Report: Pneumococcal conjugate vaccine reduced dosing schedule: a systematic review and meta-analysis

11 March 2025

AUTHORS

Eleanor Neal[1, 2]

Yonatan Mesfin[1]

Cattram Nguyen[1,2]

Qiongyu Liang[3]

Sue Brennan[4]

Joanne McKenzie[5]

Mariama Badjie Hydara[1]

Joshua Szanyi[1]

Fiona Russell[1, 2]

[1] Asia-Pacific Health, Murdoch Children's Research Institute, Parkville, Australia.

[2] Department of Paediatrics, The University of Melbourne, Parkville, Australia.

[3] School of Population Health and Global Health, The University of Melbourne, Parkville, Australia.

[4] Melbourne GRADE Centre, Cochrane Australia, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

[5] Melbourne GRADE Centre, Methods in Evidence Synthesis Unit, School of Public Health and Preventive Medicine, Monash University Melbourne, Australia.

WORKING GROUP

Professor Fiona Russell led the working group from the Centre for International Child Health, Department of Paediatrics, The University of Melbourne (WHO Collaborating Centre for Child and Neonatal Research and Training) and Asia-Pacific Health Group, Murdoch Children's Research Institute (MCRI). Dr Eleanor Neal (MCRI) coordinated the project and led the systematic review and team. Dr Yonatan Mesfin (MCRI) contributed his epidemiological skills on meta-analysis. Dr Cattram Nguyen (MCRI) led the statistical analysis plan. Qiongyu Liang (School of Population and Global Health, The University of Melbourne) and Dr Mariama Badjie Hydara (MCRI) conducted screening and data extraction. Dr Joshua Szanyi led the ROB with Prof Fiona Russell. Dr Sue Brennan and Professor Joanne McKenzie from the Melbourne GRADE Centre, Cochrane Australia, School of Public Health and Preventive Medicine, Monash University, provided guidance on the systematic review and meta-analysis protocol development and statistical methods. Administrative information can be found in Appendix 1.

Table of Contents

ABBREVIATIONS

CoP	Correlate of protection
cRCT	cluster randomised controlled trial
DTP	Diphtheria, tetanus, pertussis
EMBASE	Excerpta Medica Database
GMC	Geometric mean concentration
GMT	Geometric mean titre
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICC	Intra-cluster correlation
IgG	Immunoglobulin G
IPD	Invasive pneumococcal disease
IRR	Incidence rate ratio
LMIC	Lower-middle income countries
MCRI	Murdoch Children's Research Institute
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical subject headings
NRSIs	Non-randomised studies
NVT	Non-vaccine serotype
OIs	Opsonisation indices
OPA	Opsonophagocytic activity
PCV	Pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PCV9	9-valent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PR	Prevalence ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	The International Prospective Register of Systematic Reviews
RCT	Randomised controlled trial
RoB2	Cochrane Risk of Bias for randomised trials tool, version 2
ROBINS-I	Cochrane Risk of Bias in Non-Randomised Studies of Interventions tool
ROB-ME	Risk of Bias due to Missing Evidence
WHO	World Health Organization
1p+1	One primary plus one PCV booster dose
2p+1	Two primary plus one PCV booster dose
3p+0	Three primary plus zero PCV booster doses

3p+1	Three primary plus one PCV booster dose
95% CI	95% confidence interval

ACKNOWLEDGEMENTS

We would like to sincerely thank the researchers who contributed to this systematic review by sharing their data. Dr Courtney Olwagen, Prof Yoshida Lay Mint, and Dr Anand Kawade provided data that were not extractable directly from their published studies. We also thank Prof Grant Mackenzie and Dr Manish Sadarangani for sharing additional unpublished data from their trials.

We are grateful to all authors who conducted studies in this review, enabling us to extract valuable data for our analysis. Their efforts in generating high-quality research have been instrumental to the success of this review, and we sincerely appreciate their contributions and collaboration.

EXECUTIVE SUMMARY

Background

Pneumococcal diseases, including invasive pneumococcal disease (IPD), pneumonia, and meningitis, are a substantial global health challenge, particularly for children under five. Pneumococcal conjugate vaccines (PCV) have been instrumental in preventing these diseases by reducing vaccine-type (VT) carriage and disease through direct and indirect effects. The most recent WHO Position Paper (2019) recommends that countries may use either three primary doses without a booster (3p+0) or two primary doses with a booster (2p+1). Some countries also use a 3p+1 schedule. Further research has suggested that reduced dose schedules (1p+1 schedule) could provide similar protection to a three-dose schedule. At least seven clinical trials have been conducted comparing a 1p+1 schedule to three dose schedules, and many of these have been completed. A reduced dose schedule may allow immunisation programmes to reduce the number of injections and immunisation program costs.

Aims

This systematic review and meta-analyses aim to determine the efficacy and effectiveness of a two-dose PCV schedule (1p+1) in preventing pneumococcal disease in children, focusing on disease incidence, immunogenicity, and pneumococcal nasopharyngeal carriage.

Methods

A systematic literature search was conducted to identify studies assessing the effect of 1p+1 PCV schedules on IPD, pneumonia, pneumococcal nasopharyngeal carriage, and immunogenicity among children under five years. Three databases were searched: MEDLINE, PubMed, and EMBASE, along with clinical trial registries. Inclusion criteria were randomised controlled trials (RCTs) and non-randomised observational studies published from January 2000 onwards, reporting on pneumococcal disease or pneumonia incidence, immunogenicity, and pneumococcal nasopharyngeal carriage; among children receiving their first PCV dose before six months and their final dose by 18 months of age in any of the following schedules: 1p+1, 2p+1, 3p+0, 3p+1, or zero doses.

Two reviewers independently screened titles, abstracts, and full texts to determine eligibility, with a third reviewer resolving disagreements. Data were extracted using standardised forms, and the risk of bias was assessed using appropriate tools for each study design. The time points for immunogenicity and carriage outcomes were post-primary, one month after the first dose for 1p+1, the second dose for 2p+1, and the third dose for 3p+0 and 3p+1; and pre-and post-final dose to less than two years of age; and post-final dose between two and five years of age. IPD and pneumonia outcomes were assessed for children under five years of age. Data were synthesised using random-effects meta-analysis models, using separate models for each outcome, comparison, and timepoint where data allowed. Sub-analyses were performed for PCV7 and PCV9. Sensitivity analyses were performed excluding cluster RCTs (cRCT) from the meta-analyses for relevant outcomes and timepoints.

This review was registered with PROSPERO (CRD42024560160) and reported in line with PRISMA guidelines.

Results

There were 3,219 articles screened and 16 met the inclusion criteria for this systematic review. Of these, 15 were articles generated from seven individually randomised RCTs, two cRCTs, and one observational study. There were six RCTs and one cRCT for PCV13, five RCTs and one cRCT for PCV10 (GSK), zero for PCV10 (PneumoSil), zero for PCV9 and two RCTs for PCV7. The nine trials were conducted across five WHO regions (Africa, the Americas, Europe, South-East Asia, and the Western-Pacific) and conducted in low, lower-middle, upper-middle, and high-income settings. The observational PCV13 study was conducted in England. There were limited data available for PCV7 and none for PCV9.

For the outcome of IPD, data on incidence rates were available from a single surveillance study in England comparing 1p+1 versus 2p+1 schedules in children under five years of age, while no data were available for comparisons of 1p+1 versus 3p+0, 3p+1, or 0p+0 schedules, nor for VT or serotype-specific IPD for any schedule.

This study reported no difference in VT IPD in children under five years old during the 1p+1 period compared with the 2p+1 period. The commonest VTs were serotype 3 (8%, a known vaccine failure) with increases in 19A (7%) and 19F (4.4%) and some increase in 9V and 23F in 2022-2023 compared with pre-pandemic years.

For the outcome of pneumonia data on the incidence of radiological pneumonia was available from a single non-inferiority cRCT of 1p+1 vs 3p+0 using PCV13 in The Gambia. This cRCT enrolled 33,000 infants through EPI clinics between 22 August 2019 and 31 October 2023, with 18,356 in the 1p+1 group (35 clusters) and 14,644 in the 3p+0 group (33 clusters). Among 18,355 1p+1 group participants, there were 254 events of radiological pneumonia, and 196 events in the 14,464 3p+0 group participants. The incidence of radiological pneumonia was 0.014 (95% CI 0.012 to 0.017)) in the 1p+1 group and 0.013 (95% CI 0.011 to 0.016)in the 3p+0 group. The adjusted incidence proportion ratio comparing the 1p+1 to the standard 3p+0 schedule was 1.06 (95% CI 0.81 to 1.39), indicating a similar risk of radiological pneumonia between schedules.

Post-primary series

1p vs 0p: For PCV13, neither the 1p nor 0p were favoured for VT carriage. There were no non-vaccine type (NVT) carriage data.

For PCV10, the 1p was favoured compared to 0p for VT carriage, while there was no difference between 1p and 0p for NVT and serotype-specific carriage.

There were no serotype-specific IgG level or OPA data for either vaccine.

1p vs 2p: For PCV13 1p vs 2p, there was no difference for VT carriage; 2p was favoured for all serotype-specific IgG levels except serotype 3, for which results favoured neither 2p or 1p.

For PCV10, neither 1p nor 2p was favoured for VT carriage, and sensitivity analyses excluding the cRCT found minimal difference in the overall findings. Neither 1p nor 2p was favoured for NVT carriage, while 2p was favoured for IgG levels for all serotypes.

There were no OPA data for either vaccine.

1p vs 3p: For PCV13 neither 1p nor 3p were favoured for VT carriage. For serotype-specific IgG, 3p was favoured compared with 1p for all serotypes except for serotype 3, for which neither 1p nor 3p was favoured.

For PCV10, neither 1p nor 3p was favoured for VT carriage. Results from the sensitivity analyses excluding the cRCT were similar to the combined analysis including both individually randomised RCTs and cRCTs. Neither 1p nor 3p was favoured for NVT carriage. For serotype-specific IgG, limited data found 3p was favoured for all serotypes compared with 1p.

There were no OPA data for either vaccine.

Sub-analyses with PCV7 and PCV9: Data were available for post-primary shared PCV7-type carriage data for 1p vs 0p, 1p vs 2p, and 1p vs 3p, along with IgG data for 1p vs 2p and 1p vs 3p. Additionally, very limited post-primary PCV9 shared serotype data (serotypes 1 and 5) were available, with IgG data for 1p vs 2p and 1p vs 3p only.

For the seven serotypes shared across PCV7, PCV9, PCV10, and PCV13, sub-analyses of serotype-specific carriage did not consistently favour 1p, 2p, or 3p. 2p and 3p were favoured over 1p for serotype-specific IgG GMC. No OPA data were available. These findings suggest similar carriage outcomes across schedules, with higher IgG levels in 2p and 3p regimens.

For sub-analyses of the additional serotypes 1 and 5 shared across PCV9, PCV10, and PCV13, there were no carriage data for 1p, preventing comparisons. For serotype-specific IgG, 2p and 3p were favoured vs 1p. No OPA data were available. These findings suggest that 2p and 3p schedules may result in higher IgG levels for both serotypes.

Pre-final dose

1p vs 0p: There were no data.

1p vs 2p: For PCV13 serotype-specific IgG GMC, 2p was favoured over 1p for 5/13 serotypes (1, 6A, 6B, 9V, and 14), while there was no difference between 1p and 2p for other 8/13 serotypes. There were no carriage or OPA data.

