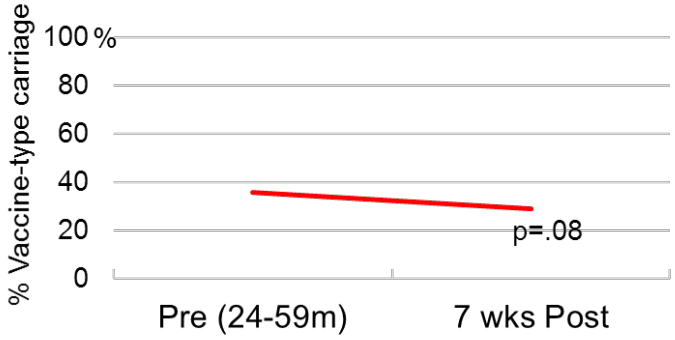
A Finnish head-to-head RCT (Vesikari-2016) compared 2 doses of PCV10 in toddlers administered 6 months apart (at 12-18m of age and at 18-24m of age) to controls immunized with hepatitis A vaccine. The outcome measured was the proportion of the children who had VT carriage 3 months following the second dose of PCV. They observed non-statistically significant 26% lower VT carriage at 1 month post dose 2 in the PCV10 group (20.3%) compared to the HepA group (27.5%), but 3 months after post dose 2 both there was no difference in VT colonization (PCV10 %VT=18.9% compared to 20.9% in HepA group,) [40]. Since the follow up period was very limited, the conclusions about protection from acquisition are limited.

Figure 74: Impact on NP colonization of catch-up immunization with 2-doses in toddlers administered 6 months apart (at 12-18m and 18-24m of age) compared to HepA-vaccinated controls (Finland, Vesikari 2016)



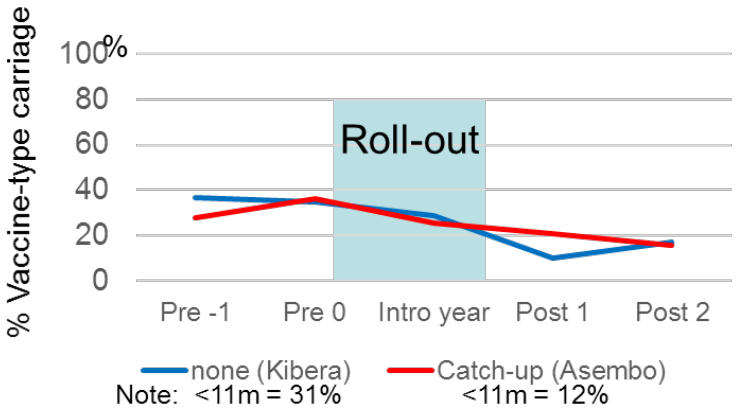
A **single-arm clinical trial** in Venezuela (Verhagen-2016) compared NP colonization prevalence before and 7 weeks after 1 PCV dose in children 24-59m of age. They observed a relative reduction of 20% in VT carriage (from 36% pre-vaccine to 29% post vaccine; p=.08; **Figure 75**) [137]. This provides some evidence from a time series that a single dose of PCV may reduce the prevalence of VT carriage in directly immunized children. This may be a combination of direct effect from the single PCV dose plus any indirect effects from immunization the birth cohort in the community or just a seasonal secular trend in circulation of VT pneumococci. This study had no contemporaneous control group who was also monitored over time, which would have helped in interpreting the time series data. This study also assessed indirect effects in the older siblings (5-10y) and caregivers of the immunized children. However, carriage was too low and sample size too small to observe any significant changes and again there is no comparator group without PCV catch up vaccination: pre-vaccine VT carriage=14% compared to post-vaccine VT carriage 12% (14% relative reduction, p=0.6).

Figure 75: NP colonization pre vs. 7 weeks post catch-up immunization with 1-dose in toddlers 24-59m of age (Venezuela, Verhagen 2016)



There was also an **observational head-to-head study** (Kim, 2016; **Figure 76**) in Kenya that assessed change in carriage prevalence in a 2-year pre-PCV period compared to a period 2 years post PCV introduction (skipping 1 year during the introduction period) in a community that had catch-up (Kibera) compared with another without catch-up (Asembo)[139]. Catch-up consisted of up to 2 doses in children 1-4 years old and was in the context of 3+0 PCV10 introduction in children at 6, 10 and 14 weeks of age (both sites) [139]. NIP coverage with PCV10 was 85% by the end of the year of introduction. The proportion of children <5 years of age with VT carriage did not differ across the two types of communities, with and without the catchup program. In the community with PCV catch up the pre-PCV VT carriage rate was 38.5% compared with 18.1% in the 2-years following the catch-up campaign. In the community without catchup the prevaccine VT prevalence was 40% compared with 18.6% in the 2-years following PCV introduction in infants but with no PCV catchup in the older children. Although the 2-year post carriage measures may not represent the children who received the catch up, since up to half of them will have aged out of the observed group and up to half would have received the 3+0 primary series a year or two earlier, there was also no indication during the year of roll-out or year 1 post introduction of lower carriage in the catch-up community. However, there was a considerable difference in the age distribution sampled between the sites (31% <11m in the catch-up community vs. 12% in the community without catch-up), and there were annual fluctuations in %VT carriage in the pre-PCV period, both of which likely confound the results.

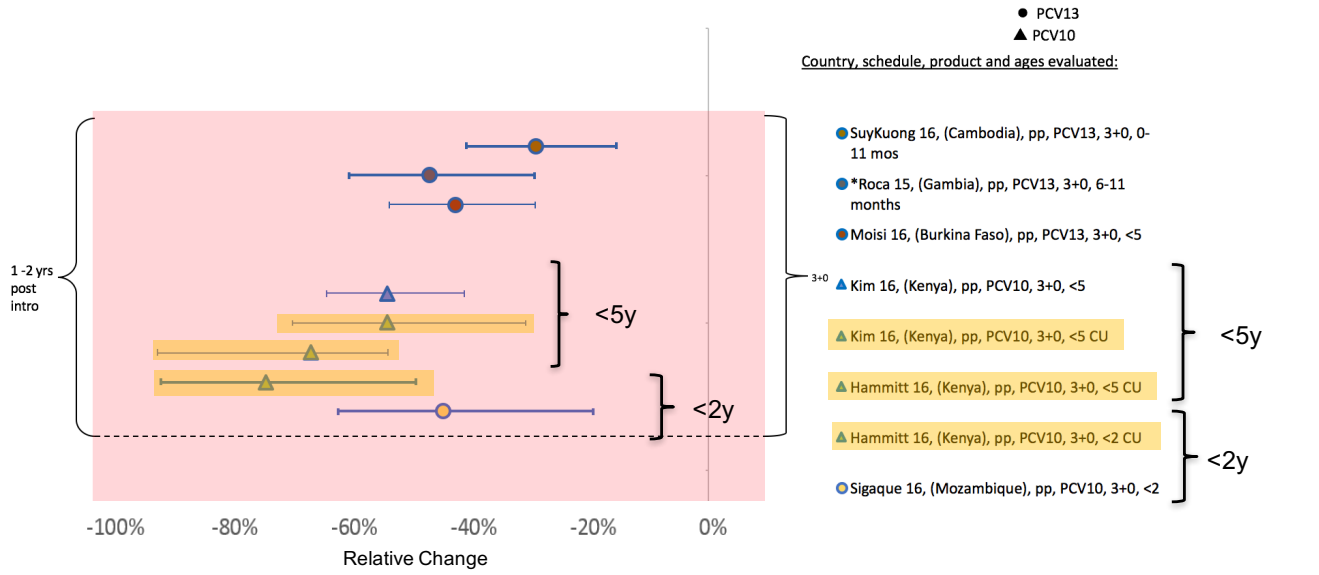
Figure 76: Impact on NP colonization of catch-up immunization with up to 2 doses in children 1-4 years of age compared to a community without catch-up (Kenya, Kim 2016)



PICO III: Catch-Up

Another **observational study** in Kenya (same national infant PCV introduction as the Kim study), assessed VT carriage after introduction of PCV10 among infants, but with a catch-up campaign (1 or 2 doses) in children <5 years of age[47, 140]. There was no comparison group but their results can be compared to counties that did not use a catch-up campaign (**Figure 77** and **Figure 78**). They observed a large, significant decline in VT carriage in children <2 years of age in the first year after introduction, from approximately 40% to 12% (70% relative change), and in children <5 years of age, from approximately 35% to 13% (63% relative change). This impact was larger than for any of the other studies that did not use catch-up (range 30-55%).

Figure 77: Relative change in VT NP carriage pre- to post-PCV10/13 in routine use settings that had catch-up (yellow highlighted) compared to those that did not.



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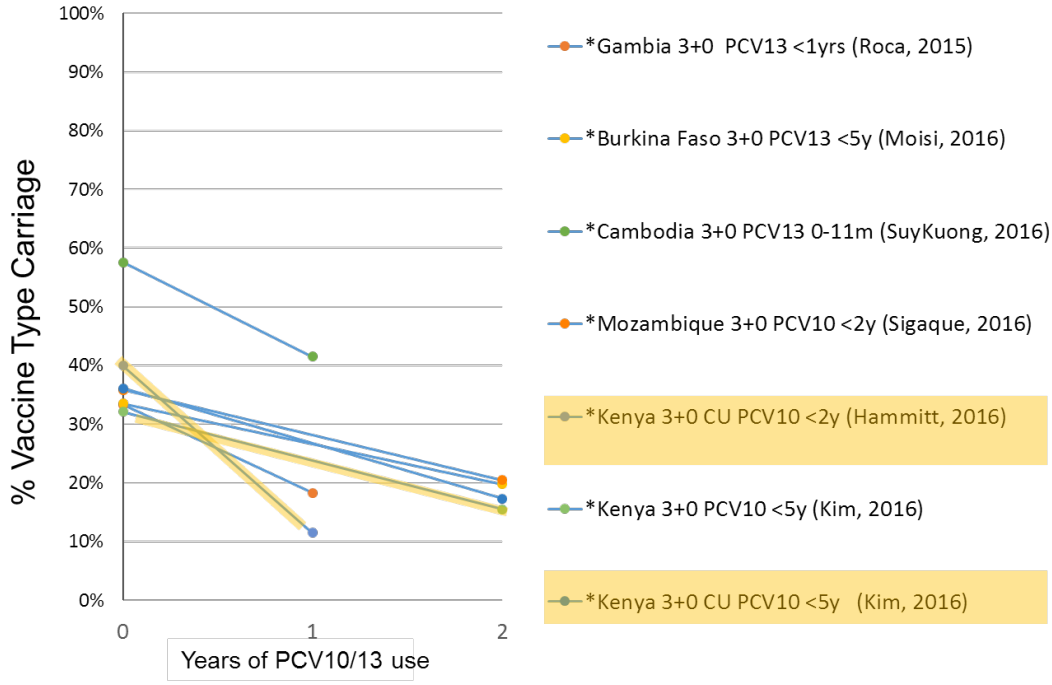
Footnote: All used 3+0 schedule and evaluated carriage 1 to 2 years after PCV10/13 introduction.
*Note that The Gambia had 1.5 years of PCV7 prior to switching to PCV13.

Figure 78: Decline in VT NP carriage pre- to post-PCV10/13 in routine use settings that had catch-up (yellow highlighted) compared to those that did not.



Footnote: Ages specified in the labels (e.g., '<2y') describes the age group in whom NP colonization was measured.

*p<.05 change from pre-PCV10/13 period.

5.3 Nasopharyngeal Carriage Indirect Effects And Catch-Up:

Three studies (from Finland, Fiji and the Netherlands) reporting on VT carriage did not use catch up programs while introducing PCV. In these studies, between 3 years and 4.5 years after PCV10 introduction, there was 57%-100% reduction of VT carriage.[55-57] In Kilifi, Kenya, where a catch up campaign targeting all children under 5 years was used to introduce PCV10, there was a 65% reduction (95% CI: 46, 78) in PCV10 VT carriage among all persons over 5 years of age achieved in a period that averaged just two years post PCV10.[58] After 4 years of PCV10 use in Kilifi, there was 52%-100% reduction in VT carriage in various age groups.[58]

5.4 Invasive Pneumococcal Disease Direct Effects and Catch-Up:

There were no studies available to adequately assess the value of catch-up on invasive pneumococcal disease in the vaccine targeted cohort.

5.5 Invasive Pneumococcal Disease Indirect Effects and Catch-Up:

A number of factors, including variability in the number of years post PCV10/13 introduction as well as regional differences in serotype distribution and disease epidemiology, make it difficult to draw any conclusions about the indirect impact of catch up campaigns on the incidence of VT IPD. Eight studies are from countries that did not have a catch-up campaign, and ten studies from countries that did employ a catch-up campaign at the time of PCV introduction. Catch up present (cu+) or absent (cu-) is marked in the IPD figures for PICO1 and PICO2 figures.

5.6 Pneumonia Direct Effects and Catch-Up:

There were no observational studies that evaluated the value of catch-up on pneumonia in the vaccine targeted cohort.

5.7 Pneumonia Indirect Effects and Catch-Up:

Four studies did not use catch up campaigns and six studies did. In a Finnish study reporting during an average period of 2.5 years after PCV10 introduction without catch up, there was a significant reduction in clinical pneumonia (18%) and pneumococcal pneumonia (70%) in children 19-71 months [79]. This study suggests that even without catch up in this setting, PCV10 introduction had relatively swift and marked impact on children just above the vaccinated cohort. A Kenyan study in 5-12 year olds, in contrast, did not find significant reductions in clinical or radiological pneumonia after 4 years of PCV10 use and with catch up used for all children under 5 years of age at the time of PCV10 introduction [101]. Factors beyond the presence or absence of catch up campaigns are likely at play and intermingling to produce the composite impact that is varied and highly context.

6.0. MORTALITY

SUMMARY:

- Data on PCV-10 and PCV-13 impact on child mortality are limited. To provide the most inclusive evidence base possible for consideration by policy-makers, data on mortality rates (incidence of death) and case fatality rate (CFR) for all-cause, pneumonia, and IPD deaths, before and after introduction of PCV-10 and/or -13 were considered.
- No head-to-head comparisons of PCV products or dosing schedules are available for evaluating impact on mortality.
- 13 studies provide data on mortality impact following PCV10/13 introduction in a 3-dose schedule: 7 on 2+1 schedules [140] [68] [141] [142] [86] [35] [28]and 6 on 3+0 schedules [102] [18] [143] [103] [144] [37]. With a few exceptions, they are largely from countries with low infant and child mortality.
    - Due to limited data availability for PCV-10 and PCV-13, data on 4-dose schedules (3+1) were brought in for consideration as well (n=5 studies). [145-147] [148] [149]
        - All studies evaluating a 2+1 and 3+1 schedule were conducted in high-income (high or upper-middle) settings.
        - Due to inherent differences in study populations where a 2+1 schedule versus a 3+0 schedule was used (e.g. income strata, underlying infant mortality, etc.) comparisons of observed PCV impact by dosing schedule would be confounded by these factors. Thus, comparisons of impact across dosing schedules are not appropriate to make with the mortality data available from included studies.
- Of the 18 included studies, 11 evaluate PCV10 and 7 evaluate PCV13.
    - Due to inherent differences in study populations where a PCV10 versus PCV13 was used (e.g. income strata, underlying infant mortality, etc.) comparisons of observed PCV impact by product would be confounded by these factors. Thus, comparisons of impact across PCV product are not appropriate to make with the mortality data available from included studies.
- No studies directly compare settings with and without catch-up immunization (above the birth cohort). Ten of the studies were conducted in settings with catch-up vaccination at the time of introduction; 8 were conducted in settings without catch-up.
    - Four of the 10 studies conducted in settings with catch-up evaluated a 3+1 dosing schedule.
    - The amount of evidence on mortality impact in relation to the added value of catch-up immunization is limited, and the lack of direct measurement in comparable populations with and without catch-up immunization (the intervention of interest) makes the evaluation of this policy question inappropriate using this evidence alone.
- Quantitative comparisons across studies should not be interpreted to mean there are true differences in impact on mortality; these observational studies are highly heterogeneous for factors that themselves would impact mortality (study method, analysis approach, years of PCV use, age strata, outcome, secular trends)
- Nevertheless, most published studies demonstrate an impact (albeit statistically non-significant) of PCV on mortality rates and case fatality ratios in children under-5; it is unknown how many studies have been conducted that found no impact and did not publish the findings
- The data do not indicate that there are any significant differences in mortality impact by PCV product and/or schedule

MORTALITY CHANGES:

- All-cause, IPD (and pneumococcal meningitis), and pneumonia mortality rates before and after introduction were all considered. Figure 28-30 demonstrate the reduction in mortality rates for each endpoint, by schedule and product.

The range of observed reduction was as follows for each endpoint:

  - All-cause mortality rates: 22 to 37%
  - Pneumonia mortality rates: -5 (increase) to 71.5%
  - IPD mortality rates: 69 to 88%

CFR CHANGES:

- The reason to study changes in CFR as a result of PCV use is based on the hypothesis that vaccine serotype pneumococcal cases are more at risk of death than non-VT pneumococcal, or non-pneumococcal cases. If the fraction of the cases that are VT pneumococcal decreased, as a result of PCV use, then the CFR would be expected to fall.
- The range of observed reduction across all-cause, IPD, and pneumonia case fatality rates (CFR) is from 100 to -62%
- Ten studies studied the change in case fatality ratio of all-cause syndromes or pneumococcal specific syndromes, however no reductions were significant.
  - Six studies for IPD (n=4) and pneumococcal meningitis (n=2)
    - Reductions ranged from 100% to -62% (i.e. an increase of 62%)
    - Of these studies, 2 evaluated 2+1 using PCV10, and 1 evaluated 3+0 using PCV13
      - Three evaluated a 3+1 schedule, all using PCV10
  - Four studies for pneumonia
    - Reductions ranged from 12.5% to 57%, which could reflect the lower fraction of bacterial disease among these cases, which are known to have a higher CFR than non-bacterial cases
    - Of these studies, 2 evaluated a 2+1 schedule using PCV13 and 2 evaluated a 3+0 schedule, 1 with PCV10 and 1 with PCV13.
  - One study evaluated all-cause CFR (reporting a non-significant reduction of 50%) for PCV10 in a 2+1 schedule
  -

REGIONAL REPRESENTATIVENESS :

- Studies are available from Europe (n=2 for each of PCV10 and PCV13), Africa (n=1 for PCV10 and n=2 for PCV13), Latin America (n=7 for PCV10 and n=2 for PCV13) and Oceania (n=1 for each PCV10 and PCV13)
  - 5 of the 9 Latin America studies are of a 3+1 dosing schedule
- No studies of mortality for PCV10 or PCV13 are available from South East Asia or the Middle Eastern geographic regions

Evaluating the impact of PCV10 and PCV13 on mortality is of high priority for policy decision-makers but these studies are among the most technically difficult to conduct because of the relative rarity of mortal outcomes. Furthermore, there are many other interventions that can affect the mortality rate absent PCV, and these confound the conclusions from mortality analyses. All studies are time-series studies looking at mortality rates, or fatality counts, before and after PCV introduction, leaving these highly susceptible to changes unrelated to PCV use.

Therefore, any mortality results from observational studies should be interpreted relative to the mortality observations from randomized controlled trials, where inferences about causality are substantially lessened through randomization and the inclusion of a contemporaneous control group. The PCV9/3+0 trial in the Gambia concluded that there was a 16% reduction in all-cause mortality for infants 3-29 months of age [150]. This allows some benchmarking of the changes that might be expected in other settings.

There are 18 studies (n=11 PCV10; n=7 PCV13) with mortality outcome following the use of PCV10 or PCV13 in a 3- or 4-dose schedule ([140] [68] [141] [142] [86] [35] [28] [18] [143] [103] [144] [37] [145-147] [148] [149]). The outcomes include mortality rates and changes in case fatality ratio. These are assessed according to all-cause mortality, IPD mortality, and pneumonia mortality (**Annex B: TABLE Mort 1**). The observed reductions are not all statistically significant and their magnitude in some cases is surprisingly large, suggesting either that pneumococcus is a much greater contributor to mortality than evidenced by other work, that herd effects are contributing to the overall measured benefit, or that the studies suffer from one or more methodological issues just described.

Regardless, most published studies have documented a reduction in mortality following the routine use of PCV, including use of both products, for both 3+0 and 2+1 schedules, in a range of high and low-income countries, across geographies. The magnitude in some cases is surprisingly large, suggesting either that pneumococcus is a much greater contributor to mortality than evidenced by other work, that herd effects are contributing to the overall measured benefit, or that the studies suffer from some of the methodological issues just described.

