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*Shuo Feng, Julie McLellan, Nicola Pidduck, Nia Roberts, Julian PT Higgins, Yoon Choi, Alane Izu, Mark Jit, Shabir A Madhi, Kim Mulholland, Andrew J Pollard, Simon Procter, Beth Temple and Merryn Voysey*

*DOI 10.3310/YWHA3079*

# Immunogenicity and seroefficacy of pneumococcal conjugate vaccines: a systematic review and network meta-analysis

Shuo Feng[1], Julie McLellan[2], Nicola Pidduck[2], Nia Roberts[3], Julian PT Higgins[4], Yoon Choi[5], Alane Izu[6], Mark Jit[8], Shabir A Madhi[6,7], Kim Mulholland[8,9,10], Andrew J Pollard[1,11], Simon Procter[8], Beth Temple[8,9,10] and Merryn Voysey[1,11*]

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# Abstract

## Immunogenicity and seroefficacy of pneumococcal conjugate vaccines: a systematic review and network meta-analysis

Shuo Feng[1] Julie McLellan[2] Nicola Pidduck[2] Nia Roberts[3] Julian PT Higgins[4] Yoon Choi[5] Alane Izu[6] Mark Jit[8] Shabir A Madhi[6,7] Kim Mulholland[8,9,10] Andrew J Pollard[1,11] Simon Procter[8] Beth Temple[8,9,10] and Merryn Voysey[1,11*]

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**Background:** Vaccination of infants with pneumococcal conjugate vaccines is recommended by the World Health Organization. Evidence is mixed regarding the differences in immunogenicity and efficacy of the different pneumococcal vaccines.

**Objectives:** The primary objective was to compare the immunogenicity of pneumococcal conjugate vaccine-10 versus pneumococcal conjugate vaccine-13. The main secondary objective was to compare the seroefficacy of pneumococcal conjugate vaccine-10 versus pneumococcal conjugate vaccine-13.

**Methods:** We searched the Cochrane Library, EMBASE, Global Health, MEDLINE, ClinicalTrials.gov and trialsearch.who.int up to July 2022. Studies were eligible if they directly compared either pneumococcal conjugate vaccine-7, pneumococcal conjugate vaccine-10 or pneumococcal conjugate vaccine-13 in randomised trials of children under 2 years of age, and provided immunogenicity data for at least one time point. Individual participant data were requested and aggregate data used otherwise.

Outcomes included the geometric mean ratio of serotype-specific immunoglobulin G and the relative risk of seroinfection. Seroinfection was defined for each individual as a rise in antibody between the post-primary vaccination series time point and the booster dose, evidence of presumed subclinical infection.

Each trial was analysed to obtain the log of the ratio of geometric means and its standard error. The relative risk of seroinfection ('seroefficacy') was estimated by comparing the proportion of participants with seroinfection between vaccine groups.

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The log-geometric mean ratios, log-relative risks and their standard errors constituted the input data for evidence synthesis. For serotypes contained in all three vaccines, evidence could be synthesised using a network meta-analysis. For other serotypes, meta-analysis was used.

Results from seroefficacy analyses were incorporated into a mathematical model of pneumococcal transmission dynamics to compare the differential impact of pneumococcal conjugate vaccine-10 and pneumococcal conjugate vaccine-13 introduction on invasive pneumococcal disease cases. The model estimated the impact of vaccine introduction over a 25-year time period and an economic evaluation was conducted.

**Results:** In total, 47 studies were eligible from 38 countries. Twenty-eight and 12 studies with data available were included in immunogenicity and seroefficacy analyses, respectively. Geometric mean ratios comparing pneumococcal conjugate vaccine-13 versus pneumococcal conjugate vaccine-10 favoured pneumococcal conjugate vaccine-13 for serotypes 4, 9V and 23F at 1 month after primary vaccination series, with 1.14- to 1.54-fold significantly higher immunoglobulin G responses with pneumococcal conjugate vaccine-13. Risk of seroinfection prior to the time of booster dose was lower for pneumococcal conjugate vaccine-13 for serotype 4, 6B, 9V, 18C and 23F than for pneumococcal conjugate vaccine-10. Significant heterogeneity and inconsistency were present for most serotypes and for both outcomes. Twofold higher antibody after primary vaccination was associated with a 54% decrease in risk of seroinfection (relative risk 0.46, 95% confidence interval 0.23 to 0.96).

In modelled scenarios, pneumococcal conjugate vaccine-13 or pneumococcal conjugate vaccine-10 introduction in 2006 resulted in a reduction in cases that was less rapid for pneumococcal conjugate vaccine-10 than for pneumococcal conjugate vaccine-13. The pneumococcal conjugate vaccine-13 programme was predicted to avoid an additional 2808 (95% confidence interval 2690 to 2925) cases of invasive pneumococcal disease compared with pneumococcal conjugate vaccine-10 introduction between 2006 and 2030.

**Limitations:** Analyses used data from infant vaccine studies with blood samples taken prior to a booster dose. The impact of extrapolating pre-booster efficacy to post-booster time points is unknown. Network meta-analysis models contained significant heterogeneity which may lead to bias.

**Conclusions:** Serotype-specific differences were found in immunogenicity and seroefficacy between pneumococcal conjugate vaccine-13 and pneumococcal conjugate vaccine-10. Higher antibody response after vaccination was associated with a lower risk of subsequent infection. These methods can be used to compare the pneumococcal conjugate vaccines and optimise vaccination strategies. For future work, seroefficacy estimates can be determined for other pneumococcal vaccines, which could contribute to licensing or policy decisions for new pneumococcal vaccines.

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# List of abbreviations

| | |
|---|---|
| AIC | Akaike information criterion |
| CCR | case : carrier ratio |
| CDSR | Cochrane Database of Systematic Reviews |
| CET | cost-effectiveness threshold |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CRM | cross-reacting material |
| DTaP | diphtheria, tetanus, acellular pertussis |
| DTwP | diphtheria, tetanus, whole-cell pertussis |
| ELISA | enzyme-linked immunosorbent assay |
| GMC | geometric mean concentration |
| GMR | geometric mean ratio |
| HBV | hepatitis B vaccine |
| Hib-TT | *Haemophilus influenzae* type b tetanus toxoid conjugate vaccine |
| ICTRP | International Clinical Trials Registry Platform |
| IgG | immunoglobulin G |
| iNMB | incremental net monetary benefit |
| IPV | inactivated polio vaccine |
| mcg/ml | micrograms per millilitre |
| MenC | group C meningococcal vaccine |
| NCT | National Clinical Trial |
| NMA | network meta-analysis |
| OPV | oral polio vaccine |
| PCV | pneumococcal conjugate vaccine |
| PCV10-SII | Pneumosil |
| QALY | quality-adjusted life-year |
| RCT | randomised controlled trial |
| RoB | risk of bias |
| RR | relative risk |
| SE | standard error |
| TT | tetanus toxoid |
| WHO | World Health Organization |

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# Plain language summary

Pneumococcal disease is a serious illness caused by a bacterial infection that can result in death. Children in the United Kingdom receive a vaccine to prevent this disease that protects against 13 different types of pneumococcal diseases. It is very effective, but other vaccines are also available, such as one that contains 10 types of pneumococcal diseases. Vaccines in the United Kingdom are bought by the government and the choice of which vaccine to provide is based on the cost of the vaccine as well as the benefits to our health. However, there is very little information comparing different vaccines and it is often assumed they are the same.

We did a large analysis combining all studies of the two main licensed pneumococcal vaccines to determine which vaccine provides better protection against infection and how this affects costs. We used information from studies published in medical journals, and also data from studies done by the companies that own the vaccines.

Our results showed that pneumococcal conjugate vaccine-13 vaccine provided better protection than pneumococcal conjugate vaccine-10 for 5 of the 10 serotypes that are contained in both vaccines. When we used these results to model what might have happened had either of these vaccines been introduced into the United Kingdom vaccination programme in 2006, we found that both vaccines caused a rapid decrease in the amount of disease, but that the decrease in disease was faster with pneumococcal conjugate vaccine-13 than pneumococcal conjugate vaccine-10. This resulted in 2808 cases of diseases prevented over a 25-year time frame with pneumococcal conjugate vaccine-13 compared with pneumococcal conjugate vaccine-10.

Our methods can be used to compare other vaccines and we recommend this type of study be done in future when making decisions on vaccine product choice.

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# Scientific summary

*Streptococcus pneumoniae* (pneumococcus) causes severe diseases, including bacterial pneumonia, meningitis and sepsis, leading to substantial morbidity and mortality worldwide, with the highest disease burden being in young children and older adults. Three pneumococcal conjugate vaccines (PCVs) have been widely deployed worldwide in the past two decades: PCV7 (Prevnar; Pfizer, headquartered in New York City, New York, USA), PCV10 (Synflorix; GlaxoSmithKline, headquartered in Brentford, London, UK) and PCV13 (Prevenar 13; Pfizer, headquartered in New York City, New York, USA), resulting in substantial reduction in disease. Between 2009 and 2011, PCV7 was gradually replaced by PCV13 and PCV10 and is no longer available.

The World Health Organization (WHO) does not preferentially endorse one PCV over another. Both PCV13 and PCV10 have been shown to provide both direct and indirect protection against pneumococcal pneumonia, invasive pneumococcal disease and nasopharyngeal carriage. Although there are 10 common serotypes in these 2 vaccines, the components of the vaccines differ, with different carrier proteins used in the conjugation process, as well as different amounts of polysaccharide, and these differences may contribute to differences in protection. Large randomised controlled trials directly comparing different PCVs with invasive pneumococcal disease as the primary outcome are not feasible. We previously used 'seroinfection' as an outcome for analysis of PCVs, where seroinfection is defined as an increase in antibody levels between the primary vaccination series (typically complete at 5–7 months of age) and the booster dose (typically administered at 9–18 months of age). Seroinfection can be regarded as evidence of exposure to the pathogen and a resultant subclinical infection, given antibody responses wane rapidly during this period otherwise. Seroinfection rates for different vaccines can be compared by calculating the relative risk (RR) of seroinfection, referred to herein as 'seroefficacy'.

We meta-analysed data from studies of PCVs to compare the immunogenicity and seroefficacy of PCV10 with PCV13 for each serotype. We aimed to determine if serotype-specific immune responses were higher for either vaccine and whether this resulted in greater protection again seroinfection. In addition, we explored the overall relationship between the higher immune response and protection against seroinfection in infants.

Following this, we show how serotype-specific estimates of seroefficacy can be incorporated in vaccine cost-effectiveness models.

## Objectives

The primary objective of the systematic review was to compare the immunogenicity of PCV10 versus PCV13 for each serotype contained in the vaccines.

The secondary objectives were:

1. to compare the seroefficacy of PCV10 versus PCV13 for each serotype contained in the vaccines
2. for PCV10 and PCV13 separately, to estimate immunogenicity and seroefficacy in comparison with the older PCV7 vaccine
3. to determine how the comparisons of immunogenicity and efficacy of PCV10 to PCV13 are affected by the co-administration of different routine vaccines.

## Methods

### *Systematic review*

We conducted a systematic review identifying studies that compared the immunogenicity of licensed PCVs in trials which randomised children to one of two different PCVs. The PCVs included in the review

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were PCV7 (Prevnar; Pfizer), PCV10 (Synflorix; GlaxoSmithKline) and PCV13 (Prevenar 13; Pfizer); PCV7 was included even though no longer available, so that we could compare PCV13 and PCV10 indirectly through them each being compared with PCV7 for the same serotypes.

### *Data sources*

The databases searched were Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials, EMBASE, Global Health and MEDLINE. The trial registers searched were ClinicalTrials.gov (https://clinicaltrials.gov/) and WHO International Clinical Trials Registry Platform (https://trialsearch.who.int/). The search comprised title/abstract keywords and subject headings for pneumococcal vaccines and children. A methodological search filter for randomised controlled trials taken from the Cochrane Handbook was used to limit to randomised controlled trials. Pharmaceutical company websites (GlaxoSmithKline and Pfizer) were also hand-searched for relevant studies. No date or language limits were applied.

### *Study selection*

Randomised controlled trials were included if they provided direct comparisons of either PCV7, PCV10 or PCV13 among infants and children < 2 years of age, and if they provided estimates of antibody responses [serotype-specific anti-pneumococcal immunoglobulin G (IgG) to PCVs for at least one time point of 1] between 4 and 6 weeks after the primary vaccination series and/or 1 month after a booster vaccination.

Individual participant-level data were retrieved if available. Aggregate data from publications were extracted if individual participant data were not available.

Risk of bias in results of the included studies was assessed independently by two reviewers using the Cochrane Risk of Bias Tool.

### *Data synthesis*

Each trial with individual participant-level data available was analysed to obtain the log of the ratio of geometric means (log-GMR) and its standard error (SE) for each serotype and time point of interest.

The RR of seroinfection was estimated by comparing the proportion of participants with seroinfection between vaccine groups. When no seroinfection occurred in any group (numerator of absolute risk was 0), a small non-zero value (0.5) was added to both sero-infected and sero-non-infected groups to allow estimation of the RR.

The log-GMRs, log-RRs and their SEs constituted the input data for evidence synthesis. Only trials supplying individual participant data were included in seroefficacy analyses. For serotypes contained in all three vaccines, evidence could be synthesised using a network meta-analysis (NMA) of all comparisons. For other serotypes, meta-analysis was used for evidence synthesis.

To estimate the overall association between antibody geometric mean ratio (GMR) and RR across all serotypes, we fitted a mixed-effect model regressing study-level RRs of seroinfection on GMRs across serotypes, weighted by the sample size of each study. Fixed effects included GMR, serotype and interactions between GMR and serotype (allowing serotype-specific association), while study was included as a random effect.

### *Mathematical modelling and retrospective economic evaluation*

To illustrate the use of serotype-specific estimates of seroefficacy in modelling vaccine impact and cost-effectiveness, we developed a serotype-specific mathematical model of pneumococcal transmission dynamics to compare the differential impact of PCV10 and PCV13 introduction on invasive pneumococcal disease cases with vaccine serotypes in England and Wales. The model estimated the impact over a 25-year time period from 2006 to 2030.

We subsequently assessed the cost-effectiveness of introducing infant vaccination with PCV13 compared with introducing PCV10 from a healthcare payer perspective in England and Wales. More specifically, we retrospectively estimated the *additional* threshold price per dose below which PCV13 would be more cost-effective than PCV10 had they both been available at the time of introduction of the PCV vaccine programme in England and Wales in 2006.

## Results

Database registry and hand searches identified 4699 publication records of which 47 studies (78 publication reports) satisfied our eligibility criteria. Nineteen studies (24 publication reports) were excluded from the analysis: 6 studies did not provide individual patient or aggregate data and 13 studies (18 publication reports) were studies with the vaccines of interest, but it was not possible to form a loop within the NMA to provide indirect evidence. The remaining 28 studies (54 publication records) from 2009 to 2023 were included in the NMAs. Twenty-two studies provided individual participant data with a further five studies reporting aggregate data.

### *Immunogenicity*

Geometric mean ratios for comparisons between PCV13 versus PCV10 for any primary series schedule were higher for PCV13 for serotypes 4, 7F, 9V and 23F at 1 month after primary vaccination series, with 1.14- to 1.54-fold higher IgG responses with PCV13. Additional serotypes contained only in the PCV13 vaccine (3, 6A and 19A) also favoured PCV13 as expected. GMRs were similar for the remaining serotypes (1, 5, 6B, 14, 18C and 19F). GMRs favoured PCV7 over either PCV13 or PCV10 for serotypes 4, 6B, 9V, 14 and 23F. There was no difference in GMRs for serotypes 18C and 19F across three vaccines.

At the pre-booster time point, data were available from 18 cohorts. IgG responses were lower with PCV13 compared with PCV10 for all PCV7 serotypes except for serotype 14, with the point estimates of GMRs comparing PCV13 versus PCV10 ranging from 0.44 to 0.78. IgG responses were higher for PCV13 for serotypes 1, 5 and 7F. GMRs comparing PCV13 versus PCV7 showed higher IgG with PCV7 for serotypes 4, 6B, 9V, 14 and 23F and higher IgG with PCV13 for serotype 19F.

At 28 days post booster, data were available from 26 cohorts. GMRs favoured PCV13 over PCV10 for serotype 6B, 9V, 14 and 23F and favoured PCV10 over PCV13 for serotype 18C. For serotype 1, 5 and 7F, antibody responses were higher in PCV13 compared with PCV10. PCV7 recipients had higher geometric mean concentrations (GMCs) compared with PCV13 for all PCV7 serotypes except 6B for which there was no difference, and 19F, which favoured PCV13. For PCV13-only serotypes (3, 6A and 19A), GMRs favour PCV13 at all three time points.

Substantial heterogeneity and network inconsistency were present for most serotypes at all three time points.

To explore potential reasons for the observed heterogeneity, we summarised cohort-level GMRs and RRs for each vaccine comparison. These descriptive analyses revealed a lack of consistency in the direction of study-level estimates within each vaccine comparison, resulting in the significant heterogenicity. There was also no observable pattern in any trial-level variable (region, co-administered vaccines, vaccine schedule), from which one might propose a mechanism that would adequately explain this variation in GMRs.

### *Seroefficacy*

There were 12 studies (15 cohorts) with available individual participant antibody data at both post-primary and prior to the booster dose, allowing serotype-specific estimation of seroefficacy from a total

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of 5152 participants. Of these 15 cohorts, 6 compared PCV10 versus PCV7, 3 compared PCV13 versus PCV7 and 6 compared PCV13 versus PCV10.

Among PCV7 serotypes, the risk of seroinfection was lower with PCV13 than PCV10 for serotypes 4, 6B, 9V, 18C and 23F, while no difference was seen for serotype 14 and 19F. The RRs of seroinfection (PCV13 vs. PCV10) for PCV7 serotypes ranged from 0.32 (95% CI 0.19 to 0.52) for serotype 4 to 1.28 (95% CI 0.95 to 1.74) for serotype 14.

For serotypes 1, 5 and 7F, evidence was summarised from six studies directly comparing PCV13 with PCV10. Comparisons between PCV13 and PCV7 favoured neither vaccine over the other, whereas comparisons between PCV7 and PCV10 favoured PCV7 for serotypes 5, 6B, 9V, 18C and 23F.

The $I^2$ and *p*-values indicated some heterogeneity for all PCV7 serotypes except for serotype 4 and 19F.

In the mixed-effects model of all serotypes combined, vaccines that produced the same amount of antibody (GMR = 1) had very similar protection (adjusted RR 0.80, 95% CI 0.41 to 1.58). The model estimate indicates that for each twofold increase in antibody response, the risk of seroinfection was halved (GMR of 2.0; RR 0.46, 95% CI 0.23 to 0.96).

### *Mathematical model and economic evaluation*

Mathematical model results showed that in the absence of any vaccine programme, an increase in invasive pneumococcal disease cases caused by all five serotypes would be seen over the 25-year time frame. With the introduction of either PCV13 or PCV10 vaccine programmes in 2006, case counts would have decreased, achieving near eradication of all serotypes within the time frame modelled. The decrease in cases was most rapid for serotype 6B and least rapid for serotype 4. The decrease in cases was less rapid for PCV10 than for PCV13 due to the lower seroefficacy.

The introduction of an infant PCV13 programme was predicted to avoid an additional 2808 (95% CI 2690 to 2925) cases of invasive pneumococcal disease compared with PCV10 introduction between 2006 and 2030. This includes an estimated 326 cases of meningitis, 578 cases of sepsis, 1770 cases of invasive pneumonia and 30,680 cases of non-invasive pneumonia. Under base-case assumptions, this resulted in discounted healthcare savings of £13 million (95% CI £12 to £14 million). Including non-invasive pneumonia increased the savings to £27 million (95% CI £25 to £29 million).

## Conclusions

In our study, we used a novel methodology to define seroinfection from immunogenicity data to compare the relative efficacy of PCVs in preventing infection. Our results using individual-level data from a global meta-analysis provide the first estimates of the comparative protection afforded by different pneumococcal vaccines and show that for many serotypes, carriage events are less common after PCV13 than PCV10, likely due to a higher antibody response. In addition, we quantify the relationship between the immune response to vaccination and protection against infection, measured serologically, and show that higher antibody responses in infants are associated with greater protection from infection.

Licensure of new vaccines is based on non-inferiority comparisons with current vaccines and the proportion of antibody responses above the agreed threshold as a minimum requirement. Once a vaccine meets this 'at-least-as-good-as' immunogenicity criteria, it has previously not been clear whether exceeding it is of benefit, and the WHO position paper on pneumococcal vaccines states *'It is unknown whether a lower serotype-specific GMC of antibody indicates less efficacy'*. Our results show that lower protection against subclinical infection does indeed follow from lower antibody production and that two vaccines that produce a similar level of antibody will provide similar levels of protection.

The implications of these findings are of greatest importance when a new vaccine roll-out is being considered. Lower antibody production or lower seroefficacy for one vaccine product does not necessarily imply limited effectiveness against invasive pneumococcal diseases when considering vaccines such as PCV10 and PCV13 which are highly effective vaccines in many settings. Instead, lower antibody responses lead to less rapidly observed indirect protection after implementation into a national programme as a smaller proportion of transmission events are blocked by the vaccine. This is evident in the mathematical modelling which showed less rapid decreases in the number of cases of invasive disease when introducing PCV10 compared with PCV13.

### *Implications for practice*

This evidence of differences in serotype-specific protection can be incorporated into cost-effectiveness models used to compare vaccine products. Cost-effectiveness studies have highlighted the lack of evidence of comparative efficacy for different PCVs, resulting in previous cost-effectiveness models that ignore serotype-specific differences and assume equivalent efficacy for all serotypes covered by different PCVs. Our study fills this evidence gap and allows researchers and policy-makers to use more accurate vaccine-specific models in decision-making.

Our cost-effectiveness analysis of a hypothetical scenario showed that introducing infant PCV13 was predicted to avert a higher burden of pneumococcal disease compared with PCV10. This would have realised a small saving of £13 million discounted over 24 years.

When considering the introduction of new pneumococcal vaccines into the routine immunisation schedule, we recommend that differences in antibody responses for different vaccines be considered in modelling scenarios as higher antibody responses result in reduced transmission and greater impact on invasive diseases. Vaccine-specific threshold prices can then be determined for cost-effective vaccines. Our analysis showed that due to its higher efficacy against some serotypes, a higher threshold price per dose could be paid for PCV13 while remaining cost-effective.

## Study registration

This study is registered as PROSPERO CRD42019124580.

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# **Chapter 1** Background

## Introduction

*Streptococcus pneumoniae* (pneumococcus) causes severe diseases, including bacterial pneumonia, meningitis and sepsis, leading to substantial morbidity and mortality worldwide, with the highest disease burden being in young children and older adults.[1,2] There have been more than 100 serotypes of pneumococcus documented as of 2020, not all of which cause severe diseases, and the distribution of these serotypes varies substantially between countries.[1,2] Three pneumococcal conjugate vaccines (PCVs) have been widely deployed worldwide in the past two decades: PCV7 (Prevnar; Pfizer), PCV10 (Synflorix; GlaxoSmithKline) and PCV13 (Prevenar 13; Pfizer), resulting in substantial reduction in disease.[1,3] New PCVs such as PCV15, PCV20 and PCV10-SII have been licensed in some countries but have yet to be widely deployed.

Between 2009 and 2011, PCV7 was gradually replaced by PCV13 and PCV10 and is no longer available. Currently, three PCVs are recommended by the World Health Organization (WHO) for infants worldwide: PCV13, PCV10 and a new 10-valent PCV manufactured by Serum Institute of India (PCV10-SII, Pneumosil) which was prequalified by WHO in December 2019.[3,4] PCV13 provides additional serotypes (3, 6A and 19A) to the 10 serotypes included in PCV10 (serotype 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). PCV10-SII covers serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. The licensure of PCVs is benchmarked against anticapsular immunoglobulin G (IgG) antibody responses above a threshold of 0.35 mcg/ml for all vaccine serotypes, which was established using data from three randomised controlled efficacy trials.[5] Real-world evidence suggests that correlates of protection and effectiveness against invasive pneumococcal disease vary across serotypes.[6]

The WHO does not preferentially endorse one PCV over another. Both PCV13 and PCV10 have been shown to provide both direct and indirect protection against pneumococcal pneumonia, invasive pneumococcal disease and nasopharyngeal carriage.[3,7] Although there are 10 common serotypes in these two vaccines, the content of the vaccines differs, with different carrier proteins used in the conjugation process, as well as different amounts of polysaccharide, and these differences may contribute to differences in protection. In 2017, a systematic review of studies directly comparing PCV10 with PCV13 showed differences in anti-pneumococcal IgG responses between vaccines. However, no meta-analysis has been included in this review, and there remains uncertainty over whether one vaccine is consistently more immunogenic and whether differences in immunogenicity result in clinically important differences in protection. Large randomised controlled trials (RCTs) directly comparing different PCVs with invasive pneumococcal disease as the primary outcome are not feasible. Studies that assessed the impact of different PCVs on nasopharyngeal carriage have reported very few or no differences.[8,9] Episodes of nasopharyngeal carriage often last only a few days or weeks, and therefore cross-sectional swabbing studies may misclassify participants when swabs are not taken at the time of infection, resulting in underpowered comparisons. We previously used 'seroefficacy' as an outcome for estimating correlates of protection for PCVs against pneumococcal carriage,[10] where seroinfection is defined as an increase in antibody levels between the primary vaccination series (typically complete at 5–7 months of age) and the booster dose (typically administered at 9–18 months of age). Seroinfection can be regarded as evidence of exposure to the pathogen and a resultant subclinical infection, given antibody responses wane rapidly during this period otherwise.[10]

In this study, we meta-analysed individual participant data from studies of PCVs to compare the immunogenicity and seroefficacy of PCV10 with PCV13 for each serotype. We aimed to determine if serotype-specific immune responses were higher for either vaccine and whether this resulted in greater protection again carriage (seroefficacy) for the same serotypes. In addition, we explored the overall relationship between the higher immune response and protection against carriage in infants.

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# Chapter 2 Methods

Our systematic review is reported in line with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement plus the extension statements for network and individual patient data systematic reviews.[11–13]

## Primary and secondary objectives

The primary objective was to compare the immunogenicity of PCV10 versus PCV13 for each serotype contained in the vaccines.

The secondary objectives were:

4. to compare the seroefficacy of PCV10 versus PCV13 for each serotype contained in the vaccines
5. for PCV10 and PCV13 separately, to estimate immunogenicity and seroefficacy in comparison to the older PCV7 vaccine
6. to determine how the comparisons of immunogenicity and efficacy of PCV10 to PCV13 are affected by the co-administration of different routine vaccines.

## Outcomes

The primary outcome was serotype-specific anticapsular pneumococcal IgG antibodies measured at three time points: (1) 1 month after the primary series of one to three doses of vaccine in infancy, (2) prior to a booster dose and (3) 1 month after a booster dose.

The outcome for seroefficacy analyses was a binary variable for seroinfection defined as a rise in anti-serotype-specific IgG between the post-primary time point and the booster dose. As a binary variable, seroinfection was equivalent to 1 if antibody levels increased by any amount during this period, or 0 otherwise. This outcome was only able to be derived if individual participant data were available at both time points.

## Systematic review

We conducted a systematic review identifying studies that compared the immunogenicity of licensed PCVs for infants or children in randomised trials. The PCVs included in the systematic review were:

1. 7-valent pneumococcal conjugate vaccine (PCV7: Prevnar; Pfizer), containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, each conjugated to diphtheria cross-reacting material (CRM).
2. 13-valent pneumococcal conjugate vaccine (PCV13: Prevenar 13; Pfizer), containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, each conjugated to diphtheria CRM.
3. 10-valent pneumococcal conjugate vaccine (PCV10: Synflorix; GlaxoSmithKline), containing serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, conjugated to non-typeable *Haemophilus influenzae* protein D, for eight serotypes, or tetanus or diphtheria protein (serotypes 18C and 19F, respectively).

PCV7 was included even though no longer available, so that we could compare PCV13 and PCV10 indirectly through them each being compared with PCV7 for the same serotypes.

The search strategy was devised and conducted by an information specialist (NR). Five databases and two trial registers were searched from database inception to 27 July 2022. The original search was run

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in June 2019, with an update search run in July 2022. The databases searched were Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL; Cochrane Library, Wiley) (Issue 7 of 12, July 2022), EMBASE (OvidSP) (1974–present), Global Health (OvidSP) (1973–2022 Week 29) and MEDLINE (OvidSP) (1946–present). The trial registers searched were ClinicalTrials.gov (https://clinicaltrials.gov/) and WHO International Clinical Trials Registry Platform (https://trialsearch.who.int/). The search comprised title/abstract keywords and subject headings for pneumococcal vaccines and children. A methodological search filter for RCTs taken from the Cochrane Handbook was used to limit to RCTs.[10,11] Pharmaceutical company websites (GlaxoSmithKline and Pfizer) were also hand-searched for relevant studies. A full list of search terms for each database is summarised in *Appendix 1*. No date or language limits were applied. References were exported to EndNote 20 for de-duplication.

### *Study selection*

Two reviewers (JM, NP) independently reviewed the title and abstract of each reference and identified potentially relevant references. Two reviewers (JM, NP) independently selected studies to be included in the review from retrieved full-text papers using pre-determined inclusion criteria. Disagreements about study inclusion were resolved by a third reviewer (MV).

Randomised controlled trials were included if they provided direct comparisons of either PCV7, PCV10 or PCV13 among infants and children < 2 years of age and if they provided estimates on antibody responses (serotype-specific anti-pneumococcal IgG) to PCVs for at least one time point of 1 between 4 and 6 weeks after the primary vaccination series and/or 1 month after a booster vaccination. Trials were eligible only if they included at least one of the three currently licensed (PCV10 and PCV13) or previously licensed (PCV7) vaccines.

Trials were excluded if they did not contain a randomised comparison of eligible vaccines, contained only a single vaccine or enrolled immunocompromised (e.g. HIV) children.

### *Data retrieval*

For all eligible trials, the publication authors/data owners were approached for trial and individual participant-level data. Baseline characteristics and potential effect modifiers were extracted on participants' age, sex, country, immunogenicity assays, co-administered study vaccines and vaccine schedules. The following study-level data were extracted from trial registries/published studies:

- trial registration number/study identifier;
- study country;
- PCV vaccination schedule, for example, two priming doses followed by a booster (2 + 1) or three priming doses followed by a booster (3 + 1).

Individual participant-level data were retrieved if available for following variables:

- vaccines administered (both study vaccines and vaccines administered concomitantly as part of the routine immunisation schedule)
- vaccination dates
- details of laboratory assays conducted, including where assays were run, units of measurement and the lower limit of quantification
- participants' age at enrolment
- participants' sex
- serotype-specific anti-pneumococcal IgG measured by enzyme-linked immunosorbent assay at all time points.

Aggregate data from publications were extracted if individual participant data were not available. Data extraction of published results and individual participant-level data were independently completed by SF and MV.

## Statistical analysis

### *Immunogenicity*

Each trial that had individual participant-level data available was analysed to obtain the log of the ratio of geometric means (log-GMR) and its standard error (SE) for each serotype and time point of interest. If individual participant data were unavailable, published geometric mean ratio (GMR) estimates and confidence intervals (CIs) were used. The estimates combined from individual participant data and aggregate data formed the input data for data synthesis. Sensitivity analyses for immunogenicity results were conducted by restricting analyses to only those studies providing data for all three time points of interest.

### *Seroefficacy*

The relative risk (RR) of seroinfection was estimated by comparing the proportion of participants with seroinfection between vaccine groups. When no seroinfection occurred in any group (numerator of absolute risk was 0), a small non-zero value (0.5) was added to both numerator and denominator to allow estimation of the RR. The log-RRs and their SEs were then the input data for evidence synthesis. Only trials supplying individual participant data were included in seroefficacy analyses.

### *Data synthesis by network meta-analysis and meta-analysis*

Serotypes 4, 6B, 9V, 14, 18C, 19F and 23F were contained in all three vaccines; therefore, evidence could be synthesised using a network meta-analysis (NMA) of all comparisons between PCVs, including PCV7. Serotypes 1, 5, 7F, 3, 6A and 19A are only included in PCV10 and PCV13 vaccines; therefore, for these serotypes, evidence was synthesised by meta-analysing studies that directly compared PCV13 versus PCV10.

For the analysis of immunogenicity, we synthesised evidence for all PCV13 serotypes. However, seroefficacy could only be assessed in situations where the serotypes of interest were included in both vaccines being compared (PCV10 and PCV13), and, therefore, seroefficacy of serotypes 3, 6A and 19A could not be assessed as these are only included in one vaccine (PCV13).

### *Association between ratios of immunogenicity and seroefficacy*

To estimate separate serotype-specific relationships between the GMRs and RRs, study-level data were combined regressing the RR of seroinfection on the GMR using linear regression models weighted by the sample size of the study. Weighted Pearson's correlation coefficients were calculated.

To estimate the overall association between antibody GMR and RR across all serotypes, we fitted a mixed-effect model regressing study-level RRs of seroinfection on GMRs across serotypes, weighted by the sample size of each study. Fixed effects included GMR, serotype and interactions between GMR and serotype (allowing serotype-specific association), while study was included as a random effect. As a sensitivity analysis, we reversed both RRs and GMRs estimated (i.e. PCV13 vs. PCV7 was changed to PCV7 vs. PCV13). By shifting comparators, we aimed to evaluate the stability of the association estimates.

Model fit was evaluated through a comparison of fixed-effects and mixed-effects models, as well as between models with and without interactions between GMR and serotype. The final model was selected based on the Akaike information criterion (AIC), with preference given to the model yielding the lowest AIC score, thus indicating the best fit.

Pneumococcal conjugate vaccine-10 and PCV13 are manufactured slightly differently, with different carrier proteins, conjugation process, polysaccharide concentrations and sources. To evaluate if these differences between two products change the relationship between antibody levels and protection against seroinfection, we assessed the association between immunogenicity and seroefficacy restricting to studies that compared PCV13 versus PCV10 and PCV7 versus PCV10 only (comparisons between

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PCV13 and PCV7 were removed from analysis, as these vaccines are from the same manufacturer). We examined whether PCVs of different manufacturers that produce equivalent levels of antibody (GMR = 1) also provide comparable seroefficacy (RR = 1).

All analyses were performed in R version 4.2.2. NMA and meta-analysis were conducted using the *netmeta* and *metafor* packages.[14,15] Code for performing NMA using the 'netmeta' function from the *netmeta* package can be found in *Appendix 7*.

## Assessment of risk of bias in included studies

Risk of bias in results of the included studies was assessed independently by two reviewers (JM, NP) using the Cochrane RoB2.[16] This considers the risk of bias (RoB) in five domains (randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result) and generates an overall RoB. Assessments were undertaken for immunogenicity of PCV7, PCV10 and PCV13 for each serotype contained in the vaccines. RoBs for seroefficacy outcomes are assumed to be identical because the data came from the same blood samples and were analysed in similar ways. The possible RoB judgements for each domain, and overall, are 'low risk of bias', 'some concerns' and 'high risk of bias'. Disagreements between reviewers were resolved by consensus. Results for the RoB assessment were presented using *robvis* (visualisation tool).[17]

## Assessment of heterogeneity and inconsistency of network meta-analysis

To assess the statistical heterogeneity and inconsistency of NMA, we evaluated the transitivity assumption by visually comparing the distribution of the baseline characteristics and potential effect modifiers across the different pairwise comparisons. We assessed the presence of heterogeneity using estimated values of the heterogeneity variance parameters ($\tau^2$) and the $I^2$ statistic and its 95% CI that measures the percentage of variability in point estimates that cannot be attributed to random error. We evaluated the inconsistency, that is, coherence between direct and indirect evidence, using a Q statistic,[15] which measures the deviation from consistency. The random-effects model was fitted following the graph-theoretical approach and using the GMR and RR as effect estimate with 95% CI.[14]

Some individual participant-level data were missing due to laboratory errors, insufficient blood sample volume or participant withdrawal. Data were not imputed and missing data were considered missing completely at random. Individual participant-level data were analysed according to the vaccine received.

# Chapter 3 Results

## Search results

Database registry and hand searches identified 4697 publication records (see *Appendix 2*, *Figure 19*), of which 47 studies (78 publication reports) satisfied our eligibility criteria.[8,9,17–93] Nineteen studies (24 publication reports) were excluded from the analysis: 6 studies did not provide individual patient or aggregate data,[70–73] and 13 studies (18 publication reports) were studies directly comparing the vaccines of interest, but it was not possible to form a loop within the NMA to provide indirect evidence (*Figure 1*).[17,74–88] Of these 13 studies, 8 reported results from different, mainly unlicensed PCVs, including a new Cuban PCV7, PCV10-SII, PCV11, PCV12, a Chinese PCV13, PCV14, PCV15, PCV20, PCV24 and PCV SP0202-VI.

The remaining 28 studies (54 publication records) from 2009 to 2023 were included in the NMAs.[8,9,18–69,89] Twenty-two studies provided individual participant data with a further six studies reporting aggregate data (see *Appendix 3*, *Tables 3* and *4*).

The 28 included studies comprised 31 cohorts of children as 1 study conducted in 2 countries reported results separately,[21,22] and 1 study included comparisons of 3 vaccination schedules[19,48] (see *Appendix 3*, *Table 3*). Studies with multiple National Clinical Trial (NCT) numbers or publications, but the same population, were counted as one cohort. These 31 cohorts were representative of 38 countries in 6 continents: Europe (*n* = 11 cohorts), Asia (*n* = 9 cohorts), North America (*n* = 3 cohorts), Africa (*n* = 3 cohorts), Oceania (*n* = 4 cohorts) and South America (*n* = 1 cohort). Four cohorts were from studies conducted in multiple countries in Europe, and analyses were combined across sites.[24,53–55,64,66]

There were 7 studies comparing PCV10 versus PCV7, 14 studies comparing PCV13 versus PCV7 and 8 studies comparing PCV13 versus PCV10. Two cohorts used a single prime, single boost (1 + 1) schedule with the first dose administered at either 6 or 14 weeks of age to South African infants and compared PCV13 with PCV10.[48] Five cohorts used a 2 + 1 prime-boost schedule: one study in Vietnam comparing PCV13 versus PCV10,[57] one in South Africa comparing PCV13 versus PCV10 with additional comparisons with 1 + 1 schedules[48] and two from studies conducted in Europe comparing PCV13 versus PCV7.[31,56] Three cohorts used a 3 + 0 schedule: one in the Gambia comparing PCV13 versus PCV10,[50] one in the USA comparing PCV13 versus PCV7[67] and one in Germany comparing PCV10 versus PCV7.[39] The remaining 20 cohorts tested a 3 + 1 schedule, with most cohorts receiving a primary series at 2–4–6 months (*n* = 9) and a booster at around 12 months (*n* = 18).

Infants' age at receipt of the first dose ranged from 1 to 3.5 months, and the age of the booster dose ranged from 9 to 18 months, resulting in an interval between primary and booster dose (used for the calculation of seroefficacy) of between 6 and 12 months. Most cohorts reported or cited types of co-administered vaccines (*n* = 24), and PCVs were commonly co-administered with routine childhood vaccine including diphtheria, tetanus and acellular/whole-cell pertussis vaccines (*n* = 23), *Haemophilus influenzae* type b tetanus toxoid (TT) conjugate vaccine (*n* = 23), hepatitis B vaccine (*n* = 20), inactivated/oral polio vaccine (*n* = 22) and group C meningococcal vaccine (*n* = 3) (see *Appendix 3*, *Table 3*). Serotype-specific IgG antibody responses were defined as primary outcomes in all studies. Studies comparing PCV10 versus PCV7 (*n* = 7) assessed serotypes included in PCV10, while all other studies assessed all serotypes included in PCV13. Geometric mean concentrations (GMCs) were reported at 28 days post-primary series (*n* = 29 cohorts), prior to a booster (*n* = 17 cohorts) and 28 days post booster (*n* = 25 cohorts). Fourteen cohorts (46.7%) reported GMC at all three time points. Individual participant data were available from 25 of 30 (83.3%) cohorts.