For PCV10 serotype-specific IgG GMC, 2p was favoured over 1p for 6/10 serotypes (6B, 9V, 14, 18C, 19F, and 23F), with no difference between 1p and 2p for the other 4/10 serotypes. There were no carriage or OPA data.

1p vs 3p: Data from a single RCT for PCV13 1p vs 3p indicated serotype-specific IgG levels favoured 3p for 4/13 serotypes (6A, 6B, 14, and 19A), for serotype 23F, 1p achieved higher IgG levels than 3p, and for the remaining 8/13 serotypes (1, 3, 4, 5, 7F, 9V, 18C and 19F) there was no difference between 1p and 3p. There were no carriage or OPA data.

A single RCT for PCV10 comparing 1p and 3p favoured 3p for 8/10 serotypes. Neither 1p nor 3p were favoured for the other 2/10 serotypes (1 and 5). There were no carriage or OPA data.

Post-final dose to less than two years

1p+1 vs 0p+0: For PCV13, one RCT found lower VT carriage following 1p+1 compared with 0p+0. For serotype-specific IgG, 1p+1 was favoured for all serotypes except 18C and 23F, for which results were similar. There were no OPA data.

For PCV10, 1p+1 was favoured for VT carriage compared with 0p+0. For NVT, neither schedule was favoured. Sensitivity analyses excluding the cRCT showed a shift in the effect estimates towards the null for VT (from 0.54 to 0.60) and NVT (from 1.23 to 0.98) and widening of 95% CI, but inferences were similar to the primary analyses. For serotype-specific IgG, 1p+1 was favoured for 8/10 serotypes, and there was no difference for the remaining two serotypes. There were no OPA data.

1p+1 vs 2p+1: For PCV13, neither 1p+1 nor 2p+1 was favoured for VT carriage. IgG results varied by serotype, with 1p+1 favoured for 5/13 serotypes (1, 4, 5, 19A, and 19F); 2p+1 was favoured for 5/13 (6A, 6B, 7F, 18C, and 23F); and neither 1p+1 nor 2p+1 favoured for 3/13 serotypes (3, 9V, and 14). For PCV13 serotype-specific OPA GMT 1p+1 was favoured for 2/13 serotypes (1, and 5); 2p+1 for 2/13 (6A and 9V); and neither 1p+1 nor 2p+1 for 9/13 serotypes (6B, 7F, 14, 19A, 19F, 18C, 23F, 3, and 4).

For PCV10, there was no difference in VT or NVT carriage between 1p+1 and 2p+1. A sensitivity analysis excluding the cRCT was conducted, and results were similar to the primary analysis. For the IgG logGMR, 1p+1 was favoured for serotype 4. 2p+1 was favoured for serotypes 6B and 18C. For the remaining serotypes (1, 5, 7F, 9V, 14, 19F, and 23F) the results did not favour either schedule 1p+1 nor 2p+1. OPA logGMRs favoured 1p+1 for serotype 5 and neither 1p+1 nor 2p+1 for 9/10 serotypes (1, 4, 6B, 7F, 9V, 14, 18C, 19F, and 23F).

1p+1 vs 3p+0: Comparing PCV13 1p+1 and 3p+0, two trials estimated a risk ratio (RR) that showed no difference in VT carriage. For serotype-specific IgG and OPA responses, the PCV13 1p+1 schedule was favoured compared with 3p+0 for all serotypes.

For PCV10, neither schedule was favoured for VT or NVT carriage. For VT carriage, sensitivity analyses excluding the cRCT found similar results to the primary analyses. For IgG GMC, the logGMR was higher for 1p+1 compared to the 3p+0 for all 10 serotypes. For PCV10 serotype-specific OPA GMT 1p+1 was favoured compared with 3p+0 for all serotypes, except for serotype 1.

1p+1 vs 3p+1: There were no data for PCV13.

PCV10 1p+1 vs 3p+1 had limited carriage data, which favoured neither 1p+1 nor 3p+1 for VT or NVT carriage. There were no PCV10 IgG or OPA data.

Final dose given at six or nine months: For this sub-analysis, there were no PCV13 data. For PCV10, post-final IgG and OPA data for 1p+1 with the final dose at six or nine months versus 2p+1 were available. For IgG GMC, when the final dose was administered at six months, 1p+1 resulted in higher IgG levels than 2p+1 for 8/10 serotypes (1, 4, 6B, 9V, 14, 18C, 19F, and 23F); but there was no difference in IgG levels for 2/10 serotypes (5 and 7F). For OPA, 2p+1 resulted in higher IgG levels for several serotypes. No carriage data were available.

Comparing 2p+1 with 1p+1 with the final dose given at nine months, 1p+1 was favoured for IgG GMC for serotype 4, 2p+1 for serotypes 6B and 18C, and neither schedule for the remaining serotypes (1, 5, 7F, 9V, 14, 19F, and 23F). For OPA neither 1p+1 nor 2p+1 were favoured. No carriage data were available.

Post-final dose two to five years

1p+1 vs 0p+0: There were no data.

1p+1 vs 2p+1: PCV13 1p+1 was favoured for VT carriage at 36 months compared with 2p+1, However, by 60 months, neither 1p+1 nor 2p+1 was favoured. Compared with PCV13 2p+1, 1p+1 was favoured for NVT carriage at 48 months but neither was favoured at later time points. There were no immunogenicity data.

For PCV10, neither 1p+1 nor 2p+1 was favoured for VT carriage at any time point, while 1p+1 was favoured at 48 months, but neither 1p+1 nor 2p+1 was favoured at other time points. There were no immunogenicity data.

1p+1 vs 3p+0: There were no data.

1p+1 vs 3p+1: There were no data.

Risk of Bias

Most randomised trials had some risk of bias, with concerns in at least one domain, though a few had a low overall risk. The non-randomised study had a moderate risk of bias due to issues in two domains.

GRADE

GRADE assessments were conducted for 1p+1 vs 2p+1 and 1p+1 vs 3p+0.

IPD: low confidence for PCV13 1p+1 vs 2p+1

Radiologic pneumonia: moderate confidence for PCV13 1+1 vs 3+0

Post primary:

VT carriage: high confidence for both PCV13 and PCV10 for 1p+1 vs 2p+1 and 1p+1 vs 3p+0.

Serotype-specific IgG ≥0.35 µg/mL: moderate confidence in the evidence for PCV13 when comparing 1p vs 2p, and low confidence for PCV10 for the same comparison, with only one study assessing 1p vs 3p for both vaccines.

Post final dose to <2 years:

VT carriage: moderate confidence for PCV13 and low confidence for PCV10.

Serotype-specific IgG logGMR: low confidence for PCV13 and moderate for PCV10.

Conclusions

Post-primary series, compared to no vaccine, 1p PCV10 reduced VT carriage, but there was no difference in VT carriage following PCV13. For 1p versus 2p or 3p post-primary series, for both vaccines there were no differences in carriage, but the duration of the effect is unknown as there were no pre-final carriage data. For both vaccines, there were differences in immunogenicity with 2p and 3p being more immunogenic than 1p. These immunogenicity findings were consistent for sub-analyses including PCV7 and PCV9 shared serotypes. Additionally, these findings persisted to the pre-final dose. There did not appear to be substantial differences for 1p+1 vs 2p+1 when the final 1p+1 dose was given at six or nine months.

Following the final dose, and before two years of age, 1p+1 had a higher reduction in VT carriage vs no dose. There were no differences in VT carriage between 1p+1 vs 2p+1 or 3p+0. Less serotype replacement was seen with 1p+1 vs 2p+1 for both vaccines at different time points. For 1p+1 vs 3p+1, there were no PCV13 data, and only VT carriage data for PCV10, which showed no difference by schedule.

There were some limitations to these analyses. Most notably were the small number of carriage events at all time points, limiting the power to find any difference. Additionally, included trials were conducted in settings where the additional efficacy gained from indirect effects varied. For instance, trials in Canada, South Africa, The Gambia, and the UK were conducted following national PCV introduction 10 or more years prior to the trial being

undertaken, while the cRCT conducted in Nha Trang, Vietnam was undertaken four years after PCV use in the clusters. In contrast, trials in Fiji, India, and the RCT in Ho Chi Minh City, Vietnam, were conducted when PCV had not been introduced into the national program and therefore no additional indirect effects. In addition, individually randomised RCTs and cRCTs may be evaluating different vaccine effects. Unlike the individually randomised RCTs, which conducted nasopharyngeal swabs at specific time points relative to vaccination, the cRCTs in The Gambia and Nha Trang, Vietnam, assessed carriage in predefined age groups through cross-sectional surveys. This design means that carriage estimates are not directly linked to specific vaccination time points, which could limit direct comparisons of carriage dynamics post-vaccination. However, our sensitivity analyses to account for potential differences in study design found that while point estimates of group comparisons changed slightly and 95% CI generally widened after exclusion of the cRCTs, the overall conclusions remained similar to the primary analyses.

Most randomised trials had some risk of bias, with concerns in at least one domain, though a few had a low overall risk. The non-randomised study had a moderate risk of bias due to issues in two domains. GRADE assessment was conducted for 1p+1 vs 2p+1 and 1p+1 vs 3p+0. Available evidence suggests low confidence in IPD outcomes for PCV13 1p+1 vs 2p+1 due to limitations inherent in observational studies, while confidence in the effect of PCV13 1+1 and 3+0 on radiologic pneumonia is moderate. Confidence in the evidence for VT carriage post-primary series is high for both PCV13 and PCV10. For serotype-specific IgG ≥0.35 µg/mL post-primary series, confidence is moderate-to-low, with PCV13 evidence rated as moderate and PCV10 evidence rated as low. Confidence in VT carriage post-final dose to <2 years is moderate for PCV13 and low for PCV10. Confidence in serotype-specific IgG logGMR post-final dose is low for PCV13 and moderate for PCV10.

INTRODUCTION

Rationale

Pneumococcal disease, including invasive pneumococcal disease (IPD), pneumonia and meningitis, pose major global public health challenges, especially in children under five years old (1, 2). Pneumococcal carriage is common and is a precursor for pneumococcal disease (3). Pneumococcal conjugate vaccines (PCV) have reduced vaccine-type (VT) pneumococcal carriage and pneumococcal disease through direct and indirect effects (4-7). Since 2007, PCV has been introduced in 166 countries, with 159 countries having a universal infant immunisation program and seven having high-risk infant immunisation programs (8).

Initially, WHO recommended PCV to be given as 3p+0 or 3p+1 (9). In 2012, the WHO expanded the recommendations so that countries may use either three primary doses without a booster (3p+0) or two primary doses with a booster (2p+1) (10). Most countries use a three-dose schedule: 82 countries use 2p+1, and 68 countries use 3p+0 (11). Fourteen countries use a 3p+1 schedule (11).

Findings from recent randomised controlled trials (RCTs) have suggested that a reduced dose schedule (1p+1) could provide similar protection as three dose schedules. At least seven RCTs comparing 1p+1 to three dose schedules have been conducted, and many of these have been completed. A reduced dose schedule may allow immunisation programmes to reduce the number of injections and costs. So far, the UK is the only country using 1p+1 (11).