Regardless, most published studies have demonstrated an impact on mortality following the routine use of PCV, including use of both products, in a range of high and low-income countries, across geographies.

Figure 79: Percent Change in all-cause mortality rates

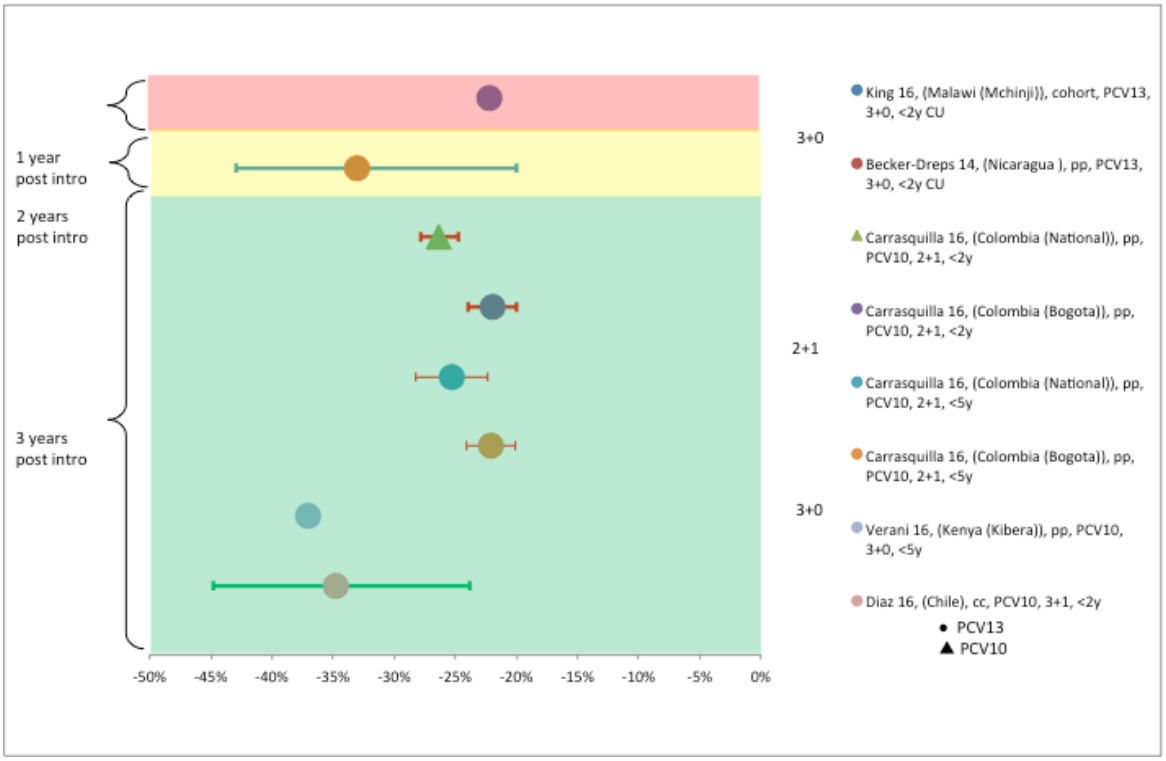


Figure 80: Percent Change in Pneumonia Mortality Rate

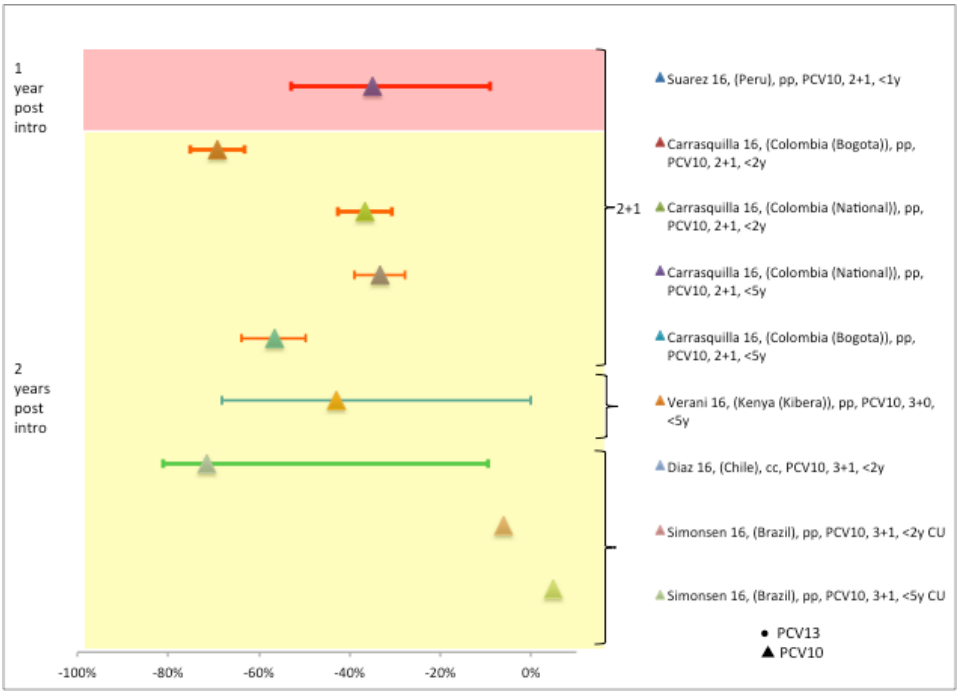
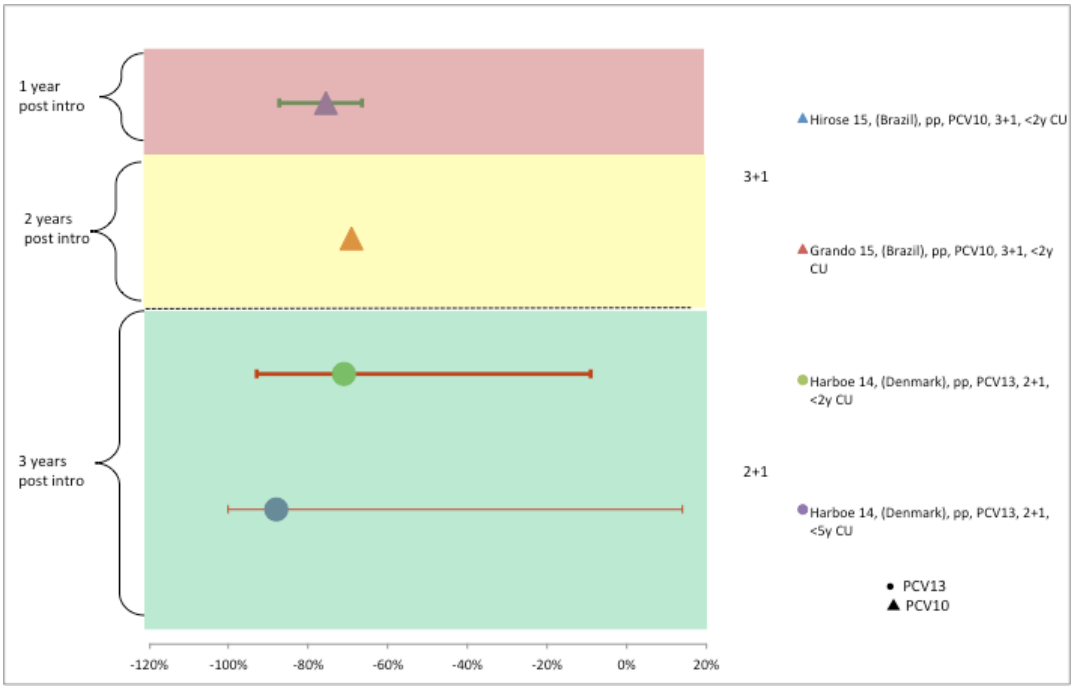


Figure 81: Percent change in all IPD (and pneumococcal meningitis) mortality rates (MR)



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ANNEX A

1. Context and background

1.1 PCV licensure and recommendations

Pneumococcal conjugate vaccines (PCV) have been authorized for use in infants since 2000, when the first product, containing seven serotypes (PCV7-Prev(e)nar) was licensed by the US Food and Drug Administration. A recommendation for inclusion of PCV in the routine infant immunization schedule was made by the US Advisory Committee on Immunization Practices (ACIP) in July 2000, which was implemented in the US later that year[1]. Soon thereafter many countries licensed and adopted a recommendation for its use. In 2007, the World Health Organization adopted a policy, as recommended by the Strategic Advisory Group of Experts on Immunization (SAGE), that all countries should include PCV as part of the routine infant immunization schedule[2]. This recommendation was made following additional evidence from two large phase III efficacy trials in Africa (the Gambia and South Africa) confirming the generalizability of efficacy beyond that observed in trials from North America and Europe. WHO pre-qualification for PCV7 was issued in the same year (2007).

Since then, two additional PCV products (PCV10-Synflorix and PCV13-Prevenar) have been pre-qualified by WHO, both of which include more serotypes than those found in PCV7-Prev(e)nar; PCV7-Prev(e)nar was replaced by PCV13-Prevenar and is no longer on the market[3]. The availability of two licensed PCV products, which differ in several ways, means that countries and vaccine programs with PCV in the routine infant vaccine schedule also need to make product selection decisions. These decisions are based on a combination of factors that fall into five categories, including: disease epidemiology, product performance, programmatic needs, supply, and financial considerations.

1.2 Product Choice Considerations

The document provides information that should be considered in a product choice decision but does not itself provide any recommendation for product choice. This document provides specific information about the two currently available, licensed PCV products along with advice about the considerations a country should weigh in making a product choice. The information here focuses on pre-qualified and globally marketed PCVs (i.e. PCV10-Synflorix and PCV13-Prevenar, see Table 2 for key descriptors of product characteristics) but does not include a systematic review of evidence from previously marketed products (i.e. PCV7-Prev(e)nar), or information on unlicensed products of the past (i.e. PCV9, PCV11), or those that are currently under evaluation. The information is presented in a framework that can be updated as new evidence on existing products and novel pneumococcal vaccine products becomes available. The document is not intended as the primary source of information to support decision-making about *whether to include PCV in the vaccine program* or on dosing schedules; comprehensive documents are otherwise available for those decisions[3-8].

Decision-makers considering a PCV product choice should weigh the evidence aiming to assure a PCV program that is optimized for disease impact and sustainability. That evidence should include an understanding of:

- Pneumococcal disease epidemiology (including pneumococcal serotype considerations)
- PCV performance, and

- PCV programmatic considerations (including product availability, cost, cold chain requirements, product presentation, wastage, product administration and training requirements)
- PCV product supply
- Financial considerations of PCV products

Vaccine performance characteristics are usually ones for which a large amount of data are available on individual products, but few data exist that offer direct product comparisons. Most data come from PCV impact evaluations in routine use settings, and by their nature most often include only the assessment of a single product. The PCV performance measures include immunogenicity, efficacy against disease and colonization (i.e. vaccine impact when given in ideal circumstances), effectiveness against disease and colonization (i.e. vaccine impact when given in routine use circumstances), duration of protection, age of administration, indirect effects (i.e. effects on those who are not immunized), serotype cross-protection, serotype replacement, and safety.

Evidence on PCV impact on pneumococcal colonization and disease from routine immunization program settings is essential for decision-makers to consider, since the question being asked is what vaccine to implement in the routine use program. Not all questions noted here have sufficient evidence to draw conclusions; where data are sparse or not available, this limitation is noted. However, there is a robust, and rapidly growing body of PCV evidence from both trials and of observational studies in routine use settings that policy-makers can rely on to make an informed product choice. To date, although the bulk of evidence remains from high-income settings, there is substantial evidence from middle- and low-income settings.

1.3 Pneumococcal disease and serotype epidemiology

World Health Organization (WHO) country specific and global burden of disease estimates are available from 2000, 2008 and will soon be released for 2015 [9-11]. In the absence of PCV use, pneumococcal disease is the leading vaccine preventable cause of mortality of infancy and childhood. Moreover, in settings where mortality is high, pneumococcus is responsible for an even greater fraction of mortality and morbidity than in lower mortality settings. Plainly stated, in places where many children die in infancy and early childhood, pneumococcal disease is a main culprit. In settings where mortality is controlled, pneumococcal disease may not cause death but it is a ubiquitous pathogen that causes pneumonia, blood stream infections and meningitis that require immediate, appropriate treatment. Pneumococcal disease, even when not fatal, incurs substantial financial treatment costs to families and to government health care systems, and can incur long-term health consequences to children who survive (e.g. sequelae of meningitis and compromised lung function among those who had pneumonia).

Having decided to introduce PCV, policy-makers will be well aware that PCVs contain only a limited number of the more than 96 different pneumococcal serotypes, and that immunity to one serotype does not necessarily confer immunity to other serotypes (i.e. there is cross-protection among a limited number of serotypes, always within a serogroup). However, since only a small subset of these 96 serotypes are responsible for the vast majority of disease and deaths, these serotypes were targeted for inclusion in available PCVs to represent those found across all geographies and epidemiologic settings[12]. Both PCV products on the market are considered global products, appropriate for any country setting.

The serotype distribution of pneumococcal disease prior to PCV use was systematically evaluated and summarized for all regions. The Pneumococcal Global Serotype Project (GSP) provides a serotype-by-serotype estimate of the fraction of disease, by geographic region, among children under 5 years of age

(Table 1) [13]. This analysis formed the basis for the pneumococcal vaccine Advanced Market Commitment (AMC) stipulation that eligible pneumococcal vaccines must account for, at a minimum, 60% of disease causing strains, and include serotypes 1, 5 and 14 [14]. The rationale for the stipulation that PCVs should account for at least 60% of disease was laid out in the TPP document. Serotypes 1 and 5 are common causes of pneumococcal disease outbreaks, and are particularly common in Africa and Asian settings and serotypes serotype 14 was found to be the most common serotype in all regions. Noted also was the observation that the 10 serotypes causing the majority of disease in Africa were the same as those in Asia suggesting more similarities than differences between populations. This systematic assessment of serotypes causing disease is considered the reference document for country deliberations.

Table 1. Serotype distribution of the top 20 global serotypes causing invasive pneumococcal disease, by region, pre-PCV among children under-5 years of age

	Africa		Asia		Europe		LAC		North America		Oceania	
	(N=11.181)		(N=4.752)		(N=10.279)		(N=18.788)		(N=11.441)		(N=3.649)	
Serotype	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
1	11.7%	9.5, 13.8	9.5%	6.6, 12.3	5.1%	4.0, 6.2	8.4%	7.2, 9.6	1.1%	0.6, 1.5	1.8%	1.0, 2.6
2	1.9%	1.0, 2.8	2.6%	1.5, 3.7	0.1%	0.0, 0.2	0.3%	0.1, 0.4	0.0%	0.0, 0.0	0.9%	0.0, 1.8
3	1.1%	0.8, 1.5	1.4%	0.8, 2.0	1.9%	1.5, 2.4	2.2%	1.8, 2.6	0.8%	0.6, 1.0	0.4%	0.2, 0.7
4	2.3%	1.7, 3.0	1.6%	1.0, 2.1	3.2%	2.6, 3.8	1.6%	1.3, 1.9	5.7%	4.7, 6.7	4.9%	3.3, 6.6
5	10.7%	7.6, 13.8	6.7%	4.5, 9.0	0.8%	0.5, 1.1	8.5%	7.2, 9.8	0.4%	0.1, 0.7	2.8%	1.5, 4.1
6A	9.4%	7.2, 11.5	3.5%	2.4, 4.6	4.4%	3.8, 5.0	4.5%	3.6, 5.4	3.6%	2.9, 4.3	3.7%	3.1, 4.3
6B	8.5%	6.3, 10.7	11.5%	9.0, 14.0	13.7%	12.2, 15.3	9.4%	8.4, 10.3	13.4%	11.7, 15.1	12.0%	9.3, 14.6
7F	0.8%	0.4, 1.3	2.0%	1.2, 2.8	3.2%	2.4, 3.9	2.5%	2.0, 3.1	1.0%	0.7, 1.4	2.0%	1.1, 2.8
8	1.1%	0.8, 1.5	0.6%	0.3, 0.9	1.0%	0.7, 1.3	0.8%	0.4, 1.1	0.1%	0.0, 0.2	0.9%	0.4, 1.5
9A	0.4%	0.2, 0.7	0.3%	0.1, 0.5	0.1%	0.1, 0.2	0.0%	0.0, 0.1	0.4%	0.2, 0.7	0.1%	0.0, 0.2
9V	2.2%	1.3, 3.1	3.1%	2.2, 4.1	4.2%	3.4, 5.1	2.7%	2.3, 3.1	5.3%	4.5, 6.0	3.9%	3.1, 4.7
12A	0.1%	0.0, 0.1	1.2%	0.7, 1.8	0.0%	0.0, 0.1	0.1%	0.0, 0.1	0.0%	0.0, 0.0	0.0%	0.0, 0.0
12F	1.7%	1.1, 2.3	1.6%	0.8, 2.3	0.7%	0.6, 0.9	0.6%	0.3, 0.9	1.2%	0.7, 1.7	2.2%	0.9, 3.5
14	13.0%	10.0, 16.0	11.6%	8.7, 14.5	23.9%	21.0, 26.8	26.5%	23.2, 29.7	29.2%	26.4, 31.9	23.7%	17.2, 30.1
15B	0.5%	0.1, 0.9	0.8%	0.4, 1.2	0.7%	0.5, 0.8	0.7%	0.4, 0.9	0.3%	0.2, 0.4	0.2%	0.0, 0.4
18C	1.4%	0.9, 2.0	2.4%	1.7, 3.2	6.9%	5.9, 8.0	4.3%	3.4, 5.2	8.0%	6.9, 9.0	5.9%	4.1, 7.7
19A	3.9%	2.5, 5.3	2.6%	1.7, 3.5	5.5%	4.6, 6.4	2.9%	2.3, 3.5	3.0%	2.4, 3.7	3.9%	2.9, 4.9
19F	5.4%	3.6, 7.1	8.1%	6.3, 9.8	8.2%	7.1, 9.3	3.6%	3.2, 4.1	10.3%	9.3, 11.3	8.9%	6.8, 11.0
23F	6.5%	4.5, 8.5	9.7%	7.6, 11.8	7.1%	6.1, 8.2	5.3%	4.4, 6.2	6.2%	4.9, 7.5	5.2%	3.7, 6.6
45	0.5%	0.0, 1.0	0.6%	0.1, 1.0	0.0%	0.0, 0.0	0.0%	0.0, 0.0	0.0%	0.0, 0.0	1.1%	0.1, 2.1
46	1.3%	0.4, 2.1	0.5%	0.1, 0.9	0.0%	0.0, 0.0	0.0%	0.0, 0.0	0.0%	0.0, 0.0	1.0%	0.0, 2.0
All Others	15.7%	12.7, 18.6	18.2%	14.7, 21.6	9.2%	7.9, 10.4	15.3%	12.5, 18.1	10.2%	7.0, 13.4	14.6%	11.1, 18.1
TOTAL	100.0%		100.0%		100.0%		100.0%		100.0%		100.0%	

CI = Confidence Interval; N= Number

Beyond the consideration of serotypes causing disease *prior to the introduction of PCV*, policy-makers may consider several other factors regarding product selection and serotypes:

- Antimicrobial resistance: Some serotypes are more commonly found among strains that exhibit antimicrobial resistance. These serotypes are largely those included in the currently licensed vaccines, but shifts in this epidemiology are possible.
- Non- PCV7 serotypes including types 3, 6A, and 19A: This document provides a specific section on the impact of both PCV13 and PCV10 on types 3, 6A, and 19A; the former includes these serotypes in the vaccine formulation while the latter relies on the possibility of cross-protection from 6B for 6A, and 19F for 19A protection. This issue is often raised for consideration because of the experience with the first generation vaccine, PCV7. Following the use of PCV7-Prev(e)nar, an increase in the disease incidence of serotypes not included in the vaccine (i.e. serotype replacement) was observed, but the magnitude of that increase was small relative to the reduction in disease incidence from

serotypes in the vaccine. Overall, there was a substantial net reduction in pneumococcal disease with the use of PCV7. However, one non-PCV7 serotype, type 19A, was observed to increase in incidence in many countries, and was a serotype commonly associated with antimicrobial resistance. Attention to evidence for PCV10 regarding 19A in particular is a focus for some decision-makers.

- Country specific serotype distribution: Most countries have few if any studies to inform local serotype distribution of pneumococcal disease in infants and young children. Even where such data exist, there are many reasons why they may be an unreliable source to estimate the long-term average serotype distribution and should not be a substantial driving factor of product choice. The regional serotype distributions provided by the GSP are considered a more robust reflection of the disease causing serotype distribution rather than local studies with small numbers of isolates whose distribution may be substantially biased relative to the true disease distribution in the country.