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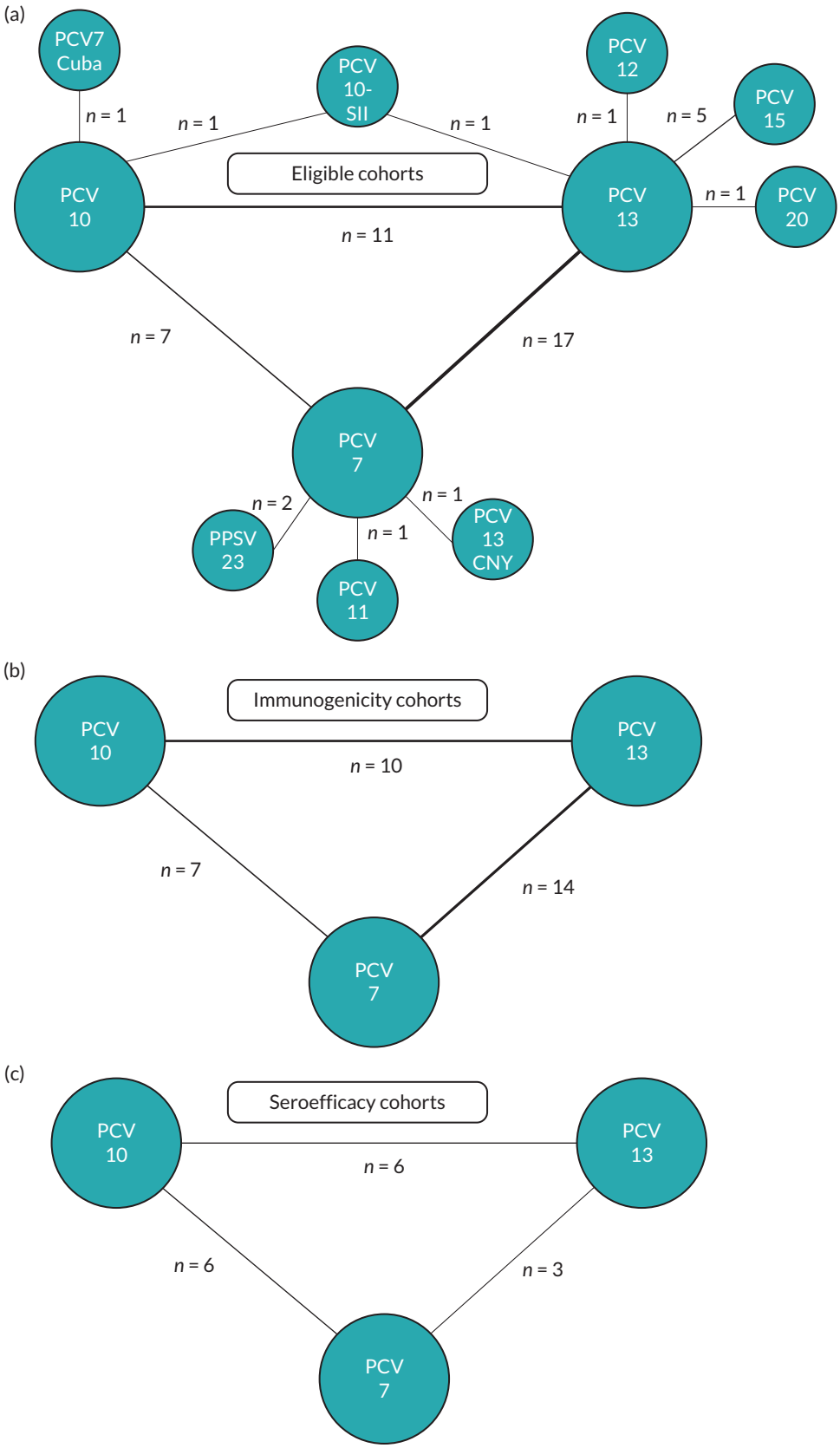



**FIGURE 1** Network of studies included for (a) all eligible cohorts, (b) immunogenicity analysis cohorts and (c) seroefficacy analysis cohorts. Studies with no closed loop to enable use of indirect evidence ($n$ = 13), or where data were unavailable ($n$ = 6), are included in panel a but not in panel b or c. PCV7 Cuba, a Cuban PCV7; PCV13 CNY, a Chinese PCV13.

## Assessment of risk of bias

Risk of bias assessments for the 28 included studies are summarised in *Appendix 4*, *Figure 20*. Results of 10 studies[31,33,36,38,51,55,56,65,67,69] were assessed to be at 'low risk of bias' across all domains and overall. Two studies[23,66] had results judged to be at 'high risk of bias' due to problems identified in one domain each: Wysocki (2009)[66] only analysed immunogenicity for a subset of participants and Bryant (2010)[23] did not report whether participants or staff delivering the intervention were blinded to the vaccine received. Lack of information was reported in Bryant (2010)[23] for the analysis, raising concerns on appropriateness of the analysis for the aggregate data obtained from this study. The remaining 16 studies[18,21,24,30,34,37,39,42,48,49,52,57,59,60,64] were judged to have 'some concerns' over RoB. These concerns predominantly arose because the randomisation process was not described and/or the study did not report if the participants or staff delivering the vaccines were blinded to which vaccines were given.

## Immunogenicity

*Figure 2* shows the number of study cohorts included in each analysis and the estimated GMR for each serotype and time point from the NMAs/meta-analyses, and *Appendix 5*, *Tables 5* and *6* summarise the heterogeneity statistics and inconsistency of the networks. Substantial heterogeneity and network inconsistency were present for most serotypes at all three time points.

Geometric mean ratios for comparisons between PCV13 and PCV10 for any primary series schedule were higher for PCV13 for serotypes 4, 7F, 9V and 23F at 1 month after primary vaccination series, with 1.14- to 1.54-fold higher IgG responses with PCV13. Additional serotypes contained only in the PCV13 vaccine (3, 6A and 19A) also favoured PCV13 as expected. GMRs were similar for the remaining serotypes (1, 5, 6B, 14, 18C, 19F; *Figure 2A*). GMRs favoured PCV7 over either PCV13 or PCV10 for serotypes 4, 6B, 9V, 14 and 23F. There was no difference in GMRs for serotypes 18C and 19F across three vaccines (see *Figure 2A*).

Direct evidence was available from studies comparing PCV10 and PCV13, and indirect evidence for the difference between PCV13 and PCV10 was provided from studies comparing either PCV10 or PCV13 with PCV7 (see *Figure 3*). GMRs from direct and indirect comparisons were very similar across time points for most serotypes. However, there were statistical inconsistencies between direct and indirect evidence identified ($p$-value for inconsistency < 0.05) for serotype 6B, 14, 18C and 19F (see *Appendix 5*, *Table 5*).

At the pre-booster time point, data were available from 18 cohorts. IgG responses were lower with PCV13 compared with PCV10 for all PCV7 serotypes except for serotype 14, with the point estimates of GMRs comparing PCV13 versus PCV10 ranging from 0.44 to 0.78. IgG responses were higher for PCV13 for serotypes 1, 5 and 7F. GMRs comparing PCV13 versus PCV7 showed higher IgG with PCV7 for serotypes 4, 6B, 9V, 14 and 23F, and higher IgG with PCV13 for serotype 19F (see *Figure 2B*).

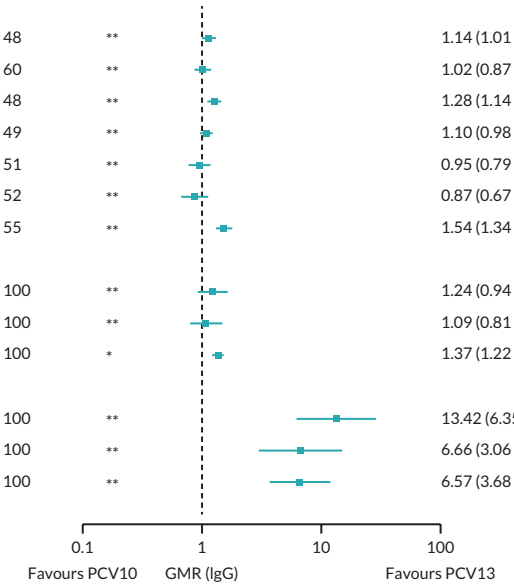
At 28 days post booster, data were available from 26 cohorts. GMRs favoured PCV13 over PCV10 for serotype 6B, 9V, 14 and 23F and favoured PCV10 over PCV13 for serotype 18C (see *Figure 2C*). For serotype 1, 5 and 7F, antibody responses were higher in PCV13 compared with PCV10. PCV7 recipients had higher GMCs compared with PCV13 for all PCV7 serotypes except 6B, for which there was no difference, and 19F, which favoured PCV13. For PCV13-only serotypes (3, 6A and 19A), GMRs favour PCV13 at all three time points. Inconsistencies were found for serotype 4 and 6B between direct and indirect evidence (see *Appendix 5*, *Table 5* and *Figure 3*).

To explore potential reasons for the observed heterogeneity, we summarised cohort-level GMRs and RRs for each vaccine comparison and present these with concomitant vaccines and vaccine schedules at all three time points in *Appendix 5*, *Figures 21–59* (GMRs) and *Figures 60–69* (RRs). These descriptive

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(a)

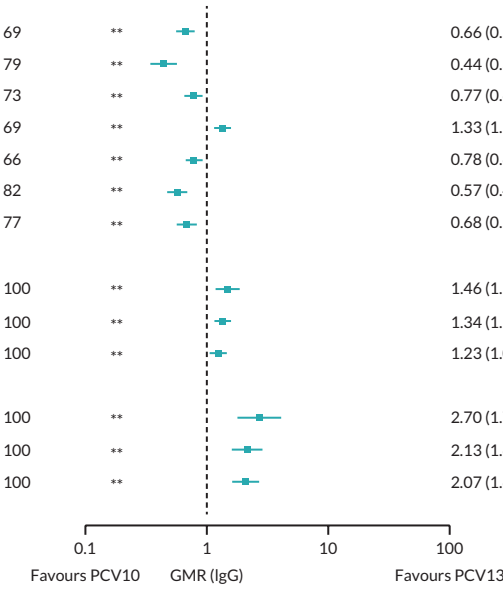
| Serotype | No. cohorts | Direct evidence (%) | | GMR at 1 month after prime PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|---|
| **4** | 28 | 48 | ** | | 1.14 (1.01 to 1.30) | 1.49 (1.32 to 1.70) | 0.77 (0.69 to 0.86) |
| **6B** | 28 | 60 | ** | | 1.02 (0.87 to 1.18) | 1.27 (1.08 to 1.49) | 0.80 (0.70 to 0.92) |
| **9V** | 28 | 48 | ** | | 1.28 (1.14 to 1.43) | 1.62 (1.45 to 1.82) | 0.79 (0.71 to 0.87) |
| **14** | 28 | 49 | ** | | 1.10 (0.98 to 1.22) | 1.31 (1.18 to 1.47) | 0.83 (0.76 to 0.92) |
| **18C** | 28 | 51 | ** | | 0.95 (0.79 to 1.16) | 1.02 (0.83 to 1.24) | 0.94 (0.79 to 1.11) |
| **19F** | 28 | 52 | ** | | 0.87 (0.67 to 1.12) | 0.89 (0.68 to 1.16) | 0.98 (0.77 to 1.23) |
| **23F** | 28 | 55 | ** | | 1.54 (1.34 to 1.76) | 1.94 (1.68 to 2.24) | 0.79 (0.70 to 0.89) |
| **1** | 9 | 100 | ** | | 1.24 (0.94 to 1.63) | 0.02 (0.01 to 0.02) | 100.26 (72.28 to 139.06) |
| **5** | 9 | 100 | ** | | 1.09 (0.81 to 1.47) | 0.04 (0.02 to 0.07) | 12.30 (7.81 to 19.39) |
| **7F** | 9 | 100 | * | | 1.37 (1.22 to 1.53) | 0.02 (0.01 to 0.02) | 87.47 (69.63 to 109.88) |
| **3** | 9 | 100 | ** | | 13.42 (6.35 to 28.36) | 0.48 (0.19 to 1.22) | 27.76 (15.54 to 49.59) |
| **6A** | 9 | 100 | ** | | 6.66 (3.06 to 14.49) | 1.04 (0.71 to 1.53) | 6.75 (5.93 to 7.69) |
| **19A** | 9 | 100 | ** | | 6.57 (3.68 to 11.73) | 1.12 (0.69 to 1.82) | 2.86 (1.84 to 4.42) |




.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

(b)

| Serotype | No. cohorts | Direct evidence (%) | | GMR at before booster PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|---|
| **4** | 17 | 69 | ** | | 0.66 (0.56 to 0.78) | 0.95 (0.80 to 1.12) | 0.70 (0.58 to 0.84) |
| **6B** | 18 | 79 | ** | | 0.44 (0.34 to 0.55) | 0.55 (0.42 to 0.73) | 0.79 (0.59 to 1.05) |
| **9V** | 18 | 73 | ** | | 0.77 (0.65 to 0.90) | 0.97 (0.81 to 1.17) | 0.79 (0.65 to 0.96) |
| **14** | 18 | 69 | ** | | 1.33 (1.15 to 1.53) | 1.56 (1.33 to 1.82) | 0.85 (0.72 to 1.00) |
| **18C** | 17 | 66 | ** | | 0.78 (0.67 to 0.91) | 0.77 (0.66 to 0.90) | 1.01 (0.85 to 1.19) |
| **19F** | 18 | 82 | ** | | 0.57 (0.47 to 0.68) | 0.39 (0.31 to 0.48) | 1.47 (1.17 to 1.85) |
| **23F** | 18 | 77 | ** | | 0.68 (0.57 to 0.81) | 0.82 (0.67 to 1.01) | 0.82 (0.67 to 1.02) |
| **1** | 8 | 100 | ** | | 1.46 (1.18 to 1.82) | 0.13 (0.11 to 0.16) | 12.77 (10.17 to 16.05) |
| **5** | 8 | 100 | ** | | 1.34 (1.16 to 1.55) | 0.18 (0.11 to 0.29) | 4.61 (2.72 to 7.82) |
| **7F** | 8 | 100 | ** | | 1.23 (1.06 to 1.44) | 0.05 (0.04 to 0.06) | 20.97 (17.43 to 25.23) |
| **3** | 7 | 100 | ** | | 2.70 (1.78 to 4.09) | 0.95 (0.51 to 1.76) | 2.90 (2.07 to 4.06) |
| **6A** | 8 | 100 | ** | | 2.13 (1.61 to 2.83) | 0.75 (0.59 to 0.95) | 2.77 (2.16 to 3.55) |
| **19A** | 8 | 100 | ** | | 2.07 (1.62 to 2.63) | 0.63 (0.47 to 0.85) | 1.50 (1.28 to 1.76) |




.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 2** Geometric mean ratios from meta-analyses at (a) 28 days post-primary vaccination series, (b) pre booster and (c) 28 days post booster. Each line in the figure shows the output from NMAs (PCV7 serotypes) or direct meta-analyses (PCV13 but non-PCV7 serotypes). Blue boxes and blue lines show the point estimates and CIs for GMRs comparing PCV13 versus PCV10. Points to the right of the vertical line are those with higher antibody responses in the PCV13 arm of the study, and points to the left are those with higher antibody responses in the PCV10 arm. The direct evidence column shows the percentage of evidence from studies directly comparing PCV13 versus PCV10 that contributes to the estimates presented in the figure in blue (PCV13 vs. PCV10). GMR of PCV13 versus PCV10 for PCV10 and PCV13 serotypes are from a meta-analysis of only studies which directly compared PCV13 with PCV10.

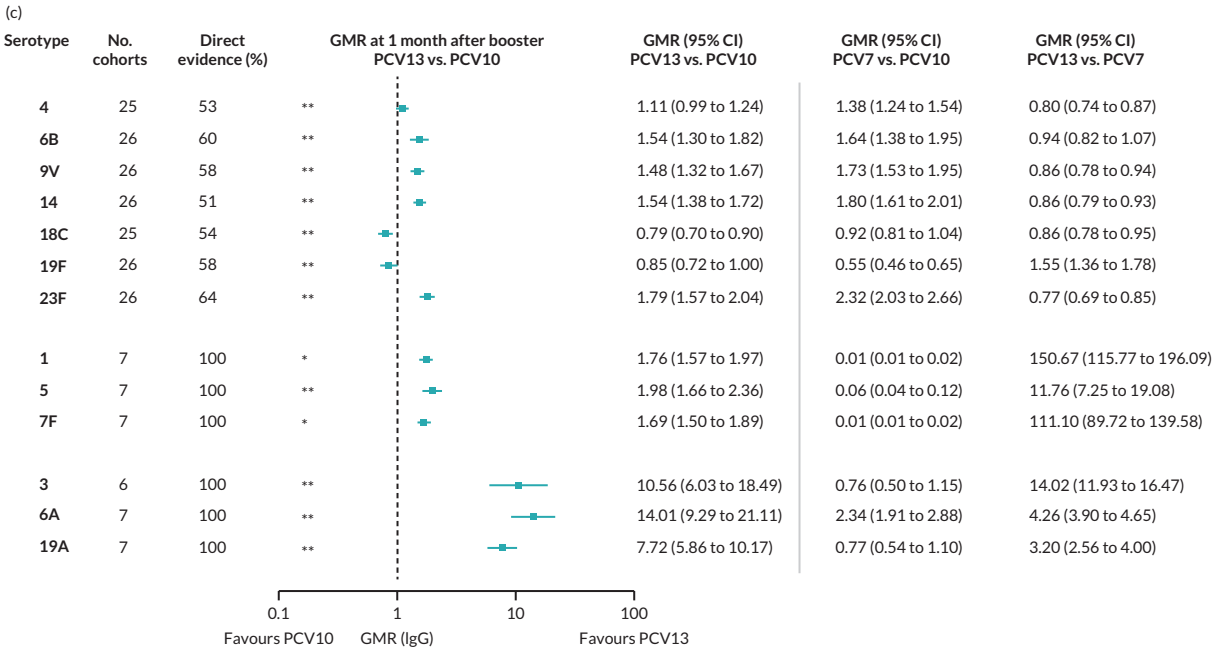



**FIGURE 2** Continued

analyses revealed a lack of consistency in the direction of study-level estimates within each vaccine comparison, resulting in the significant heterogenicity. There was also no observable pattern in any trial-level variable (region, co-administered vaccines, vaccine schedule), from which one might propose a mechanism that would adequately explain this variation in GMRs, although studies which compared vaccines with the same carrier protein seemed to have more consistent estimates. In sensitivity analysis, we restricted to 11 cohorts providing IgG results for all the three time points and observed similar results (see *Appendix 6*, *Figure 70*). Additional sensitivity analyses stratified by region and vaccine schedule demonstrated reduced heterogeneity for some serotypes and similar patterns compared with main analysis (see *Appendix 6*, *Figures 71–73*). Sensitivity analyses excluding the two studies having overall 'high risk of bias' did not provide different results. Excluding the one study comparing PCV13 and PCV10 with a 1 + 1 schedule did not affect the results.

## Seroefficacy

There were 12 studies (15 cohorts) with available individual participant antibody data at both post-primary and prior to the booster dose, allowing serotype-specific estimation of seroefficacy from a total of 5152 participants. Of these 15 cohorts, 6 compared PCV10 versus PCV7, 3 compared PCV13 versus PCV7 and 6 compared PCV13 versus PCV10 (see *Figure 1*).

The RR of seroinfection from the NMA for each serotype is summarised in *Figure 4*, and a summary of direct and indirect evidence is given in *Figure 5*. The $I^2$ and $p$-value indicate some heterogeneity for all PCV7 serotypes except for serotype 4 and 19F (see *Appendix 5*, *Table 6*).

Among PCV7 serotypes, the risk of seroinfection was lower with PCV13 than PCV10 for serotypes 4, 6B, 9V, 18C and 23F, while no difference was seen for serotype 14 and 19F (see *Figure 4*). The RRs of seroinfection (PCV13 vs. PCV10) for PCV7 serotypes ranged from 0.32 (95% CI 0.19 to 0.52) for serotype 4 to 1.28 (95% CI 0.95 to 1.74) for serotype 14. The direct evidence contributed to around 80–95% of total evidence, and we found no inconsistency between direct and indirect evidence for all but serotype 19F ($p > 0.05$; see *Appendix 5*, *Table 6* and *Figures 60–69*).

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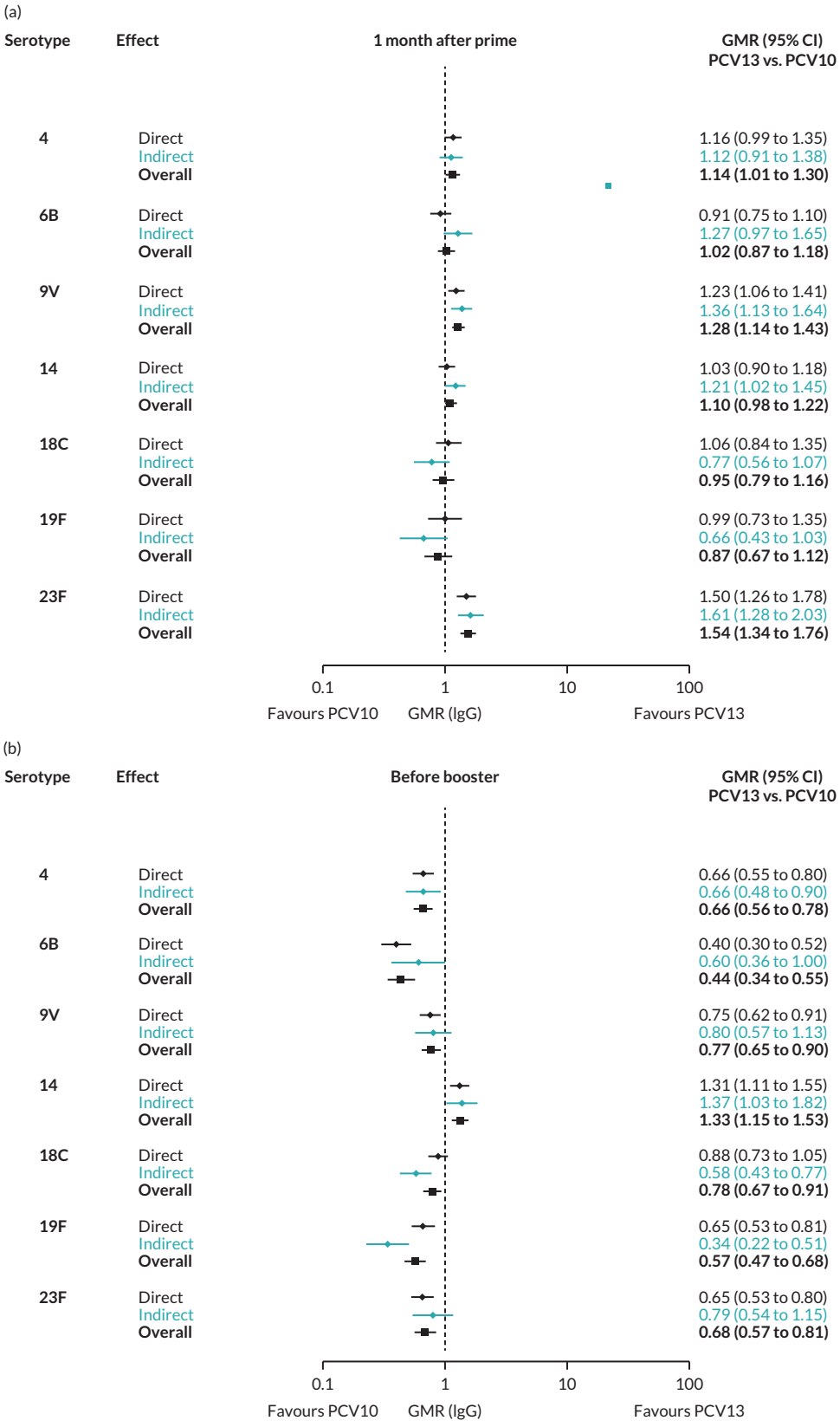



**FIGURE 3** Direct and indirect evidence on GMRs comparing PCV13 vs. PCV10 at (a) 28 days post-primary vaccination series, (b) pre booster and (c) 28 days post booster. Each line in the figure shows the output from NMAs. Dark grey diamonds and lines show the point estimates and CIs for GMRs from studies directly comparing PCV13 versus PCV10. Light grey diamonds and lines show the point estimates and CIs for GMRs from studies comparing PCV13 versus PCV10 through PCV7. Black boxes and lines show the point estimates and CIs incorporating both direct and indirect evidence.

(c)

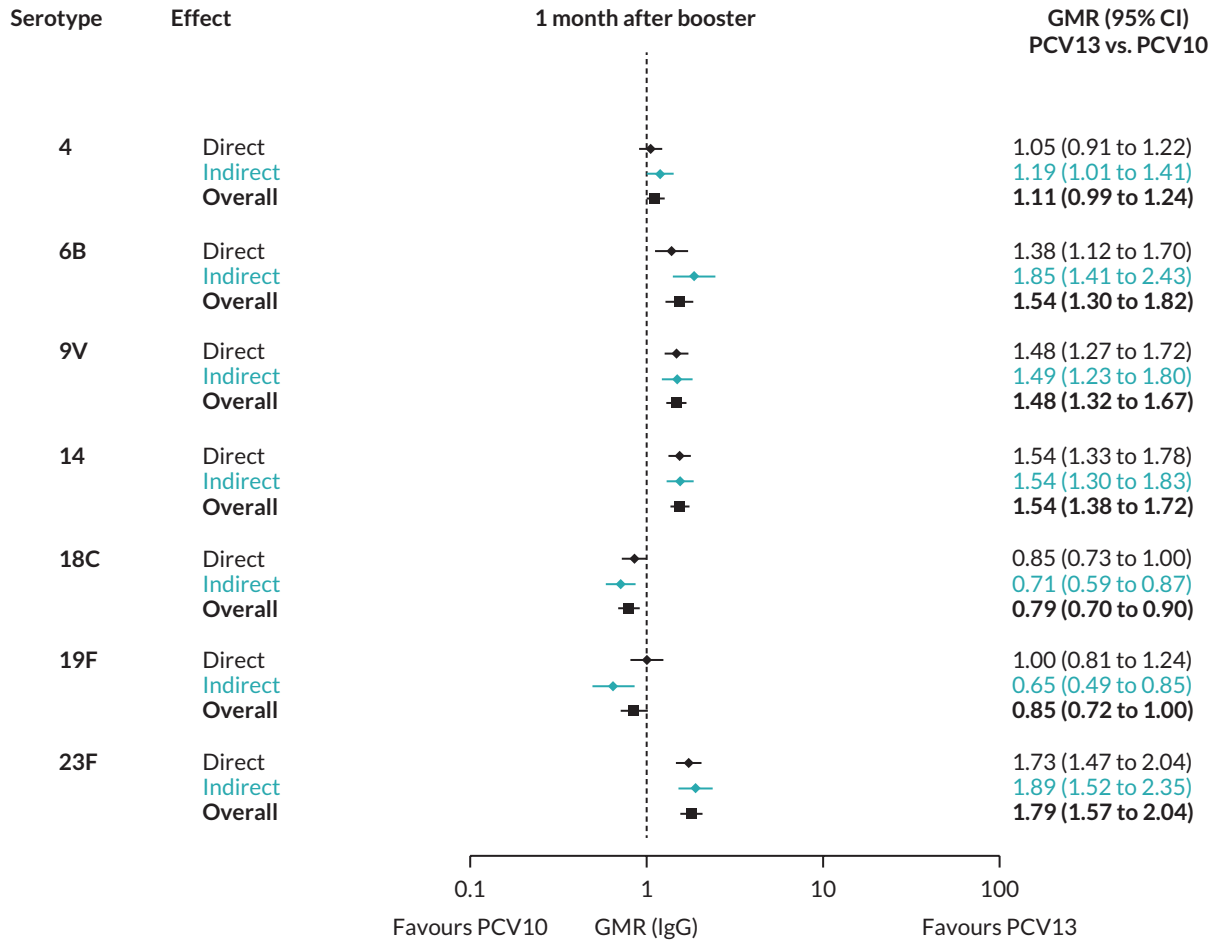



**FIGURE 3** Continued

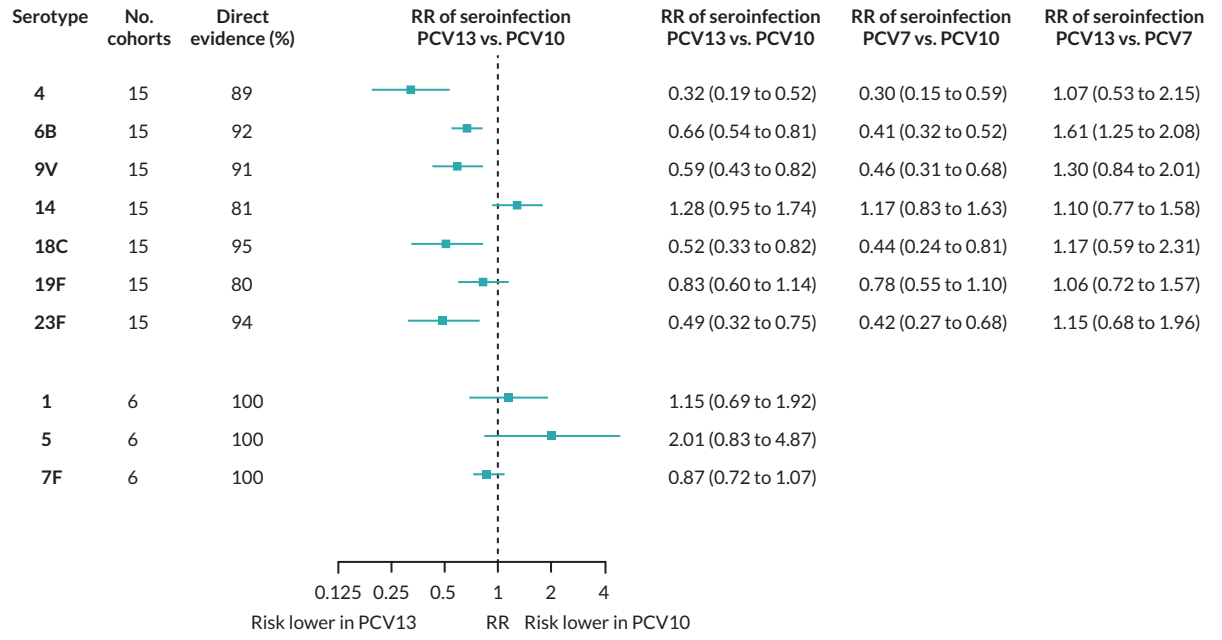



**FIGURE 4** Meta-analyses of the RR of seroinfection. Each line in the figure shows the output from NMAs (PCV7 serotypes) or direct meta-analyses (PCV10 serotypes). Blue boxes and blue lines show the point estimates and CIs of RR of seroinfection comparing PCV13 versus PCV10. The direct evidence column shows the percentage of evidence from studies directly comparing PCV13 versus PCV10. Results for PCV10 serotypes are from a meta-analysis of only studies comparing PCV13 with PCV10; therefore, estimates of PCV7 versus PCV10 and PCV13 versus PCV7 were not available.

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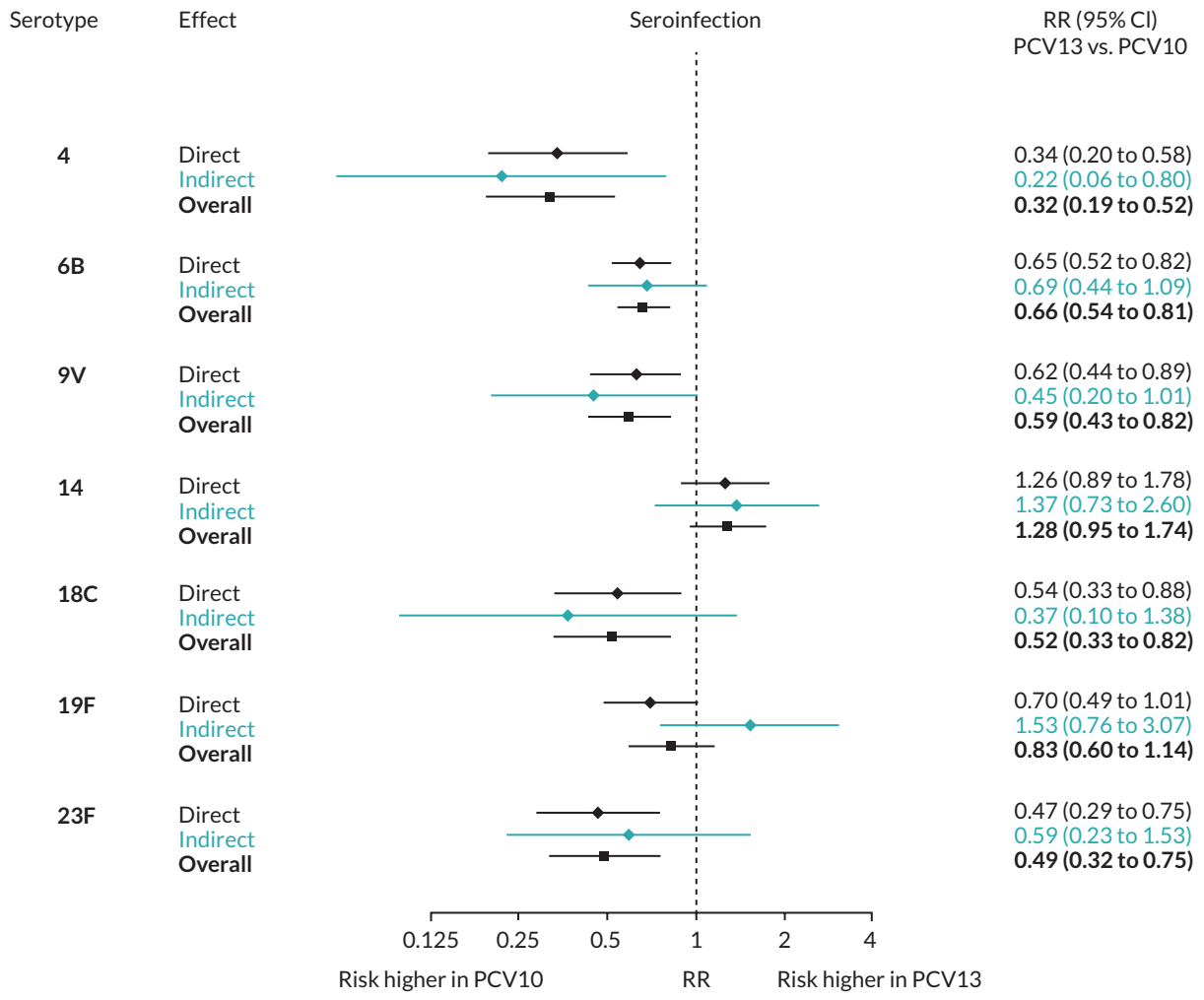



**FIGURE 5** Direct and indirect estimates of the RR of seroinfection. Each line in the figure shows the output from NMAs. Dark grey diamonds and lines show the point estimates and CIs RRs from studies directly comparing PCV13 versus PCV10. Light grey diamonds and lines show the point estimates and CIs for RRs from studies comparing PCV13 versus PCV10 through PCV7. Black boxes and lines show the point estimates and CIs incorporating both direct and indirect evidence.

For serotypes 1, 5 and 7F, evidence was summarised from six studies directly comparing PCV13 with PCV10. Heterogeneity was observed for serotype 5, and all CIs overlapped 1.0. Comparisons between PCV13 and PCV7 favoured neither vaccine over the other, whereas comparisons between PCV7 and PCV10 favoured PCV7 for serotypes 5, 6B, 9V, 18C and 23F.

Sensitivity analyses of studies conducted in Europe and, using 3 + 1 schedule, showed similar RRs as estimated from the main analysis (see *Appendix 6*, *Figures 74* and *75*). The seroefficacy analysis results remained consistent after removing one 'high risk of bias' study from the analysis.

## Association between ratios of immunogenicity and seroefficacy

*Figure 6* shows the serotype-specific relationships between trial-level immunogenicity (GMRs) and seroefficacy (RRs). Log-GMRs and log-RRs were highly or moderately correlated for all PCV7 serotypes [with weighted Pearson's correlation coefficients ($r$) ranging from −0.76 to −0.60, all $p < 0.05$] except for serotype 14 ($r = -0.30$, $p = 0.26$).

In the combined analysis across all serotypes, vaccines that produced the same amount of antibody (GMR = 1) had very similar protection (adjusted RR 0.80, 95% CI 0.41 to 1.58; see *Figure 7*). The model

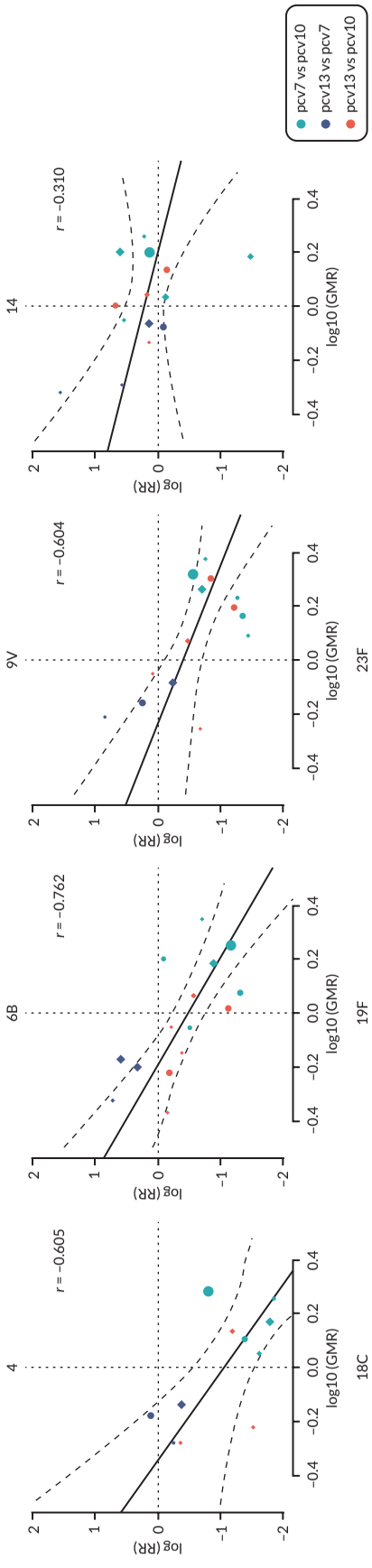



**FIGURE 6** Association between study-level GMRs and RRs of seroinfection. Each point shows results of a serotype-specific comparison between two vaccines from one study. Solid line shows the relationship between RR predicted from the crude model and GMR. Dashed line shows the CIs of predicted RR. Reference lines show GMR equivalent to one (vertical) and RR equivalent to one (horizontal) which represent values associated with no difference between vaccines. Points sizes represent sample size of the trial. Each panel shows one PCV7 serotype (4, 6B, 9V, 14, 18C, 19F and 23F).

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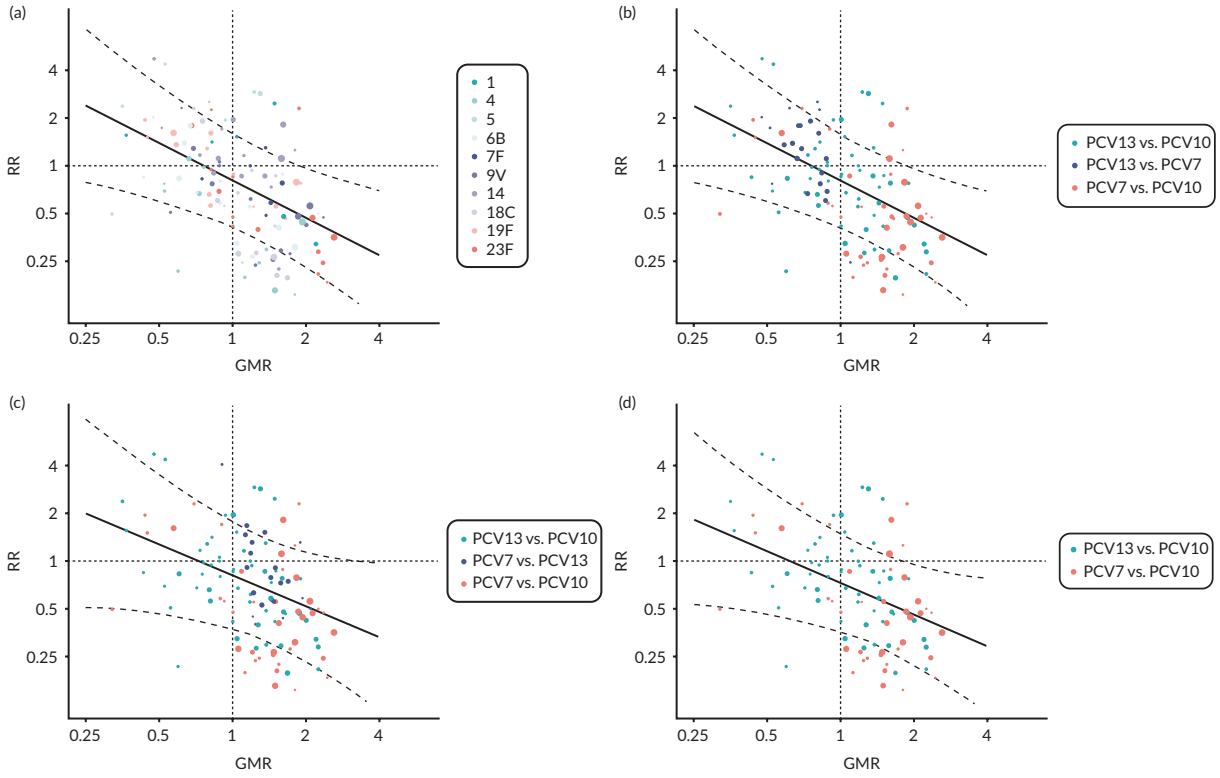



**FIGURE 7** Overall association between trial-level GMRs and RRs across all serotypes included in PCV10. Each point shows results of a serotype-specific comparison between two vaccines from one study. Solid line shows the relationship between RR predicted from the model and GMR. Dashed line shows the CIs of predicted RR. Reference lines show GMR equivalent to one (vertical) and RR equivalent to one (horizontal) which represent values associated with no difference between vaccines. Points sizes represent sample size of the trial. Panel (a) shows the relationship by 13 serotypes covered by PCV13; (b) shows the same data as panel a classified by vaccine comparison groups; (c) shows the same data as panel B; however, studies comparing PCV13 versus PCV7 are analysed and displayed as PCV7 versus PCV13 as a sensitivity analysis; and (d) shows a further sensitivity analysis that excludes studies of PCV13 versus PCV7 and only shows studies that compared vaccines from two different manufacturers.

estimate indicates that for each twofold increase in antibody response, the risk of seroinfection was halved (GMR of 2.0; RR 0.46, 95% CI 0.23 to 0.96; see *Figure 7A* and *B*). The estimates were stable when estimates of PCV13 versus PCV7 were analysed in reverse as PCV7 versus PCV13 (GMR of 2.0; RR 0.51, 95% CI 0.23 to 1.15; see *Figure 7C*).