This systematic review aims to determine the efficacy and effectiveness of 1p+1 compared with the 0p+0, 2p+1, 3p+0, and 3p+1 on IPD, pneumonia, immunogenicity, and pneumococcal nasopharyngeal carriage.

Objectives

Our primary objective was to determine the efficacy/effectiveness of PCV 1p+1, with the final dose given at or after nine months, compared with 3p+0, 2p+1, and 3p+1. We analysed PCV dose schedules, comparing two doses (1p+1) against three (2p+1, 3p+0) and four doses (3p+1). Additionally, we assessed the efficacy/effectiveness of 1p+1 compared with 0p+0.

Review Question (PICO)

In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age, compared with children who received zero, three or four doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: three primary doses and one booster (3p+1), two primary doses and one booster (2p+1), three primary doses and no booster (3p+0), or zero doses (0p+0).

METHODS

Eligibility criteria

For inclusion, studies needed to compare two doses of PCV (PCV7, PCV9, PCV10, or PCV13) with the first dose scheduled at the same time point as a dose of a DTP-containing vaccine, with a final dose at 6-18 months of age (1p+1) (intervention) with children who received three or four doses of PCV as per standard WHO-recommended schedules (3p+1, 2p+1, or 3p+0), or zero doses (comparator schedules).

Studies eligible for inclusion were RCTs assessing disease, immunogenicity, and nasopharyngeal carriage outcomes, as well as non-randomised studies, including cohort studies, case-control studies, and population-based surveillance studies reporting IPD and pneumonia. Included studies must have been conducted among children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose before 18 months of age (population).

Studies published after 1 January 2000 were considered. Only publications in English were included. Further details on eligibility criteria can be found in Appendix 4.

Information sources, strategies, and study records

A systematic literature search was conducted on 27 June 2024 to identify all relevant studies evaluating reduced-dose PCV schedules. Electronic databases searched include MEDLINE via Ovid, EMBASE via Ovid, and PubMed (See Appendix 5). The search was augmented by reviewing clinical trial databases and relevant conference abstracts. Study record information covering data management and data extraction can be found in Appendix 6.

Risk of bias

Risk of bias in individual studies

We assessed the risk of bias in each included study using tools specific to the study design. For RCTs, the risk of bias assessment was conducted using the Risk of Bias 2.0 (RoB2) tool (and extensions for variants of RCTs, including cluster RCTs (cRCT)). Non-randomised studies of interventions (NRSIs) were assessed using the ROBINS-I tool (for cohort studies) and, as necessary, an extension of the ROBINS-I tool (for case-control studies).

Outcome definitions and timing of outcome measurement

Outcome definitions and the timing of the outcome measurements are summarised in Table 1, with further details in Appendix 7. For IPD and pneumonia, analyses included age groups under five years. Nasopharyngeal carriage outcomes were assessed post-primary, pre-final dose, and post-final doses. Immunogenicity outcomes (IgG and OPA) were assessed at similar time points (Table 1). Data consistency was verified, and results are presented in GRADE tables using GRADE methodology.

Table 1 Description of outcome variables

Outcome domain	Measurement tool/definition	Outcome measure	Summary measure	Timepoint/age

Invasive pneumococcal disease (IPD)	Invasive pneumococcal disease[&]	Invasive pneumococcal disease	Incidence	Age < five years
	Vaccine-type invasive pneumococcal disease[&]	Vaccine-type invasive pneumococcal disease*	Incidence	Age < five years
	Serotype-specific invasive pneumococcal disease[&]	Serotype-specific invasive pneumococcal disease	Incidence	Age < five years
Pneumonia	Pneumococcal pneumonia[&]	Pneumococcal pneumonia	Incidence	Age < five years
	Clinical pneumonia[&]	Clinical pneumonia	Incidence	Age < five years
	Radiological (x-ray confirmed) pneumonia[&]	Radiological (x-ray confirmed) pneumonia	Incidence	Age < five years
	Hospitalised pneumonia	Hospitalised pneumonia	Incidence	Age < five years
Pneumococcal nasopharyngeal carriage	Detection of pneumococcal vaccine serotypes in a nasopharyngeal swab^	Vaccine-serotype carriage*	Proportion	Post-primary series and before booster dose
				Post-final to ≤ two years
				Post-final >two to < five years
	Detection of non-vaccine pneumococcal serotypes in a nasopharyngeal swab	Non-vaccine serotype carriage~	Proportion	Post-primary series and before booster dose
				Post-final to ≤ two years
				Post-final > two to < five years
	Detection of specific pneumococcal serotypes in a nasopharyngeal swab	Serotype-specific carriage	Proportion	Post-primary series and before booster dose
				Post-final to ≤ 2 years
				Post-final to > two to < five years
Immunogenicity	Serotype-specific antibody levels, measured as immunoglobulin G (IgG) in µg/mL[#]	Serotype-specific IgG concentration (µg/mL)	Geometric mean	One-month post-primary series
				Pre-final
				One-month post-final
		Serotype-specific IgG ≥0.35µg/mL	Proportion	One-month post-primary series
	Serotype-specific opsonophagocytic activity (OPA), (unit= opsonisation index)[#]	Serotype-specific OPA titres (OIs)	Geometric mean	Pre-final
				One-month post-final
		Serotype-specific OI≥8	Proportion	Pre-final
				One-month post-final

Footnotes: # For immunogenicity, we will include data based on all laboratory methods and record assays used; ^ For nasopharyngeal carriage, we will include carriage data based on all serotyping methods used, and record laboratory methods used; * Vaccine-type carriage is defined as detection of one or more serotypes included in the vaccine. For PCV7, vaccine serotypes are: 4, 6B, 9V, 14, 18C, 19F and 23F. For PCV9, vaccine serotypes are: 1, 4, 5, 6b, 9v, 14, 18C, 19F, 23F. For PCV10 GSK, vaccine serotypes are: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, and for PCV10 PNEUMOSIL vaccine serotypes are 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F. For PCV13, vaccine serotypes are: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F; ~Non-vaccine serotype carriage is detection of one or more serotypes that are not included in the vaccine (where vaccine types are defined separately for PCV7, PCV9, PCV10, and PCV13 above); [&] The case definitions for IPD and pneumonia may vary by study. We will include data based on all case definitions, and record the definitions used.

Methods of analysis

Appendix 7 provides details regarding descriptive summary statistics and meta-analysis methods. Our primary objective was to evaluate the effectiveness of PCV 1p+1, with the final dose given at or after nine months, compared with 3p+0, 2p+1, and 3p+1. We analysed PCV dose schedules, comparing two doses (1p+1) against three (2p+1, 3p+0) and four doses (3p+1). Additionally, we assessed the efficacy/effectiveness of 1p+1 compared with receiving zero doses of PCV (0p+0). We conducted meta-analyses for each comparison, outcome, and timepoint, separately analysing data from randomised and non-randomised studies. If all studies in a specific analysis provided results as summary measures (e.g. carriage prevalence in each group separately), these data were used in the meta-analysis. If effect measures were provided instead (e.g. prevalence ratio comparing two groups), the effect measures and standard errors were pooled in the meta-analysis. Data permitting, meta-analyses were conducted separately for each schedule comparison, outcome, and time point. Random-effects models were used to account for expected heterogeneity in clinical and methodological characteristics. For cRCTs, we have incorporated results as provided by authors; for the cRCT in The Gambia, effect measures and 95% CI adjusted for clustering; while for the Nha Trang/Vietnam cRCT, data did not account for clustered study design as per their published protocol.

Multi-arm trials were combined into single pair-wise comparisons. Subgroup analyses considered PCV formulation and timing of the booster dose (six or nine months). Sensitivity analyses were undertaken for outcomes that combined data from individually randomised trials and cRCTs, whereby data from individual randomised trials only were included. Data from eligible studies using PCV7 or PCV9, where the first dose was given before six months of age and report post-first dose data, were included in sub-analyses only (Appendix 12) as lower valency vaccines may have higher immunogenicity than PCV10/13.

RESULTS

Literature search and study selection

Out of 3,219 articles initially identified, 16 articles (from seven individually randomised RCTs, two cRCTs and one observational surveillance study, were eligible for meta-analysis after removing duplicates and exclusions based on study design, intervention, outcome, and dosing schedule. (See Appendix 10, PRISMA FLOW DIAGRAM).

Description of study characteristics

See Appendix 11, STUDY CHARACTERISTICS.

Observational studies with clinical outcomes

IPD

There was one eligible observational study assessing the effect of 1p+1 versus 2p+1 on IPD, and no studies comparing 1p+1 and 3p+0, 3p+1 or zero doses. This observational study from England using IPD surveillance data, compared IPD incidence before and after the change from 2p+1 to 1p+1 in 2020. Overall, the IPD incidence was higher in 2022–23 in children aged one to less than five years compared with 2019-20 (incidence rate ratio [IRR] 1·58 [95% confidence interval (CI) 1·16 to 2·17] p=0·004). For PCV13 VT IPD, there was no difference in incidence among children aged 1-<5 years in 2022-23 versus 2019-20 (IRR 1.54 [95% CI 0.66 – 3.60] p=0.32) and for infants (IRR 2.46 [95% CI 0.84 – 7.21] p=0.10).

Pneumonia

The cRCT in The Gambia (12), evaluating PCV13 3p+0 versus 1p+1 on radiologic pneumonia, showed that among 18,355 1p+1 group participants, there were 254 events of radiological pneumonia, while 196 events occurred among 14,644 3p+0 group participants. The incidence of radiological pneumonia was 0.014 (95% CI 0.012 to 0.017) in the 1p+1 group and 0.013 (95% CI 0.011 to 0.016) in the 3p+0 group. The adjusted incidence proportion

ratio comparing the 1p+1 to the standard 3p+0 schedule was 1.06 (95% CI 0.81 to 1.39), indicating a similar risk of radiological pneumonia between schedules.

RCTs with carriage and immunogenicity outcomes, by time point

Post-primary series

This section covers the comparison of different dosing schedules (1p vs 0p, 2p, and 3p) for PCV13 and PCV10, focusing on carriage, IgG levels and OPA.

PCV13 1p vs 0p

Carriage

For PCV13 VT carriage, one eligible study from India compared 1p and 0p, so no meta-analysis was conducted. There was no difference in VT carriage between 1p and 0p (risk ratio (RR) 1.12 [95% CI 0.72 to 1.75]).

Serotype-specific IgG and OPA

There were no data available.

PCV10 1p vs 0p

Carriage

For PCV10 VT carriage, two studies from India and Vietnam, compared 1p and 0p post-primary (Figure 1). There was little evidence of statistical heterogeneity (I^2=0%, τ^2=0.0, p=0.93). The meta-analysis favoured 1p (RR 0.40 [95% CI 0.26 to 0.63]).