2. Vaccine characteristics of currently licensed PCV products

Two PCV products are currently licensed, pre-qualified by WHO and globally marketed: PCV10 manufactured by Glaxosmithkline, marketed as Synflorix, and PCV13 manufactured by Pfizer Inc., marketed as Prevenar-13.

2.1 Serotypes included in products

All of the serotypes included in PCV10 are also included in the PCV13 product. The three additional types found in PCV13 are types 3, 6A, and 19A. Table 2 illustrates the comparison of serotypes in the two products (additional details on products are provided in Table 3). There is some evidence of cross-protection by 6B for 6A and by 19F for 19A for PCV10, which is discussed specifically in Section 3.7.

Table 2: Serotypes included in and specifications of PCV10 and PCV13 product formulations

Product	Formulation Specifications	Serotype & Carrier Protein												
		1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
PCV10	Vial Size: 2-dose Preservative: None	1µg PD		3µg PD	1µg PD		1µg PD	1µg PD	1µg PD	1µg PD	3µg TT		3µg DT	1µg PD
PCV13	Vial Size:1-dose and 4-dose Preservative: None (for 1-dose); 2- phenoxyethanol for 4-dose	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	4.4 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM	2.2 µg CRM

PD=protein D from non-typeable Haemophilus influenzae (NTHi), CRM= *Corynebacterium diphtheria*, TT=tetanus toxoid, DT=diphtheria toxoid

Serotype included in the vaccine Some evidence of cross protection

2.2 Carrier Protein

Table 2 describes the carrier proteins used for each product. PCV13 uses CRM_{197} protein as the protein carrier for each of the 13-serotypes. CRM_{197} is a cross reactive mutant of *Corynebacterium diphtheria* toxin. This is the same carrier protein found in several Hib-conjugate vaccines.

PCV10 uses protein D (derived from non-typeable *Haemophilus influenzae*) as the carrier for eight of the serotypes while one serotype (type 18C) is conjugated to tetanus toxoid and another (type 19F) is conjugated to diphtheria toxoid protein.

2.3 Therapeutic indications

PCV10 and PCV13 were each licensed and pre-qualified on the basis of immunogenicity non-inferiority to PCV7, which in turn was licensed on the basis of demonstrated efficacy against invasive pneumococcal disease. Since the time of licensure both PCV10 and PCV13 have sought and gained approval to stipulate indications beyond prevention of invasive pneumococcal disease.

Each country in which the product is licensed for marketing approves the labeling for that country. The WHO Prequalification (PQ) labeling largely mirrors that of the responsible national regulatory authority (NRA); for Prevenar-13 this is the European Medicines Agency (EMA), and Synflorix this is the Federal Agency for Medicines and Health Products in Belgium [15, 16].

The WHO PQ has approved the two vaccines for the following indications:

- PCV10: for invasive pneumococcal disease, pneumococcal pneumonia, and otitis media, with labelling by the EMA and WHO PQ that includes the prevention of serotype 19A disease [16].
- PCV13: for invasive pneumococcal disease, pneumococcal pneumonia, and otitis media caused by the 13 serotypes in the vaccine [15].

Contraindications, special warnings and precautions for use are outlined in the product labeling documents and relate specifically to those who have allergies to components in the vaccine. There are no substantive distinctions between the products [15, 16].

2.4 Formulations for PCV10 and PCV13

A description of the formulations and packaging characteristics is provided in Table 3.

Table 3: WHO Prequalified, and anticipated PCV product formulation and details [5, 6] [15, 16]

PCV	PCV10 1-dose vial preservative free	PCV10 2-dose vial Preservative free	PCV10 4-dose vial Preservative: 2-PE	PCV13 1-dose vial preservative free	PCV13 4-dose vials Preserv-ative 2-PE*
Serotypes included	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	PCV10 types plus types 3, 6A and 19A	PCV10 types plus types 3, 6A and 19A
Manu-fact.	GSK	GSK	GSK	Pfizer	Pfizer
Trade name	Synflorix	Synflorix	Synflorix	Prevnar13, Prevenar 13	Prevnar13, Prevenar 13

Carrier proteins	Protein D from NTHi, TT and DT	Protein D from NTHi, TT and DT	Protein D from NTHi, TT and DT	CRM 197 protein	CRM 197 protein
Year PQ by WHO	2009	2009	Expected in 2017 or 2018	2010	2016
Avail. from UNICEF	No	Yes	Expected	Yes	Yes
Wast-age rate	0.05	0.1	10%	0.05	0.1
Storage conditions	2-8°C, do not freeze.	2-8°C, do not freeze. An opened 2-dose vial should not be returned to the refrigerator after vaccination session or after 6 hours, whichever comes first.	2-8°C, do not freeze.	2-8°C, do not freeze	2-8°C, do not freeze
Packaging	Cartons of 1, 10 and 100 vials	Cartons of 100 vials	Info. Not Yet Available	Cartons of 50 vials	Cartons of 25 and 50 vials
Volume per dose	57.7, 11.5 and 9.7 cm3 per dose	4.8 cm3 per dose	2.4 cm^3 per dose	12 cm3 per dose	3 cm3 per dose
VVM	VVM30: quite stable under high temperatures	VVM30: quite stable under high temperatures	VVM30: quite stable under high temperatures	VVM30: quite stable under high temperatures	VVM30: quite stable under high temperatures

PQ = WHO prequalified

2.5 Safety Profile

The safety profiles of both PCV10-Synflorix and PCV13-Prevenar have been reviewed by multiple national regulatory authorities during the licensure processes, the WHO prequalification process, and the Global Advisory Committee on Vaccine Safety (GACVS) [17]. Both products have accrued extensive post-marketing safety surveillance data and both are assessed as having excellent safety profiles. There are no issues distinguishing one product from another from a safety perspective.

ANNEX B: Included Studies

SUMMARY OF EVIDENCE:
Green= Impact demonstrated
Yellow= No statistically significant effects
Red= Increases in Outcome

1. Immunogenicity:

TABLE Imm 1. Characteristics of study arms that evaluated impact of product and schedule on immunogenicity in children

	PCV10 (n=64)		PCV13 (n=56)	
Primary doses	2 dose (n=11)	3 dose (n=53)	2 dose (n=17)	3 dose (n=39)
Africa	0	4	1	1
Asia	7	16	2	6
Europe	4	26	13	18
N America	0	4	1	10
Oceania	0	1	0	2
S America	0	2	0	2
Income				
High/HMIC	4	39	14	35
Low/LMIC	7	14	3	4
Co-Vaccination				
DTaP	3	32	9	26
No DTaP	8	21	8	13
Age at Dose 1				
1m	0	1	0	2
1.5-1.75m	1	13	1	3
2m-2.25m	8	34	14	32

3m	2	5	2	1
4-4.5m	0	0	0	1
Dose 1-2 Interval				
1m	2	38	1	20
1.25-1.75m	0	4	0	0
2m-2.75	7	11	16	19
4m	2	0	0	0
Dose 2-3 Interval				
1m	NA	37	NA	20
2m	NA	13	NA	19
3m	NA	3	NA	
Age at Last Primary Dose				
3-3.5m	2	11	2	5
4-4.5m	5	20	13	13
5m	2	8	2	1
6m-7.5m	2	14	0	20
Age at Booster				
None	6**	12	3**	5
9m	3	1	3	0
10.5-14.5m	2	20	11	31
15-24m	0	20	0	3

TABLE Imm 2. Number of immunogenicity study arms included by schedule and PCV product for geographic regions and country income strata

Schedule	2p			3p		
Characteristic N=119	**PCV10** 10	**PCV13** 17	**Total** 28	**PCV10** 53	**PCV13** 39	**Total** 92
Region						
Africa	0	1	1	4	1	5
Asia	7	2	9	16	6	22
Australia/Oceania	0	0	0	1	2	3
Europe	3	13	17	26	18	44
Latin America	0	1	1	6	3	9
North America	0	0	0	0	9	9
Income						
High (High & Upper-Middle)	3	14	18	39	35	74
Low (Low & Lower-Middle)	7	3	10	14	4	18

TABLE Imm 3. Characteristics of study arms that evaluated impact of 1 or 2 catch-up doses on Immunogenicity in children 12-59 months of age, by product

	PCV10		PCV13		Total			
	1 Dose (8)	**2 Dose (10)**	**1 Dose (9)**	**2 Dose (2)**	**0+1 (16)**	**0+2 (14)**	**PCV10 (19)**	**PCV13 (11)**
Africa (14)	2	4	6	2	8	6	6	8
Asia (2)	0	2	0	0	0	2	2	0
Australia/Oceana (0)	0	0	0	0	0	0	0	0
Europe (10)	6	2	2	0	8	2	8	2
Latin America (3)	0	2	1	0	1	2	2	1
Income Status								
High Income (12)	6	4	2	0	8	4	10	2
Low Income (17)	2	6	7	2	9	8	8	9
Age at Last Dose								
12-24 months (15)	0	10	2	3	2	13	10	5

25-36 (7)	2	0	5	0	7	0	2	5
37-59(9)	6	1	2	0	8	1	8	2

2. NP Carriage Direct Effects:

TABLE NPC 1. PICO I: Characteristics of studies that evaluated impact of schedule on vaccine-type NP carriage in children, by product

Schedule:	**2+1**			**3+0**		
Characteristic:	**PCV10 (3)**	**PCV13 (9)**	**Total (12)**	**PCV10 (16)**	**PCV13 (5)**	**Total (21)**
Study Design						
Cohort				1		1
Post Survey				1	1	2
Pre Post Survey		9	9	7	3	10
RCT	1		1	3		3
RCT - Head to Head*	2		2	4	1	5
Region						
Africa		2	2	4	3	7
Asia	1		1	2	1	3
Australia/Oceania				1		1
Europe	2	7	9	6		6
Latin America				1		1
Oceana				2	1	3
Income Status						
HIC	2	9	11	9		9
LIC	1		1	7	5	12
Catch UP		2	2	2	1	3

Previous PCV7 Use		9	9	3	1	4

*Vaccine arms instead are shown for head-to-head studies.

TABLE NPC 2. PICO II: Characteristics of studies that evaluated impact of product on vaccine-type NP carriage in children, by schedule

Schedule:	**PCV10**			**PCV13**		
Characteristic:	**2+1 (3)**	**3+0 (16)**	**Total (19)**	**2+1 (9)**	**3+0 (5)**	**Total (14)**
Study Design						
Cohort		1	1			
Post Survey		1	1		1	1
Pre Post Survey		7	7	9	3	12
RCT	1	3	4			
RCT - Head to Head*	2	4	6		1	1
Region						
Africa		4	4	2	3	5
Asia	1	2	3		1	1
Australia/Oceania		1	1			
Europe	2	6	8	7		7
Latin America		1	1			
Oceana		2	2		1	1
Income Status						
HIC	2	9	11	9		9
LIC	1	7	8		5	5
Catch UP		2	2	2	1	3
Previous PCV7 Use		3	3	9	1	10

*Vaccine arms are shown for head-to-head studies.

TABLE NPC 3. PICO II: Characteristics of studies that evaluated impact of product on vaccine-type NP carriage in children, by schedule

Reference	Country	Region	Income Stratification	Study Type	Product	Schedule
Vesikari 2016	Finland	Europe	High	Head-to-Head RCT	PCV10	NA
Kim 2016	Kenya (Asembo v. Kibera)	Africa	Low	Head-to-Head Pre Post Survey	PCV10	3+0
Hammitt 2014; 2016	Kenya, Kilifi	Africa	Low	Pre Post Survey	PCV10	3+0
Verhagen, 2016	Venezuela (Warao)	South America	Low	Single Arm Trial	PCV13	NA

TABLE NPC 4. Observational studies estimating percent relative reduction against vaccine serotype NP Carriage among the general population

Region	Reference	High Income/UMIC vs Low income/LMIC	Study Type	Schedule	PCV Introduction	Number of Years Post Introduction Carriage Evaluated	Age Group (Population)	Relative Reduction[1]
PCV10								
Oceania	Fiji (Dunne; Russell 2016)	HIC/UMIC	Pre Post Survey	3+0	PCV10: 2012	PCV10: 3	5wks-23 mos (General)	84% (76%, 90%)
Oceania	Fiji (Dunne; Russell 2016)	HIC/UMIC	Pre Post Survey	3+0	PCV10: 2012	PCV10: 3	12-23 mos (General)	73% (60%, 81%)
Oceania	Fiji (Dunne; Russell 2016)	HIC/UMIC	Pre Post Survey	3+0	PCV10: 2012	PCV10: 3	5wks-6y (General)	96% (92%, 97%)

Africa	*Kenya, Asembo (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5years (General)	52% (29%, 67%)
Africa	Kenya, Kibera (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10 2	<5 years (General)	52% (40%, 62%)
Africa	*Kenya, Kilifi (Hammitt 2014; 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<2 (General)	84% (76%, 89%)
Africa	*Kenya, Kilifi (Hammitt 2014; 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5years (General)	97% (94%, 99%)
Africa	Mozambique (Sigaque; Moiane 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2013	PCV10: 2	0-23 mos (HIV -)	43% (19%, 60%)
Africa	Mozambique (Sigaque; Moiane 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2013	PCV10: 2	0-59 mos (HIV -)	30% (12%, 44%)
Australia/Oceania	Australia (Wigger, 2014)	HIC/UMIC	Post Survey	3+0	PCV7: 2005 PCV10: 2009	PCV7: 3 PCV10: 1.5	<36 months (Aboriginal)	27% (-8%, 50%)
PCV13								
Africa	Burkina Faso (Moisi 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV13: 2013	PCV13: 2	<5 years (General)	41% (28%, 51%)
Africa	Gambia (Roca 2014; 2015)	LIC/LMIC	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	45% (28%, 58%)
Africa	Malawi (Swarthout, 2016)	LIC/MIC	Post Survey	3+0	PCV13: 2011	PCV13: 4	3-5 years	NS
Asia	Cambodia (SuyKuong 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	0-11 mos (General)	28% (15%, 39%)
Asia	Cambodia (SuyKuong 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	<5 yyears (General)	11% (1%, 21%)
Africa	South Africa, Agincourt sub district (Nzenze 2016)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General)	56% (45%, 65%)

Africa	South Africa, Agincourt sub district (Nzenze 2016)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<5 years (General)	55% (47%, 62%)
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General)	42% (32%, 50%)
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<48 months (General)	62% (56%, 67%)
Europe	France (Dunais 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 2 PCV13: 2	3-40 mo (Day Care)	78% (58%, 88%)
Europe	*Isreal (Danino 2016; Ben Shimol 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2008 PCV13: 2010	PCV7: 2 PCV13 4	<5	73% (68%, 78%)
Europe	Norway (Steens 2015, Vestrheim 2008; 2010;)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (Day Care)	74% (44%, 88%)
Europe	Norway (Steens 2015, Vestrheim 2008; 2010;)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 2	<59 months (Day Care)	75% (65%, 82%)
Europe	Sweden (Galanis 2016)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	46% (NS)
Europe	UK (Devine 2016; Jones 2016; Gladstone 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 4 PCV13: 5	<4 years (General)	88.3% (59%, 97%)
Europe	*UK (Van Hoek 2014)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 3 PCV13: 3	<5 years (General)	94% (78%, 99%)

*Denotes a catch-up was used in study population

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that

switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

TABLE NPC 5. Observational studies estimating percent relative reduction against serotype 3 NP Carriage among the general population

Region	Reference	High Income/UMIC vs Low income/LMIC	Study Type	Schedule	PCV Introduction	Number of Years Post Introduction Carriage Evaluated	Age Group (Population)	Relative Reduction
PCV10								
Africa	*Kenya, Asembo (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	-32% (-166%, 35%)
Africa	Kenya, Kibera (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	-87% (-243%, -2%)
Africa	*Kenya, Kilifi (Hammitt 2014; 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<2 (General)	-9% (-403%, 76%)
Africa	*Kenya, Kilifi (Hammitt 2014; 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	42% (-40%, 76%)
Africa	Malawi (Swarthout, 2016)	LIC/MIC	Post Survey	3+0	PCV13: 2011	PCV13: 4	3-5 years	NS
Europe	Netherlands (Vissers 2016; Bosch 2015; 2014)	HIC/UMIC	Pre Post Survey	3+0	PCV7: 2006 PCV10: 2011	PCV7: 5 PCV10: 5	<2 years (General)	50% (-33%, 81%)
Europe	Netherlands (Wyllie, 2016)	HIC/UMIC	Post Survey	3+0	PCV7: 2006 PCV10: 2011	PCV7: 4 PCV10: 1	11 months (General)	17% (-169%, 74%)
PCV13								
Africa	Gambia (Roca 2014; 2015)	LIC/LMIC	Pre Post Survey	3+0	PCV7 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	Increased from zero(NS)[2]

Asia	Cambodia (SuyKuong 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	<5 (General)	65% (3%, 87%)
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General)	-60% (-354%, 44%)
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV1:3 2	<48 months (General)	49% (-16%, 78%)
Europe	France (Varon, 2015)	HIC/UMIC	Post Survey	2+1	PCV7: 2002 PCV13: 2010	PCV7: 6 PCV13: 3	6-24 months (General)	-42% (-258%, 44%)
Europe	Norway (Vestrheim 2008; 2010; Steens 2015, 2016)	HIC/UMIC	Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 4	<7 years (General)	74% (46%, 88%)
Europe	Sweden (Galanis 2016)	HIC/UMIC	Pre Post Survey	2+1	PCV7 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	-5% (NS)
Europe	UK (Devine 2016; Jones 2016; Gladstone 2015)	HIC/MIC	Pre Post Survey	2+1		PCV7: 3 PCV13: 5	<4 years <5 years (General)	100% (Decreased to zero, NS)

*Denotes a catch-up was used in study population

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

[2]Percent change not calculated because zero denominator

TABLE NPC 6. Observational studies estimating percent relative reduction against serotype 6A NP Carriage among the general population

Region	Reference	Income Status	Study Type	Schedule	PCV Introduction	Number of Years Post Introduction Carriage Evaluated	Age Group (Population)	Relative Reduction
PCV10								
Oceania	Fiji (Dunne; Russell 2016)	HIC/UMIC	Pre Post Survey	3+0	PCV10: 2012	PCV10: 3	12-23 mos (General)	28% (-41%, 63%)
Africa	*Kenya, Asembo (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	38% (-33%, 71%)
Africa	Kenya, Kibera (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	15% (-38%, 47%)
Africa	*Kenya, Kilifi (Hammitt 2014; 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<2 (General)	17% (-45%, 52%)
Africa	*Kenya, Kilifi (Hammitt 2014; 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	10% (-47%, 45%)
Europe	Netherlands (Vissers 2016; Bosch 2015; 2014)	HIC/UMIC	Pre Post Survey	3+0	PCV7 2006 PCV10: 2011	PCV7: 5 PCV10: 5	<2 years (General)	84% (20%, 97%)
PCV13								
Africa	Gambia (Roca 2014; 2015)	LIC/LMIC	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	63% (39%, 77%)
Asia	Cambodia (SuyKuong 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	<5 (General)	29% (5%, 46%)

Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General)	72% (50%, 84%)
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV1:3 2	<48 months (General)	67% (47%, 80%)
Europe	France (Varon, 2015)	HIC/UMIC	Post Survey	2+1	PCV7: 2002 PCV13: 2010	PCV7: 6 PCV13: 3	6-24 months (General)	100% (NS)
Europe	Norway (Vestrheim 2008; 2010; Steens 2015, 2016)	HIC/UMIC	Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 4	<7 years (General)	100% (Decreased to zero, NS)
Europe	Sweden (Galanis 2016)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	34% (NS)
Europe	UK (Devine 2016; Jones 2016; Gladstone 2015)	HIC/MIC	Pre Post Survey	2+1		PCV7: 3 PCV13: 5	<4 years <5 years (General)	100% (Decreased to zero, NS)

*Denotes a catch-up was used in study population

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

TABLE NPC 7. Observational studies estimating percent relative reduction against serotype 6B NP Carriage among the general population