When analyses were restricted to comparison between products from different manufacturers, the relationship between immunogenicity and seroprotection remained similar to the main analysis with a CI that incorporates 1.0 (GMR 1.0; RR 0.73, 95% CI 0.36 to 1.47; see *Figure 7D*).

# **Chapter 4** Mathematical modelling of differential impact of PCV10 and PCV13 on invasive pneumococcal diseases

To illustrate the use of serotype-specific estimates of seroefficacy in modelling vaccine impact and cost-effectiveness, we developed a mathematical model of pneumococcal transmission dynamics to compare the differential impact of PCV10 and PCV13 introduction on invasive pneumococcal disease cases with vaccine serotypes in England and Wales. The model estimated the impact over a 25-year time period from 2005–6 to 2029–30.

## Model structure and inputs

The mathematical model is a compartmental, deterministic, serotype-specific and realistic age structure model to describe the pneumococcal transmission dynamics with two PCV programmes. The model is a susceptible–infectious–susceptible model which assumes no natural immunity. When susceptibles acquire carriage infection, they become infectious for the duration of carriage. The duration of carriage for all serotypes is assumed to be age dependent, and the values were obtained from Melegaro *et al.*[94] After the duration of carriage, infectious people become susceptible again. For simplicity, invasive pneumococcal disease was assumed to occur at the time of carriage infection.

### *Serotypes*

The systematic review described in *Chapters 1–3* provided estimates of the RR of seroinfection by the time of the booster dose which is interpreted as the relative reduction in vaccine efficacy of PCV10 against carriage acquisition compared with PCV13. The systematic review found no significant difference in RRs for serotypes 1, 5, 7F, 15 and 19F among 10 serotypes common in PCV10 and PCV13. Hence, we have only included five serotypes (18C, 23F, 4, 6B and 9V) for this modelling study. For each serotype, 100 random draws were taken from the CI around the estimates of the RR of seroinfection from *Chapter 3*, assuming a normal distribution around the log-RR (see *Figure 4*).

### *Carriage*

Data for the pre-PCV equilibrium were obtained from carriage prevalence estimates from the 10-month longitudinal nasopharyngeal swab study with 3869 swabs conducted in 2001–2 in England.[95] Due to the detailed stratification for age groups and serotypes needed, there were some categories in the swabbing study with no positive samples. For simplicity, we substituted 0.5 positive sample in these groups. The carriage prevalence for the five serotypes is presented in *Figure 8*.

## Invasive disease cases

Data on the invasive pneumococcal disease cases for the five serotypes and 16 age groups were obtained for England and Wales in 2005–6 (see *Figure 9*). Similar to the carriage data, there were some groups with no positive samples, and for these groups, one positive sample was substituted to enable calculation of incidence.

### *Contact patterns*

The contact patterns for the seven age groups for the forces of infection were obtained by combining the GB POLYMOD close contact matrix,[96] and additional data on under-1-year-olds.[97]

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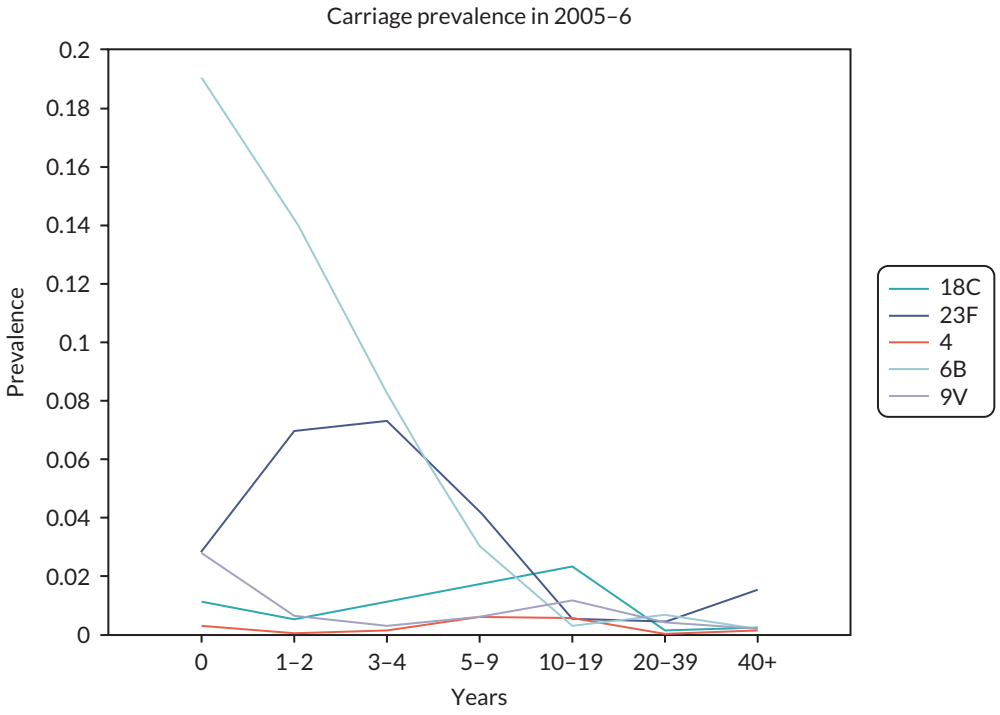



**FIGURE 8** Carriage prevalence of five serotypes (18C, 23F, 4, 6B and 9V) in seven age groups (data from Hussain *et al.*[95]).

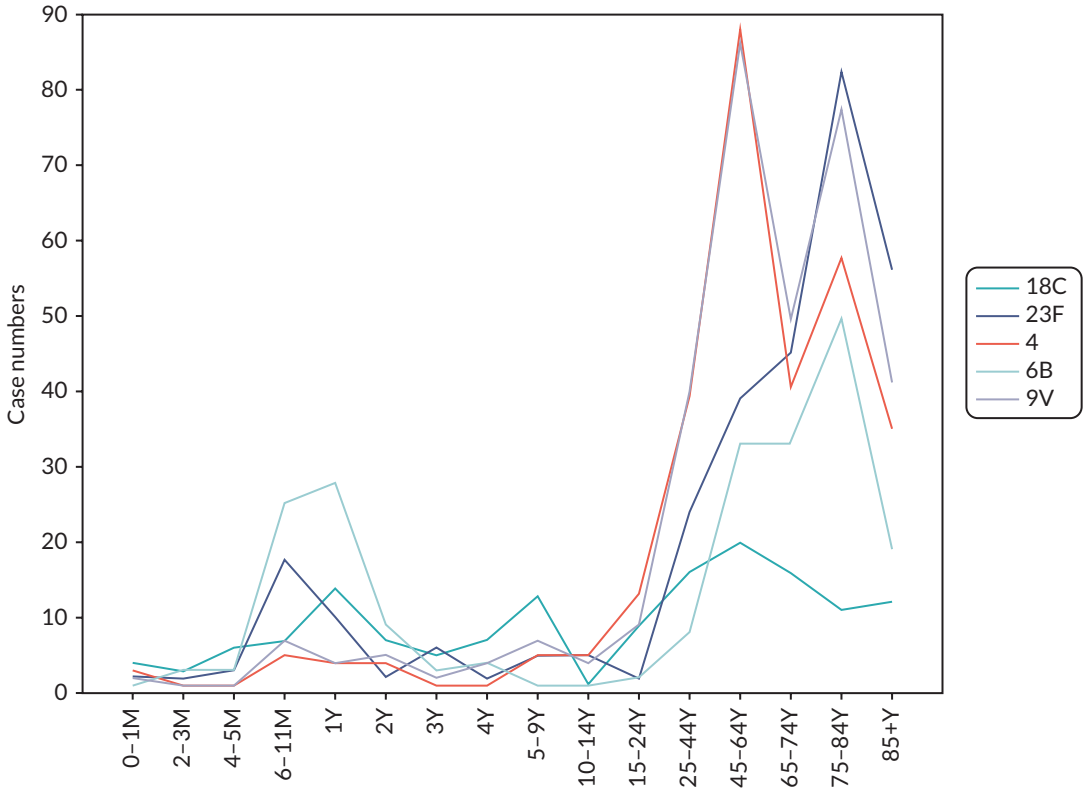



**FIGURE 9** Invasive pneumococcal disease cases for five serotypes (18C, 23F, 4, 6B and 9V) and 16 age groups in 2005–6 in England and Wales. M, months; Y, years.

### *Parameter estimations*

Using a static model, we fitted the force of infection by age groups for each target serotype (see *Figure 10*) using the carriage prevalence in *Figure 8*. Upon these forces of infection values, we calculate the transmission probabilities per contact in seven age groups (see *Figure 11*) using the 2005 England and Wales population and the contact pattern matrix.

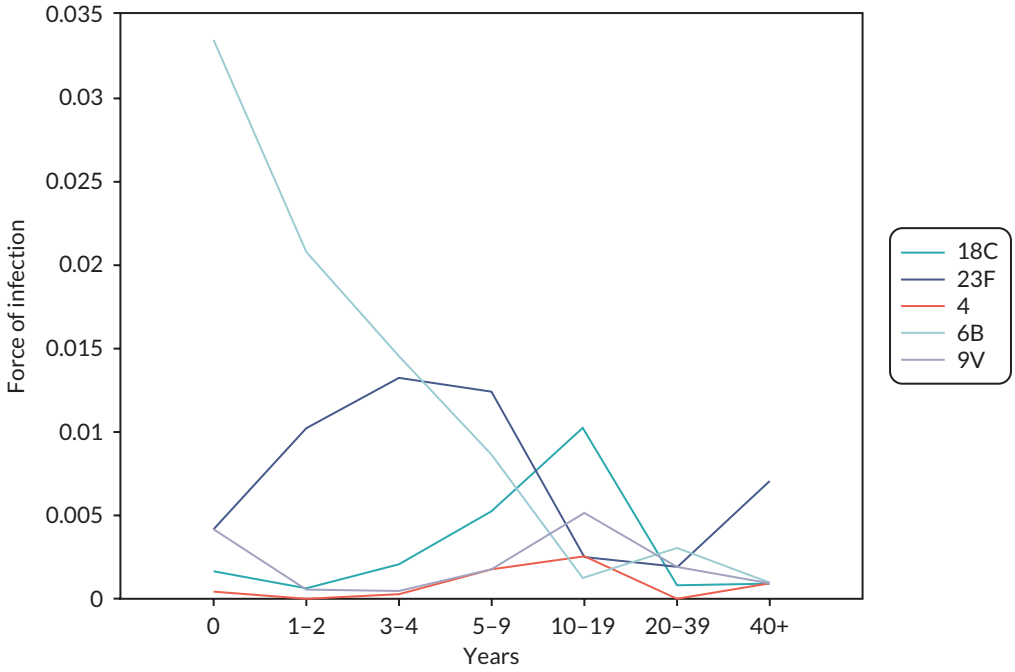



**FIGURE 10** Force of pneumococcal infection for seven age groups and five serotypes in 2005–6 obtained using the pre-PCV carriage prevalence and individual patient data cases in 2005–6 in England and Wales.[98]

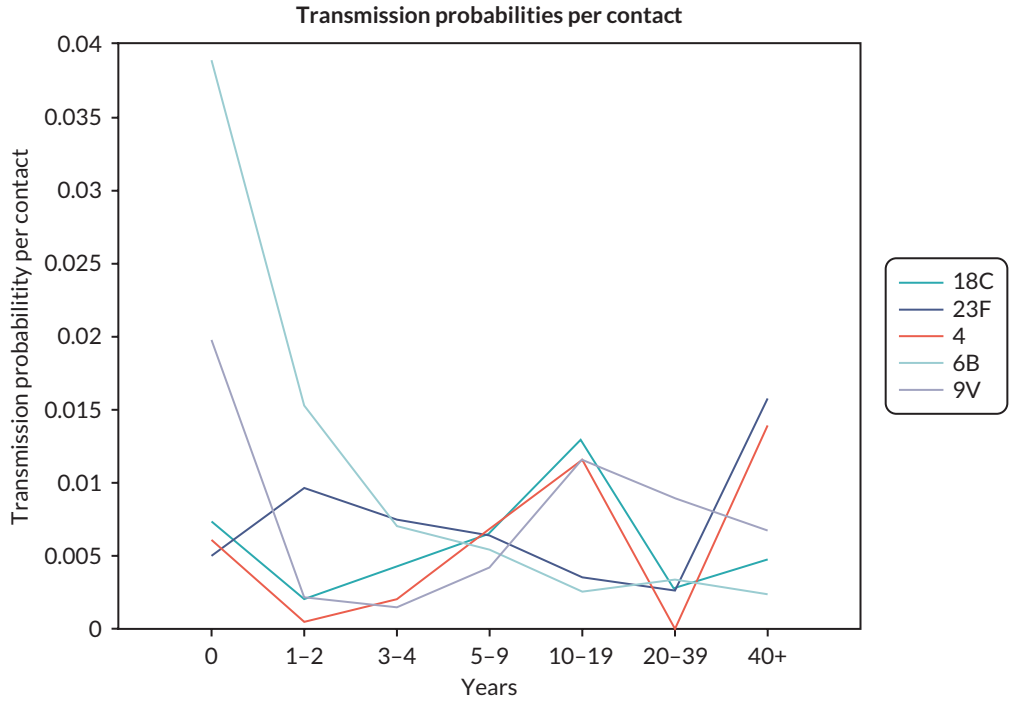



**FIGURE 11** Pneumococcal transmission probabilities per contact for seven age groups and five serotypes in 2005–6 obtained using the pre-PCV carriage prevalence and individual patient data cases in 2005–6 in England and Wales.[98]

We calculated case : carrier ratios (CCRs) (see *Figure 12*) by age groups for each serotype by dividing the number of invasive disease cases for the corresponding age group and serotype with the number of new infections during the baseline year.[98] As a sensitivity analysis, we tested an alternative assumption and used the number of infectious people instead of new infections to calculate the CCRs. Both assumptions produced almost identical results.

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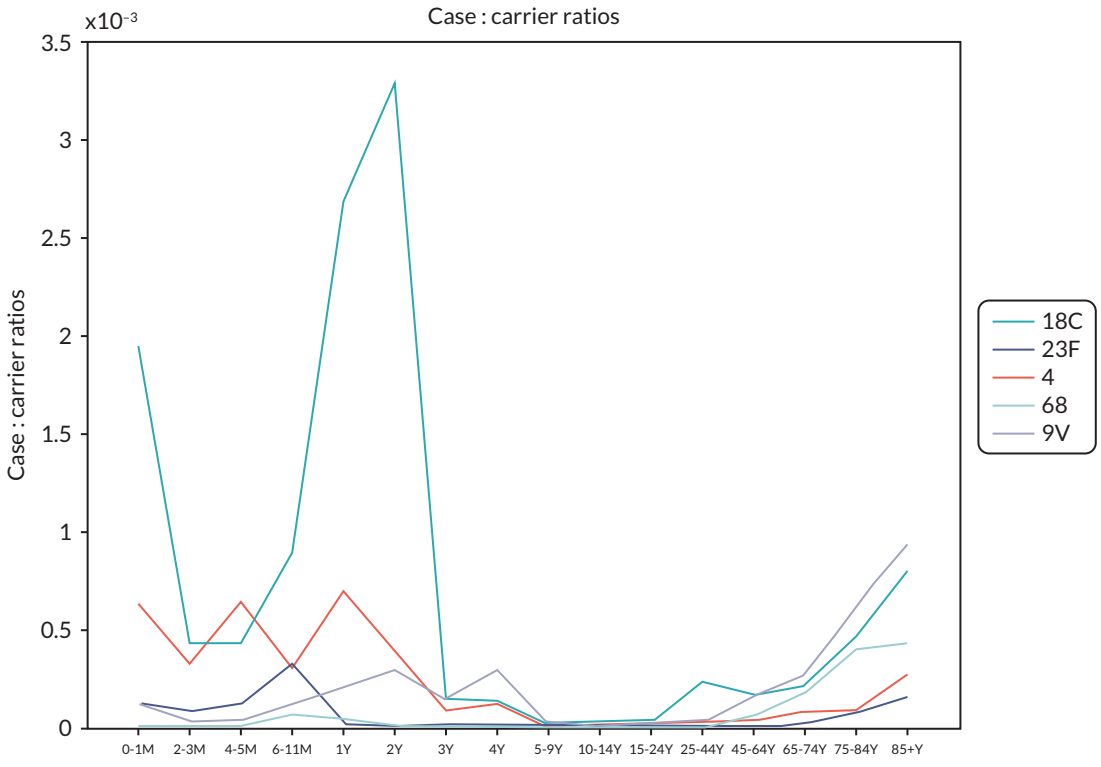



**FIGURE 12** Case : carrier ratios by 16 age groups for five pneumococcal serotypes using the pre-PCV carriage prevalence and individual patient data cases in 2005–6 in England and Wales. M, months; Y, years.[98]

### *Population*

We used the England and Wales population data from 2006/7 until 2030/1 for the long-term impact of two PCV programmes for 25 years from 2006 to 2007 (see *Figure 13*).

Baseline projections for invasive pneumococcal disease cases without PCV programmes would be increased due to these increasing population size in *Figure 13*.

### *Vaccination programme*

The PCV programme schedule was assumed to be introduced in the beginning of 2006–7 (first week of June 2006) with 2 + 1 at 2, 4 and 12 months of age in the model. The coverage for the first dose was fixed at 90%, 95% for the second dose among the first-dosed infants and 95% of the second-dosed infants for third-dose coverage. There was no catch-up programme assumed in the model. The vaccine efficacy against carriage for PCV13 was assumed to be 55% for the fully vaccinated compartments, and half this value for those partially protected. The duration of partial and full protection is assumed to be 5 years.[98] Those losing partial or full protection move to waned and partially protected compartments of the model, respectively. The average duration of full vaccine protection is assumed to be 10 years. Those in the waned and partially protected compartments move to fully protected after receiving their booster dose. The flow diagram in *Figure 14* describes the movement between compartments due to vaccine doses and waning vaccine protection.

## Results

The model showed that in the absence of any vaccine programme, an increase in invasive pneumococcal disease cases caused by all five serotypes would be seen over the 25-year time frame (*Figure 15*). With the introduction of either PCV13 or PCV10 vaccine programmes in 2006, case counts decreased, achieving near eradication of all serotypes within the time frame modelled. The decrease in cases was most rapid for serotype 6B and least rapid for serotype 4. The decrease in cases was less rapid for PCV10 than for PCV13.

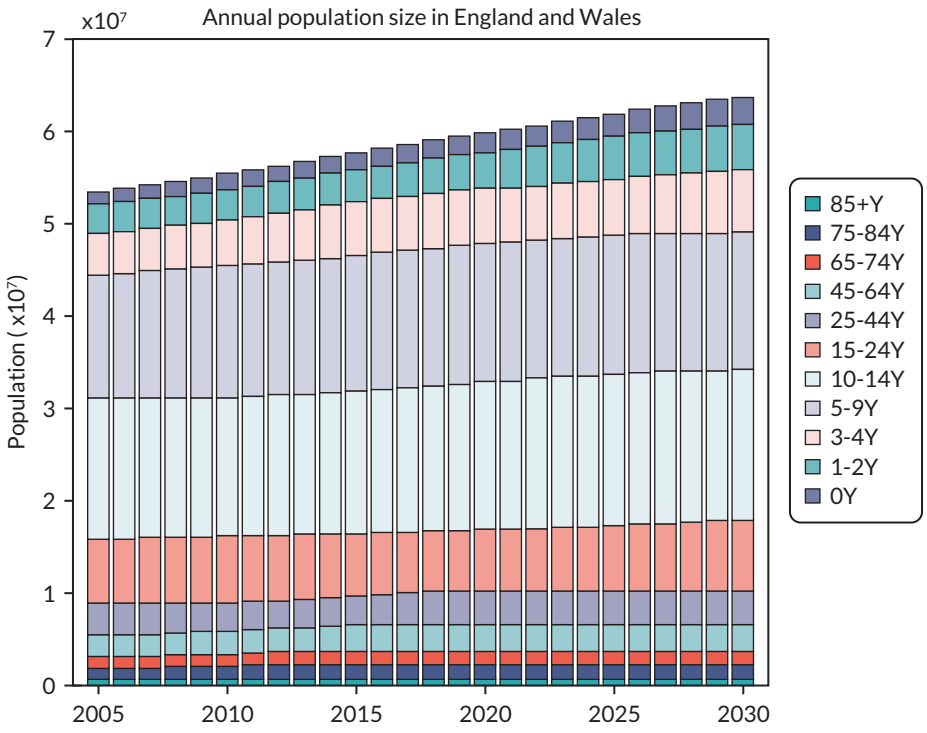



**FIGURE 13** Annual population sizes by age groups between 2005 and 2030 in England and Wales (projections obtained from the Office of National Statistics). Y, years.

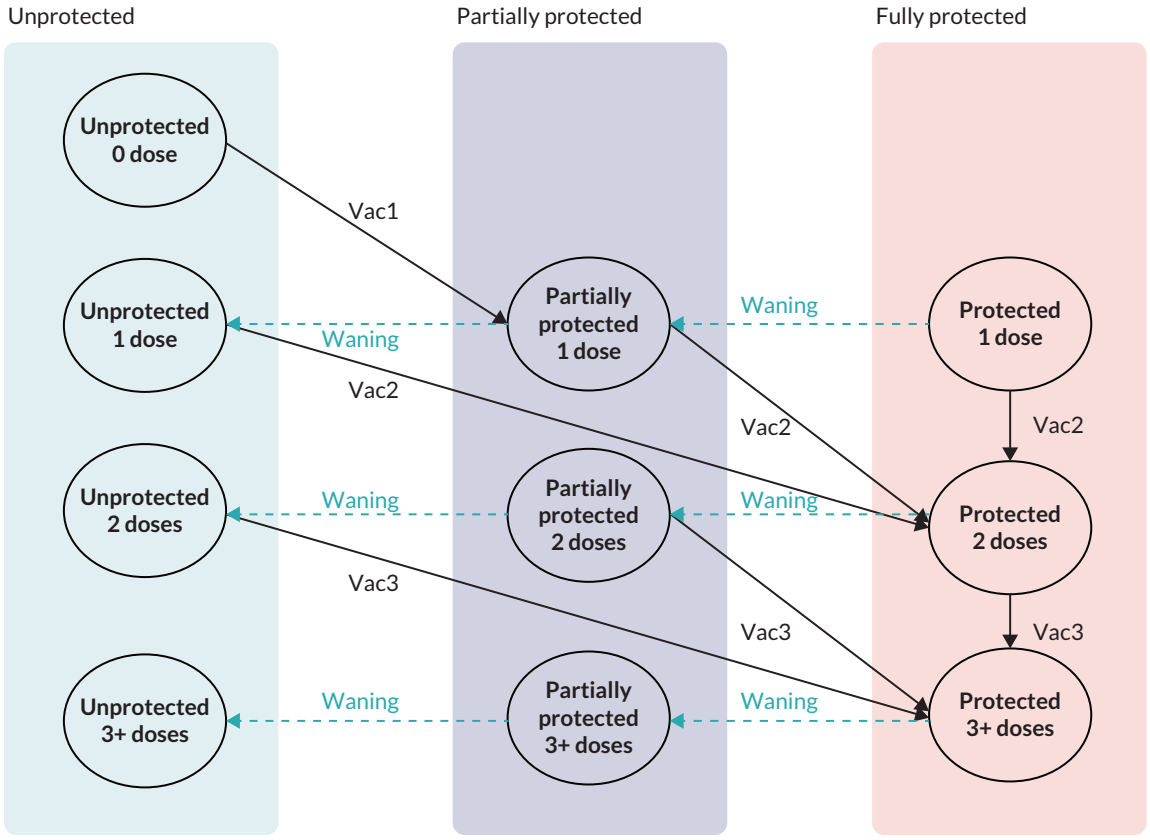



**FIGURE 14** Flow diagram showing how vaccination status of individuals is tracked in the model, based on the number of doses received and waning of vaccine protection.

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The PCV programme is assumed to be introduced in the beginning of June 2006 in the 2006–7 epidemiological year. a–e present results for five serotypes (4, 6B, 9V, 18C and 23F). Box plots show the modelled long-term impact of PCV10 on invasive pneumococcal disease cases. The dotted blue line shows the trajectory of invasive pneumococcal disease cases in the absence of any PCV programme (general increase reflects increasing population over years and age-dependent CCR by serotypes). The dark blue line shows the long-term impact of PCV13.

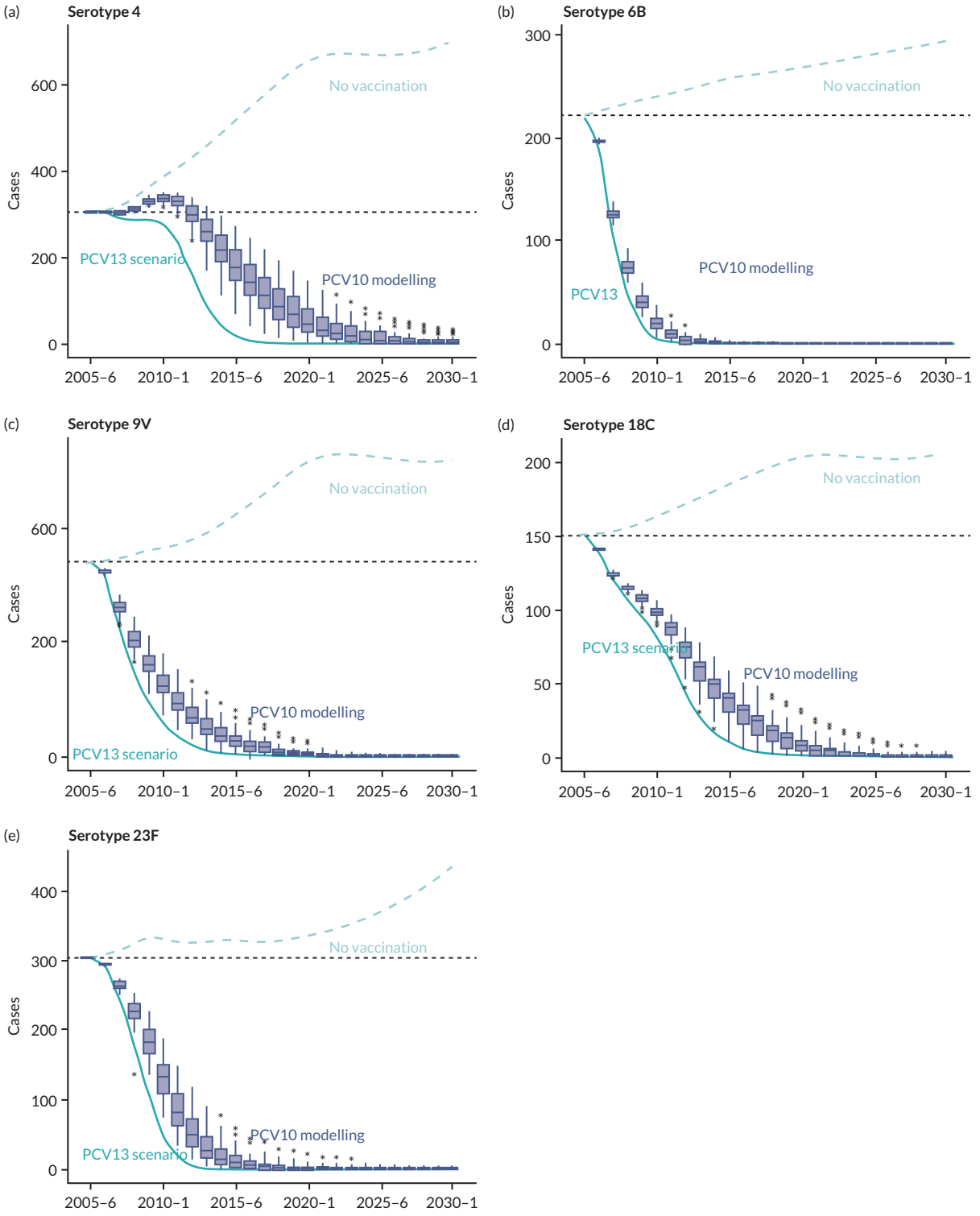



**FIGURE 15** Modelled long-term yearly number of invasive pneumococcal disease cases in England and Wales after introduction of PCV10, or PCV13 in 2006, compared with no PCV programme.

# **Chapter 5** Retrospective economic evaluation of vaccinating infants with PCV13 compared to vaccination with PCV10 to prevent pneumococcal disease in England and Wales

## Aims

We aimed to assess the cost-effectiveness of introducing infant vaccination with PCV13 compared to introducing PCV10 from a healthcare payer perspective in England and Wales. More specifically, to retrospectively estimate the *additional* threshold price per dose below which PCV13 would be more cost-effective than PCV10 had they both been available at the time of introduction of the PCV vaccine programme in England and Wales in 2006.

While these vaccines were not actually available in 2006, the eventual switch in England and Wales from PCV7 to PCV13 in 2010 was informed by a transmission dynamic model[99] combined with a health economic evaluation.[100] For those analyses, the assumption was made that PCV7 and PCV13 each fully protected against the serotypes in the vaccine, while PCV10 was not evaluated. The completion of the NMA (see *Chapters 1*–*3*) allows a retrospective comparison of PCV10 and PCV13 using serotype-specific efficacy results for the first time.

## Methods

A previously published health economic model[100] of the costs and health outcomes associated with invasive pneumococcal disease was combined with estimates of the differential number of age-specific cases of invasive pneumococcal disease following introduction of PCV10 versus PCV13 vaccination from the dynamic transmission model described in *Chapter 4*. Differences in the impact of the two vaccines on the number of cases of invasive pneumococcal disease were based on the serotype-specific RR of seroinfection with PCV13 versus PCV10 from *Chapter 3* (see *Figure 4*).

### *Vaccination programme*

The impact of a 2 + 1 infant vaccination programme (with doses given at 2, 4 and 12 months of age) was modelled from introduction in 2006 over a 25-year time horizon, by which time, the impact of PCV10 and PCV13 programmes is predicted to have reached a steady state with almost complete eradication of these serotypes (see *Figure 15*). The number of infants eligible for vaccination each year was based on the annual (historical and projected) population of children in England and Wales aged under 1 year of age.[101,102] The coverage of the first dose was assumed to be 90%, followed by 95% uptake among those eligible for the second and third doses.

### *Disease outcomes*

The risks of different invasive pneumococcal disease presentations for each case were based on the age-specific distributions presented graphically in the supplementary material of van Hoek *et al.*[100] To incorporate these distributions into the current analysis, the figures were digitised using the R package *metaDigitise* and the data were fitted to either a beta distribution (for probabilities) or gamma distributions (length of stay or non-invasive disease outcome multipliers) using the R package *fitDistrPlus*. Fitted distributions are summarised in *Table 1*.

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**TABLE 1** Parameter distributions for invasive and non-invasive disease outcomes fitted to data reported in van Hoek *et al.*

| Parameter description | Age group | Parameter distribution |
|---|---|---|
| *Invasive disease parameters* | | |
| Probability of meningitis | Under 2 years | Beta (mean = 0.44, SD = 0.017) |
| | 2–14 years | Beta (mean = 0.28, SD = 0.022) |
| | 15–64 years | Beta (mean = 0.15, SD = 0.0077) |
| | 65–74 years | Beta (mean = 0.098, SD = 0.01) |
| | Over 75 years | Beta (mean = 0.048, SD = 0.0047) |
| Probability of pneumonia | Under 2 years | Beta (mean = 0.31, SD = 0.017) |
| | 2–14 years | Beta (mean = 0.44, SD = 0.024) |
| | 15–64 years | Beta (mean = 0.61, SD = 0.01) |
| | 65–74 years | Beta (mean = 0.64, SD = 0.016) |
| | Over 75 years | Beta (mean = 0.69, SD = 0.011) |
| Probability of empyema | Under 2 years | Beta (mean = 0.028, SD = 0.0063) |
| | 2–14 years | Beta (mean = 0.05, SD = 0.0097) |
| | 15–64 years | Beta (mean = 0.024, SD = 0.0034) |
| | 65–74 years | Beta (mean = 0.018, SD = 0.0045) |
| | Over 75 years | Beta (mean = 0.0093, SD = 0.0021) |
| Probability of sepsis | Under 2 years | Beta (mean = 0.15, SD = 0.013) |
| | 2–14 years | Beta (mean = 0.15, SD = 0.017) |
| | 15–64 years | Beta (mean = 0.19, SD = 0.0086) |
| | 65–74 years | Beta (mean = 0.22, SD = 0.014) |
| | Over 75 years | Beta (mean = 0.23, SD = 0.0096) |
| Probability of other foci | Under 2 years | Beta (mean = 0.07, SD = 0.0092) |
| | 2–14 years | Beta (mean = 0.077, SD = 0.012) |
| | 15–64 years | Beta (mean = 0.032, SD = 0.0039) |
| | 65–74 years | Beta (mean = 0.03, SD = 0.0061) |
| | Over 75 years | Beta (mean = 0.015, SD = 0.0027) |
| Case fatality risk for meningitis | Under 2 years | Beta (mean = 0.048, SD = 0.0078) |
| | 2–14 years | Beta (mean = 0.068, SD = 0.015) |
| | 15–64 years | Beta (mean = 0.11, SD = 0.011) |
| | 65–74 years | Beta (mean = 0.17, SD = 0.024) |
| | Over 75 years | Beta (mean = 0.33, SD = 0.031) |
| Case fatality risk for pneumonia | Under 2 years | Beta (mean = 0.0053, SD = 0.0036) |
| | 2–14 years | Beta (mean = 0.0083, SD = 0.0037) |
| | 15–64 years | Beta (mean = 0.051, SD = 0.0034) |
| | 65–74 years | Beta (mean = 0.13, SD = 0.0086) |
| | Over 75 years | Beta (mean = 0.32, SD = 0.012) |

**TABLE 1** Parameter distributions for invasive and non-invasive disease outcomes fitted to data reported in van Hoek *et al.* (*continued*)

| Parameter description | Age group | Parameter distribution |
|---|---|---|
| Case fatality risk for empyema | Under 2 years | Beta (mean = 9.5e-08, SD = 3.6e-08) |
| | 2–14 years | Beta (mean = 1.1e–07, SD = 5.8e-08) |
| | 15–64 years | Beta (mean = 0.027, SD = 0.014) |
| | 65–74 years | Beta (mean = 0.077, SD = 0.04) |
| | Over 75 years | Beta (mean = 0.22, SD = 0.069) |
| Case fatality risk for sepsis | Under 2 years | Beta (mean = 0.041, SD = 0.012) |
| | 2–14 years | Beta (mean = 0.032, SD = 0.013) |
| | 15–64 years | Beta (mean = 0.15, SD = 0.012) |
| | 65–74 years | Beta (mean = 0.24, SD = 0.018) |
| | Over 75 years | Beta (mean = 0.41, SD = 0.018) |
| Case fatality risk for other foci | Under 2 years | Beta (mean = 0.011, SD = 0.0087) |
| | 2–14 years | Beta (mean = 0.012, SD = 0.011) |
| | 15–64 years | Beta (mean = 0.12, SD = 0.027) |
| | 65–74 years | Beta (mean = 0.14, SD = 0.039) |
| | Over 75 years | Beta (mean = 0.15, SD = 0.038) |
| Length of stay (days) for meningitis | Under 2 years | Gamma (mean = 12, SD = 0.58) |
| | 2–14 years | Gamma (mean = 11, SD = 1.7) |
| | 15–64 years | Gamma (mean = 26, SD = 2.4) |
| | 65–74 years | Gamma (mean = 29, SD = 5) |
| | Over 75 years | Gamma (mean = 23, SD = 2.8) |
| Length of stay (days) for pneumonia | Under 2 years | Gamma (mean = 5, SD = 0.48) |
| | 2–14 years | Gamma (mean = 4.8, SD = 0.56) |
| | 15–64 years | Gamma (mean = 10, SD = 0.43) |
| | 65–74 years | Gamma (mean = 15, SD = 0.82) |
| | Over 75 years | Gamma (mean = 18, SD = 0.68) |
| Length of stay (days) for empyema | Under 2 years | Gamma (mean = 17, SD = 2.7) |
| | 2–14 years | Gamma (mean = 16, SD = 1.6) |
| | 15–64 years | Gamma (mean = 32, SD = 6.1) |
| | 65–74 years | Gamma (mean = 24, SD = 4.7) |
| | Over 75 years | Gamma (mean = 39, SD = 8.6) |
| Length of stay (days) for sepsis | Under 2 years | Gamma (mean = 9.9, SD = 2.9) |
| | 2–14 years | Gamma (mean = 7.4, SD = 1.1) |
| | 15–64 years | Gamma (mean = 17, SD = 1.5) |
| | 65–74 years | Gamma (mean = 15, SD = 1.3) |
| | Over 75 years | Gamma (mean = 20, SD = 1.3) |

continued

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**TABLE 1** Parameter distributions for invasive and non-invasive disease outcomes fitted to data reported in van Hoek *et al.* (*continued*)

| Parameter description | Age group | Parameter distribution |
|---|---|---|
| Length of stay (days) for other foci | Under 2 years | Gamma (mean = 6.5, SD = 1.2) |
| | 2–14 years | Gamma (mean = 5.2, SD = 0.92) |
| | 15–64 years | Gamma (mean = 17, SD = 3.1) |
| | 65–74 years | Gamma (mean = 13, SD = 2.1) |
| | Over 75 years | Gamma (mean = 33, SD = 6.4) |
| *Non-invasive disease multipliers* | | |
| Cases of non-invasive pneumonia (GP) per case of invasive pneumococcal disease | Under 1 year | Gamma (mean = 0.88, SD = 0.32) |
| | 1 year | Gamma (mean = 2.3, SD = 0.85) |
| | 2–4 years | Gamma (mean = 3.6, SD = 1.4) |
| | 5–9 years | Gamma (mean = 6.2, SD = 2.3) |
| | Over 10 years | Gamma (mean = 4.6, SD = 1.7) |
| Cases of non-invasive pneumonia (hospital) per case of invasive pneumococcal disease | Under 1 year | Gamma (mean = 1.1, SD = 0.41) |
| | 1 year | Gamma (mean = 2.9, SD = 1) |
| | 2–4 years | Gamma (mean = 4.1, SD = 1.5) |
| | 5–9 years | Gamma (mean = 2.3, SD = 0.86) |
| | Over 10 years | Gamma (mean = 6.7, SD = 2.5) |

SD, standard deviation.

Hospitalised cases are stratified according to disease focus (meningitis, bacteraemia, empyema, pneumonia or other), which are associated with a corresponding hospital length-of-stay distribution and mortality risk. For meningitis survivors, the risk of developing different long-term sequelae was based on the results of a systematic review of sequelae due to pneumococcal meningitis in high-income countries.[103]

In a scenario analysis, the difference in impact of PCV10 versus PCV13 on non-invasive pneumonia was also included, assuming this is proportional to the impact on invasive pneumococcal disease for each age group. The number of cases of invasive pneumococcal disease averted was multiplied by age-specific factors estimated by van Hoek and co-workers to calculate the number of cases of non-invasive pneumonia due to *S. pneumoniae*.

### *Quality-adjusted life-years*

For deaths following invasive pneumococcal disease, we estimated the quality-adjusted life-year (QALY) loss as the average discounted remaining life expectancy for each age group in the model. The discounted life expectancy for each age group was calculated using the life table method and weighted according to the size of the population for each year of age with each age group. UK life tables for each year were based on medium scenario of the 2022 update of the United Nations World Population Prospects estimates,[104] which account for expected changes in underlying population mortality over the period 2006–30.

For non-fatal outcomes, the QALY loss for different outcomes of the acute episode was based on the QALY loss used by van Hoek and co-workers. For meningitis sequelae, a reduced health state utility was assumed to apply for each year of remaining life based on the values reported by Oostenbrink *et al.*[105]

Conservatively, it was assumed that meningitis survivors with sequelae did not experience any reduction in life expectancy.

In the base-case analysis, QALYs were discounted to the year 2006 at an annual discount rate of 3.5%. As a sensitivity analysis, an annual discount rate of 1.5% was also used.

### *Costs*

Healthcare costs were parameterised using distributions reported by van Hoek *et al.*[100] after adjustment to 2006 prices (see *Table 2*). This adjustment was performed using the Hospital and Community Health Services Index.[106] All costs were discounted annually at 3.5%.