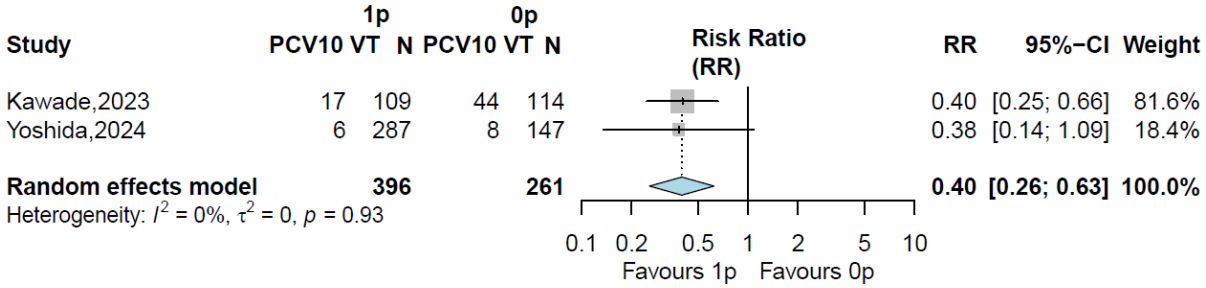


Figure 1 PCV10 vaccine-type carriage post-primary series, comparing 1p and 0p

For PCV10 NVT and serotype-specific carriage, only one study, the Vietnam-based cRCT was analysed. For PCV10 NVT carriage, there was no difference between 1p and 0p (RR 1.16 [95% CI 0.65 to 2.06]).

Sensitivity analyses to determine the effect of trial design (individually randomised vs cRCT) on VT and NVT carriage, were not undertaken as there was only one individually randomised trial.

For PCV10 serotype-specific carriage, serotypes 1, 4, 5, 7F, 9V, and 18C had no events (Figure 2). For the other four serotypes (6B, 14, 19F, 23F) there were limited carriage events and no difference between 1p and 0p.

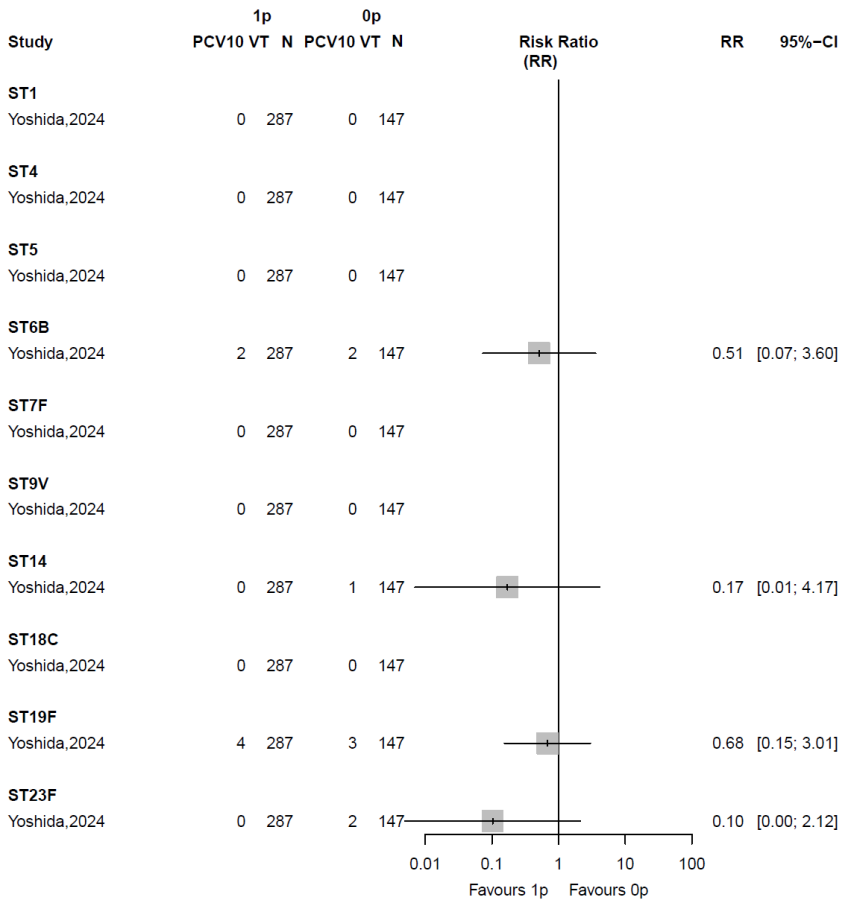


Figure 2 PCV10 serotype-specific carriage post-primary series, comparing 1p with 0p

Serotype-specific IgG and OPA

There were no data available.

PCV13 1p vs 2p

Carriage

For PCV13, one RCT conducted in India compared PCV13 VT carriage between 1p and 2p, finding no difference in prevalence (RR 1.01 [95% CI: 0.67 to 1.51]). No data were available for PCV13 NVT or serotype-specific carriage.

Serotype-specific IgG

For PCV13 serotype-specific IgG GMC, a meta-analysis of data from three studies conducted in the UK, India, and South Africa compared 1p and 2p (Figure 3). There was statistical heterogeneity for most serotypes. The meta-analysis results favoured 2p for all serotypes, except serotype 3 for which results favoured neither 1p nor 2p.

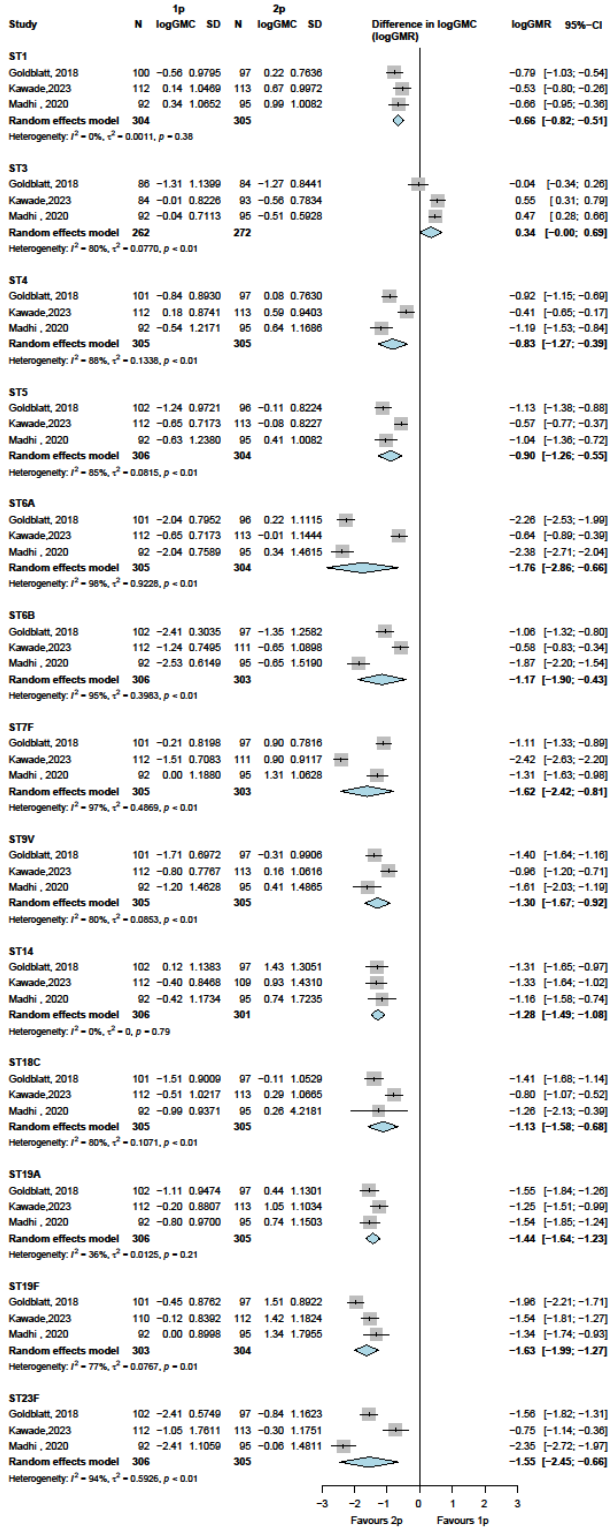


Figure 3 PCV13 serotype-specific IgG logGMR post-primary series, comparing 1p and 2p

For PCV13 serotype-specific IgG ≥0.35 µg/mL, four studies from the UK, India, South Africa, and Canada compared 1p and 2p (Figure 4). Statistical heterogeneity was observed for most serotypes. The meta-analysis results favoured 2p for all serotypes, except serotype 3, for which results favoured neither 1p nor 2p.

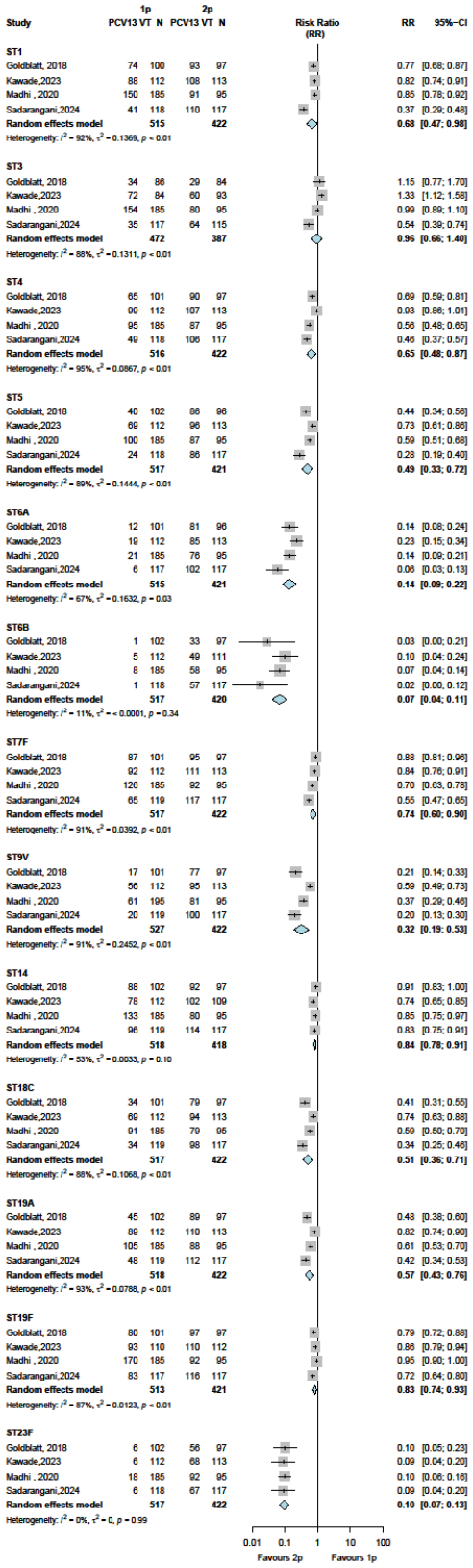


Figure 4 Proportion achieving PCV13 serotype-specific IgG ≥0.35µg/mL post-primary series, comparing 1p and 2p

Serotype-specific OPA

For PCV13, there were no data available.

PCV10 1p vs 2p

Carriage

For PCV10 VT type carriage, two eligible RCTs from India (individually randomised) and Vietnam (cRCT) compared 1p and 2p (Figure 5). There was little evidence of statistical heterogeneity (I^2=0%, τ^2=0, p=0.55). The meta-analysis results favoured neither schedule (RR 0.80 [95% CI 0.48 to 1.33]). To determine the effect of trial design (individually randomised vs cRCT), sensitivity analysis was not undertaken as there was only one individually randomised trial. The estimate from the trial in India had an estimate of (0.74 [95% CI 0.42 to 1.30]), showing minimal change from the combined result (0.80 [95% CI 0.48 to 1.33]), as this trial already had 80% weighting due to the higher number of carriage events.