Region	Reference	Income Status	Study Type	Schedule	PCV Introduction	Number of Years Post Introduction Carriage Evaluated	Age Group (Population)	Relative Reduction
PCV10								
Oceania	Fiji (Dunne; Russell 2016)	HIC/UMIC	Pre Post Survey	3+0	PCV10: 2012	PCV10: 3	12-23 mos (General)	100.0% (NS)
Africa	*Kenya, Asembo (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	98% (56%, 100%)
Africa	Kenya, Kibera (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	73% (53%, 85%
PCV13								
Africa	Gambia (Roca 2014; 2015)	LIC/LMIC	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	100.0% (NS)
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General)	58% (12%, 80%
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7; 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<48 months (General)	59% (23%, 78%
Europe	France (Varon, 2015)	HIC/UMIC	Post Survey	2+1	PCV7: 2002 PCV13: 2010	PCV7: 6 PCV13: 3	6-24 months (General)	-5% (-523%, 82%)
Europe	UK (Devine 2016; Jones 2016; Gladstone 2015)	HIC/MIC	Pre Post Survey	2+1		PCV7: 3 PCV13: 5	<4 years <5 years (General)	100% (Decreased to zero, NS)

*Denotes a catch-up was used in study population

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

TABLE NPC 8. Observational studies estimating percent relative reduction against serotype 6C NP Carriage among the general population

Region	Reference	Income Status	Study Type	Schedule	PCV Introduction	Number of Years Post Introduction Carriage Evaluated	Age Group (Population)	Relative Reduction
PCV10								
Oceania	Fiji (Dunne; Russell 2016)	HIC/UMIC	Pre Post Survey	3+0	PCV10: 2012	PCV10: 3	12-23 mos (General)	Increased fron 0 (NS)
Europe	Netherlands (Vissers 2016; Bosch 2015; 2014)	HIC/UMIC	Pre Post Survey	3+0	PCV7 2006 PCV10: 2011	PCV7: 5 PCV10: 5	<2 years (General)	-65% (-165%, - 2.5%)
PCV13								
Europe	France (Varon, 2015)	HIC/UMIC	Post Survey	2+1	PCV7: 2002 PCV13: 2010	PCV7: 6 PCV13: 3	6-24 months (General)	45% (-65%, 82%)
Europe	Norway (Vestrheim 2008; 2010; Steens 2015, 2016)	HIC/UMIC	Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 4	<7 years (General)	71% (43%, 85%
Europe	UK (Devine 2016; Jones 2016; Gladstone 2015)	HIC/MIC	Pre Post Survey	2+1		PCV7: 3 PCV13: 5	<4 years <5 years (General)	71% (3%, 91%

*Denotes a catch-up was used in study population

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

TABLE NPC 9. Observational studies estimating percent relative reduction against serotype 19A NP Carriage among the general population

Region	Reference	Income Status	Study Type	Schedule	PCV Introduction	Number of Years Post Introduction Carriage Evaluated	Age Group (Population)	Relative Reduction
PCV10								
Oceania	Fiji (Dunne; Russell 2016)	HIC/UMIC	Pre Post Survey	3+0	PCV10: 2012	PCV10: 3	12-23 mos (General)	Increased from Z (NS)[2]
Africa	*Kenya, Asembo (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	-1778% (NS)
Africa	Kenya, Kibera (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	-659% (-1597%, -239%)
Africa	*Kenya, Kilifi (Hammitt 2014; 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<2 (General)	-344% (-1269%, -
Africa	*Kenya, Kilifi (Hammitt 2014; 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	-369% (-1178%, -
Europe	Netherlands (Vissers 2016; Bosch 2015; 2014)	HIC/UMIC	Pre Post Survey	3+0	PCV7: 2006 PCV10: 2011	PCV7: 5 PCV10: 5	<2 years (General)	68% (52%, 78%)

Europe	Netherlands (Wyllie, 2016)	HIC/UMIC	Post Survey	3+0	PCV7: 2006 PCV10: 2011	PCV7: 4 PCV10: 1	11 months (General)	23% (-14%, 48%)
PCV13								
Africa	Gambia (Roca 2014; 2015)	LIC/LMIC	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	24% (-30%, 56%)
Asia	Cambodia (SuyKuong 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV13: 2015	PCV13: 0.5	<5 (General)	-20% (-324%, 66%
Europe	France (Dunais 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2006 PCV13: 2010	PCV7: 2 PCV13: 2	3-40 mo (Day Care)	57% (14%, 79%)
Europe	Norway (Vestrheim 2008; 2010; Steens 2015, 2016)	HIC/UMIC	Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 4	<7 years (General)	76% (11%, 94%)
Europe	France (Varon, 2015)	HIC/UMIC	Post Survey	2+1	PCV7: 2002 PCV13: 2010	PCV7: 6 PCV13: 3	6-24 months (General)	52% (-4%, 78%)
Europe	Sweden (Galanis 2016)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2007 PCV13: 2010	PCV7: 3 PCV13: 4	<6 years (General)	33% (NS)
Europe	UK (Devine 2016; Jones 2016; Gladstone 2015)	HIC/MIC	Pre Post Survey	2+1		PCV7: 3 PCV13: 5	<4 years <5 years (General)	81% (59%, 91%)

*Denotes a catch-up was used in study population

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

[2]Percent change not calculated because zero denominator

TABLE NPC 10. Observational studies estimating percent relative reduction against serotype 19F NP Carriage among the general population

Region	Reference	Income Status	Study Type	Schedule	PCV Introduction	Number of Years Post Introduction Carriage Evaluated	Age Group (Population)	Relative Reduction
PCV10								
Oceania	Fiji (Dunne; Russell 2016)	HIC/UMIC	Pre Post Survey	3+0	PCV10: 2012	PCV10: 3	12-23 mos (General)	100% (NS)
Africa	*Kenya, Asembo (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	69% (31%, 86%)
Africa	Kenya, Kibera (Kim 2016)	LIC/LMIC	Pre Post Survey	3+0	PCV10: 2011	PCV10: 2	<5 (General)	-326% (-851%, -91%)
Europe	Netherlands (Wyllie, 2016)	HIC/UMIC	Post Survey	3+0	PCV7: 2006 PCV10: 2011	PCV7: 4 PCV10: 1	11 months (General)	50% (-97%, 87%)
PCV13								
Africa	Gambia (Roca 2014; 2015)	LIC/LMIC	Pre Post Survey	3+0	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 1	6-11 months (General)	70% (25%, 88%)
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7: 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<2 years (General)	48% (19%, 66%)
Africa	South Africa, Soweto (Nzenze 2015)	HIC/UMIC	Pre Post Survey	2+1	PCV7; 2009 PCV13: 2011	PCV7: 2 PCV13: 2	<48 months (General)	40% (10%, 60%)
Europe	France (Varon, 2015)	HIC/UMIC	Post Survey	2+1	PCV7: 2002 PCV13: 2010	PCV7: 6 PCV13: 3	6-24 months (General)	52% (-16%, 81%)

Europe	Norway (Vestrheim 2008; 2010; Steens 2015, 2016)	HIC/UMIC	Post Survey	2+1	PCV7: 2006 PCV13: 2011	PCV7: 2 PCV13: 4	<7 years (General)	81% (64%, 90%)
Europe	UK (Devine 2016; Jones 2016; Gladstone 2015)	HIC/MIC	Pre Post Survey	2+1		PCV7: 3 PCV13: 5	<4 years <5 years (General)	Increased from 0% (NS)[2]

*Denotes a catch-up was used in study population

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

[2]Percent change not calculated because zero denominator

TABLE NPC 11. Randomized Controlled Trials estimating percent relative reduction against NP Carriage of the Vaccine-Type Serotypes, Serotype 3, Serotype 6A, and Serotype 19A among the general population.

Study Information				PCV10 or PCV 13		Serotype 3		Serotype 6A		Serotype 6b		Serotype19A		Serotype 19F	
Region	Country (Reference)	Income Status	Dosing Schedule	Baseline	% Reduction	Baseline	% Reduction	Baseline	% Reduction	Baseline	% Reduction	Baseline	% Reduction	Baseline	% Reduction
PCV10															
Eur	Finland, (Jokinen 2016)	HIC/UMIC	2+1	13.20 %	61% (35, 76)										
Asia	Vietnam, (Mullholand 2017, Temple,	LIC/LMIC	2+1	9.10%	53% (-18, 81)	0.00%	NS	9.9%	52% (-16, 80)	1.3%	61% (-109,93)	1.6%	-88% (-724, 57)	3.8%	71%(-68, 95)

	Smith-Vaguhan 2016)														
Asia	Nepal, (Hamaluba 2015)	LIC/LMIC	3+0	8.87%	6% (-118, 60)	0.81%	-15% (-1714, 93)	6.45%	43% (-85, 82)	3.00%	-23% (-395, 69)	3.2%	100% (NS)	1.00%	0% (-1202, 92)
Asia	Vietnam, (Mullholand 2017, Temple, Smith-Vaguhan 2016)	LIC/LMIC	3+0	9.10%	18% (-74, 61)			9.9%	93% (44, 99)			1.6%	-181% (-1005, 28)		
S Amr	COMPAS, (Borys 2012)	HIC/UMIC	3+0	16.10 %	27% (7, 43)										
Eur	Czech Repubic (Prymula 2011)[2]	HIC/LMIC	3+0	16%	34% (4, 55)										
Eur	Finland, (Vesikari 2016)	HIC/UMIC	3+0	18.2%	30% (17, 41)			1.9%	-26.3% (-104, 21)			1.0%	50.2% (-16, 80)		
Eur	Finland, (Vesikari 2016)	HIC/UMIC	2+1	20.1%	38% (25, 49)			2.3%	15.5% (-42.8, 51.1)			1.2%	1.4% (-103, 54)		
PCV13															
Asia	Vietnam, (Mullholand 2017, Temple,	LIC/LMIC	2+1	9.1%	23% (-48, 60)	0%	0% (NS)	9.9%	74% (35, 89)	2.2%	33%(-113,79)	1.6%	-6% (-373, 76)	3.8%	42%(-78, 81)

	Smith-Vaguhan 2016)														
Eur	Isreal (Dagan 2013)[3]	HIC/MIC	3+0									7%	36% (5, 56)		

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

[2] Cohort Study

[3] PCV7 Control

TABLE NPC 12. Head to Head Randomized Controlled Trials comparing NP Carriage in PCV10 and PCV13 among the general population

Region	Country (Reference)	Dosing Schedule	Product	% Carriage							
				All Carriage	PCV10	PCV13	3, 6A, 19A	6A	6B	19A	19F
Asia	Papau New Guinea (Pomat 2016, Orami 2016) ** Data taken from the Orami paper 9 mos group*	3+0	PCV13	89.0%	22%	30%	8%	--	--	--	--
			PCV10	90.0%	19%	32%	14*	--	--	--	--
				All Carriage	PCV10	PCV13	3	6A	6B	19A	19F
Asia	Vietnam, (Mullholand 2017, Temple, Smith-Vaguhan 2016)	2+1	PCV10	25.0%	4%		1.4%	4.8%	1.3%	3%	1.1%
			PCV13	25.0%	7%		0.0%	2.6%	2.2%	1.7%	2.2%

			Control	28.9%	9%		0.0%	7.0%	3.3%	1.6%	3.8%

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

TABLE NPC 13. Head to Head Randomized Controlled Trials comparing NP Carriage in 2+1 and 3+0 among the general population

Region	Country (Reference)	Product	Dosing Schedule	% Carriage				
				All Carriage	PCV10	PCV13	6A	19A
Asia	Vietnam, (Mullholand 2017, Temple, Smith-Vaguhan 2016)	PCV10	2+1	24.7%	4.3%	12.1%	4.8%	3%
			3+0	25.4%	7.5%	13.2%	0.70	4.5%
			Control	28.9%	9.1%	17.4%	9.9%	1.6%
				All Carriage	PCV10	PCV13	6A	19A
Europe	Finland (Vesikari 2016)	PCV10	2+1	30.2%	15.6%	15.6%	2.0%	1.1%
			Control	35.2%	20.1	23.6%	2.3%	1.2%
			3+0	28.0%	15.7%	15.6%	2.4%	0.5%
			Control	32.2%	18.2%	21.1%	1.9%	1.0%

[1]Relative change in VT carriage, defined for observational studies of routine use as (pre% - post%)/pre% where 'pre' is prior to or at time of PCV10/13 introduction, and for clinical trials and non-randomized comparisons as (unvaccinated% - vaccinated%)/unvaccinated% where 'unvaccinated' is a non-PCV control group. Observational studies include countries that switched from PCV7 to PCV10/13; only those that had carriage prevalence data at the time PCV10/13 was introduced were included in figure.

3. NP Carriage Indirect Effects:

TABLE NPC Ind Eff 1. Randomized Controlled Trials and Observational Studies estimating % Relative Reduction on NP Carriage in the Non- Vaccine Targeted Cohort

Study Information									% Relative Reduction (95% CI) Compared to		
Region	Country (Reference)	Country Income Status	Study Design	Dosing Schedule	Catch Up Used	PCV Introduction	Number of Years Post Introduction	Age Group (Population)	Baseline (no PCV)	PCV7 Period	Comments
PCV10											
PCV10 VT Carriage											
2+1											
EUR	Finland (Jokinen 2016)	HIC/UMIC	RCT and post survey	2+1 in NIP, after FinIP trial with 2+1, 3+1 or control arms	No	PCV10: 2010	PCV10: 3	3-9 years (Older siblings of controls in RCT)	63%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post) compared to 20 (early post)
							PCV10: 4	3-9 years (Older siblings of PCV recipients in RCT)	57%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post) compared to 20 (early post)
EUR	Netherlands (Vissers 2016)	HIC/UMIC	Pre Post Survey	3+1 then 2+1	No	PCV7: 2006 PCV10: 2011	PCV7: 3 years PCV10: 4.5 years	Adults (General)	100%	No carriage in PCV7 period	
3+0											

WPR	Fiji (Dunne 2016)	HIC/UMIC	Pre Post Survey	3+0	No	PCV10: 2012	PCV10: 3 years	5-8 week olds (General)	100%	--	
								Adults (General)	100%	--	
AFR	Kenya (Hammitt 2016)	LIC/LMIC	Pre Post Survey	3+0	Yes	PCV10: 2011	PCV10: median of 2 years	≥ 5 years (General)	65% (46%, 78%)*	--	Adjusted prevalence rat
							PCV10: 4 years	5-9 years (General)	52%	--	baseline 2009-2(
								10-14 years (General)	67%	--	
								15-19 years (General)	100%	--	
								20-39 years (General)	54%	--	
								40-49 years (General)	100%	--	
								50-59 years (General)	100%	--	
								≥ 60 years (General)	100%	--	
3/6A/19A (PCV13-nonPCV10 serotypes)											
2+1											
EUR	Netherlands (Vissers 2016)	HIC/UMIC	Pre Post Survey	3+1 then 2+1	No	PCV7: 2006 PCV10: 2011	PCV7: 3 years PCV10: 4.5 years	Adults (General)	100%	100%	Carriage went up PCV7 period (fr 3.6% to 4.5%) a then came down 0%. No carriage 3+ serotypes in period.
Serotype 3											
2+1											
EUR	Finland (Jokinen 2016)	HIC/UMIC	RCT and post survey	2+1 in NIP, after FinIP trial with 2+1,	No	PCV10: 2010	PCV10: 3	3-9 years (Older siblings of controls in	-31%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post)

				3+1 or control arms				RCT)			compared to 20 (early post)
							PCV10: 4	3-9 years (Older siblings of PCV recipients in RCT)	-121%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post) compared to 20 (early post)
Serotype 6A											
2+1											
EUR	Finland (Jokinen 2016)	HIC/UMIC	RCT and post survey	2+1 in NIP, after FinIP trial with 2+1, 3+1 or control arms	No	PCV10: 2010	PCV10: 3	3-9 years (Older siblings of controls in RCT)	55%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post) compared to 20 (early post)
							PCV10: 4	3-9 years (Older siblings of PCV recipients in RCT)	55%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post) compared to 20 (early post)
Serotype 19A											
2+1											
EUR	Finland (Jokinen 2016)	HIC/UMIC	RCT and post survey	2+1 in NIP, after FinIP trial with 2+1, 3+1 or control arms	No	PCV10: 2010	PCV10: 3	3-9 years (Older siblings of controls in RCT)	-88%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post) compared to 20 (early post)
							PCV10: 4	3-9 years (Older siblings of	-61%	--	Baseline is 1 ye post PCV10 introduction in N

								PCV recipients in RCT)			2013 (post) compared to 20 (early post)
Serotype 6C											
2+1											
EUR	Finland (Jokinen 2016)	HIC/UMIC	RCT and post survey	2+1 in NIP, after FinIP trial with 2+1, 3+1 or control arms	No	PCV10: 2010	PCV10: 3	3-9 years (Older siblings of controls in RCT)	-39%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post) compared to 20 (early post)
							PCV10: 4	3-9 years (Older siblings of PCV recipients in RCT)	-130%	--	Baseline is 1 ye post PCV10 introduction in N 2013 (post) compared to 20 (early post)

*Adjusted

4. Invasive Pneumococcal Disease Direct Effects:

TABLE IPD 1. ST1 Impact Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Country schedule	Catch up	Products	Pre-PCV years	Post-PCV7/pre-PCV10-13 years	Post-PCV10-13 years	Serotype	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Red on vs PCV7 perio
PCV7 followed by PCV13, 2+1															
Lepoutre et al. Vaccine 2015	VT-IPD, <2	France	Europe	high	PCV13_2,4,11mo		PCV7, PCV13	2	2	1	1	N/A	N/A	.	96 (73,10
Waight et al. Lancet Inf Dis 2015	VT-IPD, <5	England and Wales	Europe	high	PCV13_2/4/13	No	PCV7, PCV13	5	4	4	1	N/A		.	91 (68
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	PCV13_2/4/12	No	PCV7, PCV13	4	1	1	1	3.8 ± 1.5	5.2	84 (58,94)	88(71
Ben-Shimol(2015)	Bact. Pneu., <5	Israel	Middle East	high	PCV7_2 mos/4mos/12mos	Yes	PCV7, PCV13	4	2	2	1	2.2 ± 0.6	4.1	78(35, 93)	88(66
Ben-Shimol(2015)	NBP IPD, <5	Israel	Middle East	high	PCV7_2 mos/4mos/12mos	Yes	PCV7, PCV13	4	2	2	1	1.6 ± 0.9	1.1	92(38, 99)	89(16
Von Gottbergh (2014)	VT IPD, <2 years	South Africa	Africa	High	PCV13_6,14 wks,9mos	No	PCV7, PCV13	4	2	1	1	N/A	N/A	57 (79,16)	
Diawara et al 2015 (1536)	VT IPD, <2 years	Morocco	Africa	Low	PCV13_2/4/12	No	PCV7, PCV13	4		4	1	1.75		51	
PCV7 followed by PCV10, 2+1															
Naucler et al (2017)	IPD, <5	Sweden	Europe	High	2+1	No	PCV7, PCV13 *select counties	0.5	1	4.5	1	0 (0, 3.7)	0 (0,1.2)	-	-

TABLE IPD 2. ST 1 Impact Demonstrated: Case Control Studies

Study				VE compared to no vaccine (95%CI)		
Country (Reference)	Study Design	Population age	PCV product (Country Schedule)	Serotype	≥1 dose	≥2 doses
PCV13, 2+1						
United Kingdom (Andrews et al., 2014)	Indirect cohort	4 to ≤56 months	PCV13 (2+1)	1	--	84% (54-95%)[1]

TABLE IPD 3: ST 1 Non-Significant/No Direct Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Country schedule	Catch up	Products	Pre-PCV years	Post-PCV7/pre-PCV10-13 years	Post-PCV10-13 years	Serotype	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Re on v PCV7 perio
PCV7 followed by PCV13, 2+1															
Harboe et al. CID 2014	VT-IPD, <2	Denmark	Europe	high	PCV13 3,5,12mo		PCV7, PCV13	7	3	3	1	1.6 (1-2.60)	1.3 (.5-3.0)	.	No chan
I. Galanis(2016)	IPD, All ages	Sweden	Europe	high	PCV13 3/5/12mos		PCV7, PCV13	2	4	4	1	.	.	13 (-69,56)	23 (-55,6
Naucler et al (2017)	IPD, <5 years	Sweden	Europe	High	2+1	No	PCV7, PCV13 *select counties	0.5	1	4.5	1	0± 1.6 (0,1.6)	0.1 (0.02, 1.0)	-	0 (10 1200
PCV7 followed by PCV13, 3+0															
Jayasinghe (2016)	IPD, <2	Australia	Oceania	high	PCV13 2m/4m/6m	Yes	PCV7, PCV13	3	6.5	3.5	1	.	0.13	.	100 (1386 100)

TABLE IPD 4. ST 1 Non-Significant/No Direct Effects Demonstrated: Case Control Studies

Study				VE compared to no vaccine (95%CI)		
Country (Reference)	Study Design	Population age	PCV product (Country Schedule)	Serotype	≥1 dose	≥2 doses