For hospitalised cases, the cost per case was calculated by multiplying the length of stay by the corresponding cost per bed-day based on NHS reference costs. Cases were assumed to incur the cost of one primary care consultation along with the cost of an antibiotic prescription prior to hospitalisation. Survivors of meningitis with no long-term sequelae were assumed to incur the cost of one follow-up outpatient appointment, whereas the annual healthcare costs for those with meningitis sequelae were based on previous estimates from Melegaro and Edmunds.[107]

**TABLE 2** Parameter distributions for invasive and non-invasive disease outcomes fitted to data reported in van Hoek *et al.*

| Parameter description | Mean value | Parameter distribution |
|---|---|---|
| *Healthcare costs (£2010)*[a] | | |
| Primary care consultation | 35 | Fixed |
| Prescription (pneumonia) | 10.74 | Fixed |
| Prescription (sepsis or meningitis) | 2.14 | Fixed |
| Hospital bed-day (sepsis) | 308 | Log-normal (mean = 5.73, SD = 0.40) |
| Hospital bed-day (meningitis) | 261 | Log-normal (mean = 5.56, SD = 0.29) |
| Hospital bed-day (pneumonia) | 270 | Log-normal (mean = 5.60, SD = 0.26) |
| Outpatient follow-up (meningitis) | 346 | Log-normal (mean = 5.85, SD = 0.44) |
| Annual cost of meningitis sequelae (first year) | 6080 | Log-normal (mean = 8.71, SD = 0.36) |
| Annual cost of meningitis sequelae (subsequent year) | 185 | Log-normal (mean = 5.22, SD = 0.44) |
| *QALY loss per case* | | |
| Hospitalisation (sepsis or pneumonia) | 0.079 | Beta (mean = 0.079, SD = 0.0031) |
| Hospitalisation (meningitis) | 0.023 | Beta (mean = 0.023, SD = 0.0083) |
| Pneumonia (outpatient visit) | 0.0037 | Beta (mean = 0.037, SD = 0.0012) |
| *Health state utility of meningitis sequelae* | | |
| Deafness | 0.81 | Beta (mean = 0.81, SD = 0.0028) |
| Mild hearing loss | 0.91 | Beta (mean = 0.91, SD = 0.0015) |
| Epilepsy | 0.83 | Beta (mean = 0.83, SD = 0.0015) |
| Mild mental retardation | 0.62 | Beta (mean = 0.62, SD = 0.0021) |
| Paresis | 0.67 | Beta (mean = 0.67, SE = 0.0023) |

a Cost deflator of 0.843 was used to adjust all cost inputs to £2006 prices.

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For non-invasive disease costs, it was assumed that 1% of otitis media cases would require an outpatient appointment. For non-invasive pneumonia resulting in hospitalisation, in the absence of length-of-stay data, the cost was based on the reference cost for an admission.

The delivery costs for each dose of vaccine were assumed to be the same for PCV10 and PCV13 and, therefore, would not impact the threshold vaccine price.

### *Threshold price analysis*

To estimate the additional price per dose below which PCV13 becomes more cost-effective than PCV10, the additional QALY gain with PCV13 was monetised by valuing each QALY according to different cost-effectiveness threshold (CET) values. This was then used to calculate the incremental net monetary benefit (iNMB) combining the value of the QALY gain with the healthcare savings minus any extra costs of the PCV13 vaccine programme. The vaccine threshold price is then the additional cost per dose at which the iNMB equals zero.

In the base case, the additional threshold price was calculated using a CET of £20,000 per QALY, and a CET of £30,000 per QALY was used as a sensitivity analysis.

## Results

The introduction of an infant PCV13 programme was predicted to avoid an additional 2808 (95% CI 2690 to 2925) cases of invasive pneumococcal disease compared with PCV10 introduction between 2006 and 2030. This includes an estimated 326 cases of meningitis, 578 cases of sepsis, 1770 cases of invasive pneumonia and 30,680 cases of non-invasive pneumonia. Under base-case assumptions, this resulted in discounted healthcare savings of £13 million (95% CI £12 to £14 million). Including non-invasive pneumonia increased the savings to £27 million (95% CI £25 to £29 million). A breakdown of healthcare cost savings by disease presentation is shown in *Figure 16*.

In the base case, averting additional cases of invasive pneumococcal disease resulted in a gain of an additional 4545 (95% CI 4465 to 4724) discounted QALYs, which increased to a gain of 6625 (95% CI 6352 to 6899) QALYs when using a discount rate of 1.5%. Again, inclusion of non-invasive disease had only a small impact (see *Figure 17*).

*Figure 18* shows the maximum additional price that should be paid for a PCV13 dose under different scenarios. In the base-case analysis, introduction of PCV13 instead of PCV10 in 2006 would have been cost-effective in England and Wales provided the price of PCV13 was no more than an additional £3.57 (95% CI £3.42 to £3.71) per dose higher than PCV10, at a CET of £20,000 per QALY. Using a higher CET of £30,000 per QALY, additional threshold price increased to £5.13 (95% CI £4.92 to £5.33).

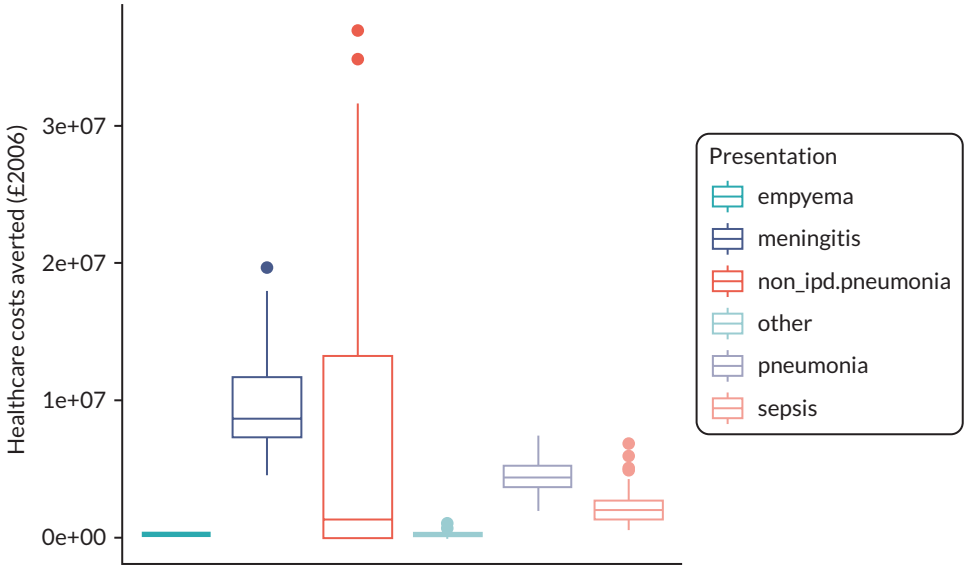



**FIGURE 16** Discounted healthcare costs averted (£2006) by an infant PCV13 introduction compared with a PCV10 programme between 2006 and 2030, stratified by disease presentation.

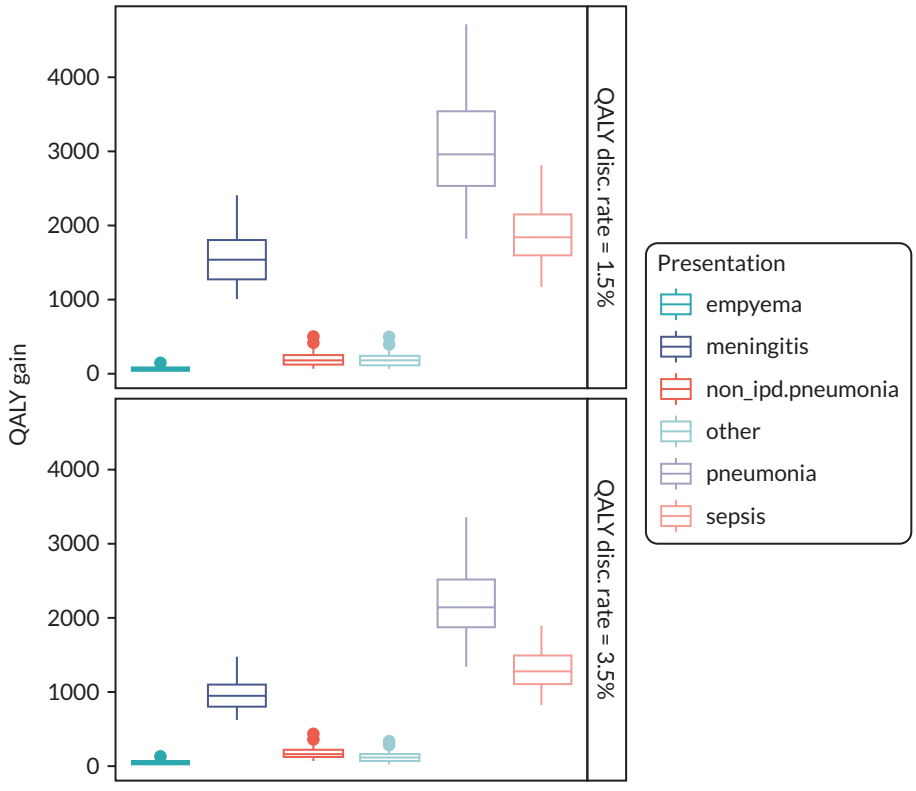



**FIGURE 17** Discounted QALYs gained by an infant PCV13 programme introduction compared to PCV10 introduction between 2006 and 2030 stratified by disease presentation under different scenario assumptions.

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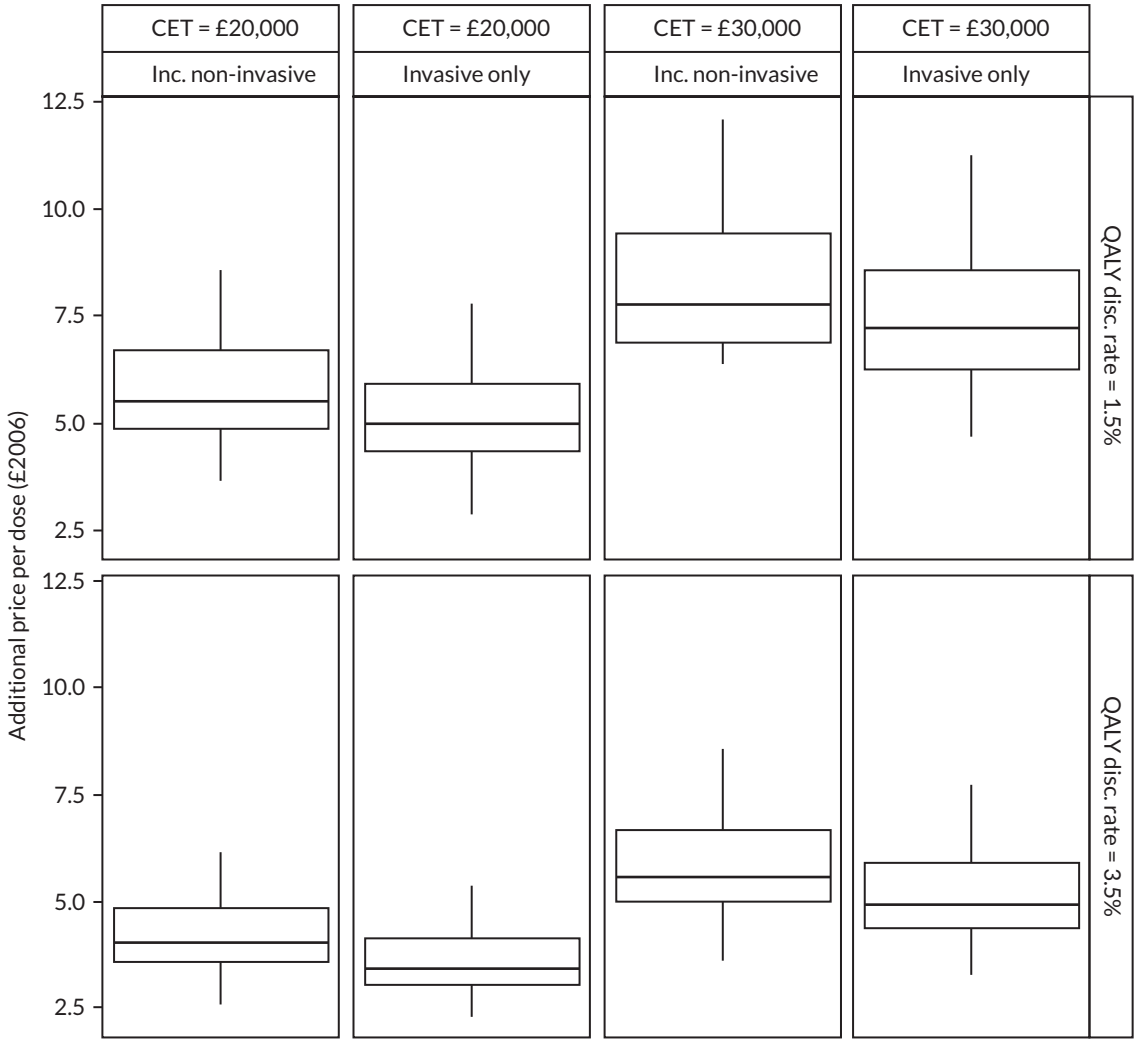



**FIGURE 18** Additional threshold price per dose in £2006 at which PCV13 becomes cost-effective compared to PCV10 under different scenario assumptions.

# **Chapter 6** Discussion

In our study, we used a novel methodology to define seroinfection from immunogenicity data to compare the relative efficacy of PCVs in preventing infection. Our results using individual-level data from a global meta-analysis provide the first estimates of the comparative protection afforded by different pneumococcal vaccines and show that for many serotypes, carriage events are less common after PCV13 than PCV10, likely due to a higher antibody response. In addition, we quantify the relationship between the immune response to vaccination and protection against infection, measured serologically, and show that higher antibody responses in infants are associated with greater protection from infection.

The observed heterogenicity in immune responses was unexpected. We assumed that if one vaccine is able to induce more antibody than another, then it would do so with some degree of consistency across all trials. However, this was not what was observed. Comparisons of the same vaccines in different studies gave widely varying estimates, and although we have reported the summary GMR estimates in our immunogenicity meta-analyses, the large degree of between-study heterogeneity in these models means these overall estimates are difficult to interpret. In some settings, PCV13 performed better; yet, in others, PCV10 was the more immunogenic vaccine. Although there was no single study-level factor that could be identified that might explain the variation in estimates, only three candidate factors could be considered (location, schedule and co-administered vaccines) and data reporting on co-administered vaccines were not always comprehensive. The assays used have been WHO standardised and unlikely to cause this variation, and additionally, only studies directly comparing the two vaccines were included.

Of note, comparisons between vaccines from the same manufacturer (PCV13 vs. PCV7) were more consistent than comparisons between vaccines from different manufacturers. Immune interference ('bystander effects') has been noted when vaccines with similar components are co-administered,[108] and this may affect the responses to one vaccine over another. It is interesting that 18C and 19F were serotypes that showed a very large degree of between-study heterogeneity. These two serotypes in PCV10 have different carrier proteins (18C is conjugated to TT and 19F is conjugated to diphtheria toxoid) and may be more susceptible than other serotypes to the co-administration of vaccines containing tetanus or diphtheria components. An additional potential confounder that is unmeasured in these studies is the degree of exposure to circulating serotypes of pneumococcus in each setting, which also has the potential to influence the immune response to vaccines.

These diverse immunogenicity findings from studies of the same vaccines raise the question of whether such differences in immunogenicity lead to meaningful differences in protection. If so, it may be important to know which vaccine performs better in which setting and further investigation into the predictors of the immune response to vaccines may be warranted. We addressed this question by modelling the relationship between seroefficacy estimates and immunogenicity comparisons (GMRs), analysed at the trial level across all serotypes and studies. This method capitalises on the observed between-study heterogenicity rather than being hindered by it. In our model, vaccines with higher antibody levels were also those with greater protection against subclinical infections in general. A vaccine with twice the antibody production was predicted to halve the rate at which carriage occurred.

Licensure of new vaccines is based on non-inferiority comparisons with current vaccines and the proportion of antibody responses above the agreed threshold as a minimum requirement. Once a vaccine meets this 'at-least-as-good-as' immunogenicity criteria, it has previously not been clear whether exceeding it is of benefit, and the WHO position paper states *'It is unknown whether a lower serotype-specific GMC of antibody indicates less efficacy'*.[3] Our results show that lower protection against subclinical infection does indeed follow from lower antibody production and that two vaccines that produce a similar level of antibody will provide similar levels of protection, even if they are from different manufacturers.

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The implications of these findings are of greatest importance when a new vaccine roll-out is being considered. Lower antibody production or lower seroefficacy for one vaccine product does not necessarily imply limited effectiveness against invasive pneumococcal diseases when considering vaccines such as PCV10 and PCV13 which are highly effective vaccines in many settings. Instead, lower antibody responses lead to less rapidly observed indirect protection after implementation into a national programme as a smaller proportion of transmission events are blocked by the vaccine. This is evident in the mathematical modelling in *Chapter 4* which showed less rapid decreases in the number of cases of invasive disease when introducing PCV10 compared with PCV13.

For serotypes where protective impact has not been observed (serotype 3), new vaccines with substantially higher antibody responses may be needed. A Phase II clinical trial of PCV15 compared with PCV13 reported almost twice the antibody level for serotype 3 at 28 days post-primary series for PCV15 (GMR 1.93, 95% CI 1.71 to 2.18).[82] Based on our modelled association between GMR and RR, the RR of seroinfection with PCV15 versus PCV13 would be 0.48 (95% CI 0.21 to 0.87). Previously reported vaccine effectiveness estimates against nasopharyngeal carriage of serotype 3 include −27% (95% CI −180 to 44) and 1% (95% CI −106 to 52),[30,109] and these translate to point estimates of 39% (95% CI −16% to 66%) and 52% (95% CI 9% to 79%) vaccine effectiveness against carriage of this serotype with PCV15 based on the relationship: $(VE_{(pcv15)} = (1 - RR_{(pcv15\ vs\ pcv13)} \times (1 - VE_{(pcv13)}/100\%)) \times 100\%)$.

## Implications for practice

This evidence of differences in serotype-specific protection can be incorporated into cost-effectiveness models used to compare vaccine products.[16] Cost-effectiveness studies have highlighted the lack of direct evidence of comparative efficacy of different PCVs, resulting in previous cost-effectiveness models that ignore serotype-specific differences and assume equivalent efficacy for all serotypes covered by different PCVs.[110–112] Our study fills this evidence gap and allows researchers and policy-makers to use more accurate vaccine-specific models in decision-making.

Our cost-effectiveness analysis of a hypothetical scenario showed that introducing infant PCV13 was predicted to avert a higher burden of pneumococcal disease compared to PCV10. This would have realised a small saving of £13 million discounted over 24 years.

When considering the introduction of new pneumococcal vaccines into the routine immunisation schedule, we recommend that differences in antibody responses for different vaccines be considered in modelling scenarios as higher antibody responses result in reduced transmission and greater impact on invasive diseases. Vaccine-specific threshold prices can then be determined for cost-effective vaccines. Our analysis showed that due to its higher efficacy against some serotypes, a higher threshold price per dose could be paid for PCV13 while remaining cost-effective. Seroefficacy estimates can also be determined for new pneumococcal vaccines and could contribute to licensing or policy decisions in the future.

## Strength and limitations

Seroefficacy analyses need to be restricted to serotypes contained in both vaccines. Comparing a vaccinated cohort to a cohort that is unvaccinated, or receives a vaccine that does not contain the serotype of interest, will result in biased estimates as the immune response after exposure to a pathogen will differ in children whose immune system is primed for that pathogen, when compared with a naïve population. For this reason, we restricted our seroefficacy analysis to shared serotypes between vaccines. While seroinfection is most likely an indicator of nasopharyngeal carriage, it may also represent cases of asymptomatic bacteraemia.

Our analyses are based on a large set of studies conducted in infants for the most commonly used vaccines and make use of data originally collected for a different purpose than ours. We used the time points available in these studies. However, the time points one might use if designing a study for the purpose of calculating seroefficacy may differ and would likely include an additional time point 6–9 months after the booster dose. Without this time point, we are extrapolating pre-booster efficacy to post-booster time periods, and the impact of this assumption is unknown.

The mathematical and economic models used were based on outputs from our NMA models which contained significant heterogeneity. The potential for bias when using inconsistent data for modelling scenarios in this situation is hard to quantify but needs to be considered.

### *Public and patient involvement*

The Oxford Vaccine Group public and patient involvement (PPI) group was involved at the design stage in the development of the plain language summary for the submitted grant proposal. Due to the nature of the project being a reanalysis of data from previously completely studies, there was no involvement of the PPI group in the data collection or analysis. Dissemination of results was discussed with the PPI lead, but as the conclusions and recommendations are relevant only to policy-makers and academics and as decision on vaccine product choice and purchases are made by the Department of Health for the whole of England, not by individuals, the PPI lead felt that further PPI review for the project would not be a good use of the PPI volunteer time.

### *Equality, diversity and inclusivity*

The research team for the project was small but reflected contributions from under-represented groups. In particular, a large proportion of the key contributors were female, including first, second and senior authors, including the principal investigator. Junior members of the team are fully acknowledged with authorship on the final report and all publications arising from the project.

Data from individual studies included in the systematic review were from a wide range of countries and regions.

## Conclusions

In conclusion, we estimated serotype-specific difference in both seroefficacy and immunogenicity between PCV10 and PCV13. Higher IgG antibody levels confer better protection against seroinfection. This methodology can be further used to compare novel high-valent PCVs and to inform cost-effectiveness models.

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# Additional information

## Contributions of authors

**Shuo Feng (https://orcid.org/0000-0001-7855-0991)** (Statistician/Epidemiologist) contributed to the study methods, obtained the individual participant data, extracted the aggregated data, analysed the data and wrote the first draft of the manuscript.

**Julie McLellan (https://orcid.org/0000-0002-2868-8631)** (Senior Systematic Reviewer) contributed to the study methods, conducted the study selection and assessment of bias and contributed to data interpretation and manuscript development.

**Nicola Pidduck (https://orcid.org/0000-0002-6491-1159)** (Research Assistant) conducted the study selection and assessment of bias.

**Nia Roberts (https://orcid.org/0000-0002-1142-6440)** (Senior Outreach Librarian) contributed to the study methods, devised and conducted the search strategy.

**Julian PT Higgins (https://orcid.org/0000-0002-8323-2514)** (Professor of Evidence Synthesis) contributed to the study methods, data interpretation and reviewed the final version of the manuscript.

**Yoon Choi (https://orcid.org/0000-0001-5561-4366)** (Infectious disease modeller) conducted the mathematical modelling and manuscript development.

**Alane Izu (https://orcid.org/0000-0002-5547-7223)** (Senior Statistician) contributed to data collection and interpretation and reviewed the final version of the manuscript.

**Mark Jit (https://orcid.org/0000-0001-6658-8255)** (Professor of Vaccine Epidemiology) contributed to the study methods, conducted health economic analyses and manuscript development.

**Shabir A Madhi (https://orcid.org/0000-0002-7629-0636)** (Professor of Vaccinology) contributed to data collection and interpretation and reviewed the final version of the manuscript.

**Kim Mulholland (https://orcid.org/0000-0001-7947-680X)** (Professor of Child Health) contributed to data collection and interpretation and reviewed the final version of the manuscript.

**Andrew J Pollard (https://orcid.org/0000-0001-7361-719X)** (Ashall Professor of Infection and Immunity) contributed to data interpretation and reviewed the final version of the manuscript.

**Simon Procter (https://orcid.org/0000-0002-0380-1503)** (Research Fellow, Department of Infectious Disease Epidemiology) conducted health economic analyses, data interpretation and manuscript development.

**Beth Temple (https://orcid.org/0000-0002-4885-9848)** (Epidemiologist) contributed to data collection and interpretation and reviewed the final version of the manuscript.

**Merryn Voysey (https://orcid.org/0000-0001-6324-6559)** (Associate Professor of Statistics in Vaccinology) conceived and designed the study, obtained study funding, obtained the individual participant data and extracted the aggregated data and provided study oversight.

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## Data-sharing statement

Data were obtained through third-party resources (Pfizer data through Vivli Inc. and data from GlaxoSmithKline through clinicalstudydatarequest.com) and were made available for a limited period of time to conduct these analyses. The authors do not have continuing access to the data sets. Vivli, clinicalstudydatarequest.com, Pfizer Inc. and GlaxoSmithKline have not contributed to or approved, and are not in any way responsible for, the contents of this publication. All other queries should be addressed to the corresponding author.

## Ethics statement

This is a meta-analysis of anonymised data from previously conducted clinical trials and as such does not require review by an ethics committee. Each individual study included in the meta-analysis had ethical approval in place. Data-sharing agreements were entered into with entities providing anonymised individual-level data.

## Information governance statement

There was no personal information handled as part of this work.

## Disclosure of interests

**Full disclosure of interests:** Completed ICMJE forms for all authors, including all related interests, or available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/YWHA3079.

**Primary conflicts of interest:** Andrew J Pollard is Chair of the UK DHSC Joint on Vaccination and Immunisation and was a member of the Strategic Advisory Group of Experts on Immunization to the World Health Organization (WHO) until 2022. Andrew J Pollard, Merryn Voysey and Shuo Feng are contributors to COVID-19 vaccine intellectual property licensed by Oxford University Innovation to AstraZeneca. Shabir A Madhi reports grants to his institution from the Bill and Melinda Gates Foundation, Pfizer and GlaxoSmithKline and is member of the Strategic Advisory Group of Experts on Immunization to the WHO. Kim Mulholland is an investigator on grants from MSD and Pfizer and reports grants to his institution from the Bill and Melinda Gates Foundation and the WHO. Mark Jit reports grants to his institution from Bill and Melinda Gates Foundation, Gavi the Vaccine Alliance, NIHR, RCUK, European Commission and Wellcome Trust. All other authors declare no competing interests. The remaining authors declare no competing interests. The views expressed in this article do not necessarily represent the views of the DHSC, JCVI, NIHR or WHO.

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# **Appendix 1** Search strategy

MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) 1946–present.

| |
|---|
| Streptococcus pneumoniae/ |
| (pneumococc* or s pneumoniae or strep* pneumoniae or strep* p).ti,ab. |
| 1 or 2 |
| vaccines/ or bacterial vaccines/ or streptococcal vaccines/ or Vaccines, Conjugate/ |
| (vaccin* or immuni?ation? or immuni?e? or inoculat* or conjugate).ti. |
| (conjugate adj2 vaccin*).ti,ab. |
| (7 valent or 7valent or seven valent or heptavalent or hepta-valent).ti,ab. |
| (9 valent or 9valent or nine valent or nonavalent or nona-valent).ti,ab. |
| (10 valent or 10valent or ten valent or decavalent or deca-valent).ti,ab. |
| (13 valent or 13valent or thirteen valent).ti,ab. |
| 4 or 5 or 6 or 7 or 8 or 9 or 10 |
| 3 and 11 |
| exp Pneumococcal Vaccines/ |
| ((pneumococc* or s pneumoniae or strep* pneumoniae or strep* p) adj5 (vaccin* or immuni?ation? or immuni?e? or inoculat* or conjugate)).ti,ab. |
| (pcv7 or pcv 7 or pncrm* or pnccrm* or 7vpnc or 7vcrm).ti,ab. |
| (pcv9 or pcv 9).ti,ab. |
| (pcv10 or pcv 10 or phidcv or phid cv).ti,ab. |
| (pcv13 or pcv 13 or 13vcrm).ti,ab. |
| (pneumovax or pneumopur or streptopur or streptorix or prevnar or prevenar or synflorix or gsk 1024850a or gsk1024850a).ti,ab. |
| 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 |
| exp child/ or infant/ |
| (child* or infan* or baby or babies or toddler? or preschool* or pre-school* or p?ediatric?).ti,ab. |
| 21 or 22 |
| 20 and 23 |
| randomized controlled trial.pt. |
| controlled clinical trial.pt. |
| randomized.ab. |
| placebo.ab. |
| drug therapy.fs. |
| randomly.ab. |
| trial.ab. |
| groups.ab. |

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25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

exp animals/ not humans.sh.

33 not 34

24 and 35

limit 24 to ('reviews (maximizes specificity)' or 'systematic review')

36 or 37

(2019* or 2020* or 2021* or 2022*).ed,ez,yr.

38 and 39

## EMBASE 1974–present

Streptococcus pneumoniae/

(pneumococc* or s pneumoniae or strep* pneumoniae or strep* p).ti,ab.

1 or 2

vaccine/ or bacterial vaccine/ or streptococcus vaccine/

(vaccin* or immuni?ation? or immuni?e? or inoculat* or conjugate).ti.

(conjugate adj2 vaccin*).ti,ab.

(7 valent or 7valent or seven valent or heptavalent or hepta-valent).ti,ab.

(9 valent or 9valent or nine valent or nonavalent or nona-valent).ti,ab.

(10 valent or 10valent or ten valent or decavalent or deca-valent).ti,ab.

(13 valent or 13valent or thirteen valent).ti,ab.

4 or 5 or 6 or 7 or 8 or 9 or 10

3 and 11

pneumococcus vaccine/

((pneumococc* or s pneumoniae or strep* pneumoniae or strep* p) adj5 (vaccin* or immuni?ation? or immuni?e? or inoculat* or conjugate)).ti,ab.

(pcv7 or pcv 7 or pncrm* or pnccrm* or 7vpnc or 7vcrm).ti,ab.

(pcv9 or pcv 9).ti,ab.

(pcv10 or pcv 10 or phidcv or phid cv).ti,ab.

(pcv13 or pcv 13 or 13vcrm).ti,ab.

(pneumovax or pneumopur or streptopur or streptorix or prevnar or prevenar or synflorix or gsk 1024850a or gsk1024850a).ti,ab.

12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

exp child/

(child* or infan* or baby or babies or toddler? or preschool* or pre-school* or p?ediatric?).ti,ab.

21 or 22

20 and 23

randomized controlled trial/

single blind procedure/ or double blind procedure/

crossover procedure/

random*.tw.

(((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab.

25 or 26 or 27 or 28 or 29

(exp animals/ or nonhuman/) not human/

30 not 31

24 and 32

limit 24 to ('systematic review' or 'reviews (maximizes specificity)')

33 or 34

(2019* or 2020* or 2021* or 2022*).yr,dd,dc.

35 and 36

## Global Health <1973 to 2022 Week 29>

streptococcus pneumoniae/

(pneumococc* or s pneumoniae or strep* pneumoniae or strep* p).ti,ab.

1 or 2

vaccines/ or conjugate vaccines/

(vaccin* or immuni?ation? or immuni?e? or inoculat* or conjugate).ti.

(conjugate adj2 vaccin*).ti,ab.

(7 valent or 7valent or seven valent or heptavalent or hepta-valent).ti,ab.

(9 valent or 9valent or nine valent or nonavalent or nona-valent).ti,ab.

(10 valent or 10valent or ten valent or decavalent or deca-valent).ti,ab.

(13 valent or 13valent or thirteen valent).ti,ab.

4 or 5 or 6 or 7 or 8 or 9 or 10

3 and 11

((pneumococc* or s pneumoniae or strep* pneumoniae or strep* p) adj5 (vaccin* or immuni?ation? or immuni?e? or inoculat* or conjugate)).ti,ab.

(pcv7 or pcv 7 or pncrm* or pnccrm* or 7vpnc or 7vcrm).ti,ab.

(pcv9 or pcv 9).ti,ab.

(pcv10 or pcv 10 or phidcv or phid cv).ti,ab.

(pcv13 or pcv 13 or 13vcrm).ti,ab.

(pneumovax or pneumopur or streptopur or streptorix or prevnar or prevenar or synflorix or gsk 1024850a or gsk1024850a).ti,ab.

12 or 13 or 14 or 15 or 16 or 17 or 18

exp children/ or infants/

(child* or infan* or baby or babies or toddler? or preschool* or pre-school* or p?ediatric?).ti,ab.

20 or 21

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19 and 22

(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*).mp.

23 and 24

(2019* or 2020* or 2021* or 2022*).yr.

25 and 26

## ClinicalTrials.gov – 1 June 2019

(pneumococcal OR pneumococcus OR 'streptococcus pneumoniae' OR 'streptococcal pneumoniae' OR 'streptococcus p' OR 'streptococcal p') AND (vaccine OR vaccines OR vaccination OR immunisation OR immunization OR immunise OR immunisation OR inoculate) | Child

(pneumococcal OR pneumococcus OR 'streptococcus pneumoniae' OR 'streptococcal pneumoniae' OR 'streptococcus p' OR 'sterptococcal p') AND (conjugate OR valent) | Child

pcv7 or pcv 7 or pncrm or pnccrm or 7vpnc or 7vcrm or pcv9 or pcv 9 or pcv10 or pcv 10 or phidcv or phid cv or pcv13 or pcv 13 or 13vcrm

pneumovax or pneumopur or streptopur or streptorix or prevnar or prevenar or synflorix or gsk 1024850a or gsk1024850a | Child

**ClinicalTrials.gov – 2022 – Added since 1 June 2019**

Other terms = (pneumococcal OR pneumococcus OR 'streptococcus pneumoniae' OR 'streptococcal pneumoniae' OR 'streptococcus p' OR 'streptococcal p') AND (vaccine OR vaccines OR vaccination OR immunisation OR immunization OR immunise OR immunisation OR inoculate) | Child | First posted from 06/01/2019 to 01/01/2024

Title = (pneumococcal OR pneumococcus OR 'streptococcus pneumoniae' OR 'streptococcal pneumoniae' OR 'streptococcus p' OR 'streptococcal p') AND (vaccine OR vaccines OR vaccination OR immunisation OR immunization OR immunise OR immunisation OR inoculate) | Child | First posted from 06/01/2019 to 01/01/2024

Condition = (pneumococcal OR pneumococcus OR 'streptococcus pneumoniae' OR 'streptococcal pneumoniae' OR 'streptococcus p' OR 'streptococcal p') AND Intervention = (vaccine OR vaccines OR vaccination OR immunisation OR immunization OR immunise OR immunisation OR inoculate) | Child | First posted from 06/01/2019 to 01/01/2024

Other terms = (pneumococcal OR pneumococcus OR 'streptococcus pneumoniae' OR 'streptococcal pneumoniae' OR 'streptococcus p' OR 'streptococcal p') AND (conjugate OR valent) | Child

Title = (pneumococcal OR pneumococcus OR 'streptococcus pneumoniae' OR 'streptococcal pneumoniae' OR 'streptococcus p' OR 'streptococcal p') AND (conjugate OR valent) | Child

Condition = (pneumococcal OR pneumococcus OR 'streptococcus pneumoniae' OR 'streptococcal pneumoniae' OR 'streptococcus p' OR 'streptococcal p') AND Intervention = (conjugate OR valent) | Child

Other terms = pcv7 or pcv 7 or pncrm or pnccrm or 7vpnc or 7vcrm or pcv9 or pcv 9 or pcv10 or pcv 10 or phidcv or phid cv or pcv13 or pcv 13 or 13vcrm | Child

Title = pcv7 or pcv 7 or pncrm or pnccrm or 7vpnc or 7vcrm or pcv9 or pcv 9 or pcv10 or pcv 10 or phidcv or phid cv or pcv13 or pcv 13 or 13vcrm | Child

Intervention = pcv7 or pcv 7 or pncrm or pnccrm or 7vpnc or 7vcrm or pcv9 or pcv 9 or pcv10 or pcv 10 or phidcv or phid cv or pcv13 or pcv 13 or 13vcrm | Child

Other terms = pneumovax or pneumopur or streptopur or streptorix or prevnar or prevenar or synflorix or gsk 1024850a or gsk1024850a | Child

Title = pneumovax or pneumopur or streptopur or streptorix or prevnar or prevenar or synflorix or gsk 1024850a or gsk1024850a | Child

Intervention = pneumovax or pneumopur or streptopur or streptorix or prevnar or prevenar or synflorix or gsk 1024850a or | Child

WHO ICTRP

| |
|---|
| pneumococcal vaccine OR pneumococcus vaccine OR pneumococcal conjugate OR pneumococcus conjugate OR pcv OR pneumovax OR pneumopur OR streptopur OR streptorix OR prevnar OR prevenar OR synflorix OR gsk 1024850a OR gsk1024850a - TRIALS IN CHILDREN |

Cochrane (CDSR – limited to publication date: 1 June 2019–27 July 2022, CENTRAL – limited to added to database date: 1 June 2019–27 July 2022)

| ID | Search |
|---|---|
| #1 | MeSH descriptor: [Streptococcus pneumoniae] explode all trees |
| #2 | (pneumococc* or 's pneumoniae' or 'streptococcus pneumoniae' or 'streptococcus p' or 'streptococcal pneumoniae' or 'streptococcal p') |
| #3 | #1 or #2 |
| #4 | MeSH descriptor: [Vaccines] this term only |
| #5 | MeSH descriptor: [Bacterial Vaccines] this term only |
| #6 | ((vaccin* or immunization* or immunize* or immunisation* or immunise* or inoculat* or conjugate or valent)):ti,ab,kw |
| #7 | #4 or #5 or #6 |
| #8 | #3 and #7 |
| #9 | MeSH descriptor: [Pneumococcal Vaccines] explode all trees |
| #10 | ((pcv7 or 'pcv 7' or pncrm* or pnccrm* or 7vpnc or 7vcrm)):ti,ab,kw |
| #11 | ((pcv9 or 'pcv 9')):ti,ab,kw |
| #12 | (pcv10 or'pcv 10' or phidcv or 'phid cv'):ti,ab,kw |
| #13 | (pcv13 or 'pcv 13' or 13vcrm):ti,ab,kw |
| #14 | pneumovax or pneumopur or streptopur or streptorix or prevnar or prevenar or synflorix or gsk 1024850a or gsk1024850a |
| #15 | #8 or #9 or #10 or #11 or #13 or #14 |
| #16 | MeSH descriptor: [Child] explode all trees |
| #17 | MeSH descriptor: [Infant] this term only |
| #18 | (child* or infan* or baby or babies or toddler* or preschool* or pre-school* or pediatric* or paediatric*):ti,ab,kw |
| #19 | #16 or #17 or #18 |
| #20 | #15 and #19 |

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# **Appendix 2** PRISMA flow diagram

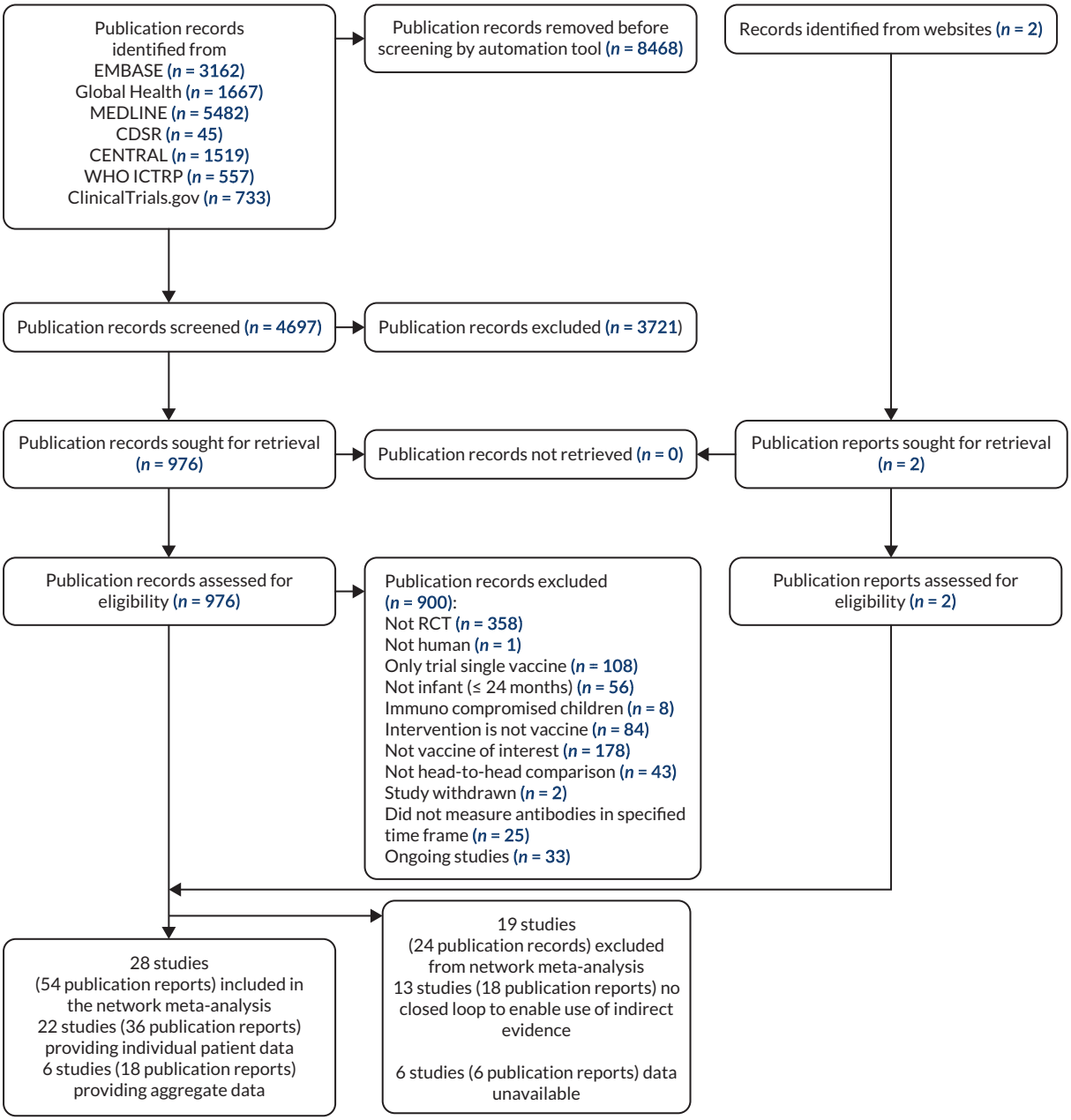



**FIGURE 19** PRISMA flow diagram. CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; ICTRP, International Clinical Trials Registry Platform.