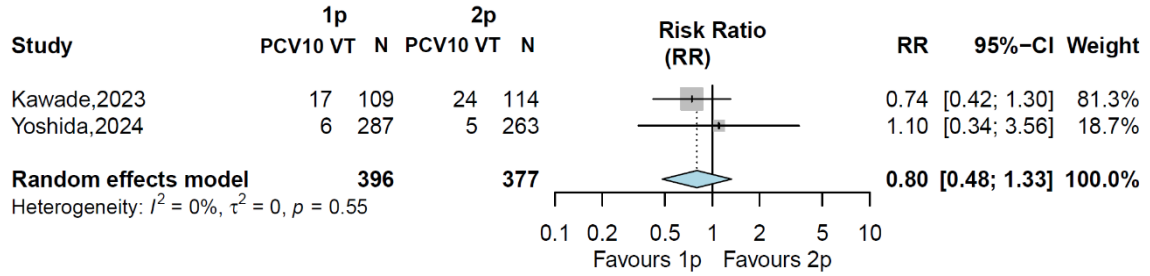


Figure 5 PCV10 vaccine-type carriage post-primary series, comparing 1p and 2p

For PCV10 NVT and serotype-specific carriage, one cRCT from Vietnam provided data comparing 1p and 2p. For PCV10 NVT carriage there was no difference between 1p and 2p (RR 1.04 [95% CI 0.64 to 1.59]). For 8/10 serotypes PCV10 serotypes there were no carriage, so no RR were calculated (Figure 6). For the other two serotypes (6B and 19F), there was no difference between 1p and 2p.

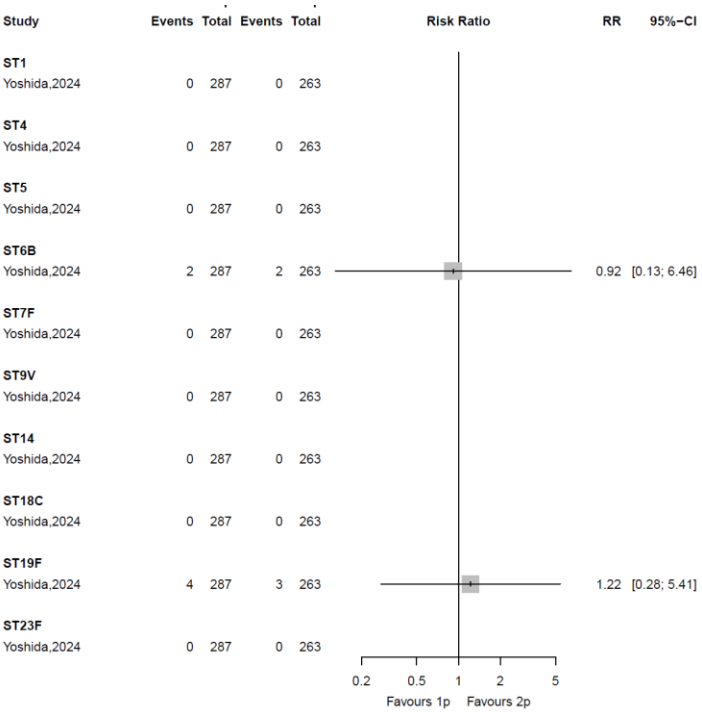


Figure 6 PCV10 serotype-specific carriage post-primary series, comparing 1p and 2p

Serotype-specific IgG

For PCV10 serotype-specific IgG GMC, a meta-analysis of data from two RCTs in India and South Africa compared 1p and 2p (Figure 7). Statistical heterogeneity was observed for most serotypes. 2p was favoured for all serotypes.

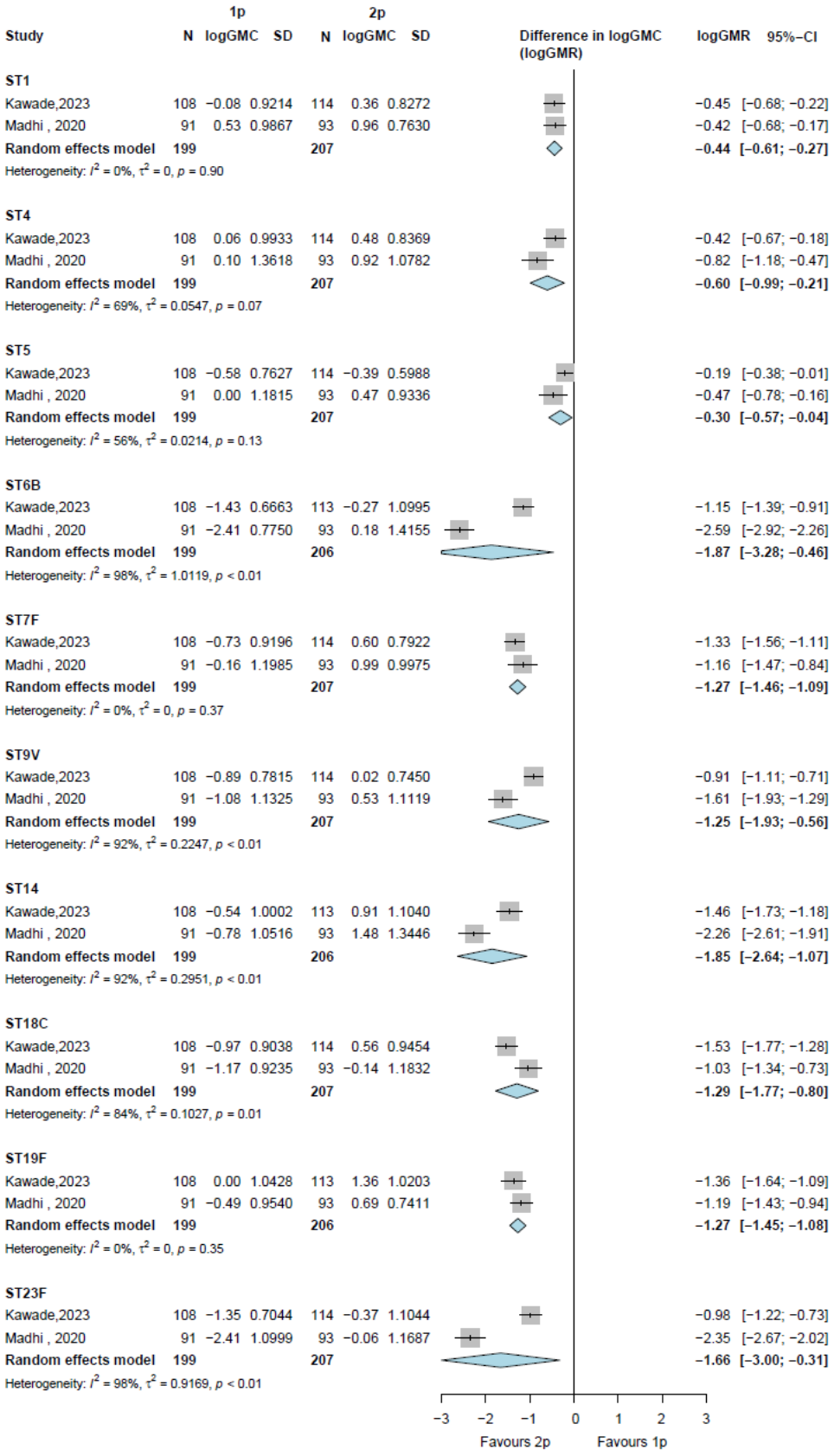


Figure 7 PCV10 serotype-specific IgG logGMR post-primary series, comparing 1p and 2p

For PCV10 serotype-specific IgG ≥0.35 µg/mL, the same two RCTs from India and South Africa compared 1p and 2p (Figure 8). Statistical heterogeneity was observed for most serotypes. 2p was favoured for all serotypes.

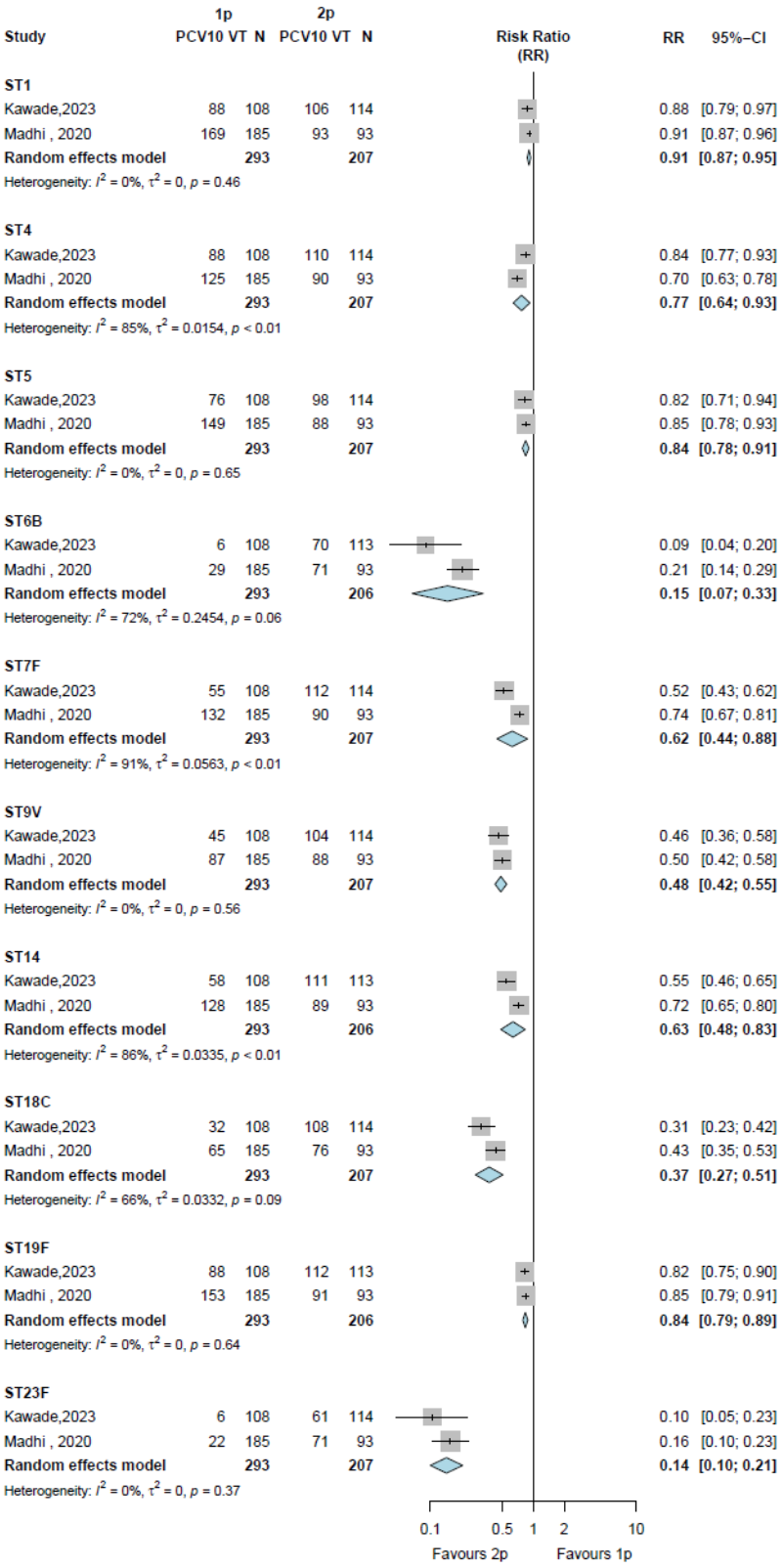


Figure 8 Proportion achieving PCV10 serotype-specific IgG >0.35µg/mL post-primary series, comparing 1p and 2p

Serotype-specific OPA

For PCV10, there were no data available.