PCV13, 2+1						
UK (Miller et al., 2011)	Case-control	2.5 to <24 months	PCV13 (2+1)	1	62%(-112 to 92)	--

TABLE IPD 5. ST 3 Direct Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Catch up	Post-PCV10-13 years	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reductio PCV7 peri
PCV7 followed by PCV13 2+1										
Lepoutre et al. Vaccine 2015	VT-IPD, <2	France	Europe	high		1	N/A	N/A	.	85 (36,96)
Waight et al. Lancet Inf Dis 2015	VT-IPD, <5	England and Wales	Europe	high	Yes	4	N/A		.	68 (6,89)
Diawara et al 2015 (1536)	VT IPD, <2 years	Morocco	Africa	Low	No	4	1.75		80	

TABLE IPD 6. ST3 Non-Significant/No Direct Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Catch up	Post-PCV10-13 years	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV10, 2+1										
Rinta-Kokko et al. ISPPD 2016	IPD, <2	Finland	Europe	high	No	5	0.4		-194 (-1224,17)	
PCV7 followed by PCV10, 2+1										
Naucler e al (2017)	IPD, <5	Sweden	Europe	High	No	4.5	0 (0, 3.7)	0.7 (0.2, 2.7)	Not calculable	29 (-431, 99)
PCV7 followed by PCV13 2+1										
Harboe et al. CID 2014	VT-IPD, <2	Denmark	Europe	high		3	0.6 (.2–1.3)	1.3 (.5–3.0)	.	No change
Von Gottberg et al. NEJM	VT-IPD, <2	South	Africa	high	No	2	0.6		41 (-54, 79)	

2014		Africa								
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	No	1	0.3 ± 0.3	0.8	-145(-1380, 36)	-13(-237, 62)
Ben-Shimol(2015)	Bactpneu, <5	Israel	Middle East	high	Yes	2	0.1 ± 0.1	0.7	-688(-14536, 58)	23(-168, 79)
Ben-Shimol(2015)	NBP IPD, <5	Israel	Middle East	high	Yes	2	0.3 ± 0.3	0.1	-75(-856, 68)	-283(-3331, 57)
I. Galanis(2016)	IPD, All Ages	Sweden	Europe	high		4		.	-62 (-132,-13)	-5 (-47,25)
Naucler et al (2017)	IPD, <5	Sweden	Europe	High	No	4.5	0 (0,1.6)	0.7 (0.2,1.8)	Not calculable	23 (-200,80)
PCV7 followed by PCV13 3+0										
Jayasinghe(2016)	IPD, <2	Australia	Oceania	high	Yes	3.5		1.11	.	-35 (-227,45)

TABLE IPD 7. ST 3 Non-Significant/No Direct Effects Demonstrated: Case Control Studies

Study				VE compared to no vaccine (95%CI)	
Country (Reference)	**Study Design**	**Population age**	**PCV product (Country Schedule)**	**≥1 dose**	**≥2 doses**
PCV10, 3+1					
Brazil (Domingues et al 2014)	Matched Case-control	<5 years	PCV10 (3+1), catch up for 12-23 months	7.8% (–271.9 to 77.1%)[2]	
PCV13, 2+1					
United Kingdom (Andrews et al., 2014)	Indirect cohort	4 to ≤56 months 2.5 to <24	PCV13 (2+1)		26% (–69,68%)[1]

(Miller et al., 2011) (1130)	Case-control	months		66%(-17 to 90)	
PCV13, 3+1					
Germany (Weinnberger et al., 2016)	Indirect cohort	2.5-56 months	PCV13 (3+1)		0% (-791 to 89)

TABLE IPD 8. Increases In ST3 IPD Observed In Directly Vaccinated Age Groups: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Catch up	Post-PCV10-13 years	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV10, 2+1										
Jokinen (2015)	IPD, 3 to 42 months	Finland	Europe	high	No	4	0.5		-354 (-2006,-26)	.

TABLE IPD 9. ST 6A Direct Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Catch up	Post-PCV10-13 years	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV10 2+1										
Rinta-Kokko et al. ISPPD 2016	IPD, <2	Finland	Europe	high	No	5	2.8		100(67,100)	.
Jokinen (2015)	IPD, 3 to 42 months	Finland	Europe	high	No	4	2.2	.	100 (41,100)	.

PCV7 followed by PCV13 2+1										
Waight et al. Lancet Inf Dis 2015	VT-IPD, <5	England and Wales	Europe	high	Yes	4	N/A	.	.	100 (62,100)
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	No	1	3.3 ± 0.9	0.7	92(72, 98)	61(-100, 92)
Ben-Shimol(2015)	NBP IPD, <5	Israel	Middle East	high	Yes	2	2.6 ± 0.8	0.4	91(60, 98)	36(-282, 89)
Naucler(2017)	IPD, <5	Sweden	Europe	High	No	4.5	1.3 (0.4, 4.2)	0.6 (0.2, 1.6)	100 (62, 100)	100 (24,100)
PCV7 followed by PCV13 2+1										
Von Gottberg et al. NEJM 2014	VT-IPD, <2	South Africa	Africa	high	No	2	6.3	.	85 (91 to 76)	

TABLE IPD 10. ST 6A No/Non-Significant Direct Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Catch up	Post-PCV10-13 years	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV7 followed by PCV13 3+0										
Jayasinghe(2016)	IPD, <2	Australia	Oceania	high	Yes	3.5	.	0.13	.	100 (-1386,100)
PCV7 followed by PCV13 2+1										
Porat et al. Vaccine 2016	VT-IPD, <2	Israel	Middle East	high	Yes	3	7.1	1.6	86(-9, 98)	36(-921, 96)
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	No	1	3.3 ± 0.9	0.7	92(72, 98)	61(-100, 92)
Ben-Shimol(2015)	Bact pneu, <5	Israel	Middle East	high	Yes	2	0.8 ± 0.5	0.3	93(-20, 100)	81(-299, 99)
Ben-Shimol(2015)	NBP IPD, <5	Israel	Middle East	high	Yes	2	2.6 ± 0.8	0.4	91(60, 98)	36(-282, 89)
I. Galanis(2016)	IPD, All ages	Sweden	Europe	high		4	.	.	41 (-7,68)	34 (-29,66)
PCV7 followed by PCV10, 2+1										
Naucler (2017)	IPD <5	Sweden	Europe	High	No	4.5	2.0 (0.5, 8.3)	1.0 (0.3, 3.1)	78 (-54, 97)	56 (-166, 93)

TABLE IPD 11: ST 6A Direct Effects Demonstrated: Case Control Studies

Study				VE compared to no vaccine (95%CI)		
Country (Reference)	**Study Design**	**Population age**	**Catch Up**	**Serotype**	**≥1 dose**	**≥2 doses**
PCV7 followed by PCV13, 2+1						
United Kingdom (Andrews et al., 2014)	Indirect cohort	4 to ≤56 months	No	6A		98% (64, 99%)[1]

TABLE IPD 12. ST 6A No/Non-Significant Direct Effects Demonstrated: Case Control Studies

Study				VE compared to no vaccine (95%CI)		
Country (Reference)	**Study Design**	**Population age**	**Catch Up**	**Serotype**	**≥1 dose**	**≥2 doses**
PCV10, 3+1						
Brazil (Domingues et al 2014)	Matched Case-control	<5 years	Catch up for 12-23 months	6A	14.7% (–311.6, 82.3%)[2]	
(Verani et al 2015)	Indirect cohort				62.2% (–42.2, 89.9%)[2]	

TABLE IPD 13. ST 6B Impact Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Country schedule	Catch up	Products	Pre-PCV years	Post-PCV7/pre-PCV10-13 years	Post-PCV10-13 years	Serotype	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV7, followed by PCV13, 2+1															
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	PCV13_ 2/4/12	No	PCV7, PCV13	4	1	1	6B	6.1 ± 1.1	0.7	95(84, 99)	61(-100, 92)
Ben-Shimol(2015)	Bactpneu, <5	Israel	Middle East	high	PCV13_ 2mos/4mos/12mos	Yes	PCV7, PCV13	4	2	2	6B	1.8 ± 0.3	0.3	93(49, 99)	52(-429, 96)
Ben-Shimol(2015)	IPD, <5	Israel	Middle East	high	PCV13_ 2mos/4mos/12mos	Yes	PCV7, PCV13	4	2	2	6B	4.1 ± 1.2	0.4	97(78, 100)	68(-207, 97)
I. Galanis(2016)	IPD, All Ages	Sweden	Europe	high	PCV13_ 3/5/12 mos		PCV7, PCV13	2	4	4	6B	.	.	84 (71,91)	45 (-19,74)

TABLE IPD 14: ST 6B Non-Significant/No Direct Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Country schedule	Catch up	Products	Pre-PCV years	Post-PCV7/pre-PCV10-13 years	Post-PCV10-13 years	Serotype	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV7, followed by PCV13, 2+1															
Porat et al. Vaccine 2016	VT-IPD, <2	Israel	Middle East	high	PCV13_ 2/4/12	No	PCV7, PCV13	8	2	3	6B	7.1		86 (-9,98)	36 (-921,96)
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	PCV13_ 2/4/12	No	PCV7, PCV13	4	1	1	6B	6.1 ± 1.1	0.7	95(84, 99)	61(-100, 92)
Ben-Shimol(2015)	Bactpneu, <5	Israel	Middle East	high	PCV13_ 2mos/4mos/12mos	Yes	PCV7, PCV13	4	2	2	6B	1.8 ± 0.3	0.3	93(49, 99)	52(-429, 96)

Ben-Shimol(2015)	NBP IPD, <5	Israel	Middle East	high	PCV13_ 2mos/4 mos/12 mos	Yes	PCV7, PCV13	4	2	2	6B	4.1 ± 1.2	0.4	97(78, 100)	68(-207, 97)
I. Galanis(2016)	IPD, All ages	Sweden	Europe	high	PCV13_ 3/5/12 mos		PCV7, PCV13	2	4	4	6B	.	.	84 (71,91)	45 (-19,74)

TABLE IPD 15. ST6C No Direct Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Catch up	Post-PCV10-13 years	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV7 followed by PCV13 2+1										
I. Galanis(2016)	IPD, All Ages	Sweden	Europe	high		4			-81(-297, 18)	15(-63, 56)
Waight et al. Lancet Inf Dis 2015	VT-IPD, <5	UK	Europe	high	No	4				63(-238, 96)
N. Porat(2016)	<2	Israel	Middle East	high	Yes	3	0	1.6	-132(-3605, 86)	36(-921, 96)
PCV7 followed by PCV13 3+0										
Jayasinghe(2016)	IPD, <2	Australia	Oceania	high	Yes	3.5		0.91		59(-74, 96)

TABLE IPD 16. ST 19A Impact Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Catch up	Post-PCV10-13 years	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV10 2+1										
Rinta-Kokko et al. ISPPD 2016**	IPD, <2	Finland	Europe	high	No	5	6.8		74 (47, 89)	
Jokinen, 2015**	IPD, 3 to 42 mos	Finland	Europe	high	No	4	5.5	.	62 (20,85)	.
PCV7 followed by PCV13 2+1										
Lepoutre et al. Vaccine 2015	VT-IPD, <2	France	Europe	high		1	N/A	N/A	.	83 (72,90)
Waight et al. Lancet	VT-IPD, <5	UK	Europe	high		4	N/A		.	91 (75,97)

Inf Dis 2015										
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	No	1	5.1 ± 0.7	5	69(42, 84)	68(41, 83)
Ben-Shimol(2015)	Bactpneu, <5	Israel	Middle East	high	Yes	2	2.0 ± 0.7	1.6	69(13, 89)	63(-3, 87)
Ben-Shimol(2015)	NBP IPD, <5	Israel	Middle East	high	Yes	2	3.3 ± 0.1	3.4	74(41, 89)	75(43, 89)
Von Gottberg et al. NEJM 2014	VT-IPD, <2	South Africa	Africa	high	No	2	4.5		70 (55,81)	
Ladhani (UNPUBLISHED 2017)	IPD, <5	UK	Europe	High	No	5	Not specified	Not specified		83 (62, 93)
Naucler (2017)	IPD, <5	Sweden	Europe	High	No	4.5	1.5 (0.3, 5.1)	1.4 (0.7, 2.9)	100 (62,, 100)	100 (67, 100)
PCV7 followed by PCV13 3+0										
Jayasinghe(2017)	IPD,2-4*	Australia	Oceania	high	Yes	3.5	.	5.74	.	75 (57,88)
Jayasinghe(2017)	IPD, <2	Australia	Oceania	high	Yes	3.5	.	15.63	.	77 (65,87)
PCV7 followed by PCV10, 2+1										
Naucler (2017)	IPD, <5	Sweden	Europe	High	No	4.5	0 (0, 3.7)	0.7 (0.2, 3.0)	Not calculable	-54 (-697, 70)

*Age group has both directly immunized and unimmunized children (both direct and indirect effects)
**Unpublished data indicate no effect when taking into account pre-vaccine trends

TABLE IPD 17. ST 19A No Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Catch up	Post-PCV10-13 years	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV7 followed by PCV13 2+1										
Harboe et al. CID 2014	VT-IPD, <2	Denmark	Europe	high		3	1.3 (.8–2.2)	3.8 (2.3–6.3)	.	Decreased to pre-PCV7 Level*
Ben-Shimol(2015)	Bact pneu, <5	Israel	Middle East	high	Yes	2	2.0 ± 0.7	1.6	69(13, 89)	63(-3, 87)
I. Galanis(2016)	IPD, All Ages	Sweden	Europe	high		4	.	.	-31 (-116,21)	33 (-4,56)

*Statistically significant reductions were observed when compared to PCV7 period

TABLE IPD 18 ST 19A Impact Demonstrated: Case Control Studies

Country (Reference)	Population age	Study Design	≥1 dose	≥2 doses
PCV10 2+1				
Canada (Deceuninck et al., 2015)	2-59 months	Case-control	71% (24–89%)	
Brazil (Domingues et al 2014)	<5 years	Matched Case-control	82.2% (10.7 to 96.4%)[2]	
PCV13 2+1				
UK (Andrews et al., 2014)	4 to ≤56 months	Indirect cohort		67% (33 to 84) [1]
UK (Miller et al., 2011)	2.5 to <24 months	Case-control	70% (10 to 90%)	
Canada (Deceuninck et al., 2015)	2-59 months	Case-control	74% (11-92%)	
South Africa (Von Gottberg et al. ISPPD 2016)	6 weeks-9 months	Case-control		94% (44-100%)
PCV13 3+1				
Germany (Weinnberger et al., 2016)	2.5-56 months	Indirect cohort		83(41 to 95) [1]
Taiwain (Su et al 2016)	<2 years	Case-control	81%(47 to 93) [4]	

TABLE IPD 19. ST 19A No Effects Demonstrated: Case Control Studies

Country (Reference)	Population age	Study Design	≥1 dose	≥2 doses
PCV10 2+1				
Finland (Auranen et al. ISPPD 2014)	≥3 months, PCV10 eligible	Indirect cohort		29% (-631 to 93%)
Netherlands (Knol et al. ISPPD 2016)	2-54 months	Indirect cohort	61% (-79- 92%)	
Brazil (Verani et al. 2015)		Indirect cohort	63.4% (−16.8 to 88.6%) [2]	

TABLE IPD 20. ST 19F Impact Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Country schedule	Catch up	Products	Pre-PCV years	Post-PCV7/pre-PCV10-13 years	Post-PCV10-13 years	Serotype	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV7 followed by PCV 13, 2+1															
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	PCV13_ 2/4/12	No	PCV7, PCV13	4	1	1	19F	2.4 ± 0.9	0.3	94(61, 99)	52(-435, 96)
Ben-Shimol(2015)	NBP IPD, <5	Israel	Middle East	high	PCV7_2 mos/4 mos/12 mos	Yes	PCV7, PCV13	4	2	2	19F	1.8 ± 0.7	0.3	93(49, 99)	68(-207, 97)
I. Galanis(2016)	IPD, All Ages	Sweden	Europe	high	PCV13_ 3/5/12 mos		PCV7, PCV13	2	4	4	19F		.	75 (51,87)	-43 (-341,54)
Diawara et al 2015 (1536)	VT IPD, <2 years	Morocco	Africa	Low	PCV13_ 2/4/12	No	PCV7, PCV13	4		4	19F	3.065		-1 so 100% reduction from pre to post	
Von Gottberg et al. NEJM 2014	VT-IPD, <2	South Africa	Africa	high	PCV13_ 6/14/9	No	PCV7, PCV13	4	2	2	19F	5.6		74 (83, 61)	

TABLE IPD 21. ST 19F Non-Significant/No Direct Effects Demonstrated: Pre/Post Observational Studies

Reference	Outcome, age group	Country	Region	Income	Country schedule	Catch up	Products	Pre-PCV years	Post-PCV7/pre-PCV10-13 years	Post-PCV10-13 years	Serotype	Incidence pre-PCV	Incidence during PCV7	%Reduction vs pre-PCV period	%Reduction vs PCV7 period
PCV7 followed by PCV 13, 2+1															
Ben-Shimol(2014)	IPD, <5	Israel	Middle East	high	PCV13_ 2/4/12	No	PCV7, PCV13	4	1	1	19F	2.4 ± 0.9	0.3	94(61, 99)	52(-435, 96)

Ben-Shimol(2015)	Bactpneu, <5	Israel	Middle East	high	PCV7_2 mos/4 mos/12 mos	Yes	PCV7, PCV13	4	2	2	19F	0.6 ± 0.5	0	90(-81, 99)	4(-4731, 98)
Ben-Shimol(2015)	NBP IPD, <5	Israel	Middle East	high	PCV7_2 mos/4 mos/12 mos	Yes	PCV7, PCV13	4	2	2	19F	1.8 ± 0.7	0.3	93(49, 99)	68(-207, 97)
I. Galanis(2016)	IPD, All Ages	Sweden	Europe	high	PCV13_ 3/5/12 mos		PCV7, PCV13	2	4	4	19F		.	75 (51,87)	-43 (-341,54)

TABLE IPD 22. ST19F Non-Significant/No Direct Effects Demonstrated: Case Control Studies

Country (Reference)	Study Design	Population age	PCV product (Country Schedule)	Serotype	≥1 dose	≥2 doses
PCV10 (2+1 and 3+1)						
Finland (Auranen et al. ISPPD 2014)	Indirect cohort	≥3 months, PCV10 eligible	PCV10 (2+1)	19F		70% (-283 to 98)
Brazil (Verani et al 2015)	Indirect cohort	<5 years	PCV10 (3+1), catch up for 12-23 months	19F	77.9(-188.9 to 98.3)[2]	

5. IPD Indirect Effects:

TABLE IPD Ind Eff 1. PCV10 indirect impact on serotype-specific IPD, by schedule

							Surveillance Years Reported			Baseline Measure (per 100,000 person-years)		% Reduction (95% CI) in PCV10 period compared to		
Region	Country	Ref	Catch Up	Income Group	Case Def	Age Group Evaluated	Pre PCV	PCV7/ PCV13	PCV10	Pre PCV	PCV7	Pre PCV	PCV7	Comments
PCV7 VT														
2+1														
EUR	Netherlands	3535: Knol 2016, ISPPD10	No	HIC/UMIC	PCV7 VT IPD	5-64 years	2 years	PCV7: 5 years	PCV10 : 5 years	3.2	1.9	78%	63%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
					PCV7 VT IPD	≥ 65 years	2 years	PCV7: 5 years	PCV10 : 5 years	29.6	7.6	89%	58%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
PCV10 VT														
2+1														
EUR	Finland	63: Jokinen 2015, PLoS ONE	No	HIC/UMIC	PCV10 VT IPD	19-71 months	4 years	--	PCV10 : 2.5 years median	12.8		56% (24%,76%)		Reported: 2012/2013 compare to 2005-2008
					PCV10 VT IPD	31-72 months	2 years	--	PCV10 : 3 years	6.1		60% (-18%,91%)		Reported: 2013 compared to 2006 & 2008
EUR	Finland	3672: Nuorti 2016, ISPPD10	No	HIC/UMIC	PCV10 VT IPD	18-49 years	4 years	--	PCV10 : 3.5 years median	5.6		51% (sig)		PCV10 period 2012-2015
						18-49 years	4 years	--	PCV10 : 5 years	5.6		70%		PCV10 period 2015
						50-64 years	4 years	--	PCV10 : 3.5 years media	10.7		41% (sig)		PCV10 period 2012-2015

									n					
						50-64 years	4 years	--	PCV10 : 5 years	10.7		63%		PCV10 period 2015
						≥ 65 years	4 years	--	PCV10 : 3.5 years median	19.2		47% (sig)		PCV10 period 2012-2015
						≥ 65 years	4 years	--	PCV10 : 5 years	19.2		65%		PCV10 period 2015
3+VT IPD: PCV10-nonPCV7 serotypes														
2+1														
EUR	Netherlands	3535: Knol 2016, ISPPD10	No	HIC/UMIC	3+ VT IPD	5-64 years	2 years	PCV7: 5 years	PCV10 : 5 years	1.5	2.7	13%	52%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
					3+ VT IPD	≥ 65 years	2 years	PCV7: 5 years	PCV10 : 5 years	9.5	9.1	47%	47%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
Serotype 3														
2+1														
EUR	Finland	63: Jokinen 2015, PLoS ONE	No	HIC/UMIC	ST3 IPD	19-71 months	4 years	--	PCV10 : 2.5 years median	0.2		-125% (-17534%, 97%)		Reported: 2012/2013 compare to 2005-2008
						31-72 months	2 years	--	PCV10 : 1 year	0.4		-124% (-17515%, 97%)		Reported: 2013 compared to 2006 & 2008
EUR	Finland	3672: Nuorti 2016, ISPPD10	No	HIC/UMIC	ST3 IPD	>65 years	4 years	--	PCV10 : 3.5 years median	1.19		-299%		Calculated: pre (2005-2008), PCV10 (2012-2015)
EUR	Netherlands	3535: Knol 2016,	No	HIC/UMIC	ST3 IPD	5-64 years	2 years	PCV7: 5 years	PCV10 : 5 years	0.5	0.5	-33%	-33%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)