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# **Appendix 3** Study characteristics

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**TABLE 3** Summary of studies included in immunogenicity and seroefficacy analyses

| Cohort ID[a] | Author and year[a] | NCT | Individual participant data available/ aggregate data | Comparison | Country/region | Continent | Schedule | Schedule primary series | Schedule booster | Co-administered vaccine(s) | Assay |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[21,22] | Bermal *et al.* 2009[21] | NCT00344318 NCT00547248 | Individual | PCV10 vs. PCV7 | Philippines | Asia | 3 + 1 | 6–10–24 weeks | 12–18 months | DTPw-HBV-Hib-TT + OPV | 22F-ELISA |
| 1[21,22] | Bermal *et al.* 2009[21] | NCT00344318 NCT00547248 | Individual | PCV10 vs. PCV7 | Poland | Europe | 3 + 1 | 2–4–6 months | 12–18 months | DTPw-HBV-Hib-TT + IPV | 22F-ELISA |
| 2[37] | Kim *et al.* 2011[37] | NCT00680914 | Individual | PCV10 vs. PCV7 | Korea | Asia | 3 + 1 | 2–4–6 months | 12–18 months | Hib-TT | 22F-ELISA |
| 3[39] | Knuf *et al.* 2012[39] | NCT00307541 NCT00333450 | Individual | PCV10 vs. PCV7 | Germany | Europe | 3 + 0 | 2–3–4 months | N/A | DTPa-HBV-Hib-TT/IPV | 22F-ELISA |
| 4[53–55] | Prymula *et al.* 2017[55] | NCT01204658 | Individual | PCV13 vs. PCV10 | Czech Republic, Germany, Poland and Sweden | Europe | 3 + 1 | 2–3–4 months | 12–15 months | DTPa-HBV-Hib-TT/IPV | 22F-ELISA |
| 5[24] | Carmona Martinez *et al.* 2019[24] | NCT01616459 | Individual | PCV13 vs. PCV10 | Czech Republic, Germany, Poland and Spain | Europe | 3 + 1 | 2–3–4 months | 12–15 months | DTPa-HBV-Hib-TT/IPV + MenC-TT (SP) | 22F-ELISA |
| 6[8,46,47,57,58] | Temple *et al.* 2019[57] | NCT01953510 | Individual | PCV13 vs. PCV10 | Vietnam | Asia | 2 + 1 | 2–4 months | 9.5 months | DTPa-HBV-Hib-TT/IPV | Modified third-generation standardised ELISA |
| 7[60–62] | van den Bergh *et al.* 2011[60] | NCT00652951 | Individual | PCV10 vs. PCV7 | Netherland | Europe | 3 + 1 | 2–3–4 months | 11–13 months | DTPa-(HBV)-Hib-TT/IPV | 22F-ELISA |
| 8[64] | Vesikari *et al.* 2009[64] | NCT00307554 NCT00370396 | Individual | PCV10 vs. PCV7 | Finland, France and Poland | Europe | 3 + 1 | 2–3–4 months | 12–18 months | DTPa-(HBV)-Hib-TT/IPV | 22F-ELISA |
| 9[66] | Wysocki *et al.* 2009[66] | NCT00334334 NCT00463437 | Individual | PCV10 vs. PCV7 | Germany, Poland and Spain | Europe | 3 + 1 | 2–4–6 months | 11–18 months | DTPa-(HBV)-Hib-TT/IPV + Hib MenC-TT | 22F-ELISA |
| 10[18] | Amdekar *et al.* 2013[18] | NCT00452790 | Individual | PCV13 vs. PCV7 | India | Asia | 3 + 1 | 6–10–14 weeks | 12 months | DTwP-Hib-HBV + OPV | Standardised ELISA |

**TABLE 3** Summary of studies included in immunogenicity and seroefficacy analyses (*continued*)

| Cohort ID[a] | Author and year[a] | NCT | Individual participant data available/ aggregate data | Comparison | Country/region | Continent | Schedule | Schedule primary series | Schedule booster | Co-administered vaccine(s) | Assay |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 11[26–30,35] | Dagan *et al.* 2013[30] | NCT00508742 | Aggregate | PCV13 vs. PCV7 | Israel | Asia | 3 + 1 | 2–4–6 months | 12 months | N/A | Standardised ELISA |
| 12[31] | Esposito *et al.* 2010[31] | NCT00366899 | Individual | PCV13 vs. PCV7 | Italy | Europe | 2 + 1 | 3–5 months | 11 months | DTPa-HBV-Hib-TT/IPV | Standardised ELISA |
| 13[33] | Grimprel *et al.* 2011[33] | NCT00366678 | Individual | PCV13 vs. PCV7 | France | Europe | 3 + 1 | 2–3–4 months | 12 months | DTPa-Hib-TT/IPV | Standardised ELISA |
| 14[34] | Huang *et al.* 2012[34] | NCT00688870 | Individual | PCV13 vs. PCV7 | Taiwan | Asia | 3 + 1 | 2–4–6 months | 15 months | DTPa-(HBV)-Hib-TT/IPV | Standardised ELISA |
| 15[25,32,36] | Kieninger *et al.* 2010[36] | NCT00366340 | Individual | PCV13 vs. PCV7 | Germany | Europe | 3 + 1 | 2–3–4 months | 11–12 months | DTPa-HBV-Hib-TT/IPV | Standardised ELISA |
| 16[38,44] | Kim *et al.* 2013[38] | NCT00689351 | Individual | PCV13 vs. PCV7 | Korea | Asia | 3 + 1 | 2–4–6 months | 12 months | DTPa-HBV-Hib-TT/IPV | Standardised ELISA |
| 17[51] | Payton *et al.* 2013[51] | NCT00444457 | Individual | PCV13 vs. PCV7 | USA | North America | 3 + 1 | 2–4–6 months | 12 months | DTPa-HBV-Hib-TT/IPV | Standardised ELISA |
| 18[9,45,52,63] | Pomat *et al.* 2018[52] | NCT01619462 | Aggregate | PCV13 vs. PCV10 | Papua New Guinea | Oceania | 3 + 1 | 1–2–3 months | 9 months | DTPw-HBV-Hib-TT + OPV | WHO standardised ELISA |
| 19[56] | Snape *et al.* 2010[56] | NCT00384059 | Individual | PCV13 vs. PCV7 | UK | Europe | 2 + 1 | 2–4 months | 12–13 months | DTPa-Hib-TT/IPV/MenC + Hib-MenC-TT | Standardised ELISA |
| 20[59] | Togashi *et al.* 2015[59] | NCT01200368 | Individual | PCV13 vs. PCV7 | Japan | Asia | 3 + 1 | enr 3–6 m, 4–8 w int | 12–15 months | DTPa | Standardised ELISA |
| 21[65] | Weckx *et al.* 2012[65] | NCT00676091 | Individual | PCV13 vs. PCV7 | Brazil | South America | 3 + 1 | 2–4–6 months | 12 months | HBV-DTwP-Hib/OPV/Rotavirus | Standardised ELISA |
| 22[67] | Yeh *et al.* 2010[67] | NCT00373958 | Individual | PCV13 vs. PCV7 | USA | North America | 3 + 1 | 2–4–6 months | 12–15 months | DTPa-HBV-Hib-TT/IPV | Standardised ELISA |

continued

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**TABLE 3** Summary of studies included in immunogenicity and seroefficacy analyses (*continued*)

| Cohort ID[a] | Author and year[a] | NCT | Individual participant data available/ aggregate data | Comparison | Country/region | Continent | Schedule | Schedule primary series | Schedule booster | Co-administered vaccine(s) | Assay |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 23[68,69] | Zhu *et al.* 2016[69] | NCT01692886 | Individual | PCV13 vs. PCV7 | China | Asia | 3 + 1 | 3–4–5 months | 12 months | N/A | Standardised ELISA |
| 24[23] | Bryant *et al.* 2010[23] | NCT00205803 | Aggregate | PCV13 vs. PCV7 | USA | North America | 3 + 0 | 2–4–6 months | N/A | DTPa-HBV-Hib-TT/IPV | Standardised ELISA |
| 25[49,50] | Odutola *et al.* 2017[49] | NCT01262872 | Aggregate | PCV13 vs. PCV10 | Gambia | Africa | 3 + 0 | 2–3–4 months | N/A | DTPw-HBV-Hib-TT + OPV | GlaxoSmithKline in-house ELISA |
| 26[20,40–43] | Leach *et al.* 2021[42] | NCT01174849 | Aggregate | PCV13 vs. PCV10 | Australia | Oceania | 3 + 1 | 2–4–6 months | 12 months | DTPa-HBV-Hib-TT/IPV/ Rotavirus | Modified third-generation ELISA |
| 27[19,48] | Madhi *et al.* 2020[48] | NCT02943902 | Individual | PCV13 vs. PCV10 | South Africa | Africa | 1 + 1 | 6 weeks | 40 weeks | DTPa-HBV-Hib-TT/IPV/ Rotavirus/ Measles | In-house ELISA according to the standardised WHO protocol |
| 27[19,48] | Madhi *et al.* 2020[48] | NCT02943902 | Individual | PCV13 vs. PCV10 | South Africa | Africa | 1 + 1 | 14 weeks | 40 weeks | DTPa-HBV-Hib-TT/IPV/ Rotavirus/ Measles | In-house ELISA according to the standardised WHO protocol |
| 27[19,48] | Madhi *et al.* 2020[48] | NCT02943902 | Individual | PCV13 vs. PCV10 | South Africa | Africa | 1 + 1 | 6–14 weeks | 40 weeks | DTPa-HBV-Hib-TT/IPV/ Rotavirus/ Measles | In-house ELISA according to the standardised WHO protocol |
| 28[89] | Adigweme *et al.* 2023 | NCT03896477 | Aggregate | PCV13 vs. PCV10 | Gambia | Africa | 2 + 1 | 6–8 and 14–16 weeks | 9–18 months | DTwP-Hib-HBV/ bOPV/Rotavirus | Validated ELISA by the WHO Pneumococcal Serology Reference Laboratory |

DTwP, diphtheria, tetanus, whole-cell pertussis; ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B vaccine; Hib-TT, *Haemophilus influenzae* type b tetanus toxoid conjugate vaccine; MenC, group C meningococcal vaccine; NCT, National Clinical Trial; OPV, oral polio vaccine.

a In 'Cohort ID' column all relevant publication records are cited; in 'Author and Year' column the main studies relevant to the analysis are cited.

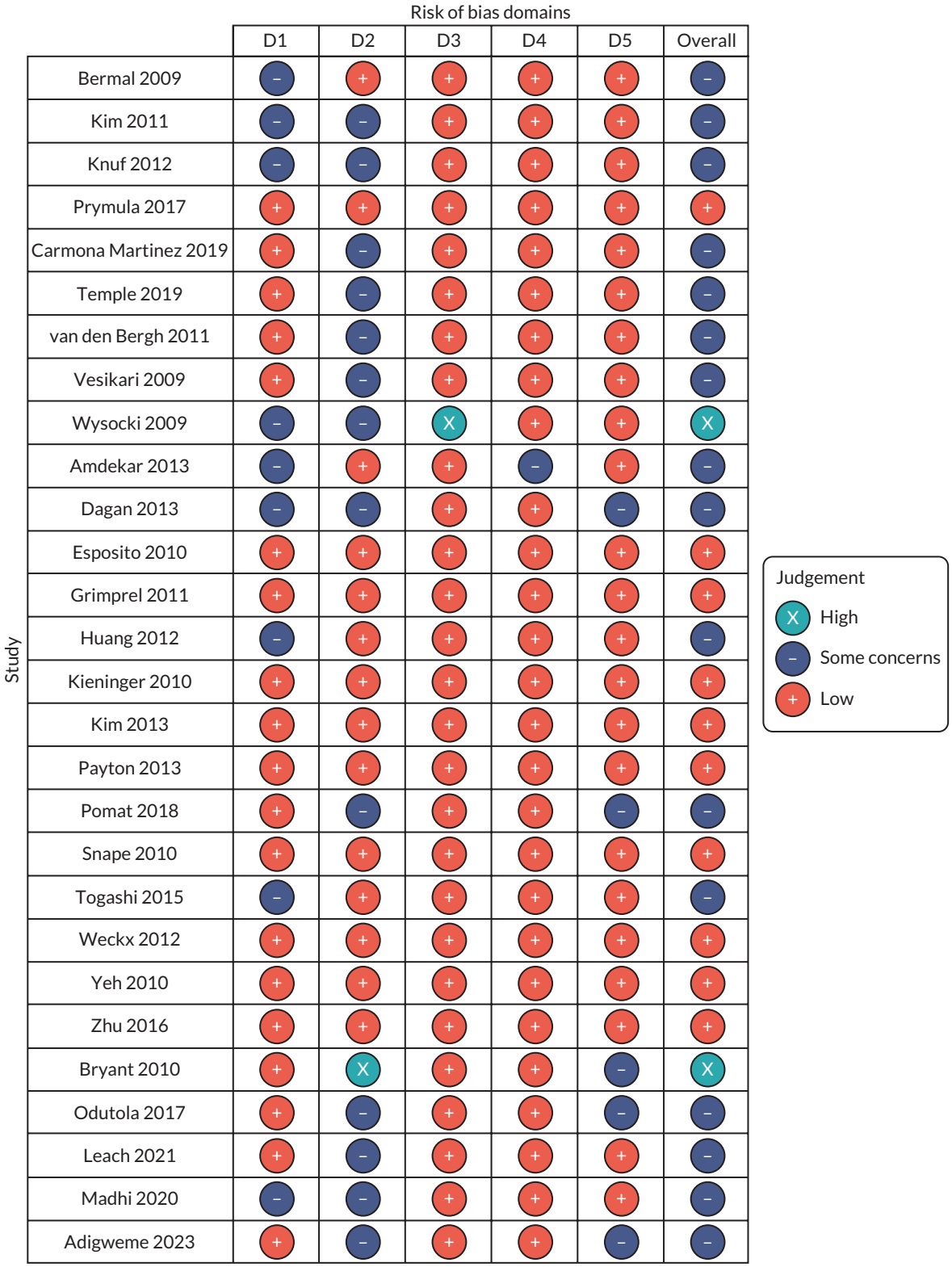
**TABLE 4** Summary of eligible studies excluded from NMA due to either no closed loop or data unavailable

| Author and year[a] | NCT | Comparison |
|---|---|---|
| Studies with no closed loop in the network | | |
| GlaxoSmithKline[113] | NCT00169481 | PCV7 vs. PCV11 |
| Dagan *et al.* 1996[79] | Not found | PCV7 vs. PPV23 |
| Greenberg *et al.* 2018[80] | NCT01215188 | PCV13 vs. PCV15 |
| Rupp *et al.* 2019[83] | NCT0251373<br>NCT02037984 | PCV13 vs. PCV15 |
| Thisyakorn *et al.* 2014[87] | NCT00594347 | PCV7 vs. PPV23 |
| Martinez *et al.* 2018[81] | RPCE00000173 | Cuban PCV7 vs. PCV10 |
| Platt *et al.* 2020[82] | NCT02987972 | PCV15 vs. PCV13 |
| Bili *et al.* 2021;[75]<br>Bili *et al.* 2023[90] | NCT03620162 | PCV15 vs. PCV13 |
| Shin *et al.* 2020[86] | NCTR20170109002 | PCV12 vs. PCV13 |
| Chen *et al.* 2016;[76]<br>Zhao *et al.* 2022[88] | NCT02736240 | PCV7 vs. Chinese PCV13 |
| Senders *et al.* 2021;[85] Senders *et al.* 2020[84] | NCT03512288 | PCV13 vs. PCV20 |
| Banniettis *et al.* 2021;[74]<br>Banniettis *et al.* 2022[91] | NCT03885934 | PCV15 vs. PCV13 |
| Lupinacci *et al.* 2022;[92]<br>Lupinacci *et al.* 2023[90] | NCT03893448 | PCV15 vs. PCV13 |
| Studies with data unavailable | | |
| Martinon-Torres *et al.* 2012[72] | NCT00474539 | PCV7 vs. PCV13 |
| Vanderkooi *et al.* 2012[73] | NCT00475033 | PCV7 vs. PCV13 |
| De Los Santos *et al.* 2017[70] | NCT01641133 | PCV10 vs. PCV13 |
| Diez-Domingo *et al.* 2013[71] | NCT00368966 | PCV7 vs. PCV13 |
| Clarke *et al.* 2020[78,a] | NCT02308540 | PCV10-SII vs. PCV13 |
| Clarke *et al.* 2021[77,a] | NCT03197376 | PCV10 vs. PCV10-SII |

PCV10-SII, 10-valent Pneumococcal conjugate vaccine by Serum Institute of India.
a Individual participant data unavailable.

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# **Appendix 4** Risk of bias




Domains:
D1: Bias arising from the randomisation process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

**FIGURE 20** Assessment of RoB for included studies.

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# **Appendix 5** Heterogeneity and inconsistency assessments

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**TABLE 5** Summary of the statistical heterogeneity and incoherence for immunogenicity analyses shown in *Figure 2*

| Serotype | Time point | Number of study | Number and proportion of study providing direct evidence | | Number of participants providing direct evidence | Number of participants providing indirect evidence | Tau (τ) | $I^2$ (%) | *p*-value (Q of heterogeneity and inconsistency; df) | *p*-value (Q of heterogeneity; df) | *p*-value (Q of inconsistency; df) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **4** | Post prime | 28 | 9 | 47.9% | 2356 | 9258 | 0.089 | 86.8 (82.0–90.4) | 0.000 (197.440; 26) | 0.000 (196.733; 25) | 0.400 (0.707; 1) |
| **6B** | Post prime | 28 | 9 | 59.7% | 2356 | 9194 | 0.109 | 82.2 (75.0–87.3) | 0.000 (145.913; 26) | 0.000 (108.043; 25) | 0.000 (37.870; 1) |
| **9V** | Post prime | 28 | 9 | 48.0% | 2360 | 9241 | 0.078 | 83.8 (77.5–88.4) | 0.000 (160.708; 26) | 0.000 (158.678; 25) | 0.154 (2.030; 1) |
| **14** | Post prime | 28 | 9 | 48.6% | 2358 | 9186 | 0.069 | 71.1 (57.4–80.4) | 0.000 (89.983; 26) | 0.000 (83.435; 25) | 0.010 (6.548; 1) |
| **18C** | Post prime | 28 | 9 | 50.9% | 2358 | 9258 | 0.147 | 93.7 (91.9–95.1) | 0.000 (413.924; 26) | 0.000 (405.782; 25) | 0.004 (8.142; 1) |
| **19F** | Post prime | 28 | 9 | 51.8% | 2358 | 9235 | 0.199 | 96.2 (95.3–96.9) | 0.000 (679.122; 26) | 0.000 (675.147; 25) | 0.046 (3.975; 1) |
| **23F** | Post prime | 28 | 9 | 55.1% | 2358 | 9211 | 0.095 | 80.6 (72.5–86.3) | 0.000 (133.979; 26) | 0.000 (131.123; 25) | 0.091 (2.856; 1) |
| **1** | Post prime | 9 | 9 | 100% | 2357 | | 0.177 | 93.8 (90.4–96.1) | 0.000 (130.029; 8) | 0.000 (130.029; 8) | |
| **5** | Post prime | 9 | 9 | 100% | 2356 | | 0.193 | 95.1 (92.5–96.7) | 0.000 (161.837; 8) | 0.000 (161.837; 8) | |
| **7F** | Post prime | 9 | 9 | 100% | 2358 | | 0.056 | 63.6 (25.3–82.3) | 0.005 (21.980; 8) | 0.005 (21.980; 8) | |
| **3** | Post prime | 9 | 9 | 100% | 2354 | | 0.495 | 99.2 (99.0–99.4) | 0.000 (1006.362; 8) | 0.000 (1006.362; 8) | |
| **6A** | Post prime | 9 | 9 | 100% | 2354 | | 0.514 | 99.0 (98.8–99.2) | 0.000 (825.778; 8) | 0.000 (825.778; 8) | |
| **19A** | Post prime | 9 | 9 | 100% | 2356 | | 0.381 | 98.1 (97.5–98.6) | 0.000 (428.259; 8) | 0.000 (428.259; 8) | |
| **4** | Prior booster | 17 | 7 | 68.9% | 1816 | 4174 | 0.098 | 83.7 (74.8–89.4) | 0.000 (92.071; 15) | 0.000 (90.267; 14) | 0.179 (1.805; 1) |
| **6B** | Prior booster | 18 | 8 | 78.7% | 2220 | 4140 | 0.161 | 90.8 (86.8–93.6) | 0.000 (173.775; 16) | 0.000 (171.746; 15) | 0.154 (2.029; 1) |
| **9V** | Prior booster | 18 | 8 | 72.7% | 2218 | 4175 | 0.108 | 87.9 (82.2–91.8) | 0.000 (132.395; 16) | 0.000 (131.952; 15) | 0.506 (0.443; 1) |
| **14** | Prior booster | 18 | 8 | 69.3% | 2224 | 4178 | 0.082 | 70.1 (50.9–81.8) | 0.000 (53.432; 16) | 0.000 (53.136; 15) | 0.586 (0.296; 1) |
| **18C** | Prior booster | 17 | 7 | 65.6% | 1806 | 4177 | 0.089 | 82.0 (71.8–88.5) | 0.000 (83.259; 15) | 0.000 (68.689; 14) | 0.000 (14.571; 1) |
| **19F** | Prior booster | 18 | 8 | 82.0% | 2215 | 4151 | 0.12 | 83.2 (74.3–89.0) | 0.000 (95.125; 16) | 0.000 (69.247; 15) | 0.000 (25.878; 1) |
| **23F** | Prior booster | 18 | 8 | 76.9% | 2216 | 4170 | 0.115 | 82.8 (73.5–88.8) | 0.000 (92.759; 16) | 0.000 (92.450; 15) | 0.578 (0.309; 1) |
| **1** | Prior booster | 8 | 8 | 100.0% | 2228 | | 0.127 | 90.1 (83.0–94.3) | 0.000 (71.032; 7) | 0.000 (71.032) | |

**TABLE 5** Summary of the statistical heterogeneity and incoherence for immunogenicity analyses shown in *Figure 2* (*continued*)

| Serotype | Time point | Number of study | Number and proportion of study providing direct evidence | | Number of participants providing direct evidence | Number of participants providing indirect evidence | Tau (τ) | $I^2$ (%) | *p*-value (Q of heterogeneity and inconsistency; df) | *p*-value (Q of heterogeneity; df) | *p*-value (Q of inconsistency; df) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **5** | Prior booster | 8 | 8 | 100.0% | 2221 | | 0.077 | 77.2 (54.7–88.5) | 0.000 (30.664; 7) | 0.000 (30.664) | |
| **7F** | Prior booster | 8 | 8 | 100.0% | 2220 | | 0.083 | 79.4 (59.8–89.4) | 0.000 (33.968; 7) | 0.000 (33.968) | |
| **3** | Prior booster | 7 | 7 | 100.0% | 1813 | | 0.236 | 95.0 (91.8–96.9) | 0.000 (119.248; 6) | 0.000 (119.248) | |
| **6A** | Prior booster | 8 | 8 | 100.0% | 2213 | | 0.169 | 92.2 (87.0–95.3) | 0.000 (89.441; 7) | 0.000 (89.441) | |
| **19A** | Prior booster | 8 | 8 | 100.0% | 2219 | | 0.132 | 84.8 (71.9–91.8) | 0.000 (46.063; 7) | 0.000 (46.063) | |
| **4** | Post booster | 25 | 6 | 53.1% | 1706 | 8457 | 0.063 | 72.9 (59.3–81.9) | 0.000 (84.813; 23) | 0.000 (75.091; 22) | 0.002 (9.722; 1) |
| **6B** | Post booster | 26 | 7 | 60.0% | 2102 | 8434 | 0.11 | 86.5 (81.3–90.3) | 0.000 (178.002; 24) | 0.000 (176.999; 23) | 0.317 (1.003; 1) |
| **9V** | Post booster | 26 | 7 | 57.9% | 2101 | 8457 | 0.076 | 82.5 (75.1–87.7) | 0.000 (136.818; 24) | 0.000 (135.005; 23) | 0.178 (1.812; 1) |
| **14** | Post booster | 26 | 7 | 51.0% | 2100 | 8446 | 0.063 | 71.7 (57.8–81.1) | 0.000 (84.914; 24) | 0.000 (84.381; 23) | 0.466 (0.532; 1) |
| **18C** | Post booster | 25 | 6 | 54.0% | 1705 | 8453 | 0.074 | 79.6 (70.3–86.0) | 0.000 (112.643; 23) | 0.000 (112.118; 22) | 0.469 (0.525; 1) |
| **19F** | Post booster | 26 | 7 | 58.1% | 2102 | 8443 | 0.111 | 87.4 (82.6–90.8) | 0.000 (190.038; 24) | 0.000 (186.332; 23) | 0.054 (3.706; 1) |
| **23F** | Post booster | 26 | 7 | 64.3% | 2100 | 8437 | 0.08 | 76.4 (65.5–83.9) | 0.000 (101.839; 24) | 0.000 (101.839; 23) | 1.000 (0.000; 1) |
| **1** | Post booster | 7 | 7 | 100.0% | 2100 | | 0.048 | 54.6 (0.0–80.6) | 0.040 (13.216; 6) | 0.040 (13.216) | |
| **5** | Post booster | 7 | 7 | 100.0% | 2101 | | 0.092 | 83.4 (67.2–91.6) | 0.000 (36.074; 6) | 0.000 (36.074) | |
| **7F** | Post booster | 7 | 7 | 100.0% | 2100 | | 0.055 | 70.0 (34.2–86.3) | 0.003 (19.981; 6) | 0.003 (19.981) | |
| **3** | Post booster | 6 | 6 | 100.0% | 1701 | | 0.299 | 96.9 (95.2–98.0) | 0.000 (162.413; 5) | 0.000 (162.413) | |
| **6A** | Post booster | 7 | 7 | 100.0% | 2099 | | 0.232 | 94.2 (90.4–96.5) | 0.000 (103.568; 6) | 0.000 (103.568) | |
| **19A** | Post booster | 7 | 7 | 100.0% | 2100 | | 0.147 | 86.4 (74.0–92.8) | 0.000 (43.957; 6) | 0.000 (43.957) | |

df, degree of freedom; $I^2$, heterogeneity statistic; Q of heterogeneity, overall heterogeneity statistic; Q of heterogeneity and inconsistency, overall heterogeneity/inconsistency statistic; Q of inconsistency, overall inconsistency statistic; tau, square-root of between-study variance.

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**TABLE 6** Summary on assessment of statistical heterogeneity and incoherence for seroefficacy analysis shown in *Figure 3*

| Serotype | Number of study | Number and proportion of study providing direct evidence | | Number of participants providing direct evidence | Number of participants providing indirect evidence | tau | $I^2$ (%) | *p*-value (Q of heterogeneity and inconsistency; df) | *p*-value (Q of heterogeneity; df) | *p*-value (Q of inconsistency; df) |
|---|---|---|---|---|---|---|---|---|---|---|
| **4** | 15 | 6 | 89.0% | 1577 | 3531 | 0.383 | 23.7 (0–59.5) | 0.198 (17.036; 13) | 0.178 (16.286; 12) | 0.386 (0.750; 1) |
| **6B** | 15 | 6 | 91.6% | 1573 | 3466 | 0.249 | 74.4 (56.7–84.9) | 0.000 (50.756; 13) | 0.000 (48.136; 12) | 0.105 (2.621; 1) |
| **9V** | 15 | 6 | 90.7% | 1574 | 3518 | 0.309 | 43.0 (0–69.6) | 0.044 (22.801; 13) | 0.049 (21.065; 12) | 0.188 (1.736; 1) |
| **14** | 15 | 6 | 81.3% | 1578 | 3524 | 0.361 | 69.6 (47.4–82.5) | 0.000 (42.834; 13) | 0.000 (40.642; 12) | 0.139 (2.192; 1) |
| **18C** | 15 | 6 | 95.1% | 1568 | 3537 | 0.474 | 49.9 (7.4–72.9) | 0.017 (25.961; 13) | 0.017 (24.657; 12) | 0.254 (1.304; 1) |
| **19F** | 15 | 6 | 80.2% | 1569 | 3497 | 0.327 | 49.1 (5.7–72.5) | 0.020 (25.541; 13) | 0.104 (18.415; 12) | 0.008 (7.126; 1) |
| **23F** | 15 | 6 | 93.6% | 1570 | 3498 | 0.557 | 83.8 (74.3–89.9) | 0.000 (80.480; 13) | 0.000 (78.982; 12) | 0.221 (1.498; 1) |
| **1** | 6 | 6 | 100% | 1581 | | 0.403 | 42.7 (0–77.3) | 0.121 (8.724; 5) | 0.121 (8.724; 5) | |
| **5** | 6 | 6 | 100% | 1573 | | 0.975 | 82.2 (62.1–91.6) | 0.000 (28.031; 5) | 0.000 (28.031; 5) | |
| **7F** | 6 | 6 | 100% | 1575 | | 0.000 | 0 (0–74.6) | 0.537 (4.084; 5) | 0.537 (4.084; 5) | |

df, degree of freedom; $I^2$: heterogeneity statistic; tau, square-root of between-study variance; Q of heterogeneity, overall heterogeneity statistic; Q of heterogeneity and inconsistency, overall heterogeneity/inconsistency statistic; Q of inconsistency, overall inconsistency statistic.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 1.13 (0.95 to 1.33) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 1.29 (1.10 to 1.50) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 1.31 (1.12 to 1.54) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.81 (1.39 to 2.36) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.52 (1.32 to 1.76) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.94 (1.78 to 2.12) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 1.50 (1.30 to 1.71) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.38 (1.10 to 1.73) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 1.66 (1.42 to 1.94) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.50 (1.31 to 1.73) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | 1.14 (0.91 to 1.43) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | 1.67 (1.41 to 1.97) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.27 (1.02 to 1.59) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.60 (0.42 to 0.86) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.53 (0.36 to 0.77) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.76 (0.55 to 1.05) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | DTwP-Hib-HBV+OPV | 0.85 (0.72 to 1.00) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 1.07 (0.99 to 1.15) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV | 0.62 (0.50 to 0.78) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.73 (0.64 to 0.84) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.79 (0.64 to 0.98) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.76 (0.68 to 0.86) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 0.53 (0.36 to 0.78) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.81 (0.71 to 0.93) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | HBV-DTwP-Hib/OPV/Rotavirus | 0.75 (0.65 to 0.87) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.67 (0.58 to 0.76) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.78 (0.70 to 0.87) |
| 24 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.72 (0.57 to 0.91) |

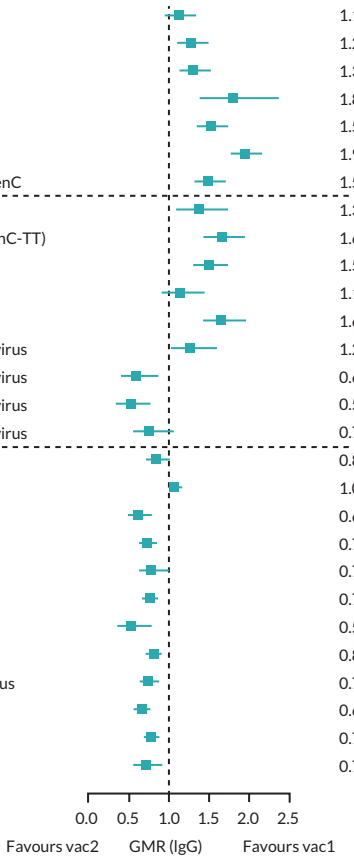



**FIGURE 21** Trial-level GMRs for serotype 4 post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available (e.g. study ID 11 and 23). Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.89 (0.66 to 1.20) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 1.60 (1.22 to 2.11) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 1.45 (1.19 to 1.77) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 2.25 (1.39 to 3.64) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.20 (0.94 to 1.55) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.80 (1.55 to 2.09) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 1.55 (1.28 to 1.88) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.18 (0.87 to 1.61) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 1.05 (0.82 to 1.33) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 0.61 (0.50 to 0.73) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | 1.20 (0.94 to 1.54) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | 1.35 (1.00 to 1.82) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.15 (0.84 to 1.57) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.71 (0.55 to 0.92) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.89 (0.73 to 1.09) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.43 (0.28 to 0.66) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | DTwP-Hib-HBV+OPV | 0.92 (0.72 to 1.19) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.98 (0.87 to 1.10) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV | 0.91 (0.70 to 1.17) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.64 (0.51 to 0.79) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 1.14 (0.86 to 1.52) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.89 (0.74 to 1.06) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 0.48 (0.29 to 0.80) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.79 (0.65 to 0.97) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | HBV-DTwP-Hib/OPV/Rotavirus | 1.24 (0.97 to 1.59) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.68 (0.53 to 0.86) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.93 (0.79 to 1.08) |
| 24 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.93 (0.61 to 1.41) |

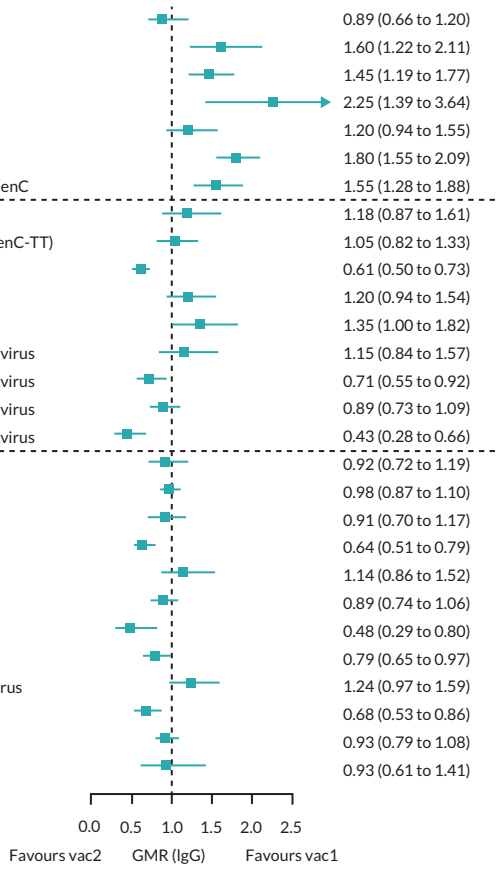



**FIGURE 22** Trial-level GMRs for serotype 6B post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available (e.g. study ID 11 and 23). Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 9V – post prime | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 1.24 (1.03 to 1.49) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 1.71 (1.44 to 2.04) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | | 1.47 (1.23 to 1.76) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 2.37 (1.78 to 3.16) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 1.47 (1.27 to 1.70) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 2.09 (1.91 to 2.29) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | | 1.85 (1.59 to 2.16) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.19 (0.96 to 1.48) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 1.57 (1.36 to 1.82) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 2.00 (1.72 to 2.33) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | | 1.19 (0.95 to 1.49) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | | 1.23 (1.00 to 1.52) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 1.55 (1.26 to 1.92) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.56 (0.41 to 0.75) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.88 (0.60 to 1.29) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.88 (0.61 to 1.28) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | DTwP-Hib-HBV + OPV | | 0.92 (0.79 to 1.08) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | | 0.98 (0.91 to 1.05) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV | | 0.67 (0.56 to 0.82) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.83 (0.73 to 0.94) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | | 0.89 (0.74 to 1.08) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | | 0.81 (0.74 to 0.90) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | | 0.62 (0.41 to 0.93) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | | 0.74 (0.64 to 0.86) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | HBV-DTwP-Hib/OPV/Rotavirus | | 0.87 (0.75 to 1.01) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | | 0.70 (0.61 to 0.80) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | | 0.77 (0.70 to 0.85) |
| 24 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | | 0.81 (0.66 to 0.99) |

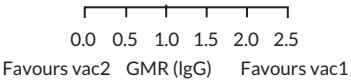



**FIGURE 23** Trial-level GMRs for serotype 9V post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available (e.g. study ID 11 and 23). Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.90 (0.70 to 1.16) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 1.55 (1.27 to 1.89) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 1.53 (1.27 to 1.83) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.80 (1.29 to 2.51) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.09 (0.95 to 1.26) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.59 )1.43 to 1.77) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 1.61 (1.34 to 1.94) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.11 (0.88 to 1.41) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 1.01 (0.85 to 1.20) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.36 (1.11 to 1.68) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | 0.73 (0.55 to 0.98) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | 1.12 (0.89 to 1.42) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.37 (1.02 to 1.84) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.73 (0.52 to 1.03) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.44 (1.04 to 1.99) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.48 (0.31 to 0.74) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | DTwP-Hib-HBV + OPV | 1.20 (0.93 to 1.55) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.89 (0.79 to 0.99) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV | 0.84 (0.67 to 1.06) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.87 (0.74 to 1.04) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.88 (0.67 to 1.16) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.83 (0.72 to 0.96) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 0.51 (0.32 to 0.84) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.82 (0.70 to 0.97) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | HBV-DTwP-Hib/OPV/Rotavirus | 0.92 (0.73 to 1.16) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.84 (0.71 to 1.00) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.91 (0.79 to 1.04) |
| 24 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.80 (0.60 to 1.08) |

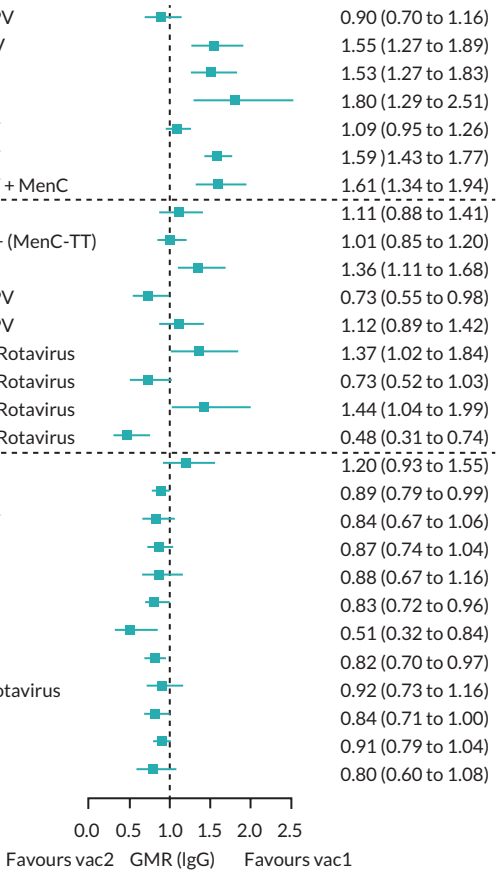



**FIGURE 24** Trial-level GMRs for serotype 14 post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available (e.g. study ID 11 and 23). Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age, and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.32 (0.26 to 0.39) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 0.69 (0.57 to 0.85) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 0.86 (0.70 to 1.06) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.93 (0.67 to 1.28) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.53 (1.29 to 1.82) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.48 (1.33 to 1.65) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 1.06 (0.91 to 1.23) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.05 (0.82 to 1.35) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 1.25 (1.05 to 1.50) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.69 (1.44 to 1.98) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | 0.88 (0.68 to 1.16) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | 0.37 (0.30 to 0.45) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.93 (0.72 to 1.20) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.50 (1.15 to 1.97) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.19 (0.92 to 1.56) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.49 (1.07 to 2.08) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | DTwP-Hib-HBV + OPV | 1.02 (0.85 to 1.22) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 1.02 (0.93 to 1.11) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV | 0.78 (0.63 to 0.97) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.87 (0.76 to 1.00) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.98 (0.81 to 1.19) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.86 (0.77 to 0.97) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 1.10 (0.76 to 1.60) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.72 (0.62 to 0.84) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | HBV-DTwP-Hib/OPV/Rotavirus | 0.90 (0.76 to 1.07) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.75 (0.66 to 0.86) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.95 (0.84 to 1.07) |
| 24 | *PCV13 vs.a PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.60 (0.49 to 0.77) |