PCV13 1p vs 3p

Carriage

For PCV13 VT carriage, two trials from India and The Gambia compared 1p and 3p (Figure 9), incorporating estimates and standard errors to account for clustering in the cRCT. Results favoured neither 1p nor 3p. No data were available for PCV13 NVT or serotype-specific carriage. Sensitivity analyses to determine the effect of trial design (individually randomised vs cRCT) on VT and NVT carriage, were not undertaken as there was only one individually randomised trial.

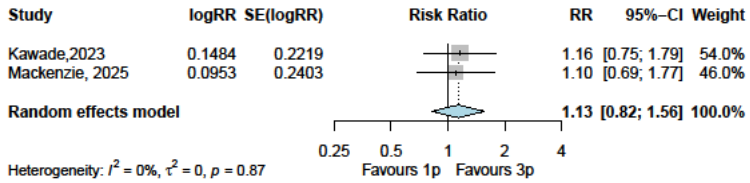


Figure 9 PCV10 vaccine-type carriage post-primary series, comparing 1p and 3p

Serotype-specific IgG

For PCV13 serotype-specific IgG GMC post-primary series, only the RCT in India had data to compare 1p and 3p, so no meta-analysis was conducted. The logGMRs show 3p as achieving higher IgG levels for all serotypes, except serotype 3, for which there was no difference between 1p and 3p (Figure 10).

Figure 10 PCV13 serotype-specific IgG logGMR post-primary series, comparing 1p and 3p

In the same RCT in India, 3p PCV13 was associated with a higher proportion achieving IgG ≥0.35 µg/mL compared with 1p for all serotypes, except serotype 3 for which there was no difference (Figure 11).

Figure 11 Proportion achieving PCV13 serotype-specific IgG ≥0.35µg/mL post-primary series, comparing 1p and 3p

Serotype-specific OPA

For PCV13, there were no data available.

PCV10 1p vs 3p

Carriage

For PCV10 VT carriage, two eligible RCTs from India (individually randomised) and Vietnam (cRCT) compared 1p and 3p post-primary (Figure 12). There was little evidence of statistical heterogeneity (I^2=14%, τ^2=0.0605, p=0.28), and meta-analysis results favoured neither 1p nor 3p. Sensitivity analyses excluding the cRCT and considering only

the individually randomised trial, found no difference between 1p and 3p (RR=0.99 [95% CI 0.54 to 1.82]), similar to the combined analysis of both trial types.

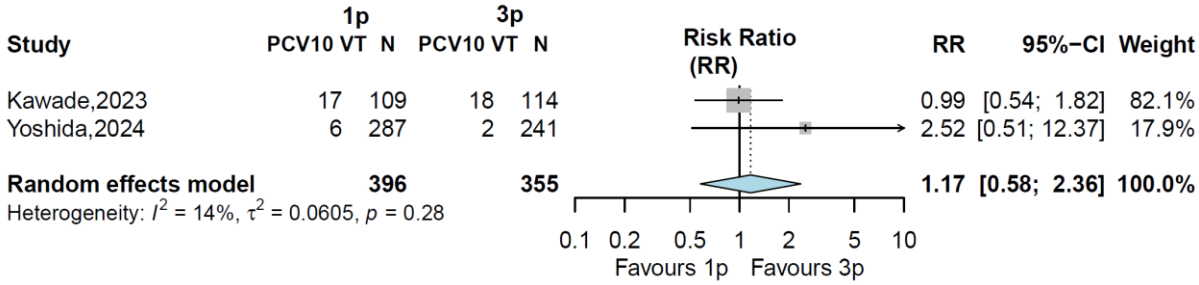


Figure 12 PCV10 vaccine-type carriage post-primary series, comparing 1p and 3p

For PCV10 NVT and serotype-specific carriage, data were available from a single cRCT in Vietnam (Figure 13). There was no difference in prevalence of PCV10 NVT between 1p and 3p (RR 1.06 [95% CI 0.66 to 1.70]). For PCV10 serotype-specific carriage, there were no carriage events for 8/10 serotypes (Figure 12). For the remaining two serotypes (6B and 19F) there were no differences by 1p and 3p, though number of events were very small.

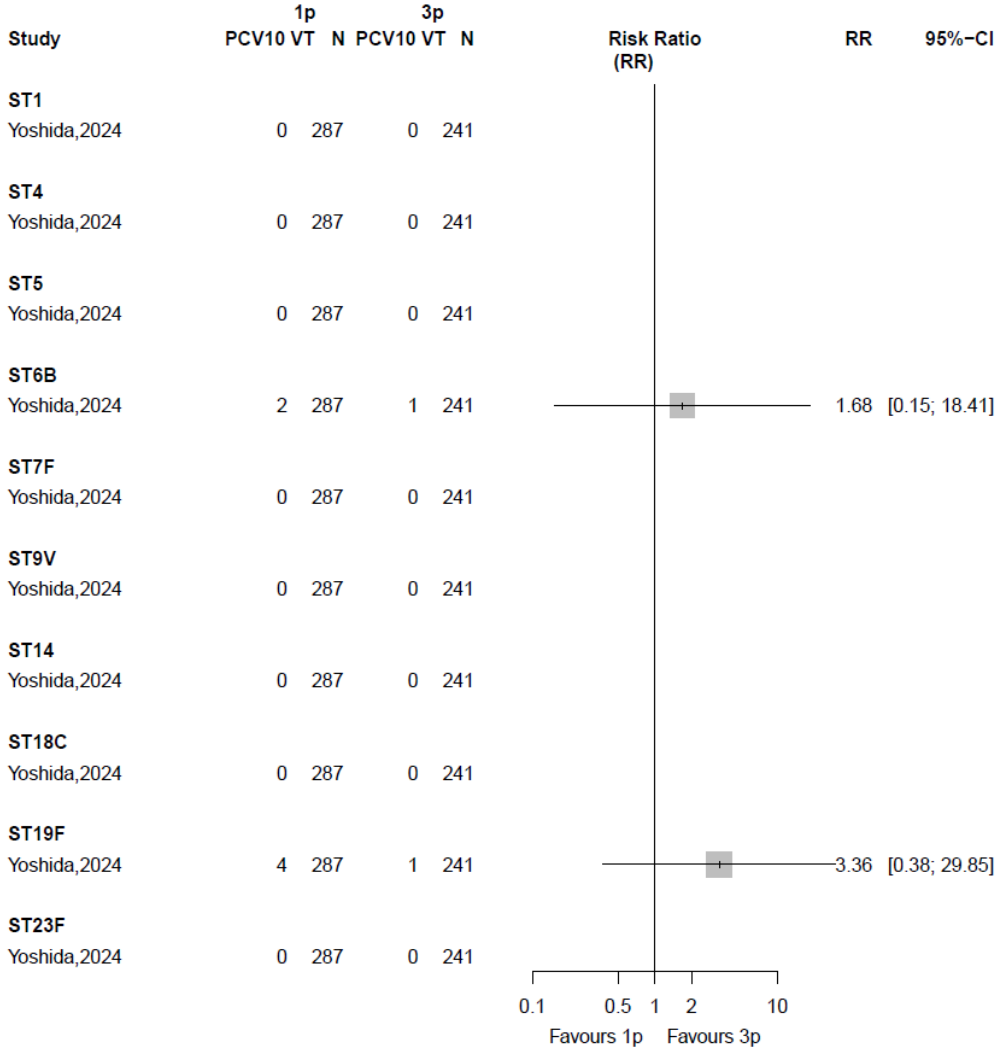


Figure 13 PCV10 serotype-specific carriage post-primary series, comparing 1p and 3p

Serotype-specific IgG

For PCV10 serotype-specific IgG GMC, one RCT from India compared 1p and 3p, so no meta-analysis was conducted. The 3p schedule was associated with higher IgG levels for all serotypes compared with 1p (Figure 14).

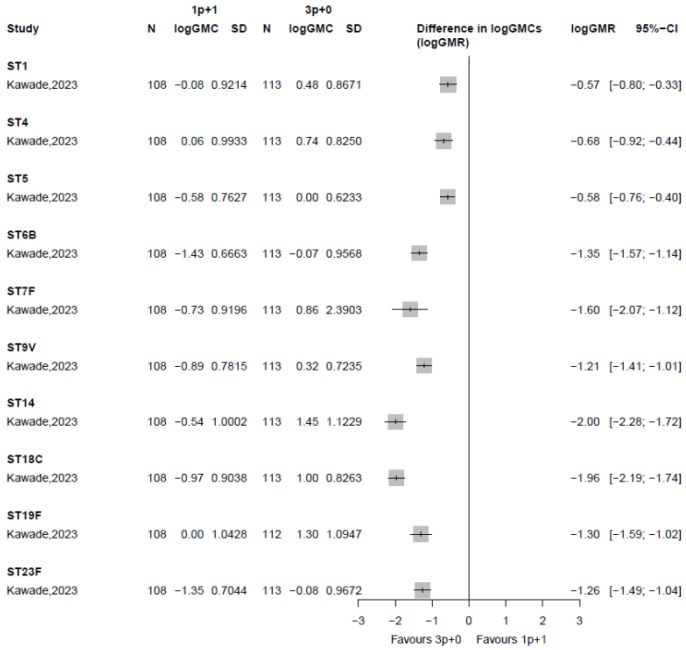


Figure 14 PCV10 serotype-specific IgG logGMR post-primary series, comparing 1p and 3p

Similarly, PCV10 3p was associated with a higher proportion achieving IgG ≥0.35 µg/mL that PCV10 1p for all serotypes (Figure 15).

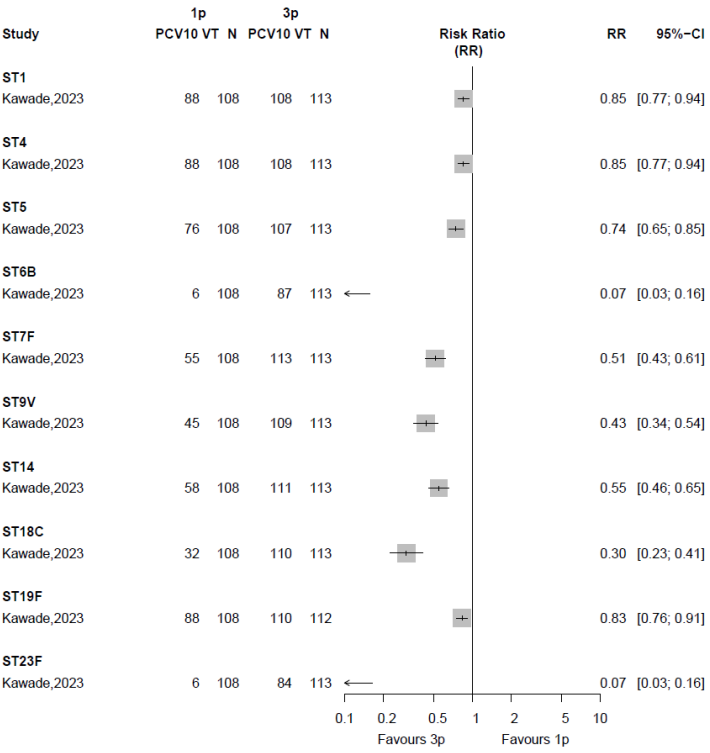


Figure 15 Proportion achieving PCV10 serotype-specific IgG ≥0.35 µg/mL post-primary series, comparing 1p and 3p

Serotype-specific OPA

For PCV10, there were no data.