		ISPPD10				≥ 65 years	2 years	PCV7: 5 years	PCV10 : 5 years	3.3	4.3	-52%	-16%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
EUR	Sweden	Naucler 2017	No	High	ST3 IPD	5-64	0.5 years	PCV7: 1 year	4.5 years	1.0 (0.5, 1.7)	0.9 (0.6, 1.3)	-31% (-149, 31)	-44 (-120, 6)	
EUR	Sweden	Naucler, 2017	No	High	ST3 IPD	>65	0.5 years	PCV7: 1 years	4.5 years	3.3 (1.8, 5.9)	4.5 (3.4, 5.9)	-55 (-189, 17)	-14 (-63, 20)	
Serotype 6A														
2+1														
EUR	Finland	63: Jokinen 2015, PLoS ONE	No	HIC/UMIC	ST6A IPD	19-71 months	4 years	--	PCV10 : 2.5 years median	0.9		-80% (-579%,56%)		Reported: 2012/2013 compare to 2005-2008
						31-72 months	2 years	--	PCV10 : 1 year	0.7		-124% (-2996%, 84%)		Reported: 2013 compared to 2006 & 2008
EUR	Finland	3672: Nuorti 2016, ISPPD10	No	HIC/UMIC	ST6A IPD	>65 years	4 years	--	PCV10 : 3.5 years median	2.22		14%		Calculated: pre (2005-2008), PCV10 (2012-2015)
EUR	Netherlands	3535: Knol 2016, ISPPD10	No	HIC/UMIC	ST6A IPD	5-64 years	2 years	PCV7: 5 years	PCV10 : 5 years	0.1	0	100%		Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
						≥ 65 years	2 years	PCV7: 5 years	PCV10 : 5 years	1.5	0.6	99%	83%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
Serotype 19A														
2+1														
EUR	Finland	63: Jokinen 2015, PLoS ONE	No	HIC/UMIC	ST19A IPD	19-71 months	4 years	--	PCV10 : 2.5 years median	0.7		-12% (-476%, 84%)		Reported: 2012/2013 compare to 2005-2008

						31-72 months	2 years	--	PCV10 : 1 year	1.1		-50% (-1206%, 88%)		Reported: 2013 compared to 2006 & 2008
EUR	Finland	3672: Nuorti 2016, ISPPD10	No	HIC/UMIC	ST19A IPD	>65 years	4 years	--	PCV10 : 3.5 years median	1.11		-171%		Calculated: pre (2005-2008), PCV10 (2012-2015)
EUR	Netherlands	3535: Knol 2016, ISPPD10	No	HIC/UMIC	ST19A IPD	5-64 years	2 years	PCV7: 5 years	PCV10 : 5 years	0.6	1.1	-117%	-18%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
						5-64 years	2 years	PCV7: 5 years	PCV10 : 5 years				-46% (-117%, 1%)	Reported: PCV7 (09/11), PCV1 (14/16)
						≥ 65 years	2 years	PCV7: 5 years	PCV10 : 5 years	2.1	4.7	-138%	-6%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
						≥ 65 years	2 years	PCV7: 5 years	PCV10 : 5 years				-23% (-69%, 11%)	Reported: PCV7 (09/11), PCV1 (14/16)
EUR	Sweden	Naucler	No	HIC/UMIC	ST19A IPD	5-64 years	0.5	1.0	4.5	0 (0, 0.26)	0.2 (0.1, 0.4)	Noncalculable	-381 (-1030, -204)	
EUR	Sweden	Naucler	No	HIV/UMIC	ST19A IPD	>65 years	0.5	1.0	4.5	0.9 (0.3, 3.0)	1.6 (1.0, 2.6)	-435 (-1700, -58)	-208 (-423, -81)	
Serotype 6C														
2+1														
EUR	Netherlands	3535: Knol 2016, ISPPD10	No	HIC/UMIC	ST6C IPD	5-64 years	2 years	PCV7: 5 years	PCV10 : 5 years	0	0			Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)
						≥ 65 years	2 years	PCV7: 5 years	PCV10 : 5 years	0.1	0.4	-1045%	-200%	Calculated: pre (05/06), PCV7 (10/11), PCV10 (15/16)

TABLE IPD Ind Eff 2. PCV13 impact on serotype-specific IPD, by schedule

							Surveillance Years Reported			Baseline Measure (per 100,000)			% Reduction (95% CI) in PCV13 period compared to			
Region	Country	Ref	Catch Up	Income Group	Case Def	Age Group Evaluated	Pre PCV	PCV7/ PCV10	PCV13	Pre PCV	PCV7	PCV10	Pre PCV	PCV7	PCV10/ 13	Comment
PCV7 VT																
2+1																
EUR	UK	137: Waight 2015, Lancet	Yes	HIC/UMIC	PCV7 IPD	5-14 years	--	PCV7: 4 years	PCV13 : 4 years		0.4			91% (33%, 99%)		Reported 2013/201 compared to 2010
					PCV7 IPD	15-44 years	--	PCV7: 4 years	PCV13 : 4 years		0.53			83% (65%, 91%)		Reported 2013/201 compared to 2010
					PCV7 IPD	45-64 years	--	PCV7: 4 years	PCV13 : 4 years		`1.55			85% (73%, 91%)		Reported 2013/201 compared to 2010
					PCV7 IPD	≥ 65 years	--	PCV7: 4 years	PCV13 : 4 years		4.58			89% (82%, 92%)		Reported 2013/201 compared to 2010
					PCV7 IPD	5-14 years	6 years	PCV7: 4 years	PCV13 : 4 years	2.09	0.34		100%	100%		Calculate
					PCV7 IPD	15-44 years	6 years	PCV7: 4 years	PCV13 : 4 years	3.19	0.31		97%	67%		Calculate
					PCV7 IPD	45-64 years	6 years	PCV7: 4 years	PCV13 : 4 years	7.43	0.97		96%	69%		Calculate
					PCV7 IPD	≥ 65 years	6 years	PCV7: 4 years	PCV13 : 4 years	17.92	2.69		97%	81%		Calculate
EUR	UK	508: Moore 2014,	Yes	High	PCV7 IPD	50-64 years	11 years	PCV7: 4 years	2 years	3.75	1		100%	100%		Calculated: P year 201

		JID			PCV7 IPD	≥ 65 years	11 years	PCV7: 4 years	2 years	16.4	2.8		95%	71%		Calculated: P year 201
EUR	UK	3501: Collins 2016, ISPPD 10	Yes	HIC/UMIC	PCV7 IPD	15-44 years	6 years	PCV7: 4 years	PCV13: 5 years	3.2	0.3		97%	67%		Calculated: P 1 year 09/1 PCV13: 1 ye 14/15
					PCV7 IPD	45-64 years	6 years	PCV7: 4 years	PCV13: 5 years	7.5	1.1		95%	64%		Calculated: P 1 year 09/1 PCV13: 1 ye 14/15
					PCV7 IPD	≥ 65 years	6 years	PCV7: 4 years	PCV13: 5 years	17.9	3.1		96%	77%		Calculated: P 1 year 09/1 PCV13: 1 ye 14/15
EUR	Denmark	262: Harboe 2014, CID	Yes	HIC/UMIC	PCV7 IPD	≥ 65 years	8 years	PCV7: 3 years	PCV13: 2 years median	27.1	14		88%	76%		Calculated comparisc between PC period (201 2013) and ea periods
					PCV7 IPD	≥ 65 years	8 years	PCV7: 3 years	PCV13: 3 years	27.1	14		91%	83%		Calculated: P year 201
EUR	Denmark	299: Slotved 2014, PLoS ONE	Yes	HIC/UMIC	PCV7 IPD	< 90 days	6 years	PCV7: 3 years	PCV13: 3 years	1.9	1.7		100%	100%		Calculated: P year 201
EUR	Sweden	2177: Galanis 2016, Eur Resp J	No	HIC/UMIC	PCV7 IPD	18-64 years	2 years	PCV7: 2 years	PCV13: 4 years	6.12	2.9		95%	87%		Calculated: P year 201
					PCV7 IPD	≥ 65 years	2 years	PCV7: 2 years	PCV13: 4 years	22.25	12		89%	79%		Calculated: P year 201
					PCV7 IPD	18-64 years	3 years	PCV7: 2 years	PCV13: 2.5 years median	6.12	2.59		38% (29%, 46%)	15% (-1%,28%)		Reported: PCV 2011-201

					PCV7 IPD	≥ 65 years	3 years	PCV7: 2 years	PCV13: 2.5 years median	22.25	10.1		85% (80%,90 %)	68% (52%,78 %)		Reported: PC 2011-201
EUR	Israel	3636: Regev-Yocha y 2016, ISPPD 10	Yes	HIC/U MIC	PCV7 IPD	≥ 18 years	--	PCV7: 2 years	PCV13: 4 years		2.5			79%		PCV13: 2014-
						18-49 years	--	PCV7: 2 years	PCV13: 4 years		0.7			61%		PCV13: 2014-
						50-64 years	--	PCV7: 2 years	PCV13: 4 years		3.2			94%		PCV13: 2014-
						≥ 65 years	--	PCV7: 2 years	PCV13: 4 years		8.6			85%		PCV13: 2014-
EUR	Israel	3674: Regev-Yocha y 2016, ISPPD 10	Yes	HIC/U MIC	PCV7 Menin gitis	≥ 18 years	--	PCV7: 2 years	PCV13: 4 years		0.23			100%		
AMR	Canada	4285: Desai 2016, CMAJ Open	No	HIC/U MIC	PCV7 IPD	≥ 65 years	--	PCV7: 2 years PCV10 : 2 years	PCV13: 4 years		3	2.4		77% (sig)	PCV13 v. PCV10: 71%	Reported: P year 2007 Comparisor PCV7 is a combined effe PCV10 and PC
AFR	South Africa	3546: von Gottb erg 2016, ISPPD 10	No	HIC/U MIC	PCV7 IPD	10-14 years	4 years	PCV7: 2 years	PCV13: 5 years	0.9	0.5		78%	60%		Calculated PCV7(2010 PCV13(201
					PCV7 IPD	15-24 years	4 years	PCV7: 2 years	PCV13: 5 years	1.1	0.7		82%	71%		
					PCV7 IPD	25-44 years	4 years	PCV7: 2 years	PCV13: 5 years	3.9	3.3		82% (78%, 85%)	79%		
					PCV7 IPD	45-64 years	4 years	PCV7: 2 years	PCV13: 5 years	2.8	2.8		71%	71%		

					PCV7 IPD	≥ 65 years	4 years	PCV7: 2 years	PCV13 : 5 years	2.1	2.2		62%	64%		
3+0																
WPR	Australia	4454: Jayasinghe 2017, CID	Yes	HIC/UMIC	PCV7 IPD	15-49 years	3 years	PCV7: 6 years	PCV13 : 3 years	3.6	0.3		92% (88%, 94%)	18%		PCV year 20
						50-64 years	3 years	PCV7: 6 years	PCV13 : 3 years	6.5	0.8		85% (80%, 90%)	-15%		PCV year 20
						≥ 65 years	3 years	PCV7: 6 years	PCV13 : 3 years	16.9	1.8		92% (89%, 94%)	28%		PCV year 20
AFR	Gambia	3835: Mackenzie 2016, Lancet	No	LIC/LMIC	PCV7 IPD	5-14 years	2 years	PCV7: 2 years	PCV13 : 3 years		2			100%		Calculate
						≥ 15 years	2 years	PCV7: 2 years	PCV13 : 3 years	0.25	1.2		100%	100%		Calculate
PCV13 VT																
2+1																
EUR	UK	137: Waight 2015, Lancet	Yes	HIC/UMIC	PCV13 IPD	5-14 years	--	PCV7: 4 years	PCV13 : 4 years		1.27			70% (43%, 84%)		Reported 2013/201 compared to 2010
					PCV13 IPD	15-44 years	--	PCV7: 4 years	PCV13 : 4 years		2.49			72% (64%, 78%)		Reported 2013/201 compared to 2010
					PCV13 IPD	45-64 years	--	PCV7: 4 years	PCV13 : 4 years		4.55			64% (55%, 71%)		Reported 2013/201 compared to 2010
					PCV13 IPD	≥ 65 years	--	PCV7: 4 years	PCV13 : 4 years		10.33			64% (57%, 70%)		Reported 2013/201 compared to 2010
					PCV13 IPD	5-14 years	6 years	PCV7: 4 years	PCV13 : 4 years	2.06	1.35		80%	69%		Calculate

					PCV13 IPD	15-44 years	6 years	PCV7: 4 years	PCV13: 4 years	2.53	2.45		73%	72%		Calculate
					PCV13 IPD	45-64 years	6 years	PCV7: 4 years	PCV13: 4 years	4.12	4.32		58%	60%		Calculate
					PCV13 IPD	≥ 65 years	6 years	PCV7: 4 years	PCV13: 4 years	6.57	10.16		48%	66%		Calculate
AMR	Canada	4285: Desai 2016, CMAJ Open	No	HIC/UMIC	PCV13 IPD	≥ 65 years	--	PCV7: 2 years PCV10: 2 years	PCV13: 4 years		7	12		24%	PCV13 v. PCV10: 56% (sig)	Reported: P year 2007 Comparisor PCV7 is a combined effe PCV10 and PC
EUR	Denmark	2197: Slotved, 2016 Vaccine	Yes	HIC/UMIC	PCV13 IPD	5-64 years	8 years	PCV7: 3 years	PCV13: 2.5 median years		0.46			38% (-26%, 69%)		Reported: P years 2008-2 compared to 2014
					PCv13 IPD	≥ 65 years	8 years	PCV7: 3 years	PCV13: 2.5 years median		2.7			48% (0%, 74%)		Reported: P years 2008-2 compared to 2014
EUR	Israel	3636: Regev-Yochay 2016, ISPPD 10	Yes	HIC/UMIC	PCV13 IPD	≥ 18 years	--	PCV7: 2 years	PCV13: 4 years		6.1			70%		PCV13: 2014-
						18-49 years	--	PCV7: 2 years	PCV13: 4 years		2.7			87%		PCV13: 2014-
						50-64 years	--	PCV7: 2 years	PCV13: 4 years		7.3			80%		PCV13: 2014-
						≥ 65 years	--	PCV7: 2 years	PCV13: 4 years		19.1			68%		PCV13: 2014-
EUR	Israel	3674: Regev-Yochay 2016, ISPPD	Yes	HIC/UMIC	PCV13 Meningitis	≥ 18 years	--	PCV7: 2 years	PCV13: 4 years		0.29			72%		

		10													
3+0															
WPR	Australia	4454: Jayasinghe 2017, CID	Yes	HIC/UMIC	PCV13 IPD	15-49 years	3 years	PCV7: 6 years	PCV13 : 3 years	4.1	2.2		63%	33% (20%, 44%)		PCV7 period 2 2011
						50-64 years	3 years	PCV7: 6 years	PCV13 : 3 years	7.8	4.6		58%	28% (13% ,41%)		PCV7 period 2 2011
						≥ 65 years	3 years	PCV7: 6 years	PCV13 : 3 years	20.6	8.7		78%	48% (38%, 56%)		PCV7 period 2 2011
AFR	Gambia	3835: Mackenzie 2016, Lancet	No	LIC/LMIC	PCV13 IPD	5-14 years	2 years	--	PCV13 : 2.5 years	10			-5% (-199%, 63%)			Reported: 20 2010 compar 2013-201
						≥ 15 years	2 years	--	PCV13 : 2.5 years	7			50% (-32%, 81%)			Reported: 20 2010 compar 2013-201
6+ PCV13-nonPCV7 VT															
2+1															
EUR	Denmark	262: Harboe 2014, CID	Yes	HIC/UMIC	6+ VT IPD	≥ 65 years	8 years	PCV7: 3 years	PCV13 : 2 years median	18.8	20.7		10%	18%		Calculated comparisc between PC period (201 2013) and ea periods
					6+ VT IPD	≥ 65 years	8 years	PCV7: 3 years	PCV13 : 3 years	18.8	20.7		39%	45%		Calculated: P year 2013
EUR	Denmark	299: Slotved 2014, PLoS ONE	Yes	HIC/UMIC	6+ VT IPD	< 90 days	6 years	PCV7: 3 years	PCV13 : 3 years	3.6	1.6		54%	250%		Calculated: P year 2013
EUR	UK	508: Moore 2014, JID	Yes	High	6+ VT IPD	50-64 years	11 years	PCV7: 4 years	2 years	2.1	4.3		5%	53%		Calculated: P year 2012
					6+ VT IPD	≥ 65 years	11 years	PCV7: 4 years	2 years	7.6	8.8		17%	28%		Calculated: P year 2012

EUR	UK	3501: Collins 2016, ISPPD	Yes	HIC/UMIC	6+ VT IPD	15-44 years	6 years	PCV7: 4 years	PCV13: 5 years	2.6	2.3		77%	74%		Calculated: P 1 year 09/1 PCV13: 1 ye 14/15
					6+ VT IPD	45-64 years	6 years	PCV7: 4 years	PCV13: 5 years	4.3	4.5		58%	60%		Calculated: P 1 year 09/1 PCV13: 1 ye 14/15
					6+ VT IPD	≥ 65 years	6 years	PCV7: 4 years	PCV13: 5 years	7	10.2		30%	52%		Calculated: P 1 year 09/1 PCV13: 1 ye 14/15
EUR	Sweden	2177: Galanis 2016, Eur Resp J	No	HIC/UMIC	6+ VT IPD	18-64 years	2 years	PCV7: 2 years	PCV13: 4 years	2.96	3.2		51%	56%		Calculated: P year 201
					6+ VT IPD	≥ 65 years	2 years	PCV7: 2 years	PCV13: 4 years	7.75	13.5		-10%	35%		Calculated: P year 201
					6+ VT IPD	18-64 years	2 years	PCV7: 2 years	PCV13: 2.5 years median	2.96	3.25		15% (-11%,34%)	22% (-3%,41%)		Reported: PCV 2011-201
					6+ VT IPD	≥ 65 years	2 years	PCV7: 2 years	PCV13: 2.5 years median	7.75	12.09		-25% (-71%,9%)	20% (-6%,40%)		Reported: PCV 2011-201
EUR	Israel	3636: Regev-Yochay 2016, ISPPD 10	Yes	HIC/UMIC	6+ VT IPD	≥ 18 years	--	PCV7: 2 years	PCV13: 4 years		3.7			66%		PCV13: 2014-
						18-49 years	--	PCV7: 2 years	PCV13: 4 years		2			96%		PCV13: 2014-
						50-64 years	--	PCV7: 2 years	PCV13: 4 years		4.2			69%		PCV13: 2014-
						≥ 65 years	--	PCV7: 2 years	PCV13: 4 years		10.5			54%		PCV13: 2014-