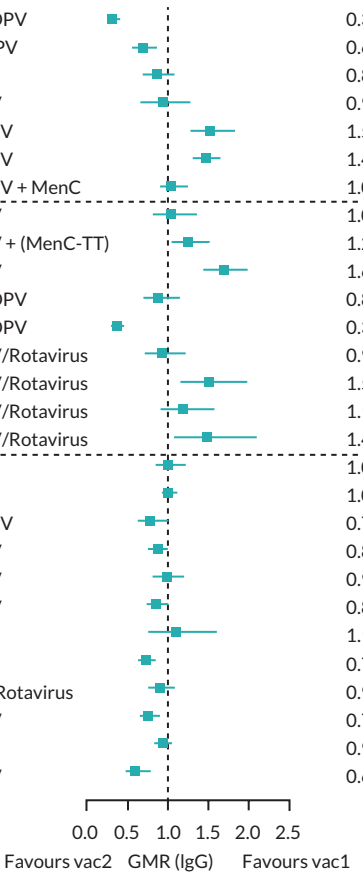



**FIGURE 25** Trial-level GMRs for serotype 18C post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available (e.g. study ID 11 and 23). Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.45 (0.37 to 0.54) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 0.44 (0.36 to 0.53) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 0.37 (0.31 to 0.43) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.22 (0.88 to 1.69) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.50 (1.27 to 1.77) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.83 (1.65 to 2.03) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 0.57 (0.50 to 0.65) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.79 (0.62 to 1.00) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 0.81 (0.69 to 0.96) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 0.80 (0.67 to 0.96) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | 1.25 (1.00 to 1.55) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | 0.60 (0.49 to 0.72) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.82 (0.62 to 1.09) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.01 (0.81 to 1.27) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.64 (1.26 to 2.14) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.90 (1.39 to 2.61) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | DTwP-Hib-HBV + OPV | 0.91 (0.75 to 1.10) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 1.30 (1.19 to 1.42) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV | 0.75 (0.60 to 0.94) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.59 (0.51 to 0.69) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.96 (0.74 to 1.24) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.96 (0.84 to 1.10) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 0.80 (0.50 to 1.30) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.87 (0.71 to 1.07) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | HBV-DTwP-Hib/OPV/Rotavirus | 0.74 (0.61 to 0.90) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.82 (0.71 to 0.94) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 1.29 (1.07 to 1.55) |
| 24 | *PCV13 vs.a PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.82 (0.65 to 1.04) |

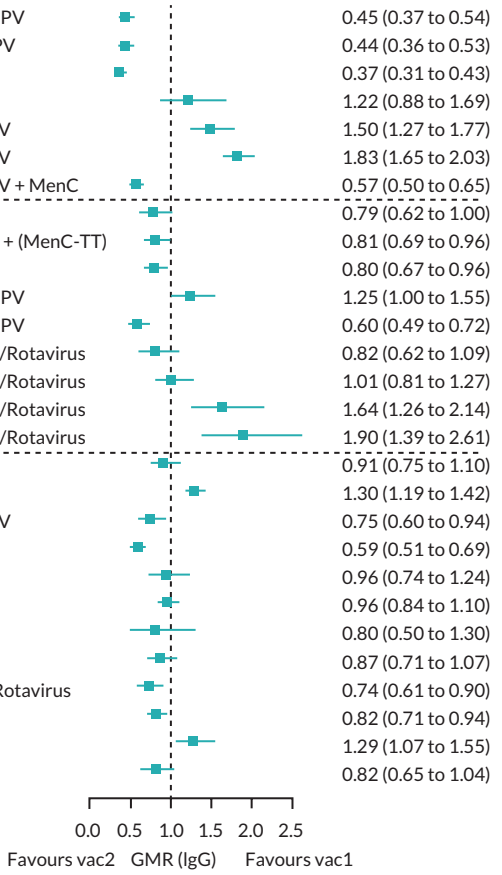



**FIGURE 26** Trial-level GMRs for serotype 19F post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available (e.g. study ID 11 and 23). Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 1.01 (0.74 to 1.36) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 1.88 (1.50 to 2.34) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 1.95 (1.57 to 2.43) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 2.45 (1.66 to 3.61) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 2.35 (1.89 to 2.93) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 2.60 (2.26 to 2.99) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 2.12 (1.73 to 2.61) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 2.25 (1.66 to 3.04) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 2.24 (1.81 to 2.78) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.28 (1.06 to 1.54) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | 1.60 (1.22 to 2.11) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | 2.39 (1.83 to 3.14) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.70 (1.28 to 2.26) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.82 (0.63 to 1.06) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.00 (0.73 to 1.38) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.00 (0.68 to 1.47) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | DTwP-Hib-HBV + OPV | 0.95 (0.77 to 1.17) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.72 (0.65 to 0.81) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV | 0.59 (0.46 to 0.76) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.88 (0.74 to 1.06) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 1.04 (0.81 to 1.35) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.70 (0.60 to 0.82) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 0.82 (0.51 to 1.32) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.81 (0.67 to 0.98) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | HBV-DTwP-Hib/OPV/Rotavirus | 0.99 (0.78 to 1.24) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.69 (0.58 to 0.82) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.90 (0.79 to 1.04) |
| 24 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.71 (0.55 to 0.92) |

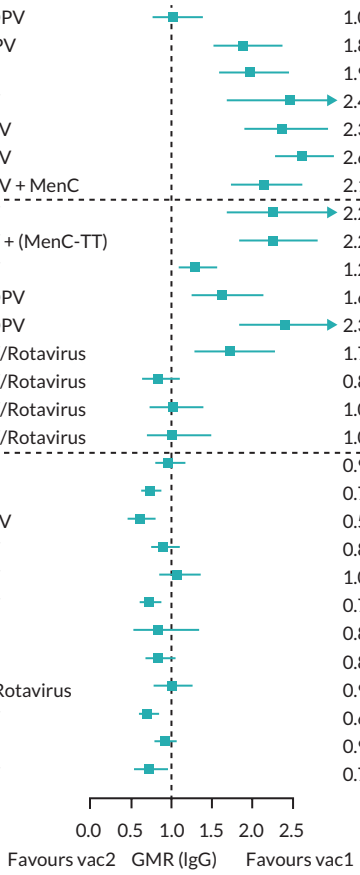



**FIGURE 27** Trial-level GMRs for serotype 23F post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available (e.g. study ID 11 and 23). Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 1 – post prime | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.49 (1.20 to 1.86) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 1.62 (1.39 to 1.88) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 2.21 (1.89 to 2.57) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | | 1.15 (0.93 to 1.42) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | | 1.63 (1.37 to 1.93) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 1.81 (1.47 to 2.24) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.37 (0.27 to 0.51) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.82 (0.61 to 1.11) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 1.04 (0.81 to 1.34) |

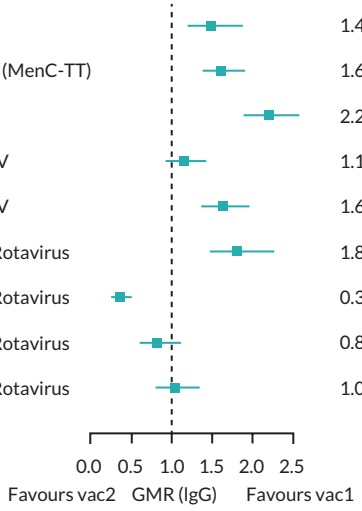



**FIGURE 28** Trial-level GMRs for serotype 1 post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 5 – post prime | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.23 (0.97 to 1.56) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 1.30 (1.12 to 1.51) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 1.88 (1.66 to 2.13) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | | 1.01 (0.85 to 1.20) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | | 1.32 (1.10 to 1.59) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 2.49 (2.01 to 3.08) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.36 (0.25 to 0.50) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.53 (0.37 to 0.75) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.94 (0.71 to 1.24) |

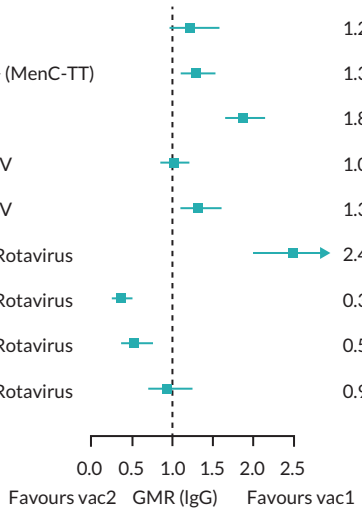



**FIGURE 29** Trial-level GMRs for serotype 5 post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.37 (1.12 to 1.67) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 1.44 (1.26 to 1.64) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.60 (1.42 to 1.82) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | 1.29 (1.08 to 1.55) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | 1.29 (1.09 to 1.53) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.72 (1.41 to 2.10) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.75 (0.52 to 1.09) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.18 (0.83 to 1.67) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.37 (1.02 to 1.84) |

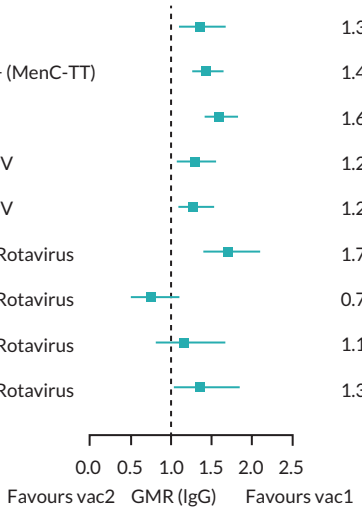



**FIGURE 30** Trial-level GMRs for serotype 7F post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitantvaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is notalways available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 4 | *PCV13 vs.. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 43.33 (33.78 to 55.58) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 44.21 (38.12 to 51.27) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 15.16 (13.17 to 17.46) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | 2.19 (1.72 to 2.78) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | 90.36 (72.44 to 112.73) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | 5.60 (4.55 to 6.90) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 11.99 (9.53 to 15.10) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 7.50 (5.88 to 9.57) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 4.84 (3.92 to 5.99) |

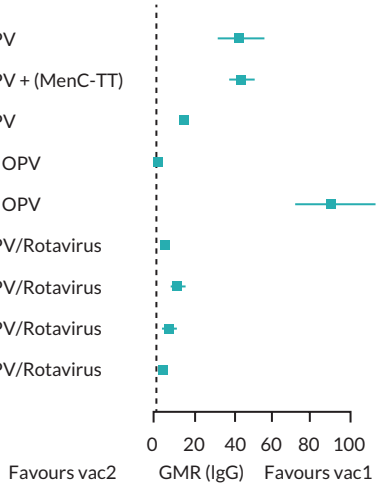



**FIGURE 31** Trial-level GMRs for serotype 3 post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 6A – post prime | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 18.67 (14.07 to 24.76) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 17.14 (13.99 to 20.99) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 6.19 (5.21 to 7.36) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | | 3.54 (2.73 to 4.60) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | | 23.17 (18.75 to 28.65) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 12.47 (9.76 to 15.94) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 1.18 (0.97 to 1.45) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 10.77 (7.74 to 14.96) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 1.00 (0.78 to 1.28) |

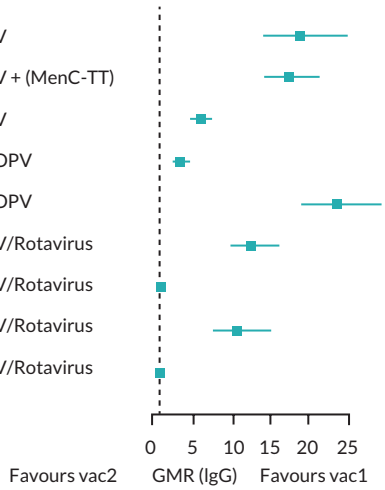



**FIGURE 32** Trial-level GMRs for serotype 6A post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 19A – post prime | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 16.30 (12.77 to 20.80) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 14.23 (11.70 to 17.32) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 6.93 (5.81 to 8.26) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | DTPw-HBV-Hib-TT + OPV | | 4.78 (3.78 to 6.04) |
| 25 | *PCV13 vs. PCV10* | Africa | 2–3–4 months | DTPw-HBV-Hib-TT + OPV | | 22.91 (17.79 to 29.50) |
| 26 | *PCV13 vs. PCV10* | Oceania | 2–4–6 months | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 3.59 (2.78 to 4.65) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 2.50 (1.90 to 3.29) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 11.04 (8.23 to 14.80) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 1.30 (0.99 to 1.71) |

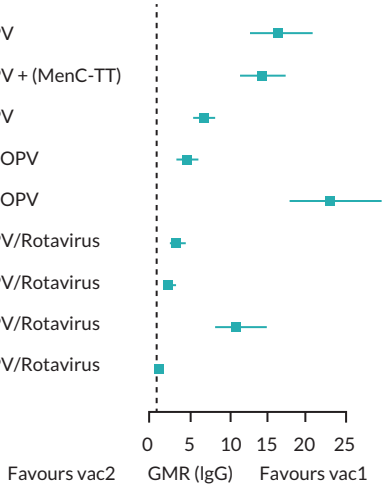



**FIGURE 33** Trial-level GMRs for serotype 19A post-primary vaccination series. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 4 – prior booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 0.60 (0.43 to 0.84) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 0.91 (0.68 to 1.20) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | NA | | 1.02 (0.74 to 1.42) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.92 (0.79 to 1.08) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 1.08 (0.94 to 1.25) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | | 1.14 (0.94 to 1.38) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.68 (0.54 to 0.84) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 0.83 (0.71 to 0.96) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 1.04 (0.90 to 1.20) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | Measles, PPV | | 0.91 (0.74 to 1.12) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 0.29 (0.21 to 0.40) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 0.48 (0.34 to 0.67) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 0.52 (0.38 to 0.71) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | | 0.68 (0.59 to 0.80) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.81 (0.70 to 0.92) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | | 0.61 (0.46 to 0.80) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | | 0.68 (0.58 to 0.79) |

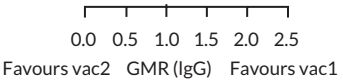



**FIGURE 34** Trial-level GMRs for serotype 4 pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 6B – prior booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 0.55 (0.32 to 0.95) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 1.01 (0.59 to 1.72) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | NA | | 0.84 (0.56 to 1.25) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.41 (0.33 to 0.51) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.59 (0.48 to 0.72) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | | 0.67 (0.52 to 0.85) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.57 (0.44 to 0.74) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 0.38 (0.31 to 0.46) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 0.39 (0.33 to 0.45) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | Measles, PPV | | 0.78 (0.62 to 0.99) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 0.18 (0.13 to 0.24) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 0.25 (0.18 to 0.35) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 0.23 (0.18 to 0.31) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 0.80 (0.68 to 0.95) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | | 0.92 (0.76 to 1.12) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.92 (0.79 to 1.07) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | | 1.35 (0.86 to 2.12) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | | 0.77 (0.64 to 0.91) |

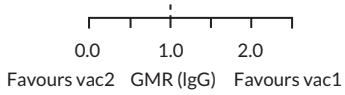



**FIGURE 35** Trial-level GMRs for serotype 6B pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

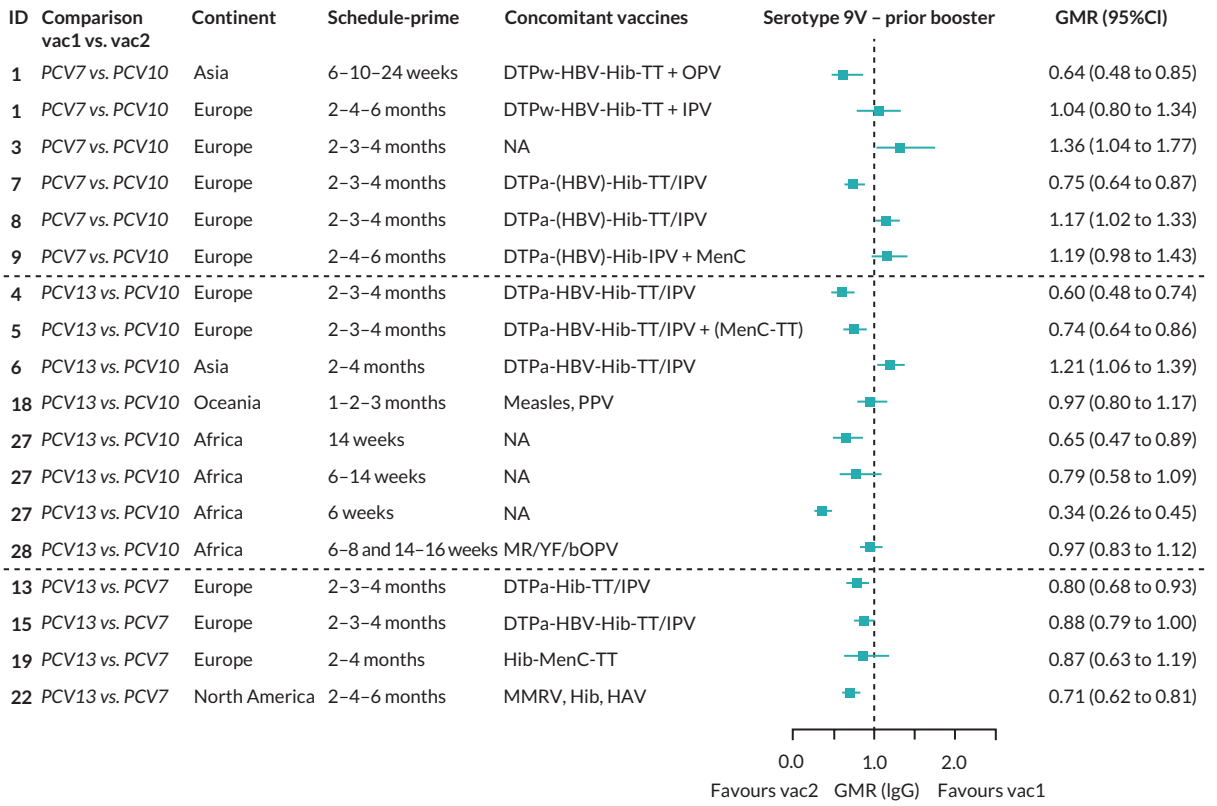



**FIGURE 36** Trial-level GMRs for serotype 9V pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

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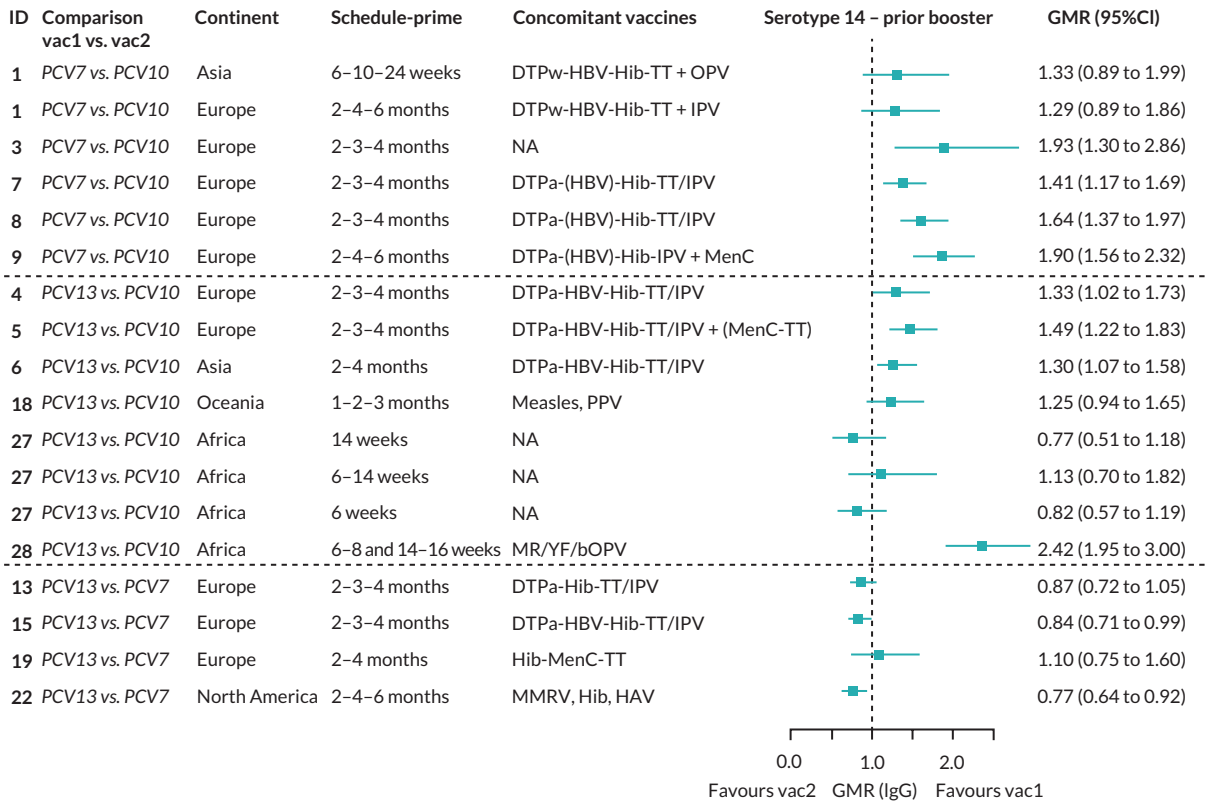



**FIGURE 37** Trial-level GMRs for serotype 14 pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

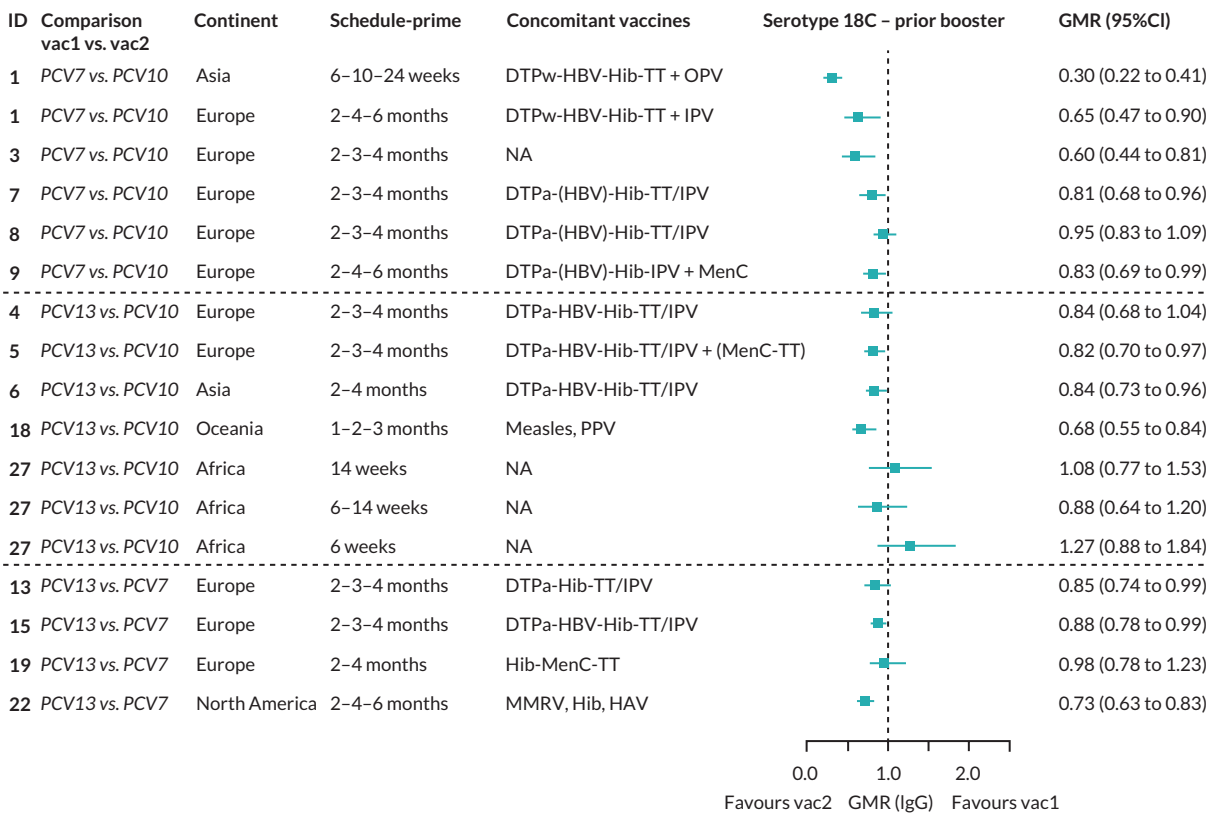



**FIGURE 38** Trial-level GMRs for serotype 18C pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 19F – prior booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 0.11 (0.07 to 0.19) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 0.32 (0.19 to 0.56) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | NA | | 0.43 (0.26 to 0.71) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.35 (0.28 to 0.45) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.47 (0.38 to 0.59) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | | 0.25 (0.19 to 0.33) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.49 (0.37 to 0.65) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 0.45 (0.37 to 0.54) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 0.55 (0.48 to 0.62) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | Measles, PPV | | 0.75 (0.60 to 0.95) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 0.88 (0.64 to 1.21) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 0.83 (0.57 to 1.22) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 1.10 (0.74 to 1.63) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 0.57 (0.48 to 0.69) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | | 0.92 (0.71 to 1.19) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.14 (0.96 to 1.35) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | | 1.33 (0.80 to 2.23) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–a6 months | MMRV, Hib, HAV | | 1.11 (0.95 to 1.31) |

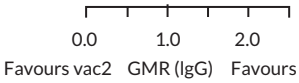



**FIGURE 39** Trial-level GMRs for serotype 19F pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

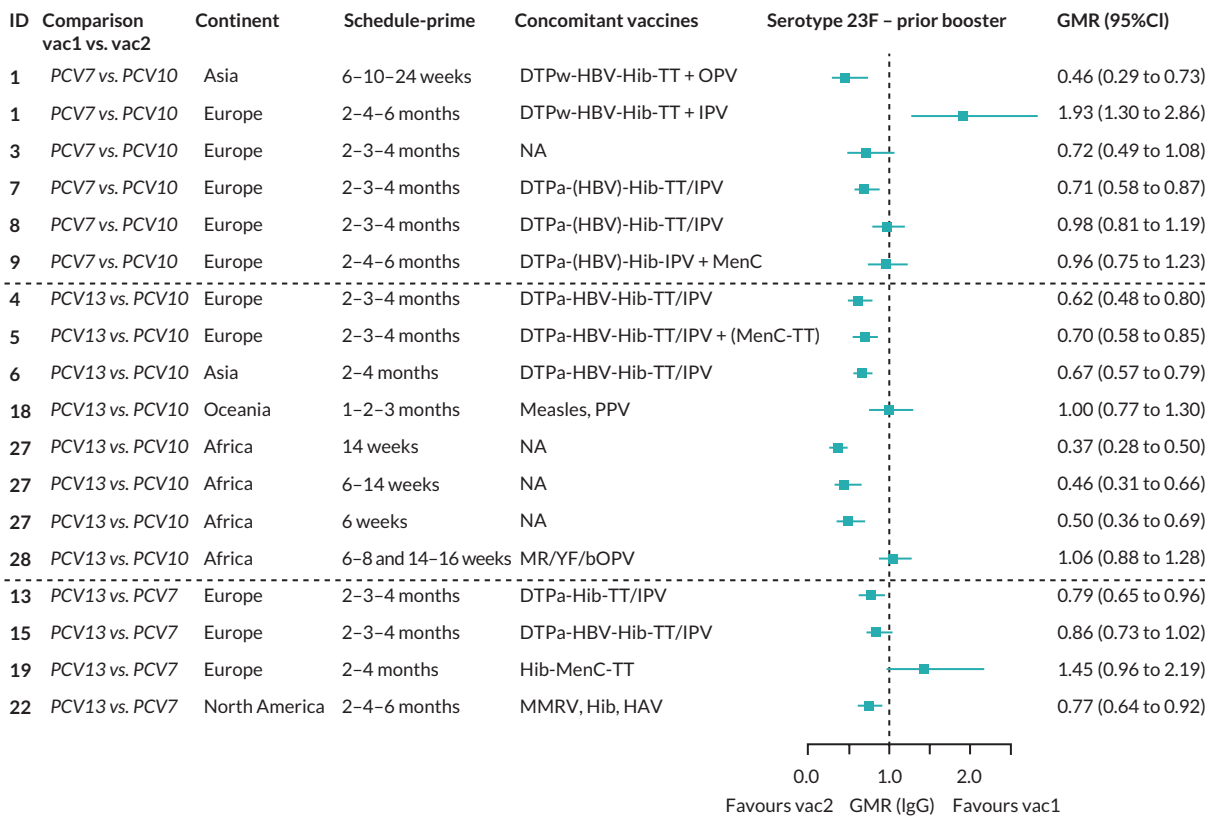



**FIGURE 40** Trial-level GMRs for serotype 23F pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

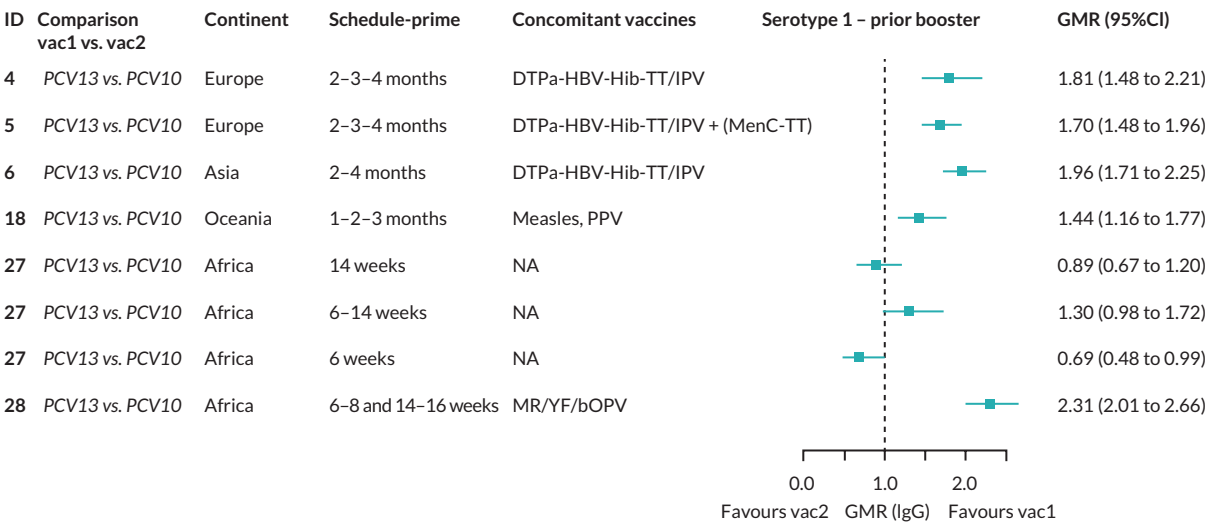



**FIGURE 41** Trial-level GMRs for serotype 1 pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 5 – prior booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.51 (1.22 to 1.87) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 1.62 (1.40 to 1.87) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 1.58 (1.40 to 1.79) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | Measles, PPV | | 1.26 (1.04 to 1.53) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 1.32 (0.95 to 1.84) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 1.23 (0.90 to 1.66) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 0.61 (0.43 to 0.87) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 1.50 (1.30 to 1.73) |

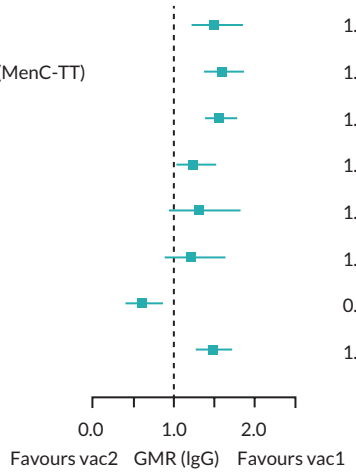



**FIGURE 42** Trial-level GMRs for serotype 5 pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 7F – prior booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.39 (1.15 to 1.68) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 1.30 (1.14 to 1.50) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 1.29 (1.13 to 1.47) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | Measles, PPV | | 1.35 (1.10 to 1.65) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 1.10 (0.79 to 1.53) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 1.18 (0.85 to 1.65) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 0.57 (0.40 to 0.80) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 1.68 (1.44 to 1.95) |

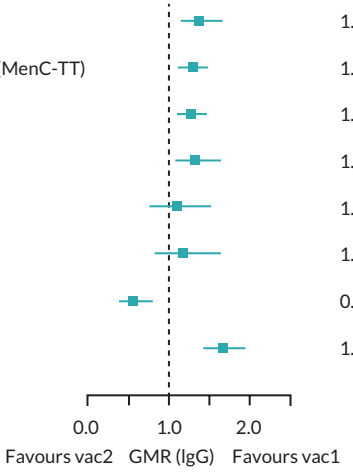



**FIGURE 43** Trial-level GMRs for serotype 7F pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

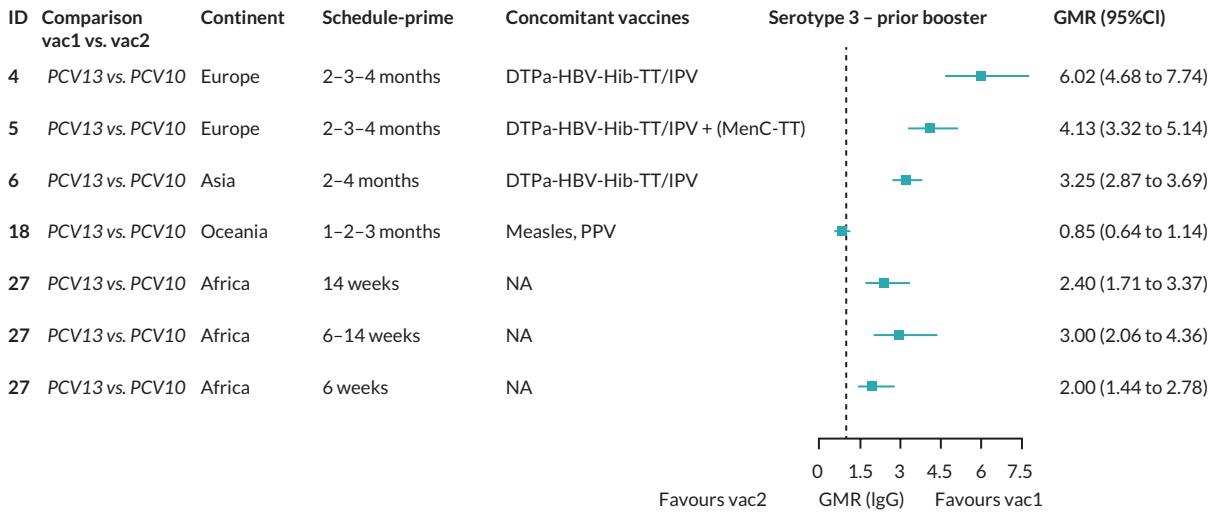



**FIGURE 44** Trial-level GMRs for serotype 3 pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

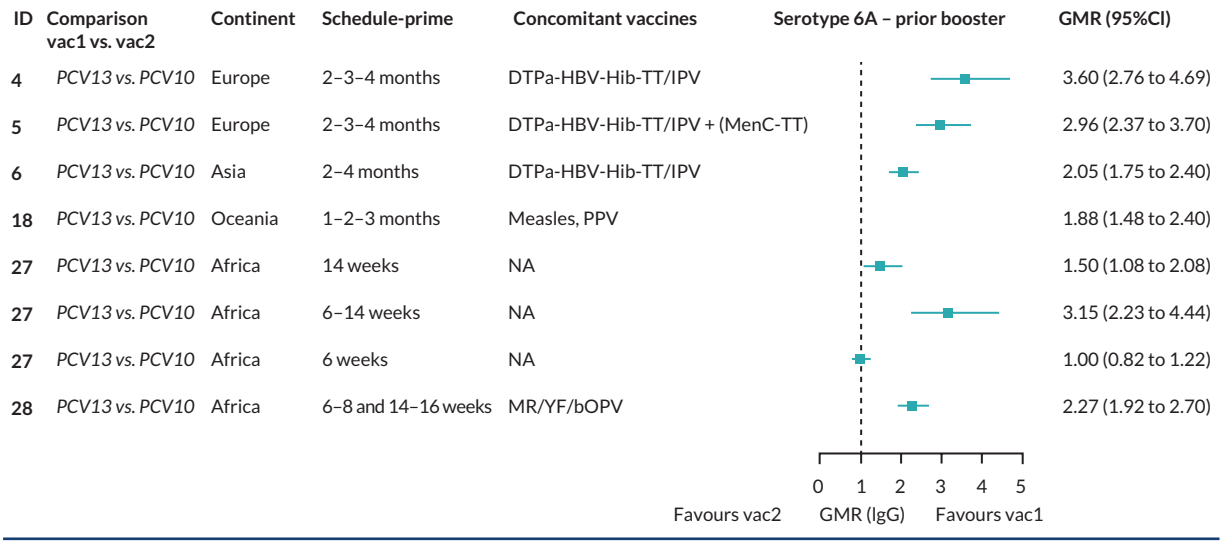



**FIGURE 45** Trial-level GMRs for serotype 6A pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 4 | *PCV13 vs.. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 3.21 (2.34 to 4.40) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 2.25 (1.79 to 2.83) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.89 (1.63 to 2.19) |
| 18 | *PCV13 vs. PCV10* | Oceania | 1–2–3 months | Measles, PPV | 1.43 (1.11 to 1.84) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | 2.00 (1.45 to 2.77) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | 3.46 (2.56 to 4.68) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | > 2.08 (0.48 to 8.91) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | 1.32 (1.09 to 1.61) |

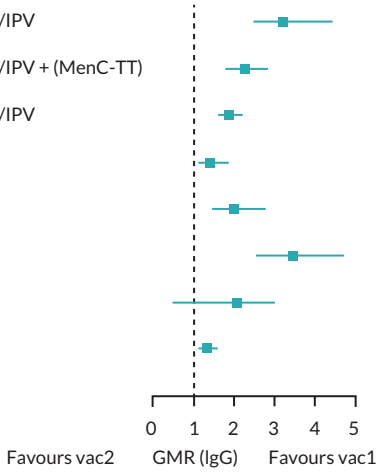



**FIGURE 46** Trial-level GMRs for serotype 19A pre booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.89 (0.65 to 1.21) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 1.58 (1.21 to 2.06) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 2.11 (1.73 to 2.57) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.25 (1.08 to 1.46) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.60 (1.41 to 1.81) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | 1.36 (1.17 to 1.65) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.09 (0.91 to 1.32) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 0.97 (0.84 to 1.11) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.12 (0.96 to 1.31) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | 1.36 (1.02 to 1.83) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | 0.84 (0.64 to 1.11) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | 1.00 (0.75 to 1.33) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | NA | 0.90 (0.75 to 1.08) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.99 (0.90 to 1.08) |
| 12 | *PCV13 vs. PCV7* | Europe | 3–5 months | DTPa-HBV-Hib-TT/IPV | 0.67 (0.58 to 0.78) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | 0.83 (0.70 to 0.98) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.64 (0.49 to 0.83) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.83 (0.71 to 0.97) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.82 (0.63 to 1.07) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMR | 0.92 (0.80 to 1.05) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | 0.61 (0.41 to 0.91) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.92 (0.76 to 1.13) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | DTwP-Hib, OPV | 0.91 (0.75 to 1.10) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | 0.69 (0.59 to 0.81) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.85 (0.75 to 0.96) |

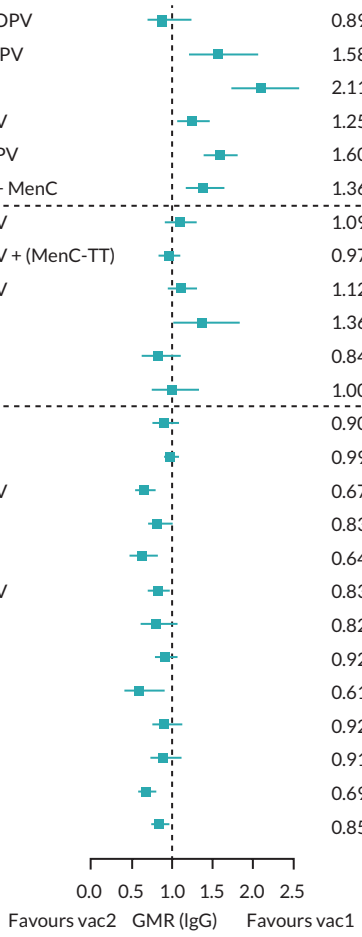



**FIGURE 47** Trial-level GMRs for serotype 4 post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 1.31 (0.92 to 1.87) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 2.68 (1.79 to 4.00) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 2.45 (1.97 to 3.06) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.72 (1.41 to 2.08) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.32 (1.12 to 1.56) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | 2.26 (1.89 to 2.71) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.38 (1.11 to 1.72) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 1.52 (1.28 to 1.80) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.54 (1.27 to 1.87) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | 0.85 (0.59 to 1.22) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | 1.60 (1.18 to 2.15) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | 0.48 (0.34 to 0.68) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | 3.13 (2.65 to 3.70) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | NA | 1.06 (0.86 to 1.30) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.91 (0.82 to 1.00) |
| 12 | *PCV13 vs. PCV7* | Europe | 3–5 months | DTPa-HBV-Hib-TT/IPV | 0.95 (0.79 to 1.14) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | 0.91 (0.76 to 1.10) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 1.03 (0.78 to 1.36) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.94 (0.79 to 1.11) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 1.12 (0.85 to 1.47) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMR | 1.07 (0.93 to 1.22) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | 1.10 (0.64 to 1.90) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 1.21 (0.97 to 1.50) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | DTwP-Hib, OPV | 1.13 (0.89 to 1.43) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | 0.73 (0.61 to 0.88) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.94 (0.81 to 1.08) |