Pre-final dose immunogenicity

This section presents results comparing serotype-specific IgG by 1p with 0p, 2p, and 3p before the final dose. There were no data to compare PCV13 or PCV10 1p vs 0p.

PCV13 1p vs 2p

Serotype-specific IgG

Two eligible RCTs from India and South Africa compared 1p and 2p one month before the final dose (Figure 16). There was little evidence of statistical heterogeneity for 3/13 serotypes (τ^2=0 and I^2=0%).

The meta-analysis of IgG logGMR results favoured 2p for 5/10 (1, 6A, 6B, 9V, and 14). For 8/13 serotypes (3, 4, 5, 7F, 18C, 19A, 19F, and 23F) results favoured neither 1p nor 2p.

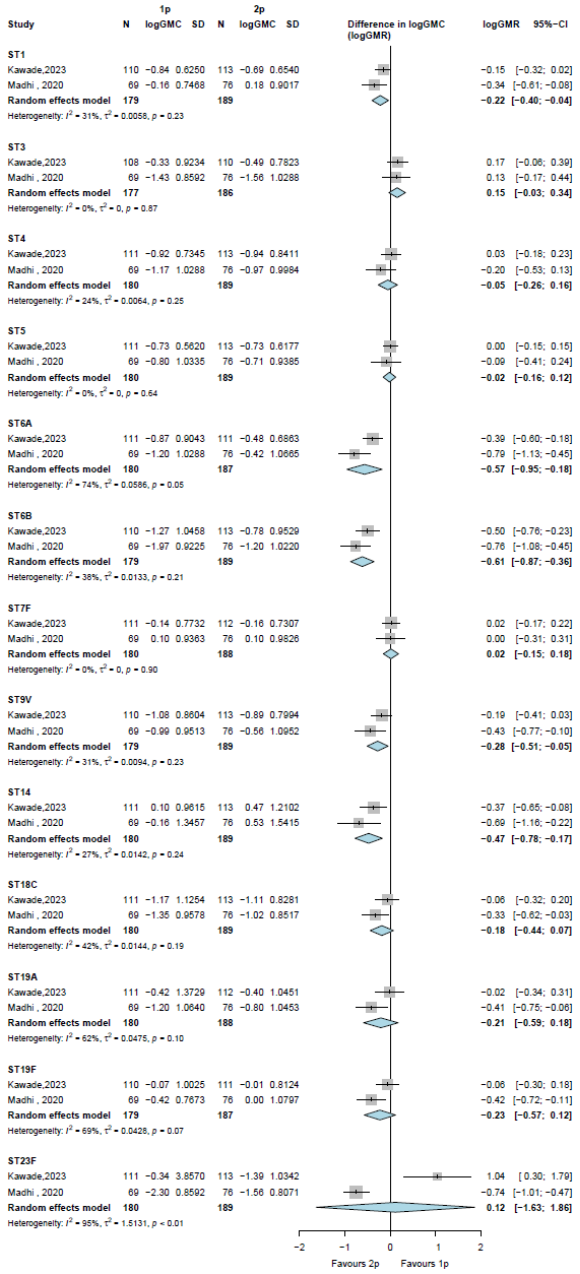


Figure 16 PCV13 serotype-specific IgG logGMR pre-final dose, comparing 1p and 2p

PCV10 1p vs 2p

Serotype-specific IgG

Two eligible RCTs from India and South Africa compared 2p and 1p one-month prior to the final dose (Figure 17). There was little evidence of statistical heterogeneity for 9/10 serotypes (τ^2=0 and I^2=0%).

The meta-analysis of the IgG logGMR results favoured 2p for 6/10 serotypes (6B, 9V, 14, 18C, 19F, and 23F). For the remaining serotypes (1,4,5, and 7F) the meta-analysis did not favour either 1p or 2p.

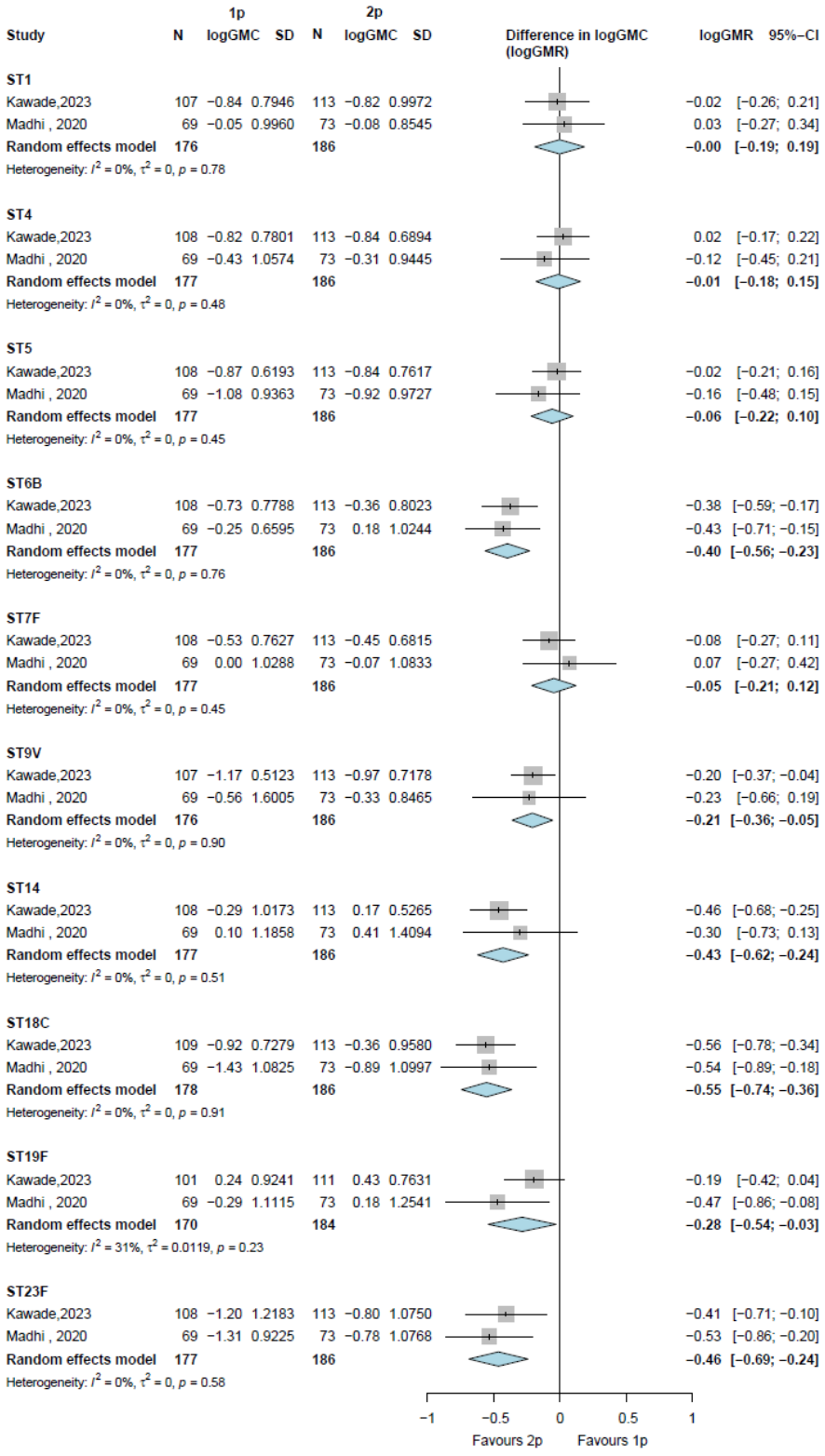


Figure 17 PCV10 serotype-specific IgG logGMR pre-final dose, comparing 1p and 2p

PCV13 1p vs 3p

Serotype-specific IgG

One RCT from India compared 1p with 3p one month prior to the final dose, so no meta-analysis was done. For 8/13 serotypes (1, 3, 4, 5, 7F, 9V, 18C and 19F) there was no difference between 1p and 3p (Figure 18). For serotype 6A, 6B, 14, and 19A, 3p achieved higher IgG levels compared with 3p. For serotype 23F, 1p achieved higher IgG levels than 3p.

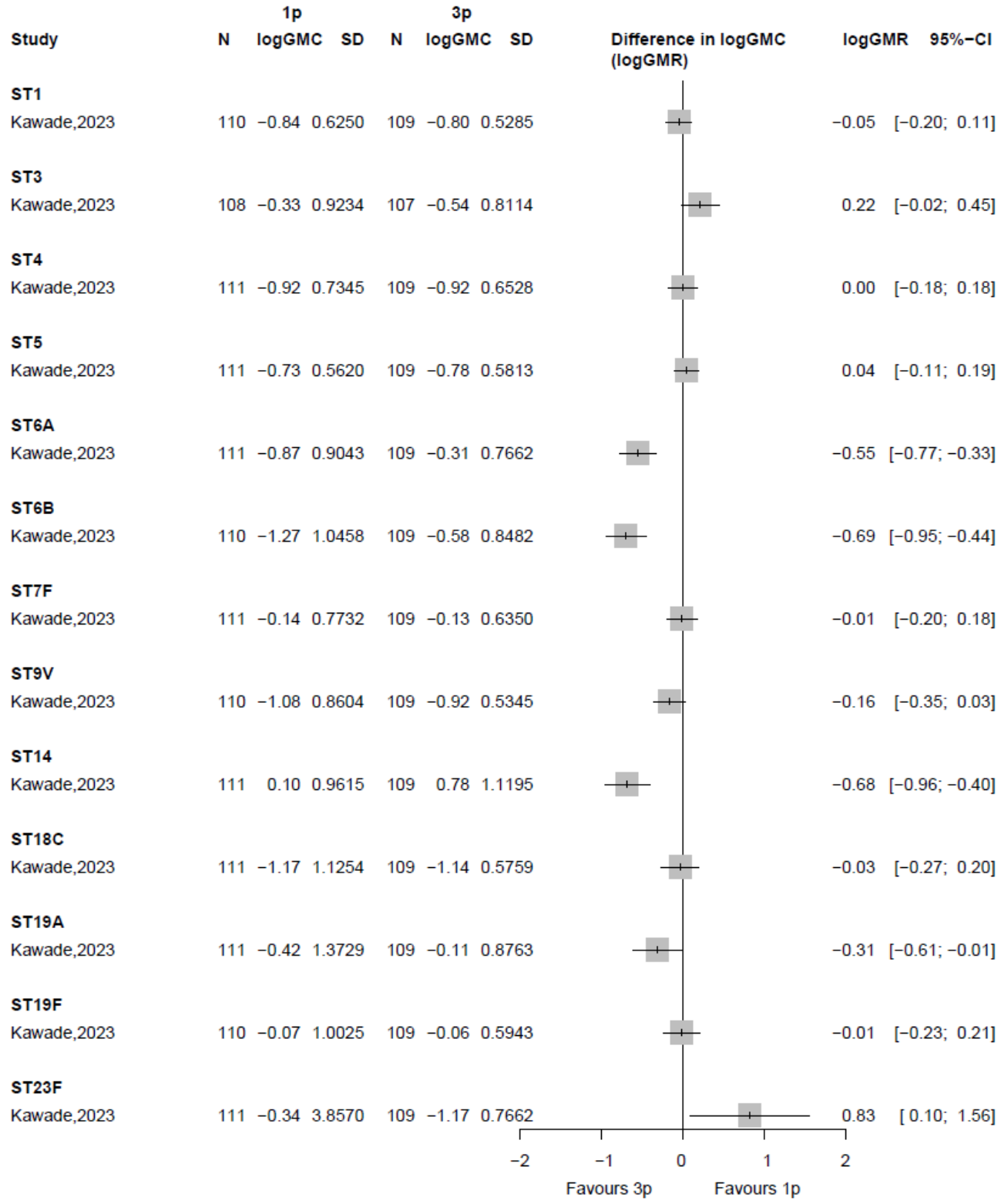


Figure 18 PCV13 serotype-specific IgG logGMR pre-final dose, comparing 1p and 3p

PCV10 1p vs 3p

Serotype-specific IgG

One RCT from India compared 1p with 3p one-month before the final dose, so no meta-analysis was done. Results are shown in Figure 19. For 8/10 serotypes (4, 6B, 7F, 19V, 14, 18C, 19F, and 23F) 3p was associated with higher IgG levels than 1p. For 2/10 serotypes (1 and 5) IgG GMCs were similar between 1p and 3p.