AMR	Canada	4285: Desai 2016, CMAJ Open	No	HIC/UMIC	6+ VT IPD	≥ 65 years	--	PCV7: 2 years PCV10: 2 years	PCV13: 4 years		4	9.8		-15%	PCV13 v. PCV10: 53% (sig)	Reported: P year 2007 Comparisor PCV7 is a combined effe PCV10 and PC
AMR	Canada	4034: Waye 2015, Drugs	No	HIC/UMIC	6+ VT IPD	10-19 years	2 years	PCV7: 9 years	PCV13: 3 years	0.75	0.4		100%	100%		Calculated reductior
						20-64 years	2 years	PCV7: 9 years	PCV13: 3 years	1.8	3.1		-11%	35%		Calculated reductior
						≥ 65 years	2 years	PCV7: 9 years	PCV13: 3 years	5.1	8.9		-24%	29%		Calculated reductior
AFR	South Africa	3546: von Gottberg 2016, ISPPD 10	No	HIC/UMIC	6+ VT IPD	10-14 years	4 years	PCV7: 2 years	PCV13: 5 years	0.9	0.9		78%	78%		Calculated PCV7(2010 PCV13(201
					6+ VT IPD	15-24 years	4 years	PCV7: 2 years	PCV13: 5 years	1.2	1.2		75%	75%		
					6+ VT IPD	25-44 years	4 years	PCV7: 2 years	PCV13: 5 years	3.7	3.8		68%	68%		
					6+ VT IPD	45-64 years	4 years	PCV7: 2 years	PCV13: 5 years	2.6	2.8		50%	54%		
					6+ VT IPD	≥ 65 years	4 years	PCV7: 2 years	PCV13: 5 years	1.7	2.5		47%	64%		
3+0																
WPR	Australia	4454: Jayasinghe 2017, CID	Yes	HIC/UMIC	6+ VT IPD	15-49 years	3 years	PCV7: 6 years	PCV13: 3 years	0.5	1.6		-132%	27%		PCV7 year 2
						50-64 years	3 years	PCV7: 6 years	PCV13: 3 years	1.3	4		-83%	40%		PCV7 year 2
						≥ 65 years	3 years	PCV7: 6 years	PCV13: 3 years	3.7	5.8		14%	45%		PCV7 year 2
AFR	Gambia	3835: Macke	No	LIC/LMIC	6+ VT IPD	5-14 years	2 years	--	PCV13: 2.5	10			5% (-176%,			Reported: 2(2010 compar

		nzie 2016, Lancet							years				68%)			2013-201
						≥ 15 years	2 years	--	PCV13 : 2.5 years	7			48% (-39%, 80%)			Reported: 20 2010 compar 2013-201
						5-14 years	2 years	PCV7: 2 years	PCV13 : 3 years	6.9	18.5		-120%	17%		Calculate
						≥ 15 years	2 years	PCV7: 2 years	PCV13 : 3 years	2.7	16.8		-43%	77%		Calculate
Serotype 3																
2+1																
EUR	UK	137: Waight 2015, Lancet	Yes	HIC/UMIC	ST3 IPD	5-64 years	6 years	PCV7: 4 years	PCV13 : 4 years		NR			59% (38%, 72%)		Reported 2013/201 compared to 2010
						≥ 65 years	6 years	PCV7: 4 years	PCV13 : 4 years		NR			44% (27%, 57%)		Reported 2013/201 compared to 2010
EUR	Denmark	262: Harboe 2014, CID	Yes	HIC/UMIC	ST3 IPD	≥ 65 years	8 years	PCV7: 3 years	PCV13 :2 years median	4.2	4.4		-7%	-2%		Calculated comparisc between PC period (201 2013) and ea periods
EUR	Denmark	2197: Slotved, 2016 Vaccine	Yes	HIC/UMIC	ST3 IPD	5-64 years	8 years	PCV7: 3 years	PCV13 : 4 years	0.51	0.69		21%	27%		Calculated: P 2010 and PC 2014
						≥ 65 years	8 years	PCV7: 3 years	PCV13 : 4 years	4.23	4.91		11%	23%		Calculated: P 2010 and PC 2014
EUR	Denmark	3773: Slotved 2016, Heliyo	Yes	HIC/UMIC	ST3 IPD	5-64 yrs	8 years	PCV7: 4 years	PCV13 : 3.5 years median	0.51			11% (-11%, 29%)			Reported: 19 2010 compar 2011-201

		n				≥ 65 years	8 years	PCV7: 4 years	PCV13: 3.5 years median	4.27			0% (-17%, 14%)			Reported: 19 2010 compar 2011-201
AMR	Canada	4285: Desai 2016, CMAJ Open	No	HIC/UMIC	ST3 IPD	≥ 65 years	--	PCV7: 2 years PCV10: 2 years	PCV13: 4 years		NR	NR		NR		
EUR	Sweden	Naucler 2017	No	HIC/UIMC	ST3 IPD	5-64 years	0.5	PCV7: 1 year	4.5 years	0.7 (0.4, 1.1)	0.6 (0.4, 0.8)	-	-10 (-99, 40)	-16 (-70, 21)		
EUR	Sweden	Naucler 2017	No	HIC/UIMC	ST3 IPD	<65 years	0.5	PCV7: 1 year	4.5 years	3.9 (2.5, 6.1)	4.1 (3.2, 5.3)	-	-53 (-142, 3)	-45 (-95, -8)		
3+0																
WPR	Australia	4454: Jayasinghe 2017, CID	Yes	HIC/UMIC	ST3 IPD	15-49 years	3 years	PCV7: 6 years	PCV13: 3 years		0.27			12% (-40%, 45%)		PCV7 period 2 2011
						50-64 years	3 years	PCV7: 6 years	PCV13: 3 years		0.71			13% (-38%, 46%)		PCV7 period 2 2011
						≥ 65 years	3 years	PCV7: 6 years	PCV13: 3 years		1.53			-5% (-46%, 24%)		PCV7 period 2 2011
Serotype 6A																
2+1																
EUR	UK	137: Waight 2015, Lancet	Yes	HIC/UMIC	ST6A IPD	5-64 years	6 years	PCV7: 4 years	PCV13: 4 years		NR			90% (56%, 97%)		Reported 2013/201 compared to 2010
						≥ 65 years	6 years	PCV7: 4	PCV13: 4		NR			95% (81%,		Reported 2013/201

								years	years					99%)		compared to 2010
EUR	Denmark	262: Harboe 2014, CID	Yes	HIC/UMIC	ST6A IPD	≥ 65 years	8 years	PCV7: 3 years	PCV13: 2 years median	2	1.5		85%	80%		Calculated comparisc between PC period (201 2013) and ea periods
AFR	South Africa	3546: von Gottberg 2016, ISPPD 10	No	HIC/UMIC	ST6A IPD	5-9 years	4 years	PCV7: 2 years	PCV13: 5 years	0.5	0.4		100%	100%		Calculated: (2005-2008 PCV7(2010 PCV13(201
						10-14 years	4 years	PCV7: 2 years	PCV13: 5 years	0.2	0.1		50%	0%		
						15-24 years	4 years	PCV7: 2 years	PCV13: 5 years	1.2	0.1		100%	100%		
						25-44 years	4 years	PCV7: 2 years	PCV13: 5 years	0.8	0.7		75%	71%		
						45-64 years	4 years	PCV7: 2 years	PCV13: 5 years	0.5	0.9		80%	89%		
						≥ 65 years	4 years	PCV7: 2 years	PCV13: 5 years	0.4	0.2		75%	50%		
EUR	Sweden	Naucler 2017	No	HIC/UIMC	ST6A IPD	5-64 years	0.5	PCV7: 1 year	4.5 years	0.4 (0.2, 0.8)	0..2 (0.1, 0.4)	-	93 (68, 98)	89 (58, 97)		
EUR	Sweden	Naucler (2017)	No	HIC/UIMC	ST6A IPD	<65 years	0.5	PCV7: 1 year	4.5 years	1.8 (0.9, 3.3)	2.8 (2.1, 3.8)	-	77 (40, 91)	85 (66, 94)		

3+0															
WPR	Australia	4454: Jayasinghe 2017, CID	Yes	HIC/UMIC	ST6A IPD	15-49 years	3 years	PCV7: 6 years	PCV13: 3 years		0.03			100% (-13%, 100%)		PCV7 period 2 2011
						50-64 years	3 years	PCV7: 6 years	PCV13: 3 years		0.2			87% (23%, 100%)		PCV7 period 2 2011
						≥ 65 years	3 years	PCV7: 6 years	PCV13: 3 years		0.67			91% (67%, 99%)		PCV7 period 2 2011
Serotype 19A															
2+1															
EUR	UK	137: Waight 2015, Lancet	Yes	HIC/UMIC	ST19A IPD	5-64 years	6 years	PCV7: 4 years	PCV13: 4 years		NR			54% (32%, 65%)		Reported 2013/201 compared to 2010
						≥ 65 years	6 years	PCV7: 4 years	PCV13: 4 years		NR			65% (53%, 75%)		Reported 2013/201 compared to 2010
EUR	Ireland	3677: Corcoran 2016, ISPPD 10	Yes	HIC/UMIC	ST19A IPD	≥ 65 years	2 years	PCV7: 2 years	PCV13: 5 years	1.2	1.85		-173%	-77%		Calculated comparisc between 20 2008 (pre), 2 (PCV7) and 2 (PCV13). 1 spiked in 20
EUR	Denmark	262: Harboe 2014, CID	Yes	HIC/UMIC	ST19A IPD	≥ 65 years	8 years	PCV7: 3 years	PCV13: 2 years median	1.6	3.3		-81%	12%		Calculated comparisc between PC period (201 2013) and ea periods
AMR	Canada	4285: Desai 2016, CMAJ Open	No	HIC/UMIC	ST19A IPD	≥ 65 years	--	PCV7: 2 years PCV10: 2 years	PCV13: 4 years		NR	NR		NR		

EUR	Sweden	Naucler	No	HIC/ UMIC	ST19A IPD	>65	0.5 years	PCV7: 1 year	PCV13 : 4.5 years	1.6 (0.6, 4.5)	2.0 (1.3, 3.2)	-	1 (-202, 68)	21 (-50, 58)		
EUR	Sweden	Naucler	No	HIC/ UMIC	ST19A IPD	5-64 years	0.5 years	PCV7: 1 year	PCV13 : 4.5 years	0.2 (0.1, 0.5)	0.2 (0.1, 0.4)	-	-60 (-434, 54)	-12 (-115, 42)		
3+0																
WPR	Australia	4454: Jayasinghe 2017, CID	Yes	HIC/UMIC	ST19A IPD	15-49 years	3 years	PCV7: 6 years	PCV13 : 3 years		0.75			62% (45%, 75%)		PCV7 period 2 2011
						50-64 years	3 years	PCV7: 6 years	PCV13 : 3 years		1.84			46% (25%, 63%)		PCV7 period 2 2011
						≥ 65 years	3 years	PCV7: 6 years	PCV13 : 3 years		3.59			74% (62%, 83%)		PCV7 period 2 2011
Serotype 6C																
2+1																
EUR	UK	137: Waight 2015, Lancet	Yes	HIC/UMIC	ST6C IPD	5-64 years	6 years	PCV7: 4 years	PCV13 : 4 years					28% (-32%, 64%)		Reported 2013/201 compared to 2010
						≥ 65 years	6 years	PCV7: 4 years	PCV13 : 4 years					30% (-6%, 55%)		Reported 2013/201 compared to 2010
EUR	Israel	3636: Regev-Yochay 2016, ISPPD 10	Yes	HIC/UMIC	ST6C IPD	>18 years	--	PCV7: 2 years	PCV13 : 4 years					-227%		Calculated: P (10/11), PCV (14/15)
3+0																
WPR	Australia	4454: Jayasinghe	Yes	HIC/UMIC	ST6C IPD	15-49 years	3 years	PCV7: 6 years	PCV13 : 3 years		0.1			34% (-48%, 76%)		PCV7 period 2 2011

		2017, CID				50-64 years	3 years	PCV7: 6 years	PCV13 : 3 years		0.33			9% (-74%, 58%)		PCV7 period 2 2011
						≥ 65 years	3 years	PCV7: 6 years	PCV13 : 3 years		1.71			34% (7%, 56%)		PCV7 period 2 2011

6. Pneumonia Direct Effects:

TABLE Pneumo 1. Characteristics of Studies Assessing Pneumonia

Schedule	2+1			3+0			TOTAL
Characteristic	PCV10 n=6	PCV13 n=23	Total n=28	PCV10 n=3	PCV13 n=4	Total n=7	N=35
Study type							
Clinical trial	1	0	1	0	0	0	1
Case-control/indirect cohort	0	3	3	0	2	2	5
Pre/post study	5	20	24	3	2	5	29
Region							
Africa	0	1	1	1	3	4	5
Americas	1	9	10	0	1	1	11
Asia	0	0	0	0	0	0	0
Australia/Oceania	0	0	0	2	0	2	2
Europe	5	13	17	0	0	0	17
Country Income Strata							
High	6	23	28	2	0	2	30

Low	0	0	0	1	4	5	5
Previous Other PCV Product Use							
PCV7	2	18	19	0	0	0	19
PCV10	--------	0	0	--------	0	0	0

TABLE Pneumo 2. Characteristics of Controlled Trials Evaluating Pneumonia

Country	Reference	Study design	Vaccine product	Dosing schedule	Endpoint and Case Definition*	Vaccine Efficacy (95% CI)		Comments
						Intent to Treat	Per Protocol	
Finland	Kilpi ISPPD 2016	RCT	PCV10 (2+1)	Doses >8 weeks apart; booster at >11 months	Hospital-diagnosed clinical pneumonia	28% (6 to 45)		
					Consolidated pneumonia	43% (19 to 61)		

TABLE Pneumo 3. Summary Characteristics and Findings of Case-Control Studies Evaluating Pneumonia

Country (Reference)	Study design	Population	PCV product and dosing schedule	Endpoint	Comparison group	VE compared to no PCV (95% CI)				Comments
						2+1	3+0	≥1 dose	≥2 doses	
2+1										
Israel (Givon-Lavi, ISPPD 2014)	Case-control	2-12 months	PCV7/PCV13 (2, 4, 12 months)	CXR-confirmed pneumonia	Children with rotavirus-negative gastroenteritis				40.6 (11.1-60.3)	49.5% of doses were PCV13
Spain (Madrid) (Tagarro, J	Case-control	2-12 months	PCV13 (2, 4, 12 months)	Bacteremic pneumonia	Children with bacterial pneumonia			86.0 (70.0-95.0) (compared	68.0 (60.0-96.0) (compared	

Pediatr 2016)								to <1 doses)	to <2 doses)	
South Africa (Madhi, Thorax 2015)	Case-control	8-103 weeks	PCV13 (6, 14, 39 weeks)	CXR-confirmed pneumonia (WHO)	Hospital	20.1(-9.3-41.6) (adjusted)				
					Community	32.1 (4.6-51.6) (adjusted)				
3+0										
The Gambia (Mackenzie, unpublished)	Case-control	3-11 months	PCV13 (2, 3, 4 months)	CXR-confirmed pneumonia (WHO)	Community		63 (-8 to 70)	-8 (-83 to 37) (1 dose)	17 (-50 to 54) (2 doses)	
		≥12 months			Community		7 (-264 to 76)	-29 (-536 to 74) (1 dose)	26 (-216 to 83) (2 doses)	
Togo (Moisi, ISPPD 2016)	Indirect cohort	<5 years	PCV13 (6, 10, 14 weeks)	CXR pneumonia	non-CXR pneumonia		58 (-100 to 99)			Early post-introduction and small sample size
				Severe pneumonia (WHO)	non-severe pneumonia		80 (-90 to 100)			
				Pneumonia with CRP >40 mg/L	pneumonia without CRP >40 mg/L		-2% (-30 to 80)			

TABLE Pneumo 4. Summary Characteristics and Findings of Pre/Post PCV10 Observational Studies Evaluating Pneumonia

							Surveillance years reported			Baseline measure (per 100,000)		% reduction at post-PCV introduction period compared to	
Region	Country	Reference	Catch up age, if applicable	income group	Case Definition	Age groups evaluated	Pre-PCV	Post-PCV7 Pre-PCV10	Post-PCV10	Pre-PCV	Post-PCV7 Pre-PCV10	Pre-PCV	Post-PCV7 Pre-PCV10
Clinical pneumonia													
2+1													

							Surveillance years reported			Baseline measure (per 100,000)		% reduction at post-PCV introduction period compared to	
Region	Country	Reference	Catch up age, if applicable	income group	Case Definition	Age groups evaluated	Pre-PCV	Post-PCV7 Pre-PCV10	Post-PCV10	Pre-PCV	Post-PCV7 Pre-PCV10	Pre-PCV	Post-PCV7 Pre-PCV10
America	Peru	Suarez (2016)		high	ICD	<1y	3	.	2	62.84	.	29.3 (8, 45.7)	
Europe	Finland	Palmu (2017)		high	ICD	3-42m	10		5	980		13 (9, 16)	
	Iceland	Kristinsson (2014)		high	Not stated	12-23m	3	.	1.5	2,800	.	36 (16, 49)	
		Sigurdsson (2015)		high	ICD	<2y	3	.	3	422	.	23 (5, 36)	
	Sweden	Berglund (2014)		high	ICD	<2y	10	1	2	654.7	504.4	21 (7, 32)	-3 (-30, 18)
3+0													
Africa	Kenya	Silaba (2016)	13-59months	low	WHO IMCI	<1y	.	.	4	.	.	30 (0, 50)	
Pacific	Fiji	Russell (2016)		high	ICD (iTaukei)	<2y	5	.	2	3747.4	.	19	
		Russell(2016)		high	ICD (FID)	<2y	5	.	2	1221.9	.	13.3	
		Tuivaga (2016)		high	ICD (severe pneumonia)	<1y	5	.	2	.	.	35 (26,43)	
Radiologically-confirmed pneumonia													
3+0													
Africa	Kenya	Silaba (2016)	13-59months	low	WHO	<1y	.	.	4	.	.	48 (14, 68)	
Pacific	Fiji	Tuivaga (2016)		high	ICD	<1y	5	.	2	.	.	15 (-23, 44)	
Pneumococcal pneumonia													
2+1													
Europe	Finland	Palmu (2017)		high	ICD	3-42m	10		5	23		77 (64, 86)	
Empyema													
2+1													
Europe	Finland	Palmu (2017)		high	ICD	3-42m	10		5	1.6		3 (-174, 70)	

TABLE Pneumo 5. Summary Characteristics and Findings of Pre/Post PCV13 Observational Studies Evaluating Pneumonia

							Surveillance years reported			Baseline measure (per 100,000)		% reduction at post-PCV introduction period compared to	
Region	Country	Reference	Catch up age, if applicable	income group	Case Definition	Age groups evaluated	Pre-PCV	Post-PCV7 Pre-pcv13	Post-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13
Clinical pneumonia													
2+1													
America	Argentina	Gentile (2016)		high	Not stated	<1y	3	.	2	195.3	.	50.4	
		Vizzotti (2016)		high	Clinical diagnosis	<1y	2	.	3	3295.1	.	27.3 (26.4, 28.2)	
		Lopez Papucci (2016)	<2 years	high	Clinical diagnosis	<1y	4	.	2	1687.21	.	43.2 (29.3, 54.4)	
	Costa Rica	Castro(2016)		high	Not stated	<2y	4	2	2	1180	850	35 (32, 38)	9 (5, 13)
	Mexico	Palacios (2016)		high	ICD	<1y	0	6	4		2443		60.5
Europe	Israel	Ben Shimol(2016)		high	Not stated	<2y	3	1	4	32.47	72.3	7 (1, 13)	
	Italy	Baldo (2016)	up to 36 months	high	ICD	<5y	4	4	2.5	379.4	211.9	4.6 (2.7, 6.5)	
	Spain	Rivero-Calle (2016)		high	ICD	<2y	6	5	2	20.7	.	58 (47.6, 67.3)	
	Sweden	Berglund (2014)		high	ICD	<2y	10	1	2	654.7	504.4	37 (26, 46)	18 (-1, 34)
	United Kingdom (UK)	Nath (2015)		high	ICD	<1y	24.	4	4	.	.		6 (-4, 16)
		Nair (2016)		high	ICD	<2y	7	3	3	293	237	30	13
		Saxena (2015)	<5y	high	ICD	<2y	5	4	4	.	.	20	-8 (-19, 2)
3+0													