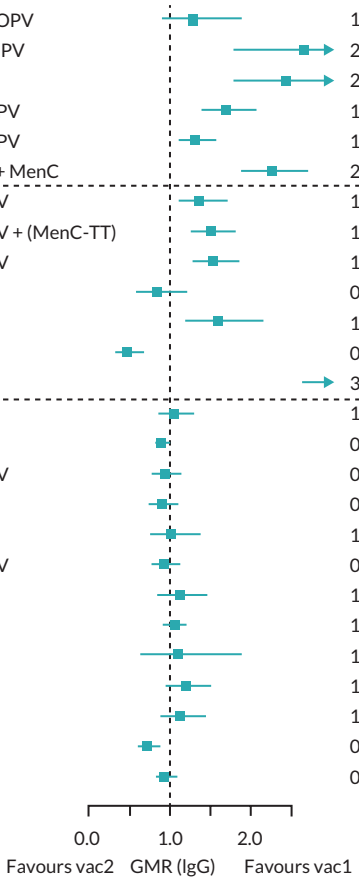



**FIGURE 48** Trial-level GMRs for serotype 6B post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 1.37 (1.03 to 1.83) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 2.86 (2.26 to 3.62) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 2.53 (2.12 to 3.01) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.47 (1.28 to 1.68) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.05 (0.92 to 1.20) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | 1.91 (1.63 to 2.24) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.26 (1.04 to 1.52) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 1.57 (1.37 to 1.80) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 1.57 (1.36 to 1.80) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | 1.53 (1.21 to 1.94) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | 1.33 (1.00 to 1.78) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | 1.47 (1.11 to 1.95) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | 1.58 (1.36 to 1.83) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | NA | 0.91 (0.77 to 1.07) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.94 (0.87 to 1.02) |
| 12 | *PCV13 vs. PCV7* | Europe | 3–5 months | DTPa-HBV-Hib-TT/IPV | 0.73 (0.64 to 0.84) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | 0.79 (0.68 to 0.92) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.83 (0.65 to 1.06) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.83 (0.73 to 0.94) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.99 (0.79 to 1.23) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMR | 0.99 (0.88 to 1.11) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | 0.78 (0.52 to 1.16) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.81 (0.67 to 0.97) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | DTwP-Hib, OPV | 1.12 (0.94 to 1.34) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | 0.72 (0.62 to 0.84) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.80 (0.71 to 0.90) |

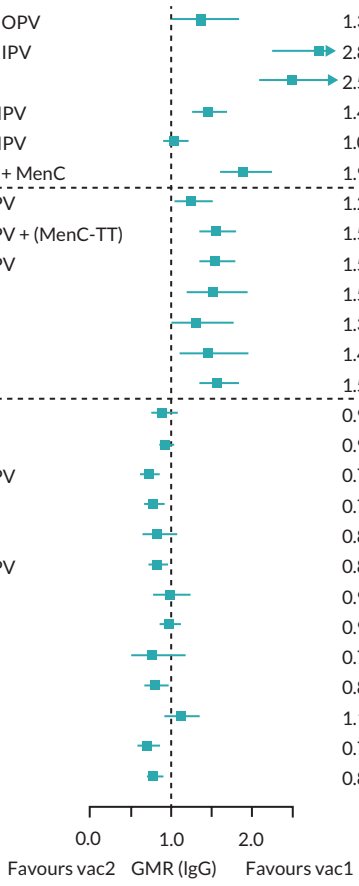



**FIGURE 49** Trial-level GMRs for serotype 9V post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 14 – post booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 1.61 (1.18 to 2.20) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 2.35 (1.74 to 3.18) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | | 2.71 (2.26 to 3.24) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 1.56 (1.33 to 1.83) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 1.24 (1.08 to 1.43) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | | 1.94 (1.62 to 2.32) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.73 (1.39 to 2.16) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 1.72 (1.47 to 2.02) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 1.31 (1.11 to 1.54) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 1.11 (0.79 to 1.56) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 1.76 (1.18 to 2.62) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 1.21 (0.76 to 1.93) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 1.82 (1.47 to 2.27) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | NA | | 0.97 (0.79 to 1.19) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | | 0.89 (0.81 to 0.98) |
| 12 | *PCV13 vs. PCV7* | Europe | 3–5 months | DTPa-HBV-Hib-TT/IPV | | 0.86 (0.74 to 1.00) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | | 0.89 (0.75 to 1.06) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | | 0.69 (0.51 to 0.92) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.77 (0.66 to 0.90) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | | 0.72 (0.57 to 0.92) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMR | | 0.85 (0.75 to 0.95) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | | 0.89 (0.61 to 1.30) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | | 0.95 (0.80 to 1.12) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | DTwP-Hib, OPV | | 1.06 (0.86 to 1.31) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | | 0.74 (0.62 to 0.88) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | | 0.88 (0.79 to 0.98) |

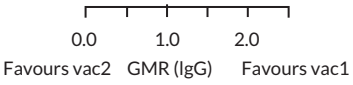



**FIGURE 50** Trial-level GMRs for serotype 14 post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | GMR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.31 (0.23 to 0.41) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 0.90 (0.67 to 1.19) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | 1.09 (0.89 to 1.33) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 0.95 (0.81 to 1.10) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.11 (0.97 to 1.27) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | 0.95 (0.81 to 1.11) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.85 (0.71 to 1.03) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 0.79 (0.68 to 0.92) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 0.84 (0.72 to 0.96) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | 1.10 (0.85 to 1.43) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | 0.71 (0.54 to 0.93) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | 0.90 (0.70 to 1.14) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | NA | 0.88 (0.74 to 1.03) |
| 11 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.99 (0.90 to 1.09) |
| 12 | *PCV13 vs. PCV7* | Europe | 3–5 months | DTPa-HBV-Hib-TT/IPV | 0.67 (0.58 to 0.77) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | 0.81 (0.68 to 0.95) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.76 (0.58 to 1.00) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.83 (0.72 to 0.96) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | 0.94 (0.74 to 1.20) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMR | 0.94 (0.82 to 1.07) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | 0.71 (0.52 to 0.98) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | 0.81 (0.67 to 0.99) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | DTwP-Hib, OPV | 0.87 (0.71 to 1.07) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | 0.68 (0.58 to 0.80) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | 0.99 (0.88 to 1.11) |

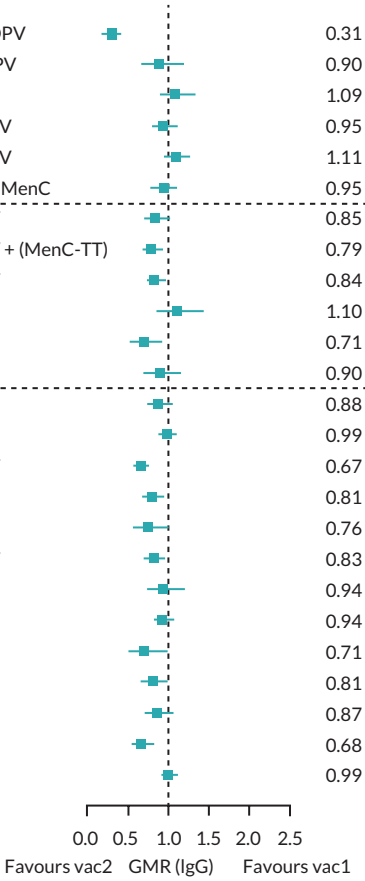



**FIGURE 51** Trial-level GMRs for serotype 18C post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 19F – post booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 0.31 (0.23 to 0.43) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 0.46 (0.34 to 0.62) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | | 0.29 (0.23 to 0.36) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.44 (0.37 to 0.51) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.84 (0.72 to 0.98) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | | 0.51 (0.44 to 0.60) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.97 (0.79 to 1.19) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 0.77 (0.67 to 0.89) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 0.72 (0.62 to 0.84) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 2.02 (1.32 to 3.11) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 1.16 (0.88 to 1.54) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 1.36 (0.90 to 2.06) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 0.87 (0.71 to 1.05) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | NA | | 1.49 (1.20 to 1.86) |
| 11 | *PCV13 vs. PCV7* | Asia | 2.–4–6 months | NA | | 2.07 (1.87 to 2.29) |
| 12 | *PCV13 vs. PCV7* | Europe | 3–5 months | DTPa-HBV-Hib-TT/IPV | | 1.10 (0.91 to 1.32) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | | 1.23 (0.98 to 1.54) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | | 1.09 (0.83 to 1.42) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.26 (1.06 to 1.50) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | | 1.42 (1.10 to 1.84) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMR | | 1.60 (1.37 to 1.86) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | | 1.56 (0.91 to 2.65) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | | 1.78 (1.42 to 2.23) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | DTwP-Hib, OPV | | 1.48 (1.19 to 1.84) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | | 1.20 (1.01 to 1.42) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | | 1.56 (1.38.1.77) |

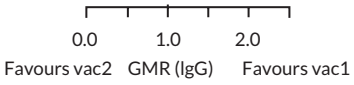



**FIGURE 52** Trial-level GMRs for serotype 19F post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 23F – post booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 1.09 (0.69 to 1.71) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 3.26 (2.18 to 4.89) |
| 2 | *PCV7 vs. PCV10* | Asia | 2–4–6 months | Hib-TT | | 3.97 (3.08 to 5.11) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 2.14 (1.76 to 2.61) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 1.72 (1.44 to 2.06) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-IPV + MenC | | 3.19 (2.61 to 3.90) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.87 (1.51 to 2.31) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 2.20 (1.86 to 2.59) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 1.73 (1.45 to 2.05) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 1.09 (0.80 to 1.48) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 1.75 (1.33 to 2.32) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 1.15 (0.81 to 1.63) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 2.30 (1.92 to 2.76) |
| 10 | *PCV13 vs. PCV7* | Asia | 6–10–14 weeks | NA | | 0.81 (0.67 to 0.99) |
| 11 | *PCV13 vs. PCV7* | Asia | 2.–4–6 months | NA | | 0.74 (0.67 to 0.83) |
| 12 | *PCV13 vs. PCV7* | Europe | 3–5 months | DTPa-HBV-Hib-TT/IPV | | 0.70 (0.59 to 0.83) |
| 13 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-Hib-TT/IPV | | 0.77 (0.64 to 0.94) |
| 14 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | | 0.69 (0.52 to 0.92) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.80 (0.66 to 0.96) |
| 16 | *PCV13 vs. PCV7* | Asia | 2–4–6 months | NA | | 1.09 (0.83 to 1.45) |
| 17 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMR | | 0.75 (0.64 to 0.87) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | Hib-MenC-TT | | 0.64 (0.46 to 0.90) |
| 20 | *PCV13 vs. PCV7* | Asia | enr 3–6 m, 4–8 w int | DTPa | | 0.83 (0.68 to 1.03) |
| 21 | *PCV13 vs. PCV7* | South America | 2–4–6 months | DTwP-Hib, OPV | | 0.86 (0.69 to 1.07) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | MMRV, Hib, HAV | | 0.65 (0.54 to 0.77) |
| 23 | *PCV13 vs. PCV7* | Asia | 3–4–5 months | NA | | 0.94 (0.80 to 1.09) |

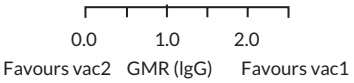



**FIGURE 53** Trial-level GMRs for serotype 23F post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 1 – post booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.55 (1.28 to 1.89) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 1.74 (1.51 to 2.00) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 1.73 (1.48 to 2.03) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 2.32 (1.74 to 3.09) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 1.25 (0.93 to 1.68) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 1.86 (1.35 to 2.56) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 2.03 (1.72 to 2.38) |

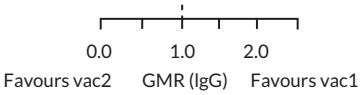



**FIGURE 54** Trial-level GMRs for serotype 1 post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 5 – post booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 2.19 (1.80 to 2.68) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 2.30 (1.99 to 2.65) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 2.52 (2.21 to 2.88) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 1.38 (1.05 to 1.83) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 1.63 (1.24 to 2.15) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 1.19 (0.84 to 1.68) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 2.55 (2.23 to 2.92) |

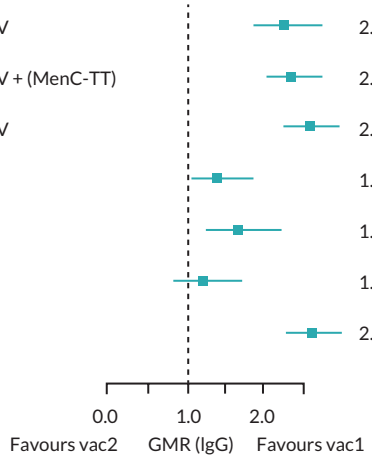



**FIGURE 55** Trial-level GMRs for serotype 5 post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 7F – post booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.57 (1.33–1.85) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 1.46 (1.29–1.66) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 1.80 (1.57–2.05) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 1.34 (1.09–1.65) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 2.00 (1.58–2.53) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 1.78 (1.39–2.28) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 2.00 (1.76–2.29) |

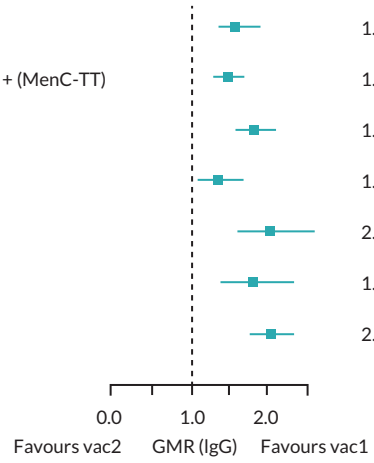



**FIGURE 56** Trial-level GMRs for serotype 7F post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 3 – post booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 28.12 (21.95–36.03) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 22.16 (17.76–27.66) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 7.16 (6.14–8.36) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 5.00 (3.78–6.62) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 7.34 (5.45–9.89) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 8.34 (6.00–11.59) |

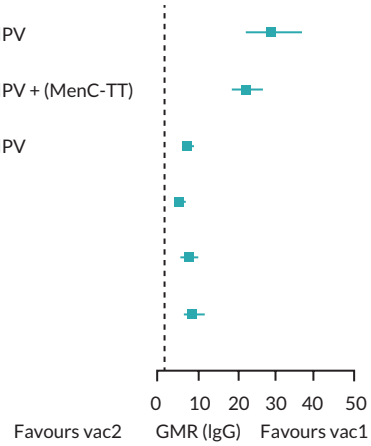



**FIGURE 57** Trial-level GMRs for serotype 3 post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; N/A, not applicable.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Concomitant vaccines | Serotype 6A – post booster | GMR (95%CI) |
|---|---|---|---|---|---|---|
| 4 | *PCV13 vs.. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 8.07 (6.13 to 10.62) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 10.30 (8.41 to 12.61) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 6.33 (5.21 to 7.70) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | NA | | 21.04 (14.86 to 29.78) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | NA | | 24.32 (16.95 to 34.90) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | NA | | 23.61 (16.53 to 33.72) |
| 28 | *PCV13 vs. PCV10* | Africa | 6–8 and 14–16 weeks | MR/YF/bOPV | | 18.24 (14.62 to 22.75) |

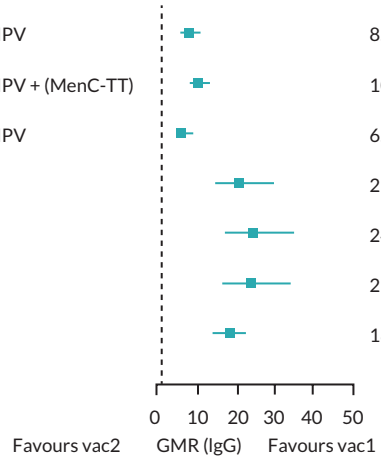



**FIGURE 58** Trial-level GMRs for serotype 6A post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

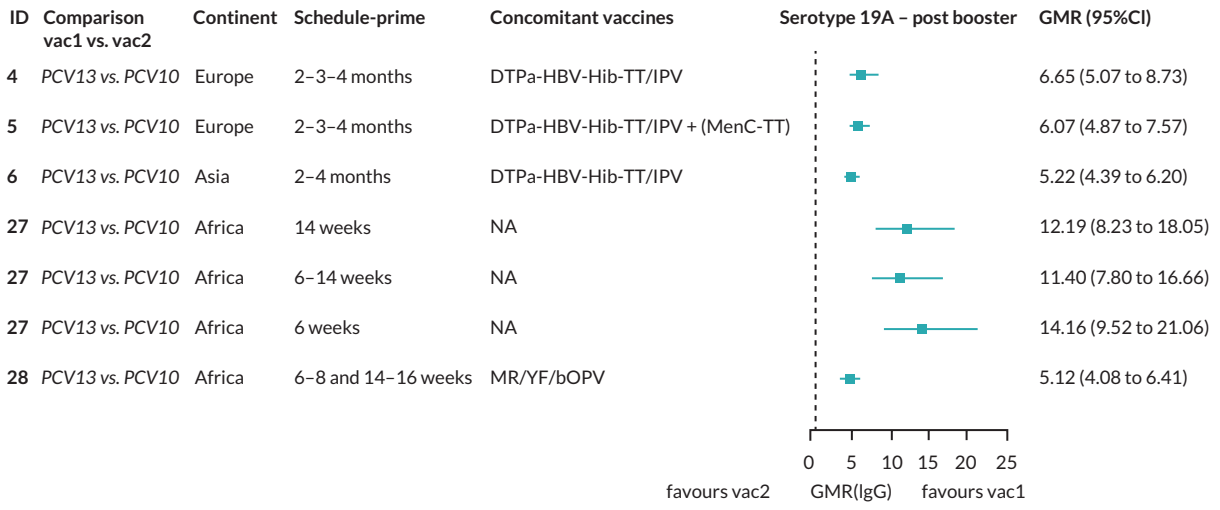



**FIGURE 59** Trial-level GMRs for serotype 19A post booster. Each solid line in the figure shows the GMR from each trial. Blue boxes and lines show the point estimates and CIs for GMRs comparing vac1 vs. vac2. Concomitant vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites. bOPV, bivalent oral poliovirus vaccine; enr 3–6 m, 4–8 w int, enrolment at 3–6 months of age and at 4–8 weeks interval of three doses primary vaccines in total; MR, measles and rubella combined vaccine; N/A, not applicable; YF, yellow fever vaccine.

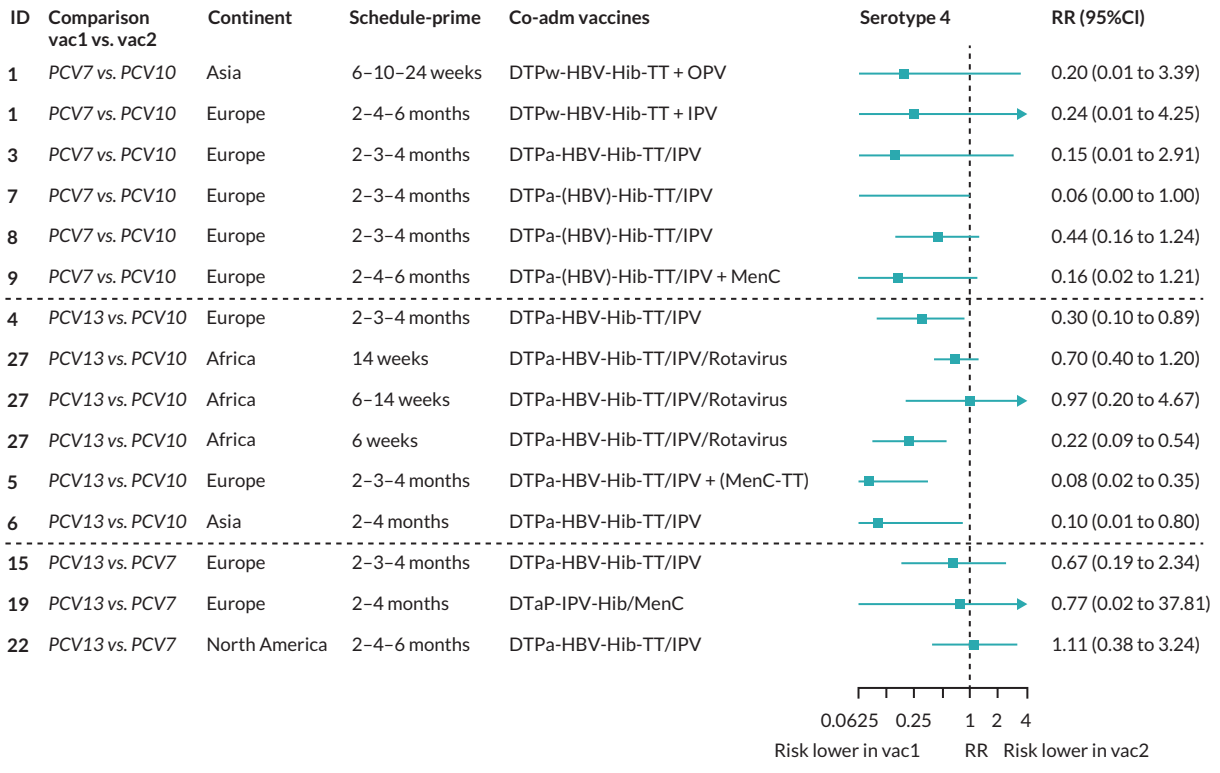



**FIGURE 60** Trial-level RR for serotype 4. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Co-adm vaccines | RR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.58 (0.28 to 1.22) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 0.88 (0.45 to 1.72) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.50 (0.28 to 0.87) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 0.27 (0.16 to 0.43) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 0.30 (0.21 to 0.43) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 0.41 (0.24 to 0.69) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.55 (0.40 to 0.76) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.80 (0.70 to 0.92) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.85 (0.57 to 1.27) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.68 (0.54 to 0.86) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 0.32 (0.23 to 0.45) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 0.83 (0.73 to 0.94) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.37 (1.13 to 1.67) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 2.02 (1.35 to 3.01) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 1.79 (1.09 to 2.94) |

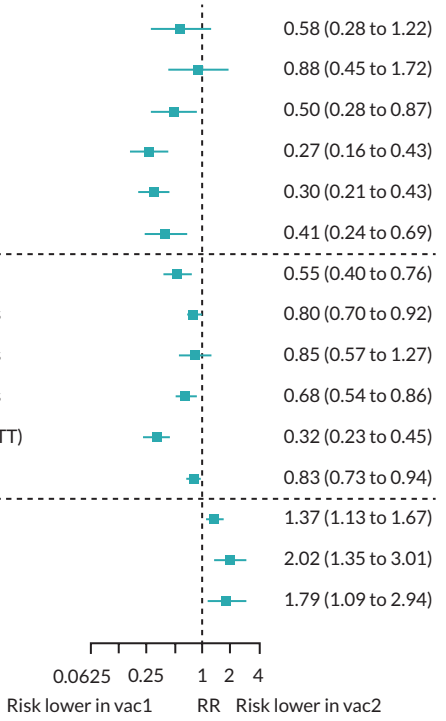



**FIGURE 61** Trial-level RR for serotype 6B. TT, tetanus toxoid conjugate; NA, not applicable. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Co-adm vaccines | RR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.24 (0.03 to 1.75) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 0.28 (0.04 to 2.10) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.47 (0.13 to 1.72) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 0.25 (0.11 to 0.58) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 0.56 (0.33 to 0.95) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 0.48 (0.24 to 0.95) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.62 (0.26 to 1.44) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.00 (0.76 to 1.32) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.06 (0.50 to 2.26) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.51 (0.32 to 0.80) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 0.29 (0.14 to 0.61) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 0.42 (0.20 to 0.90) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.77 (0.34 to 1.73) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 2.30 (0.25 to 21.18) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 1.28 (0.62 to 2.63) |

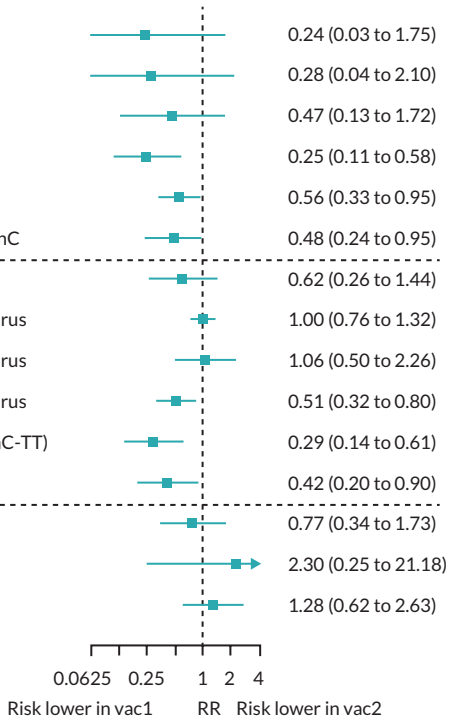



**FIGURE 62** Trial-level RR for serotype 9V. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Co-adm vaccines | RR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 1.71 (0.88 to 3.32) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 0.22 (0.03 to 1.65) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.25 (0.49 to 3.21) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 0.86 (0.52 to 1.40) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 1.11 (0.73 to 1.68) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 1.82 (1.07 to 3.11) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.16 (0.69 to 1.94) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.73 (0.57 to 0.94) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 4.73 (2.24 to 9.99) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 1.17 (0.76 to 1.79) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 1.96 (1.15 to 3.33) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 0.86 (0.62 to 1.19) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 1.11 (0.84 to 1.46) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 1.72 (0.85 to 3.51) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 0.89 (0.56 to 1.43) |

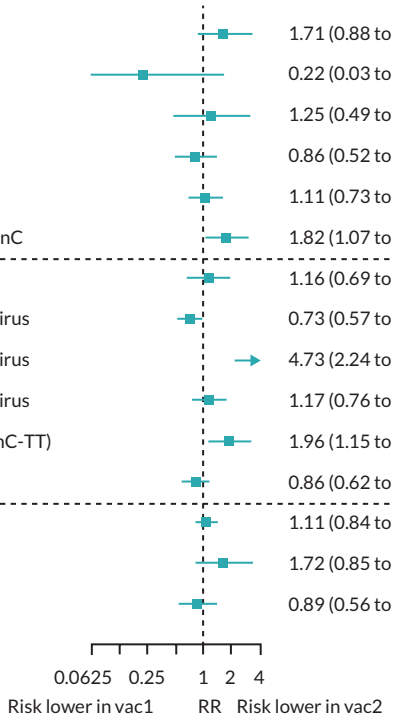



**FIGURE 63** Trial-level RR for serotype 14. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Co-adm vaccines | RR (95%CI) |
|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | 0.50 (0.06 to 4.04) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | 2.30 (0.53 to 9.90) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.56 (0.05 to 5.98) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 0.20 (0.07 to 0.55) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | 0.26 (0.08 to 0.85) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | 0.28 (0.07 to 1.18) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.67 (0.26 to 1.71) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.94 (0.65 to 1.36) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.42 (0.17 to 1.03) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | 0.86 (0.52 to 1.44) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | 0.28 (0.12 to 0.64) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | 0.20 (0.07 to 0.56) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | 0.60 (0.15 to 2.50) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | 0.25 (0.01 to 5.86) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | 1.91 (0.48 to 7.53) |

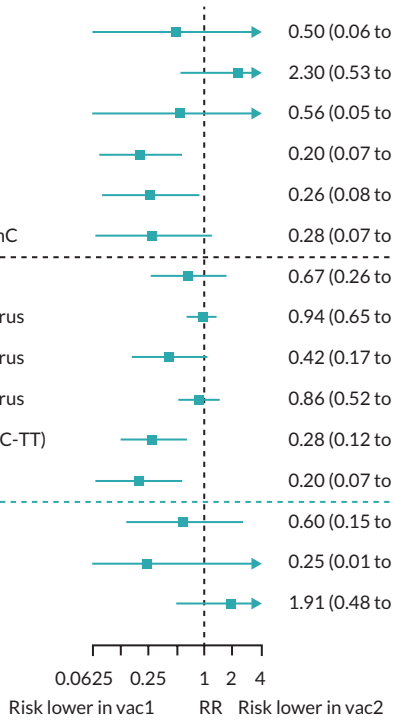



**FIGURE 64** Trial-level RR for serotype 18C. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

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| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Co-adm vaccines | Serotype 19F | RR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 1.50 (0.39 to 5.76) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 1.95 (0.80 to 4.74) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.55 (0.18 to 1.71) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.56 (0.32 to 0.96) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.78 (0.51 to 1.21) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | | 1.62 (0.85 to 3.10) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.27 (0.58 to 2.80) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.47 (0.31 to 0.70) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.78 (0.39 to 1.55) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.89 (0.51 to 1.55) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 0.56 (0.28 to 1.12) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 0.66 (0.35 to 1.25) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 1.35 (0.78 to 2.35) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | | 2.50 (0.74 to 8.43) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | | 1.59 (0.82 to 3.08) |

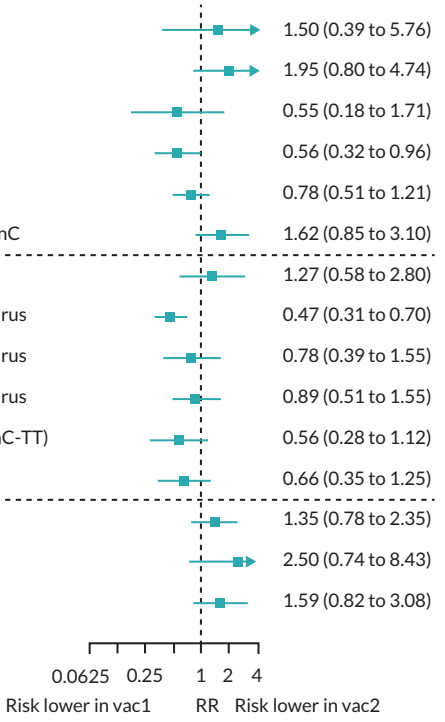



**FIGURE 65** Trial-level RR for serotype 4. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

| ID | Comparison vac1 vs. vac2 | Continent | Schedule-prime | Co-adm vaccines | Serotype 23F | RR (95%CI) |
|---|---|---|---|---|---|---|
| 1 | *PCV7 vs. PCV10* | Asia | 6–10–24 weeks | DTPw-HBV-Hib-TT + OPV | | 0.48 (0.20 to 1.15) |
| 1 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPw-HBV-Hib-TT + IPV | | 2.30 (1.03 to 5.11) |
| 3 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.18 (0.06 to 0.58) |
| 7 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.24 (0.14 to 0.43) |
| 8 | *PCV7 vs. PCV10* | Europe | 2–3–4 months | DTPa-(HBV)-Hib-TT/IPV | | 0.35 (0.23 to 0.54) |
| 9 | *PCV7 vs. PCV10* | Europe | 2–4–6 months | DTPa-(HBV)-Hib-TT/IPV + MenC | | 0.47 (0.23 to 0.97) |
| 4 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.21 (0.11 to 0.38) |
| 27 | *PCV13 vs. PCV10* | Africa | 14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.85 (0.70 to 1.04) |
| 27 | *PCV13 vs. PCV10* | Africa | 6–14 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.42 (0.20 to 0.85) |
| 27 | *PCV13 vs. PCV10* | Africa | 6 weeks | DTPa-HBV-Hib-TT/IPV/Rotavirus | | 0.95 (0.72 to 1.25) |
| 5 | *PCV13 vs. PCV10* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV + (MenC-TT) | | 0.29 (0.18 to 0.45) |
| 6 | *PCV13 vs. PCV10* | Asia | 2–4 months | DTPa-HBV-Hib-TT/IPV | | 0.39 (0.28 to 0.56) |
| 15 | *PCV13 vs. PCV7* | Europe | 2–3–4 months | DTPa-HBV-Hib-TT/IPV | | 0.69 (0.38 to 1.24) |
| 19 | *PCV13 vs. PCV7* | Europe | 2–4 months | DTaP-IPV-Hib/MenC | | 2.25 (0.90 to 5.62) |
| 22 | *PCV13 vs. PCV7* | North America | 2–4–6 months | DTPa-HBV-Hib-TT/IPV | | 1.78 (0.72 to 4.37) |

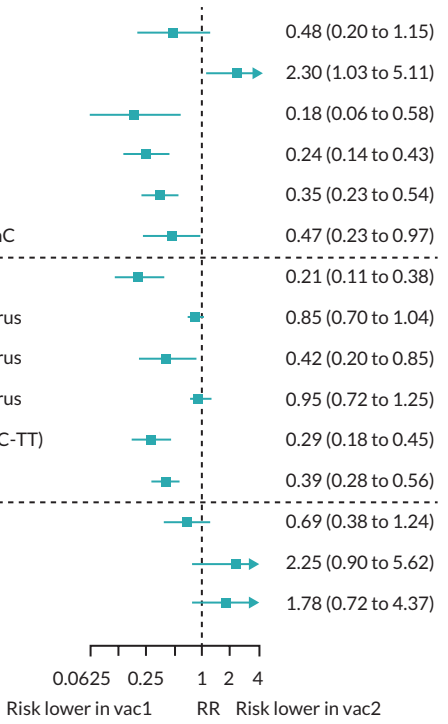



**FIGURE 66** Trial-level RR for serotype 23F. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

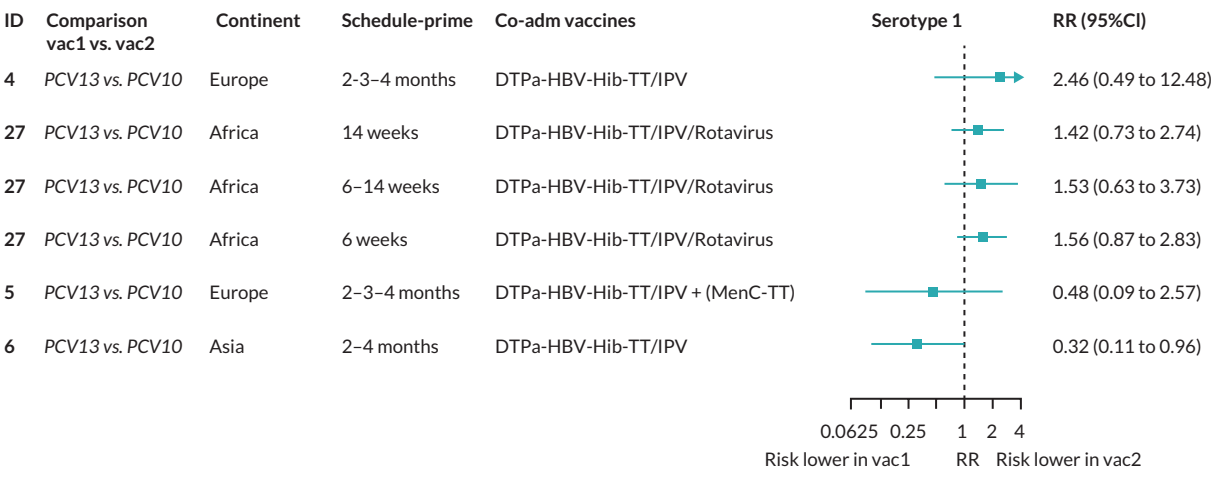



**FIGURE 67** Trial-level RR for serotype 1. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

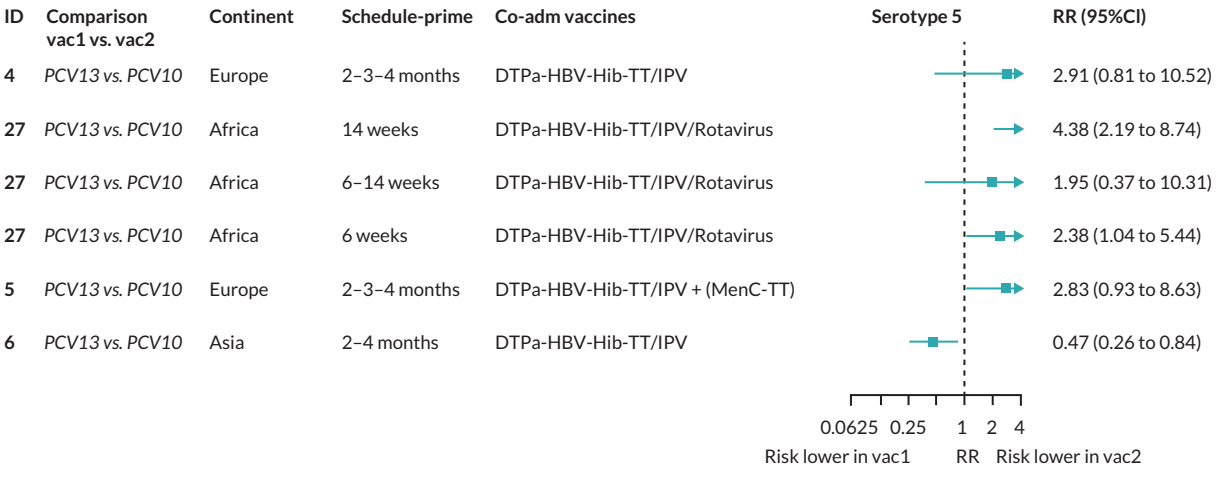



**FIGURE 68** Trial-level RR for serotype 5. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

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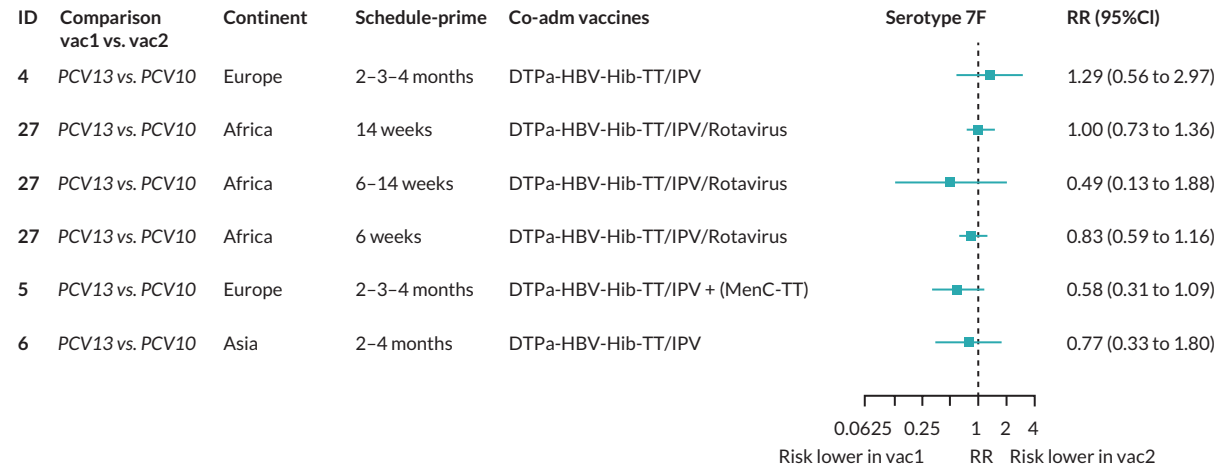
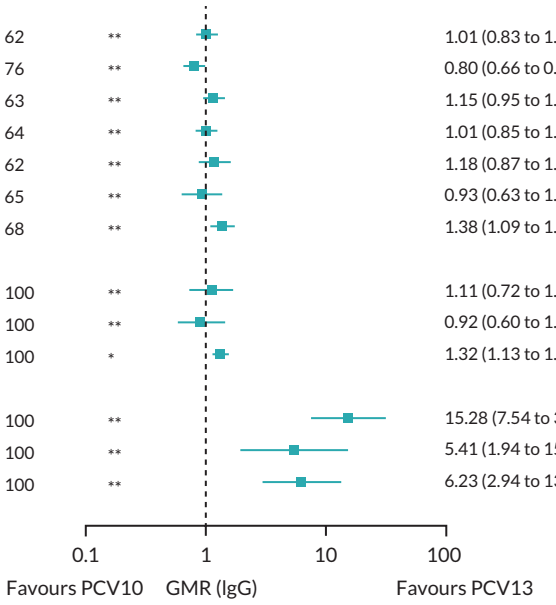



**FIGURE 69** Trial-level RR for serotype 7F. Each solid line in the figure shows the RR from each trial. Blue boxes and lines show the point estimates and CIs for RRs comparing vac1 vs. vac2. Co-adm vaccines are vaccines co-administered with PCV primary vaccine series. Information on co-administered vaccine is not always available. Concomitant vaccines in the bracket are those administered in some but not all of the study sites.