							Surveillance years reported			Baseline measure (per 100,000)		% reduction at post-PCV introduction period compared to	
Region	Country	Reference	Catch up age, if applicable	income group	Case Definition	Age groups evaluated	Pre-PCV	Post-PCV7 Pre-pcv13	Post-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13
Africa	Malawi	McCollum (2017)	14w-1y	low	WHO clinical pneumonia + hypoxemia	<5y	0.5	.	0.5	119 (hospital, 2012)	.	46.9 (-100, 100)	
Radiologically-confirmed pneumonia													
2+1													
America	Argentina	Lopez Papucci (2016)	<2 years	high	Not stated	<1y	4	.	2		.	66.2 (49.1, 77.5)	
		Gentile (2016)		high	Not stated	<5y	5	.	2	798	.	32.9 (29.7, 36)	
		Rearte (2016)		high	Not stated	<5y	4		2	732		53.3 (30, 69)	
	Uruguay	Hortal (2012)	<= 2 years	high	Not stated	12-23m		1	1.5		2087		44.9 (sig.)
Europe	Uruguay	Hortal (2014)	<= 2 years	high	Not stated	12-23m				2383	1482		37.8
	Israel	Greenberg (2015)		high	Not stated	<1y	6	2	2	1,870	2,020	34 (21, 45)	38 (26, 48)
		Givon-Lavi (2016)		high	Not stated	<2y (Jewish)	4	2	2	1,650	1,410	49 (14, 68)	40
		Givon-Lavi (2016)		high	Not stated	<2y (Bedouin)	4	2	2	2,840	2,660	51 (46 ,56)	48
		Ben Shimol (2016)		high	Not stated	<2y	3	1	4	15.47	16.3	46 (39, 53)	
3+0													
America	Nicaragua	Becker-Dreps (2014)	12-24mo	low	Clinical Diagnosis	<1y	3	.	2	6400	.	33 (25, 41)	
Pneumococcal pneumonia													
2+1													
America	Argentina	Gentile (2016)		high	Pleural effusion	<5y	5		2			72.1 (62.8, 79.1)	
Europe	Italy	Baldovin (2016)		high	ICD + isolation	<5y	.	3	3	.	1.8		70 (20, 90)
	United Kingdom (UK)	Nair (2016)		high		<2y	7	3	3	27.25	9.01	75.1	24.5
Empyema													

							Surveillance years reported			Baseline measure (per 100,000)		% reduction at post-PCV introduction period compared to	
Region	Country	Reference	Catch up age, if applicable	income group	Case Definition	Age groups evaluated	Pre-PCV	Post-PCV7 Pre-pcv13	Post-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13
2+1													
America	Argentina	Rearte (2016)		high	Pleural effusion	<5y	4		2	103		84.5 (34, 96)	
Europe	United Kingdom (UK)	Nath (2015)		high	ICD	<1y	24	4	4	.	.		53 (-14, 83)
		Saxena (2015)	<5y	high	ICD	<2y	5	4	4	.	.		42 (1, 66)
		Thomas (2013)		high	ICD	<2y	7	3	3				21 (-11,43) (st 1) 9 (-37,40) (st 3) -142 (-440,-61) (st 19F)

TABLE Pneumo 6. Summary Characteristics and Findings of Pre/Post 2+1 Observational Studies Evaluating a Pneumonia Endpoint

							Surveillance years reported			Baseline measure (per 100,000)		% reduction at post-PCV introduction period compared to	
Region	Country	Reference	Catch up age, if applicable	income group	Case Definition	Age groups evaluated	Pre-PCV	Post-PCV7 Pre-pcv13	Post-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13
Clinical pneumonia													
PCV10													
America	Peru	Suarez (2016)		high	ICD	<1y	3	.	2	62.84	.	29.3 (8, 45.7)	
	Finland	Palmu (2017)		high	ICD	3-42m	10		5	980		13 (9, 16)	
Europe	Iceland	Kristinsson (2014)		high	Not stated	12-23m	3	.	1.5	2,800	.	36 (16, 49)	
		Sigurdsson (2015)		high	ICD	<2y	3	.	3	422	.	23 (5, 36)	
	Sweden	Berglund (2014)		high	ICD	<2y	10	1	2	654.7	504.4	21 (7, 32)	-3 (-30, 18)
PCV13													
	Argentina	Gentile (2016)		high	Not stated	<1y	3	.	2	195.3	.	50.4	
America		Vizzotti (2016)		high	Clinical diagnosis	<1y	2	.	3	3295.1	.	27.3 (26.4, 28.2)	
		Lopez Papucci (2016)	<2 years	high	Clinical diagnosis	<1y	4	.	2	1687.21	.	43.2 (29.3, 54.4)	
	Costa Rica	Castro (2016)		high	Not stated	<2y	4	2	2	1180	850	35 (32, 38)	9 (5, 13)
	Mexico	Palacios (2016)		high	ICD	<1y	0	6	4		2443		60.5
Europe	Israel	Ben Shimol (2016)		high	Not stated	<2y	3	1	4	32.47	72.3	7 (1, 13)	
	Italy	Baldo (2016)	up to 36 months	high	ICD	<5y	4	4	2.5	379.4	211.9	4.6 (2.7, 6.5)	
	Spain	Rivero-Calle (2016)		high	ICD	<2y	6	5	2	20.7	.	58 (47.6, 67.3)	
	Sweden	Berglund (2014)		high	ICD	<2y	10	1	2	654.7	504.4	37 (26, 46)	18 (-1, 34)
	United Kingdom (UK)	Nath (2015)		high	ICD	<1y	24.	4	4	.	.		6 (-4, 16)
		Nair (2016)		high	ICD	<2y	7	3	3	293	237	30	13
		Saxena (2015)	<5y	high	ICD	<2y	5	4	4	.	.	20	-8 (-19, 2)
Radiologically-confirmed pneumonia													

							Surveillance years reported			Baseline measure (per 100,000)		% reduction at post-PCV introduction period compared to	
Region	Country	Reference	Catch up age, if applicable	income group	Case Definition	Age groups evaluated	Pre-PCV	Post-PCV7 Pre-pcv13	Post-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13
PCV13													
America	Argentina	Lopez Papucci (2016)	<2 years	high	Not stated	<1y	4	.	2		.	66.2 (49.1, 77.5)	
		Gentile (2016)		high	Not stated	<5y	5	.	2	798	.	32.9 (29.7, 36)	
		Rearte (2016)		high	Not stated	<5y	4		2	732		53.3 (30, 69)	
	Uruguay	Hortal (2012)	<= 2 years	high	Not stated	12-23m		1	1.5		2087		44.9 (sig.)
	Uruguay	Hortal (2014)	<= 2 years	high	Not stated	12-23m				2383	1482		37.8
Europe	Israel	Greenberg (2015)		high	Not stated	<1y	6	2	2	1,870	2,020	34 (21, 45)	38 (26, 48)
		Givon-Lavi (2016)		high	Not stated	<2y (Jewish)	4	2	2	1,650	1,410	49 (14, 68)	40
		Givon-Lavi (2016)		high	Not stated	<2y (Bedouin)	4	2	2	2,840	2,660	51 (46 ,56)	48
		Ben Shimol (2016)		high	Not stated	<2y	3	1	4	15.47	16.3	46 (39, 53)	
Pneumococcal pneumonia													
PCV10													
Europe	Finland	Palmu (2017)		high	ICD	3-42m	10		5	23		77 (64, 86)	
PCV13													
America	Argentina	Gentile (2016)		high	Pleural effusion	<5y	5		2			72.1 (62.8, 79.1)	
Europe	Italy	Baldovin (2016)		high	ICD + isolation	<5y	.	3	3	.	1.8		70 (20, 90)
	United Kingdom (UK)	Nair (2016)		high		<2y	7	3	3	27.25	9.01	75.1	24.5
Empyema													
PCV10													

							Surveillance years reported			Baseline measure (per 100,000)		% reduction at post-PCV introduction period compared to	
Region	Country	Reference	Catch up age, if applicable	income group	Case Definition	Age groups evaluated	Pre-PCV	Post-PCV7 Pre-pcv13	Post-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13	Pre-PCV	Post-PCV7 Pre-pcv13
Europe	Finland	Palmu (2017)		high	ICD	3-42m	10		5	1.6		3 (-174, 70)	
PCV13													
America	Argentina	Rearte (2016)		high	Pleural effusion	<5y	4		2	103		84.5 (34, 96)	
Europe	United Kingdom (UK)	Nath (2015)		high	ICD	<1y	24	4	4	.	.		53 (-14, 83)
		Saxena (2015)	<5y	high	ICD	<2y	5	4	4	.	.		42 (1, 66)
		Thomas (2013)		high	ICD	<2y	7	3	3				21 (-11,43) (st 1) 9 (-37,40) (st 3) -142 (-440,-61) (st 19F)

7. Pneumonia Indirect Effects:

TABLE Pneumo Ind Eff 1. Indirect effects of PCV10 on pneumonia outcomes from observational studies, by schedule

							Surveillance Years Reported			Baseline Measure (per 100,000)		% Reduction (95% CI) in PCV period compar to	
Region	Country (Ref)	Reference	Catch Up	Country Income Group	Case Definition	Age Group Evaluated	Pre PCV	PCV7/ PCV13	PCV10	Pre PCV	PCV7	Pre PCV	PCV
PCV10													
Clinical Pneumonia													
2+1													

EUR	Finland	3638: Okasha O, et al. ISPPD10 2016	No	High	all-cause pneumonia, hospitalizations	≥ 18 years	6.5 years	--	4 years	514	--	5.3% (1.2%, 8.7%)	--
						≥ 65 years	6.5 years	--	4 years	1633	--	7.3% (2.9%, 10.9%)	--
EUR	Finland	Palmu 2017, PLoS ONE	No	High	all-cause pneumonia, hospitalizations	19-71 months, unvaccinated	4 years	--	2.5 years	320	--	18% (10%, 25%)	--
EUR	Sweden	3533: Kostenniemi UD, et al. ISPPD10 2016.	No	High	Clinical pneumonia, hospitalizations	6-17 years	5 years	PCV7: 1 year PCV13: 1 year	3 years	460	600	2%*	25%
						18-64 years	5 years	PCV7: 1 year PCV13: 1 year	3 years	770	1000	-16%*	12%
						≥ 65 years	5 years	PCV7: 1 year PCV13: 1 year	3 years	3700	4100	-5%*	6%
3+0													
AFR	Kenya	3655: Silaba M, et al. ISPPD10 2016.	Yes	Low	Severe or very severe pneumonia, hospitalizations	5-12 years	9 years	--	4 years	Not reported	--	5% (-59%, 44%)	--
CXR Pneumonia													
3+0													
AFR	Kenya	3655: Silaba M, et al. ISPPD10 2016.	Yes	Low	CXR pneumonia, hospitalizations	5-12 years	9 years	--	4 years	Not reported	--	11% (-69%, 53%)	--

Pneumococcal Pneumonia													
2+1													
EUR	Finland	Palmu 2017, PLoS ONE	No	High	Pneumococcal pneumonia, hospital inpatients & outpatients	19-71 months, unvaccinated	4 years	--	2.5 years	18	--	70% (49%, 84%)	--
3+0													
AFR	Kenya	3541: Bigogo G, et al. ISPPD10 2016	Yes	Low	Pneumococcal pneumonia, surveillance	≥ 18 years, gen pop	3 years	--	3 years	1120	--	94% (90%, 98%)	--
						≥ 18 years, HIV uninfected	3 years	--	3 years	590	--	100%	--
Empyema													
2+1													
EUR	Finland	Palmu 2017, PLoS ONE	No	High	all-cause empyema, hospitalizations	19-71 months, unvaccinated	4 years	--	2.5 years	1	--	100% (-240%, 100%)	--

*Mixed effect of PCV13 followed by PCV10 use

TABLE Pneumo Ind Eff 2. Indirect effects of PCV13 on pneumonia outcomes from observational studies, by schedule

							Surveillance Years Reported			Baseline Measure (per 100,000)		% Reduction (95% CI PCV13 period compa to	
Region	Country (Ref)	Reference	Catch Up	Country Income Group	Case Definition	Age Group Evaluated	Pre PCV	PCV7/ PCV10	PCV13	Pre PCV	PCV7	Pre PCV	PCV
PCV13													
Clinical Pneumonia													
2+1													
AMR	Canada	3668: le Meur ISPPD10, 2016	Yes	High	Clinical pneumonia, hospitalized	20-64 years, mostly Indigenous	5 years	PCV7: 7 years PCV10: 2 years	3 years	562	201	44%*	-57%
						≥ 65 years, mostly Indigenous	5 years	PCV7: 7 years PCV10: 2 years	3 years	3720	4728	59%*	67%
EUR	Italy	4132: Baldo 2016, J Prev Med Hyg	Yes	High	Clinical pneumonia, hospitalized	15-64 years	2 and 5 years	PCV7: 5 and 2 years	3 years	54	45	30%	17%
						65-79 years	2 and 5 years	PCV7: 5 and 2 years	3 years	387	350	19%	10%
						≥ 80 years	2 and 5 years	PCV7: 5 and 2 years	3 years	1440	1605	-14%	-3%
EUR	Spain	3522: Rivero-Calle 2016, ISPPD10	No	High	Clinical pneumonia, hospitalized	18-49 years	6 years	PCV7: 5 years	3 years	22	28	70%	76%
						18-49 years	6 years	PCV7: 5 years	3 years	NR	NR	42.5% (35.0%, 46.9%)	--
						50-64 years	6 years	PCV7: 5 years	3 years	53	80	34%	56%

						50-64 years	6 years	PCV7: 5 years	3 years	NR	NR	30.5% (23.1%, 35.2%)	--
						≥ 64 years	6 years	PCV7: 5 years	3 years	210	350	29%	58%
						≥ 64 years	6 years	PCV7: 5 years	3 years	NR	NR	17.2% (13.9%, 20.2%)	--
EUR	UK	178: Rodrigo 2015, Eur Resp J	Yes	High	Clinical pneumonia, hospitalized	> 16 years	--	PCV7: 2 years	3 years	--	91	--	30% (2 40%
Pneumococcal Pneumonia													
2+1													
EUR	Israel	3636: Regev-Yochay 2016, ISPPD10	Yes	High	Blood culture positive pneumonia	> 18 years	0 years	PCV7: I92 years	3.5 years	NR	7.64	--	39%
EUR	UK	178: Rodrigo 2015, Eur Resp J	Yes	High	All pneumococcal pneumonia, hospitalized	> 16 years	--	PCV7: 2 years	3 years	--	35	--	40% (3 50%
EUR	UK	178: Rodrigo 2015, Eur Resp J	Yes	High	Pneumococcal pneumonia due to **PCV7** serotypes, hospitalized	> 16 years	--	PCV7: 2 years	3 years	--	11	--	79% (6 88%

EUR	UK	178: Rodrigo 2015, Eur Resp J	Yes	High	Pneumoccocal pneumonia due to **6 additional** serotypes in PCV13, hospitalized	> 16 years	--	PCV7: 2 years	3 years	--	11	--	41% (1 61%

*Mixed effect of PCV10 followed by PCV13 use.

8. Mortality

TABLE Mort 1.: Included PCV Impact on Mortality Studies

	2p1			3p0			3p1			Grand Total
Characteristic	PCV10	PCV13	Total	PCV10	PCV13	Total	PCV10	PCV13	Total	
Geographic Region										
Africa	0	0	0	1	2	3	0	0	0	3
Europe	2	2	4	0	0	0	0	0	0	4
Latin America	2	1	3	0	1	1	5	0	5	9
Oceania	0	0	0	1	1	2	0	0	0	2
Grand Total	**4**	**3**	**7**	**2**	**4**	**6**	**5**	**0**	**5**	**18**
World Bank Income Strata										
High (High & Upper-Middle)	4	3	7	1	1	2	5	0	5	14
Low (Low & Lower-Middle)	0	0	0	1	3	4	0	0	0	4
Grand Total	**4**	**3**	**7**	**2**	**4**	**6**	**5**	**0**	**5**	**18**
Catch-Up										

No	4	1	5	2	0	2	1	0	1	8
Yes	0	2	2	0	4	4	4	0	4	10
Grand Total	**4**	**3**	**7**	**2**	**4**	**6**	**5**	**0**	**5**	**18**

TABLE Mort 2. Included Studies Characteristics

Study Characteristics								% Relative Reduction
Citation Information	**Geographic Region**	**Income**	**Study Design**	**PCV10/13 (Intro Year)**	**Number of Years Post PCV10/13 Introduction**	**Age Group**	**Endpoint Measured**	**Pre-PCV vs. PCV10/13 (95% CI)**
2p+1 Dosing Schedule								
Iceland (Haraldsson A , 2014)	Europe	High	Pre/Post	PCV10 (2011)	2	<2y	IPD	100% [a]
Finland (Palmu A, 2015)	Europe	High	Pre/Post	PCV10 (2010)	3	<5y	All-Cause IPD	51% (-94, 93) 35% (-181, 90)
Scotland* (Nair H, 2016)	Europe	High	Pre/Post	PCV13 CU (2010)	2	<2y <5y	Pneumonia	12.5% [a] 41% [a]
Costa Rica (Castro J , 2016)	Latin America	High	Pre/Post	PCV13 (2012)	2	<2y	Pneumonia	35% [a]
3p+0 Dosing Schedule								
Fiji (Tuivaga E, 2016)	Oceania	High	Pre/Post	PCV10 (2012)	3	<2y	(CXR) Pneumonia Pneumonia	57% (29.6, 110) [a] 50% (29.3, 85.3) [a]
Malawi (McCollum ED, 2017)	Africa	Low	Pre/Post	PCV13 CU (2013)	1	<5y	Pneumonia	41% (21, 63)

Australia* (Toms C, 2016)	Oceania	High	Pre/Post	PCV13 CU (2011)	5	<5y	IPD	-62% 🚘
3p+1 Dosing Schedule								
Brazil (Hirose T, 2015)	Latin America	High	Pre/Post	PCV10 CU (2010)	1	<2y	Pneumococcal Meningitis	38.3% (0, 195) 🚘
Brazil (Grando I, 2015)	Latin America	High	Pre/Post	PCV10 CU (2010)	2	<2y	Pneumococcal Meningitis	36% 🚘
Brazil (Sini de Almeida RJ, 2016)	Latin America	High	Pre/Post	PCV10 CU (2010)	5	<5y	IPD	44% 🚘

CU = Catch-up at time of introduction

* = previous PCV7 use

🚘 calculated (not reported) reduction

TABLE Mort 3. Mortality Included Studies

Study Characteristics								% Relative Reduction
Citation Information	**Geographic Region**	**Income**	**Study Design**	**PCV10/13 (Intro Year)**	**Number of Years Post PCV10/13 Introduction**	**Analytic Age Group**	**Analytic Endpoint**	**Pre-PCV vs. PCV10/13 (95% CI)**
2p+1 Dosing Schedule								
Colombia, Bogota* (Carrasquilla G, 2016)	Latin America	High	Pre/Post	PCV10 (2011)	3	<2y <5y <2y <5y	Pneumonia All-Cause	69.1% (62.7–74.5) 56.8% (49.2–63.3) 22.0% (19.1–24.8) 22.1% (19.4–24.7)

Colombia, National* (Carrasquilla G, 2016)	Latin America	High	Pre/Post	PCV10 (2011)	3	<2y <5y <2y <5y	Pneumonia All-Cause	36.7% (30.9–42.1) 33.4% (27.6–38.8) 26.3% (24.7–27.8) 25.3% (23.8–26.8)
Denmark* (Harboe Z, 2014)	Europe	High	Pre/Post	PCV13 CU (2010)	3	<2y <5y	IPD	71% (-96, 100) 88% (-21, 100)
3p+0 Dosing Schedule								
Kenya, Kibera (Verani J, 2016)	Africa	Low	Pre/Post	PCV10 (2011)	3	<5y	Pneumonia All-Cause	43% (0, 68) 37%
Nicaragua (Becker-Dreps S, 2014)	Latin America	Low	Pre/Post	PCV13 CU (2010)	2	<1y	All-Cause	33% (20, 43)
Malawi (Mchinji) (King C, 2016)	Africa	Low	Cohort	PCV13 CU (2011)	1	<1y	All-Cause	22.2%
3p+1 Dosing Schedule								
Chile (Diaz J, 2016)	Latin America	High	CC	PCV10 (2011)	3	<2y	Pneumonia All-Cause	71.5 (9.0-91.8) 34.8 (23.7-44.3)
Brazil (Grando I, 2015)	Latin America	High	Pre/Post	PCV10 CU (2010)	2	<2y	Pneumococcal Meningitis	69%
Brazil (Hirose T, 2015)	Latin America	High	Pre/Post	PCV10 CU (2010)	1	<2y	Pneumococcal Meningitis	75.5% (65.6, 86.9) [a]
Brazil (Simonsen L, 2016)	Latin America	High	Pre/Post	PCV10 CU (2010)	3	<2y <5y	Pneumonia	6% -5%
Peru (Suarez V, 2016)	Latin America	High	Pre/Post	PCV10 (2011)	2	<1y	Pneumonia	35% (8.6, 53.8)