# **Appendix 6** Sensitivity analyses

(a)

| Serotype | No. cohorts | Direct evidence (%) | | GMR at 1 month after prime (SA) PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|---|
| **4** | 14 | 62 | ** | | 1.01 (0.83 to 1.23) | 1.49 (1.23 to 1.81) | 0.68 (0.54 to 0.85) |
| **6B** | 14 | 76 | ** | | 0.80 (0.66 to 0.97) | 1.36 (1.12 to 1.66) | 0.59 (0.47 to 0.73) |
| **9V** | 14 | 63 | ** | | 1.15 (0.95 to 1.41) | 1.63 (1.34 to 1.99) | 0.71 (0.56 to 0.89) |
| **14** | 14 | 64 | ** | | 1.01 (0.85 to 1.21) | 1.32 (1.11 to 1.57) | 0.77 (0.63 to 0.94) |
| **18C** | 14 | 62 | ** | | 1.18 (0.87 to 1.61) | 1.03 (0.75 to 1.42) | 1.15 (0.80 to 1.65) |
| **19F** | 14 | 65 | ** | | 0.93 (0.63 to 1.37) | 0.94 (0.63 to 1.42) | 0.99 (0.62 to 1.56) |
| **23F** | 14 | 68 | ** | | 1.38 (1.09 to 1.74) | 1.86 (1.46 to 2.37) | 0.74 (0.56 to 0.97) |
| **1** | 6 | 100 | ** | | 1.11 (0.72 to 1.70) | 0.02 (0.02 to 0.03) | 58.61 (42.73 to 80.39) |
| **5** | 6 | 100 | ** | | 0.92 (0.60 to 1.40) | 0.03 (0.01 to 0.05) | 19.07 (9.66 to 37.67) |
| **7F** | 6 | 100 | * | | 1.32 (1.13 to 1.55) | 0.02 (0.01 to 0.02) | 66.25 (52.26 to 84.00) |
| **3** | 6 | 100 | ** | | 15.28 (7.54 to 30.98) | 0.92 (0.29 to 2.85) | 16.81 (9.03 to 31.31) |
| **6A** | 6 | 100 | ** | | 5.41 (1.94 to 15.06) | 1.01 (0.52 to 1.96) | 6.21 (4.39 to 8.80) |
| **19A** | 6 | 100 | ** | | 6.23 (2.94 to 13.18) | 0.94 (0.52 to 1.67) | 2.75 (1.46 to 5.21) |

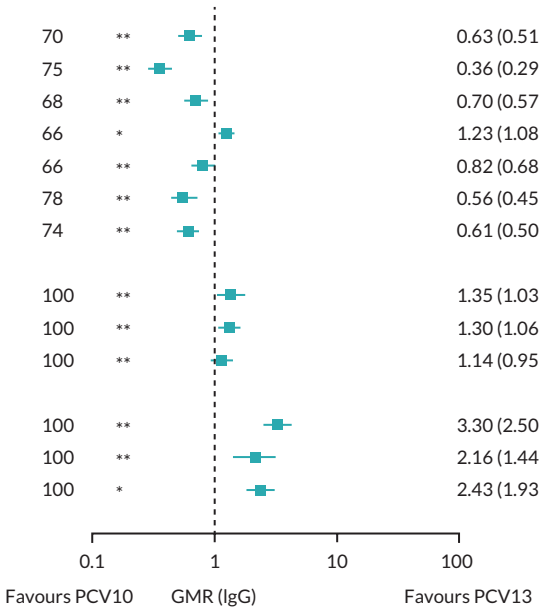



.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 70** Geometric mean ratios from sensitivity analysis restricted to studies providing data for all three time points: (a) post-primary vaccination series, (b) pre boost and (c) post boost. Each line in the figure shows the output from NMAs (PCV7 serotypes) or direct meta-analyses (PCV13 but non-PCV7 serotypes). Blue boxes and blue lines show the point estimates and CIs for GMRs comparing PCV13 vs. PCV10. Points to the right of the vertical line are those with higher antibody responses in the PCV13 arm of the study, and points to the left are those with higher antibody responses in the PCV10 arm. The direct evidence column shows the percentage of evidence from studies directly comparing PCV13 vs. PCV10 that contributes to the estimates presented in the figure in blue (PCV13 vs. PCV10). GMR of PCV13 vs. PCV10 for PCV10 and PCV13 serotypes are from a meta-analysis of only studies comparing PCV13 with PCV10. SA, sensitivity analysis.

(b)

| Serotype | No. cohorts | Direct evidence (%) | | GMR at Before booster (SA) PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|---|
| **4** | 14 | 70 | ** | | 0.63 (0.51 to 0.76) | 0.92 (0.75 to 1.12) | 0.68 (0.55 to 0.85) |
| **6B** | 14 | 75 | ** | | 0.36 (0.29 to 0.45) | 0.50 (0.39 to 0.64) | 0.72 (0.55 to 0.94) |
| **9V** | 14 | 68 | ** | | 0.70 (0.57 to 0.87) | 0.91 (0.73 to 1.13) | 0.78 (0.61 to 0.99) |
| **14** | 14 | 66 | * | | 1.23 (1.08 to 1.40) | 1.51 (1.33 to 1.72) | 0.82 (0.71 to 0.94) |
| **18C** | 14 | 66 | ** | | 0.82 (0.68 to 0.98) | 0.79 (0.65 to 0.94) | 1.04 (0.85 to 1.27) |
| **19F** | 14 | 78 | ** | | 0.56 (0.45 to 0.71) | 0.35 (0.27 to 0.46) | 1.59 (1.21 to 2.09) |
| **23F** | 14 | 74 | ** | | 0.61 (0.50 to 0.75) | 0.80 (0.64 to 0.99) | 0.77 (0.61 to 0.97) |
| **1** | 6 | 100 | ** | | 1.35 (1.03 to 1.75) | 0.12 (0.09 to 1.16) | 13.37 (10.12 to 17.67) |
| **5** | 6 | 100 | ** | | 1.30 (1.06 to 1.60) | 0.17 (0.10 to 0.29) | 4.81 (2.59 to 8.92) |
| **7F** | 6 | 100 | ** | | 1.14 (0.95 to 1.37) | 0.05 (0.04 to 0.06) | 21.71 (18.17 to 25.93) |
| **3** | 6 | 100 | ** | | 3.30 (2.50 to 4.35) | 1.07 (0.66 to 1.73) | 3.10 (2.10 to 4.58) |
| **6A** | 6 | 100 | ** | | 2.16 (1.44 to 3.22) | 0.70 (0.52 to 0.93) | 3.08 (2.22 to 4.29) |
| **19A** | 6 | 100 | * | | 2.43 (1.93 to 3.06) | 0.63 (0.44 to 0.90) | 1.53 (1.22 to 1.91) |



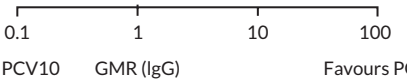

.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 70** Continued

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(c)

| Serotype | No. cohorts | Direct evidence (%) | | GMR at 1 month after booster (SA) PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|---|
| **4** | 14 | 73 | * | | 1.04 (0.93 to 1.15) | 1.38 (1.23 to 1.54) | 0.75 (0.67 to 0.85) |
| **6B** | 14 | 73 | ** | | 1.25 (1.01 to 1.55) | 1.63 (1.30 to 2.04) | 0.77 (0.60 to 0.99) |
| **9V** | 14 | 72 | ** | | 1.40 (1.18 to 1.67) | 1.68 (1.40 to 2.02) | 0.83 (0.68 to 1.02) |
| **14** | 14 | 69 | ** | | 1.43 (1.22 to 1.66) | 1.72 (1.47 to 2.00) | 0.83 (0.70 to 0.99) |
| **18C** | 14 | 73 | ** | | 0.78 (0.66 to 0.93) | 0.89 (0.74 to 1.07) | 0.88 (0.72 to 1.08) |
| **19F** | 14 | 74 | ** | | 0.93 (0.74 to 1.15) | 0.56 (0.45 to 0.70) | 1.64 (1.27 to 2.12) |
| **23F** | 14 | 76 | ** | | 1.60 (1.33 to 1.92) | 2.22 (1.81 to 2.71) | 0.72 (0.58 to 0.89) |
| **1** | 6 | 100 | .. | | 1.71 (1.51 to 1.93) | 0.02 (0.01 to 0.03) | 125.80 (71.00 to 222.91) |
| **5** | 6 | 100 | ** | | 1.87 (1.52 to 2.30) | 0.04 (0.02 to 0.10) | 25.12 (9.55 to 66.10) |
| **7F** | 6 | 100 | * | | 1.63 (1.46 to 1.82) | 0.01 (0.01 to 0.02) | 115.07 (73.61 to 179.87) |
| **3** | 6 | 100 | ** | | 10.56 (6.03 to 18.49) | 0.76 (0.33 to 1.78) | 13.92 (12.19 to 15.90) |
| **6A** | 6 | 100 | ** | | 13.40 (8.48 to 21.16) | 1.98 (1.38 to 2.83) | 4.48 (3.24 to 6.21) |
| **19A** | 6 | 100 | ** | | 8.36 (6.08 to 11.49) | 0.65 (0.36 to 1.16) | 2.46 (2.23 to 2.73) |

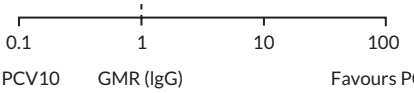



.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 70** Continued

(a)

| Serotype | No. cohorts | Direct evidence (%) | | GMR at 1 month after prime – Europe PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|---|
| **4** | 9 | 56 | ** | | 1.32 (1.06 to 1.63) | 1.68 (1.44 to 1.96) | 0.78 (0.63 to 0.97) |
| **6B** | 9 | 58 | .. | | 1.04 (0.87 to 1.25) | 1.63 (1.43 to 1.86) | 0.64 (0.53 to 0.77) |
| **9V** | 9 | 57 | ** | | 1.40 (1.17 to 1.67) | 1.84 (1.62 to 2.10) | 0.76 (0.63 to 0.91) |
| **14** | 9 | 61 | ** | | 1.08 (0.87 to 1.33) | 1.47 (1.26 to 1.71) | 0.73 (0.59 to 0.91) |
| **18C** | 9 | 51 | ** | | 1.11 (0.83 to 1.49) | 1.12 (0.90 to 1.39) | 0.99 (0.74 to 1.33) |
| **19F** | 9 | 58 | ** | | 0.74 (0.39 to 1.38) | 1.00 (0.62 to 1.59) | 0.74 (0.39 to 1.39) |
| **23F** | 9 | 55 | .. | | 2.14 (1.87 to 2.46) | 2.34 (2.14 to 2.56) | 0.92 (0.80) to 1.05) |
| **1** | 2 | 100 | .. | | 1.58 (1.39 to 1.79) | 0.03 (0.03 to 0.03) | 59.55 (52.44 to 67.62) |
| **5** | 2 | 100 | .. | | 1.28 (1.13 to 1.45) | 0.03 (0.02 to 0.05) | 16.99 (8.43 to 34.23) |
| **7F** | 2 | 100 | .. | | 1.41 (1.27 to 1.58) | 0.02 (0.02 to 0.02) | 60.35 (46.53 to 78.28) |
| **3** | 2 | 100 | .. | | 43.98 (38.72 to 49.95) | 2.29 (1.04 to 5.07) | 18.60 (7.17 to 48.24) |
| **6A** | 2 | 100 | .. | | 17.64 (14.96 to 20.80) | 1.43 (0.94 to 2.19) | 5.31 (3.93 to 7.17) |
| **19A** | 2 | 100 | .. | | 15.01 (12.88 to 17.49) | 1.04 (0.55 to 1.97) | 2.99 (1.04 to 8.53) |

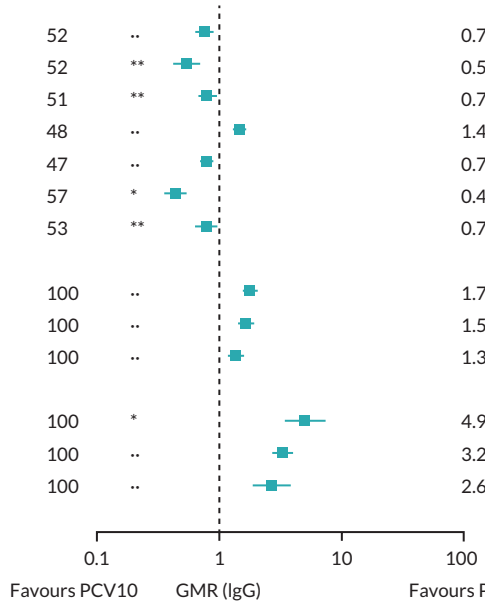



.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 71** Geometric mean ratios from sensitivity analyses restricted to studies conducted in Europe at (a) post-primary vaccination series, (b) pre boost and (c) post boost. Each line in the figure shows the output from NMSs (PCV7 serotypes) or direct meta-analyses (PCV13 but non-PCV7 serotypes). Blue boxes and blue lines show the point estimates and CIs for GMRs comparing PCV13 vs. PCV10. Points to the right of the vertical line are those with higher antibody responses in the PCV13 arm of the study, and points to the left are those with higher antibody responses in the PCV10 arm. The direct evidence column shows the percentage of evidence from studies directly comparing PCV13 vs. PCV10 that contributes to the estimates presented in the figure in blue (PCV13 vs. PCV10). GMR of PCV13 vs. PCV10 for PCV10 and PCV13 serotypes are from a meta-analysis of only studies comparing PCV13 with PCV10.

(b)

| Serotype | No. cohorts | Direct evidence (%) | GMR at before booster – Europe PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|
| **4** | 10 | 52 | .. | 0.75 (0.68 to 0.84) | 1.03 (0.94 to 1.13) | 0.73 (0.66 to 0.81) |
| **6B** | 10 | 52 | ** | 0.53 (0.41 to 0.67) | 0.58 (0.48 to 0.71) | 0.90 (0.72 to 1.13) |
| **9V** | 10 | 51 | ** | 0.77 (0.63 to 0.94) | 1.00 (0.86 to 1.18) | 0.77 (0.64 to 0.93) |
| **14** | 10 | 48 | .. | 1.42 (1.26 to 1.60) | 1.62 (1.47 to 1.78) | 0.88 (0.79 to 0.98) |
| **18C** | 10 | 47 | .. | 0.77 (0.69 to 0.87) | 0.84 (0.76 to 0.92) | 0.93 (0.83 to 1.03) |
| **19F** | 10 | 57 | * | 0.43 (0.35 to 0.53) | 0.37 (0.31 to 0.44) | 1.15 (0.95 to 1.39) |
| **23F** | 10 | 53 | ** | 0.76 (0.60 to 0.97) | 0.90 (0.74 to 1.10) | 0.85 (0.68 to 1.07) |
| **1** | 2 | 100 | .. | 1.73 (1.55 to 1.95) | 0.16 (0.13 to 0.19) | 13.06 (10.59 to 16.10) |
| **5** | 2 | 100 | .. | 1.58 (1.40 to 1.79) | 0.15 (0.08 to 0.27) | 3.84 (1.88 to 7.85) |
| **7F** | 2 | 100 | .. | 1.33 (1.19 to 1.49) | 0.05 (0.04 to 0.06) | 20.04 (15.79 to 25.43) |
| **3** | 2 | 100 | * | 4.96 (3.43 to 7.17) | 1.75 (0.88 to 3.50) | 2.80 (1.67 to 4.70) |
| **6A** | 2 | 100 | .. | 3.22 (2.67 to 3.89) | 0.86 (0.66 to 1.13) | 2.86 (1.97 to 4.14) |
| **19A** | 2 | 100 | .. | 2.64 (1.87 to 3.73) | 0.60 (0.42 to 0.87) | 1.61 (1.39 to 1.87) |

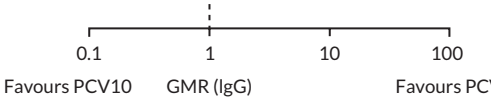



.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 71** Continued

(c)

| Serotype | No. cohorts | Direct evidence (%) | GMR at 1 month after booster – Europe PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|
| **4** | 10 | 53 | .. | 1.05 (0.94 to 1.18) | 1.42 (1.28 to 1.56) | 0.74 (0.67 to 0.82) |
| **6B** | 10 | 53 | * | 1.58 (1.31 to 1.90) | 1.75 (1.49 to 2.05) | 0.90 (0.77 to 1.06) |
| **9V** | 10 | 49 | ** | 1.36 (1.05 to 1.75) | 1.70 (1.37 to 2.12) | 0.80 (0.64 to 1.00) |
| **14** | 10 | 47 | * | 1.56 (1.29 to 1.89) | 1.75 (1.49 to 2.07) | 0.89 (0.75 to 1.05) |
| **18C** | 10 | 49 | .. | 0.78 (0.71 to 0.86) | 1.01 (0.93 to 1.10) | 0.77 (0.71 to 0.84) |
| **19F** | 10 | 58 | ** | 0.77 (0.60 to 0.98) | 0.58 (0.47 to 0.71) | 1.32 (1.06 to 1.65) |
| **23F** | 10 | 55 | ** | 1.90 (1.55 to 2.32) | 2.49 (2.08 to 2.99) | 0.76 (0.64 to 0.91) |
| **1** | 2 | 100 | .. | 1.67 (1.49 to 1.87) | 0.02 (0.01 to 0.04) | 122.09 (67.79 to 219.91) |
| **5** | 2 | 100 | .. | 2.26 (2.01 to 2.54) | 0.05 (0.02 to 0.14) | 13.50 (4.73 to 38.58) |
| **7F** | 2 | 100 | .. | 1.50 (1.36 to 1.66) | 0.02 (0.01 to 0.03) | 92.63 (54.90 to 156.27) |
| **3** | 2 | 100 | .. | 24.80 (19.65 to 31.30) | 1.85 (1.31 to 2.59) | 13.44 (10.86 to 16.64) |
| **6A** | 2 | 100 | .. | 9.29 (7.33 to 11.77) | 1.90 (1.46 to 2.46) | 4.30 (3.40 to 5.45) |
| **19A** | 2 | 100 | .. | 6.30 (5.31 to 7.47) | 0.63 (0.37 to 1.06) | 2.38 (2.19 to 2.59) |



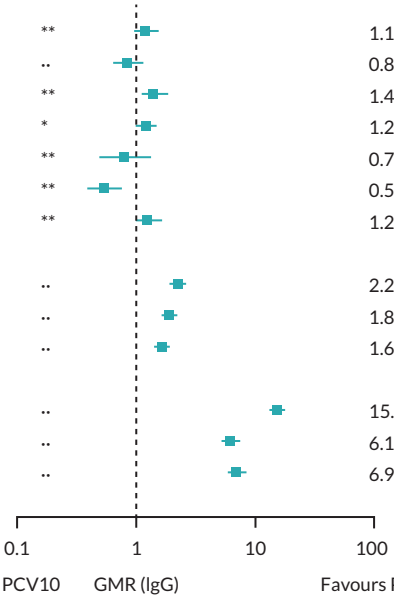

.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 71** Continued

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(a)

| Serotype | No. cohorts | Direct evidence (%) | | GMR at 1 month after prime – Asia PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|---|
| **4** | 9 | 45 | ** | | 1.18 (0.93 to 1.51) | 1.38 (1.10 to 1.73) | 0.86 (0.74 to 0.99) |
| **6B** | 9 | 48 | .. | | 0.85 (0.64 to 1.14) | 0.96 (0.73 to 1.27) | 0.88 (0.74 to 1.06) |
| **9V** | 9 | 45 | ** | | 1.42 (1.11 to 1.82) | 1.62 (1.29 to 2.05) | 0.88 (0.75 to 1.02) |
| **14** | 9 | 38 | * | | 1.20 (0.98 to 1.47) | 1.30 (1.08 to 1.57) | 0.92 (0.82 to 1.04) |
| **18C** | 9 | 48 | ** | | 0.79 (0.48 to 1.31) | 0.77 (0.48 to 1.24) | 1.03 (0.76 to 1.39) |
| **19F** | 9 | 38 | ** | | 0.53 (0.38 to 0.74) | 0.50 (0.36 to 0.68) | 1.08 (0.87 to 1.32) |
| **23F** | 9 | 51 | ** | | 1.23 to (0.95 to 1.60) | 1.49 (1.17 to 1.91) | 0.83 (0.71 to 0.96) |
| **1** | 1 | 100 | .. | | 2.21 (1.89 to 2.57) | 0.01 (0.00 to 0.03) | 217.92 (109.66 to 433.05) |
| **5** | 1 | 100 | .. | | 1.88 (1.66 to 2.13) | 0.03 (0.01 to 0.11) | 10.07 (4.07 to 24.92) |
| **7F** | 1 | 100 | .. | | 1.60 (1.42 to 1.82) | 0.01 (0.00 to 0.02) | 113.52 (68.78 to 187.37) |
| **3** | 1 | 100 | .. | | 15.16 (13.17 to 17.46) | 0.31 (0.02 to 3.93) | 49.05 (18.72 to 128.48) |
| **6A** | 1 | 100 | .. | | 6.19 (5.21 to 7.36) | 0.97 (0.74 to 1.28) | 6.24 (5.18 to 7.50) |
| **19A** | 1 | 100 | .. | | 6.93 (5.81 to 8.26) | 0.68 (0.26 to 1.80) | 3.86 (1.96 to 7.61) |

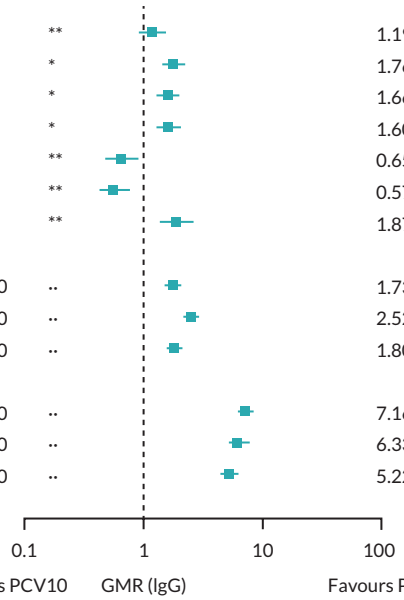



.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 72** Geometric mean ratios from sensitivity analyses of studies conducted in Asia at (a) post-primary vaccination series and (b) post boost. Each line in the figure shows the output from NMAs (PCV7 serotypes) or direct meta-analyses (PCV13 but non-PCV7 serotypes). Blue boxes and blue lines show the point estimates and CIs for GMRs comparing PCV13 vs. PCV10. Points to the right of the vertical line are those with higher antibody responses in the PCV13 arm of the study, and points to the left are those with higher antibody responses in the PCV10 arm. The direct evidence column shows the percentage of evidence from studies directly comparing PCV13 vs. PCV10 that contributes to the estimates presented in the figure in blue (PCV13 vs. PCV10). GMR of PCV13 vs. PCV10 for PCV10 and PCV13 serotypes are from a meta-analysis of only studies comparing PCV13 with PCV10.

(b)

| Serotype | No. cohorts | Direct evidence (%) | | GMR at 1 month after booster – Asia PCV13 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV10 | GMR (95% CI) PCV7 vs. PCV10 | GMR (95% CI) PCV13 vs. PCV7 |
|---|---|---|---|---|---|---|---|
| **4** | 9 | 57 | ** | | 1.19 (0.91 to 1.55) | 1.40 (1.09 to 1.80) | 0.85 (0.72 to 0.99) |
| **6B** | 9 | 52 | * | | 1.76 (1.42 to 2.19) | 1.77 (1.43 to 2.18) | 1.00 (0.88 to 1.13) |
| **9V** | 9 | 57 | * | | 1.66 (1.38 to 2.00) | 1.92 (1.60 to 2.30) | 0.87 (0.78 to 0.97) |
| **14** | 9 | 51 | * | | 1.60 (1.27 to 2.02) | 1.94 (1.55 to 2.42) | 0.83 (0.72 to 0.95) |
| **18C** | 9 | 60 | ** | | 0.65 (0.48 to 0.90) | 0.70 (0.52 to 0.94) | 0.94 (0.77 to 1.13) |
| **19F** | 9 | 61 | ** | | 0.57 (0.43 to 0.75) | 0.35 (0.27 to 0.45) | 1.64 (1.38 to 1.94) |
| **23F** | 9 | 64 | ** | | 1.87 (1.36 to 2.57) | 2.26 (1.66 to 3.08) | 0.83 (0.69 to 1.00) |
| **1** | 1 | 100 | .. | | 1.73 (1.48 to 2.03) | 0.01 (0.00 to 0.01) | 211.63 (146.41 to 305.90) |
| **5** | 1 | 100 | .. | | 2.52 (2.21 to 2.88) | 0.04 (0.01 to 0.10) | 10.09 (5.31 to 19.18) |
| **7F** | 1 | 100 | .. | | 1.80 (1.57 to 2.05) | 0.01 (0.01 to 0.01) | 109.06 (86.20 to 138.00) |
| **3** | 1 | 100 | .. | | 7.16 (6.14 to 8.36) | 0.47 (0.21 to 1.06) | 15.28 (11.15 to 20.95) |
| **6A** | 1 | 100 | .. | | 6.33 (5.21 to 7.70) | 1.67 (1.27 to 2.19) | 4.17 (3.62 to 4.79) |
| **19A** | 1 | 100 | .. | | 5.22 (4.39 to 6.20) | 0.35 (0.20 to 0.62) | 4.65 (3.60 to 6.01) |




.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 72** Continued

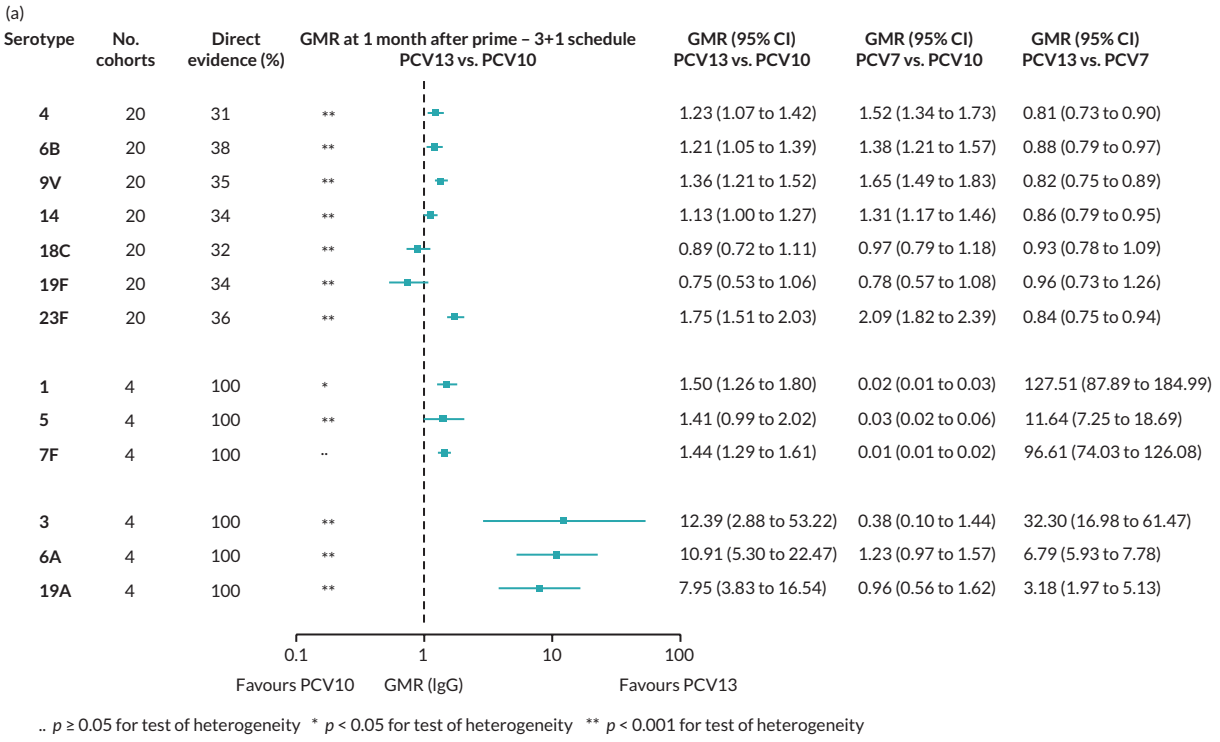



**FIGURE 73** Geometric mean ratios from sensitivity analyses of studies that used a 3 + 1 schedule at (a) post-primary vaccination series, (b) pre boost and (c) post boost. Each line in the figure shows the output from NMAs (PCV7 serotypes) or direct meta-analyses (PCV13 but non-PCV7 serotypes). Blue boxes and blue lines show the point estimates and CIs for GMRs comparing PCV13 vs. PCV10. Points to the right of the vertical line are those with higher antibody responses in the PCV13 arm of the study, and points to the left are those with higher antibody responses in the PCV10 arm. The direct evidence column shows the percentage of evidence from studies directly comparing PCV13 vs. PCV10 that contributes to the estimates presented in the figure in blue (PCV13 vs. PCV10). GMR of PCV13 vs. PCV10 for PCV10 and PCV13 serotypes are from a meta-analysis of only studies comparing PCV13 with PCV10.

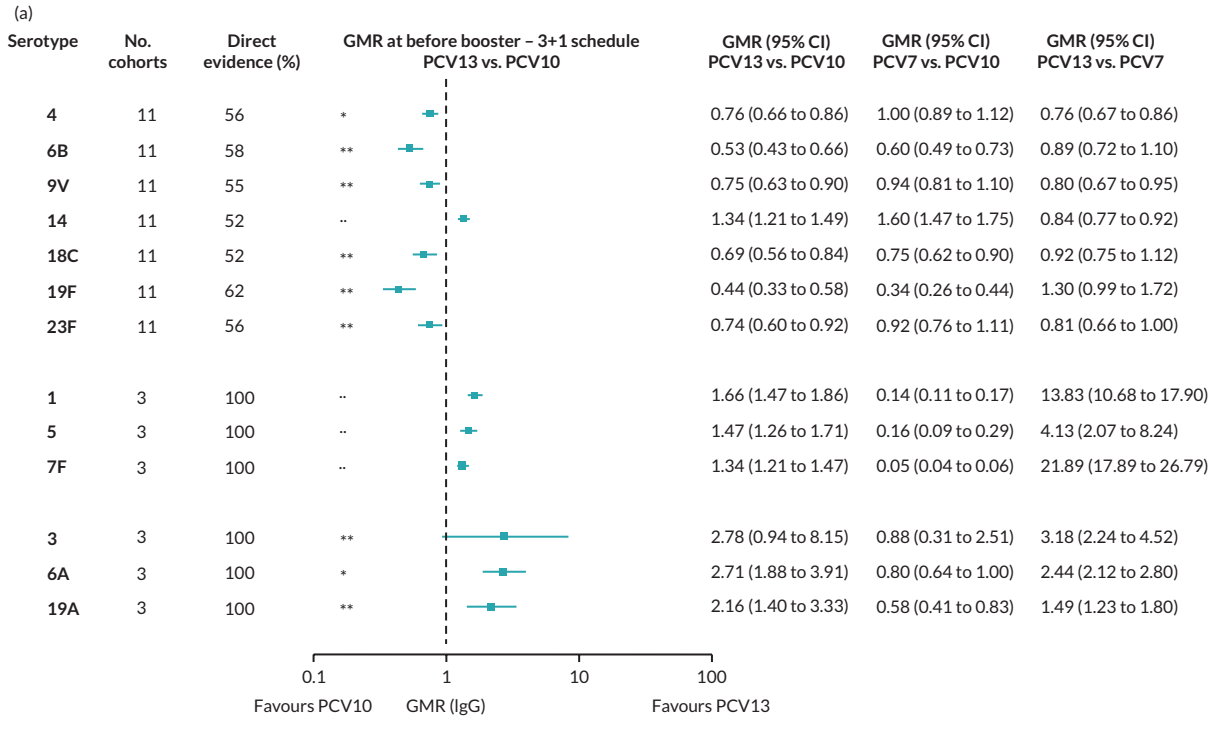
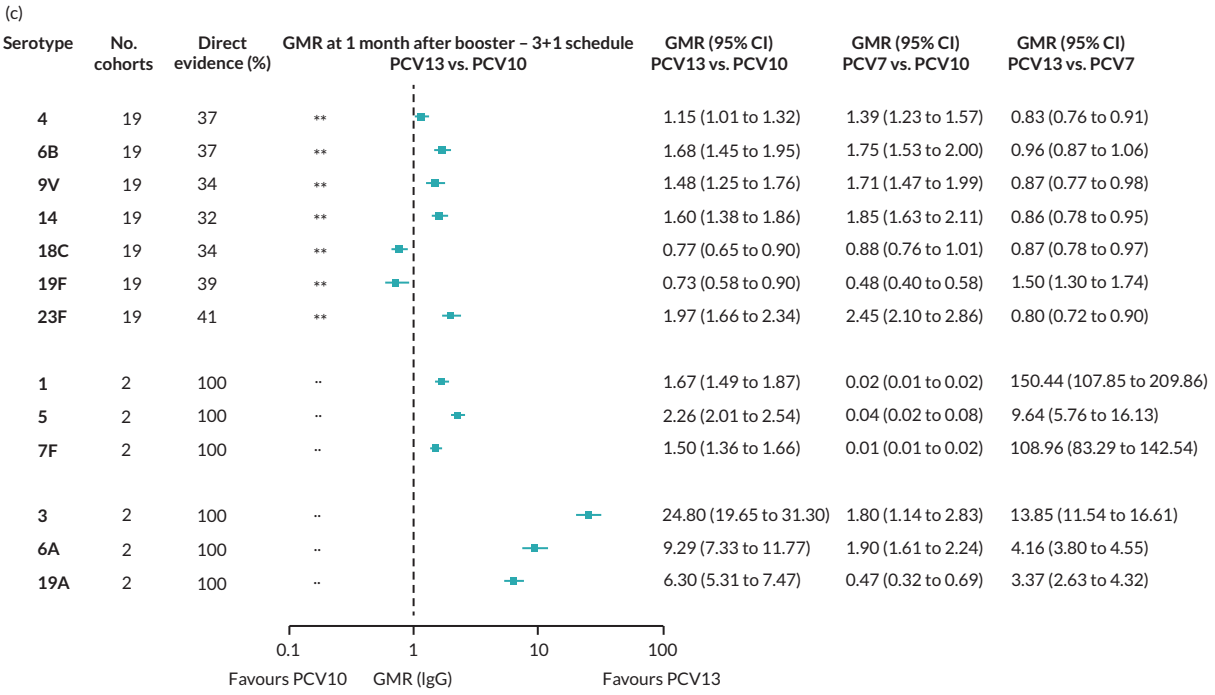



**FIGURE 73** Continued

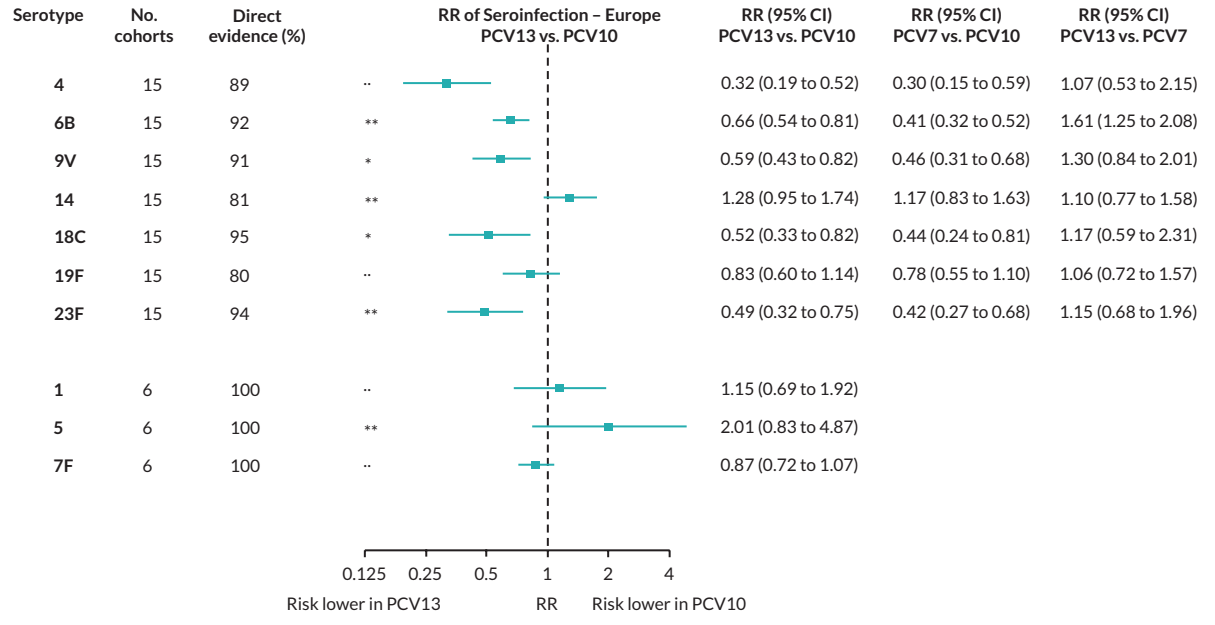
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(c)




.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 73** Continued




.. $p \geq 0.05$ for test of heterogeneity * $p < 0.05$ for test of heterogeneity ** $p < 0.001$ for test of heterogeneity

**FIGURE 74** Sensitivity analysis of RR of seroinfection for studies conducted in Europe. Each line in the figure shows the output from NMAs (PCV7 serotypes) or direct meta-analyses (PCV10 serotypes). Blue boxes and blue lines show the point estimates and CIs of RR of seroinfection comparing PCV13 vs. PCV10. The direct evidence column shows the percentage of evidence from studies directly comparing PCV13 vs. PCV10. Results for PCV10 serotypes are from a meta-analysis of only studies comparing PCV13 with PCV10; therefore, estimates of PCV7 vs. PCV10 and PCV13 vs. PCV7 were not available.

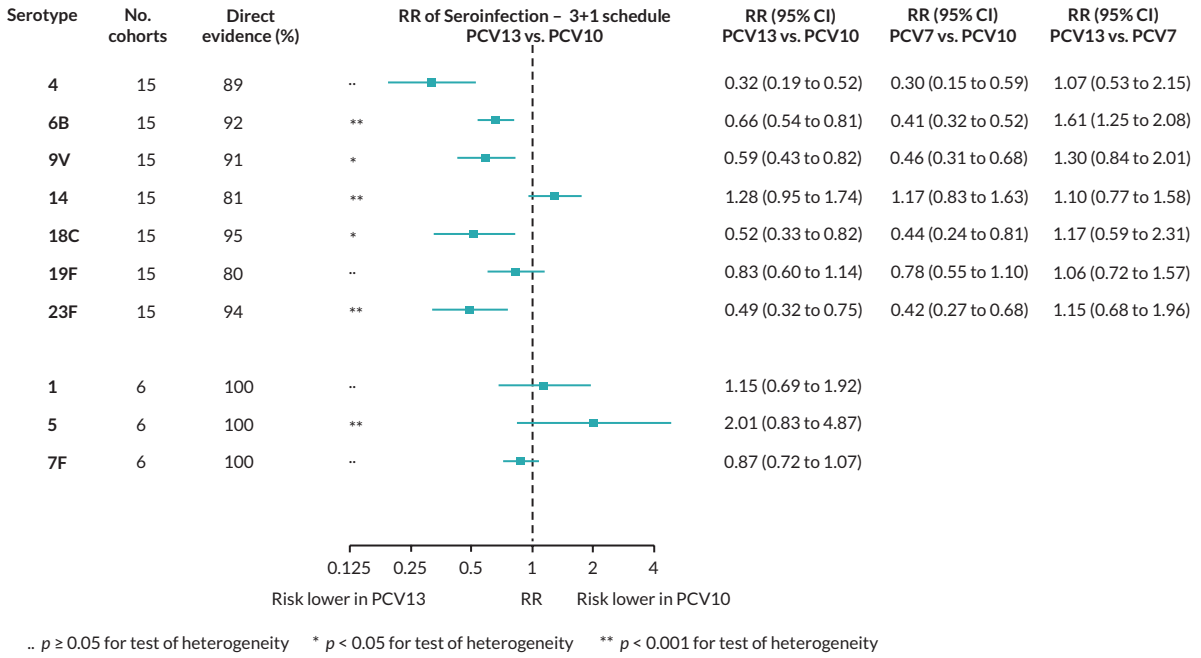



**FIGURE 75** Sensitivity analysis of RR of seroinfection for studies using a 3 + 1 schedule. Each line in the figure shows the output from NMAs (PCV7 serotypes) or direct meta-analyses (PCV10 serotypes). Blue boxes and blue lines show the point estimates and CIs of RR of seroinfection comparing PCV13 vs. PCV10. The direct evidence column shows the percentage of evidence from studies directly comparing PCV13 vs. PCV10. Results for PCV10 serotypes are from a meta-analysis of only studies comparing PCV13 with PCV10; therefore, estimates of PCV7 vs. PCV10 and PCV13 vs. PCV7 were not available.

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# **Appendix 7** R syntax

```
# network meta-analysis
library(netmeta)
net.pcv <- netmeta(TE = lgGMR, seTE = lgGMR.se, treat1 = vac2, treat2 = vac1, studlab = cohort.ID,
      data = data, sm = 'MD', reference.group = 'pcv10')
#Split direct and indirect evidence to evaluate inconsistency
net.pcv.split <- netsplit(net.pcv)
#format output
ind <- net.pcv.split$random
ind <- ind[which(ind$comparison %in% c('pcv10:pcv13', 'pcv13:pcv10')),]
output.nma$random.nma <- round(ind$TE, 3)
output.nma$random.lower <- round(ind$lower, 3)
output.nma$random.upper <- round(ind$upper, 3)
output.nma$random.se <- round(ind$seTE, 3)
output.nma$random.CI <- paste(sprintf('%0.3f', ind$TE), ' (', sprintf('%0.3f', ind$lower), ', ', sprintf('%0.3f',
      ind$upper), ')', sep = '')
# Association between immunogenicity and seroefficacy
library(lme4)
#fit linear mixed effects model
random <- lmer(logRR ~ lgGMR * sero.type + (1 | cohort.ID), data = data, weights = study.weights)
```

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