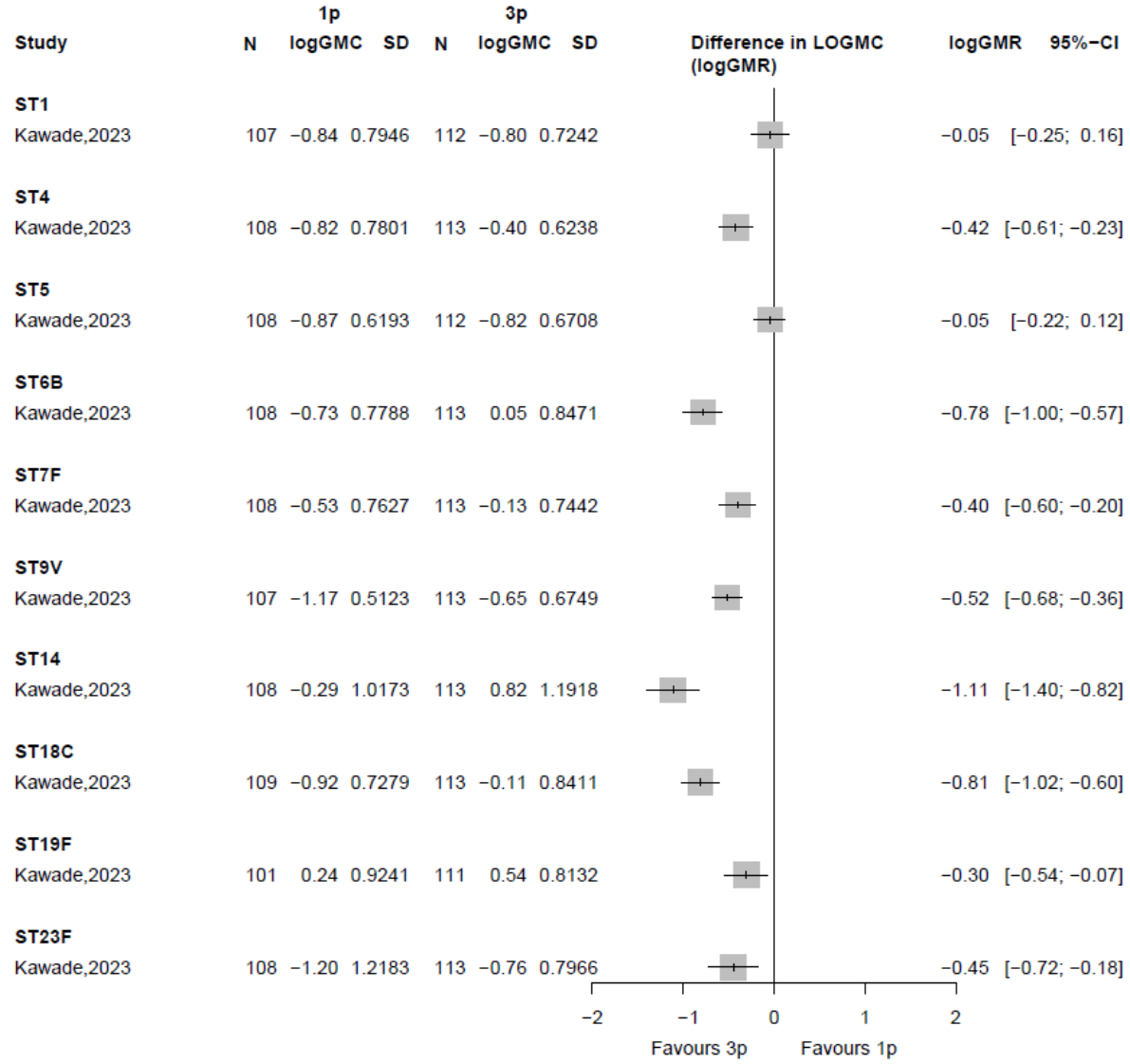


Figure 19 PCV10 serotype-specific IgG logGMR pre-final dose, comparing 1p and 3p

Post-final PCV dose to ≤ 2 years of age

This section examines the effects of different dosing schedules (1p+1, 0p+0, 2p+1, 3p+0) on VT carriage and immunogenicity outcomes in children under two years old post final dose.

PCV13 1p+1 vs 0p+0

Carriage

For PCV13 VT carriage, one eligible RCT in India compared 1p+1 and 0p+0 at 18 months of age, so meta-analysis was not done. Available data indicate prevalence of PCV13 VT carriage was lower following 1p+1 compared with 0p+0 (RR 0.65 [95%CI 0.43 to 0.99]).

Serotype-specific IgG

For PCV13, one RCT in India had with serotype-specific IgG GMC data one-month post-final dose comparing 1p+1 and 0p+0, so no meta-analysis was undertaken. Available data indicate PCV13 1p+1 achieved higher IgG levels than 1p+1 for all serotypes, except 18C and 23F, for which IgG levels were similar between 1p+1 and 0p+0 (Figure 20).

There were no data available for serotype-specific IgG ≥0.35 µg/mL.

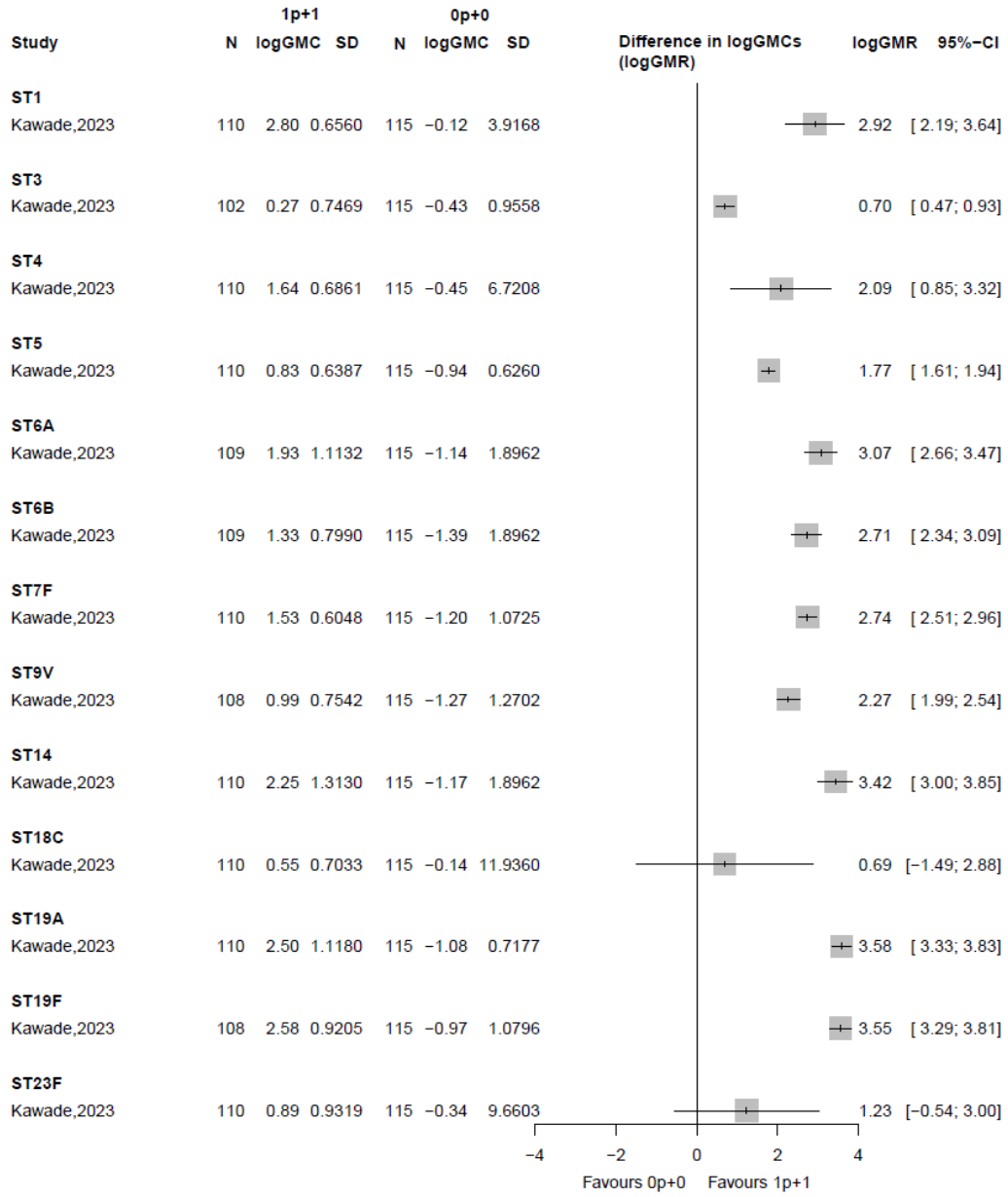


Figure 20 Serotype-specific IgG logGMR data one-month post-final dose, comparing 1p+1 and 0p+0

Serotype-specific OPA

For PCV13 there were no serotype-specific OPA GMC or OI comparing 1p+1 and 0p+0, one-month post-final dose.

PCV10 1p+1 vs 0p+0

Carriage

For PCV10 VT carriage, three RCTs compared 1p+1 and 0p at 18 months of age (Figure 21). Two RCTs were conducted in Vietnam (including one by Yoshida, a cRCT) and one in India. There was little evidence of statistical

heterogeneity (I^2=21%, τ^2=0, *P*=0.51). The meta-analysis results favoured 1p+1 (RR 0.54 [95% CI 0.37 to 0.79]). To assess the impact of trial design (individually randomised vs cRCT), a sensitivity analysis excluding the cRCT was conducted. This resulted in a slight shift in the effect estimate and precision (RR 0.60 [95% CI 0.39 to 0.92]), but the overall conclusion remained consistent, still favouring 1p+1.

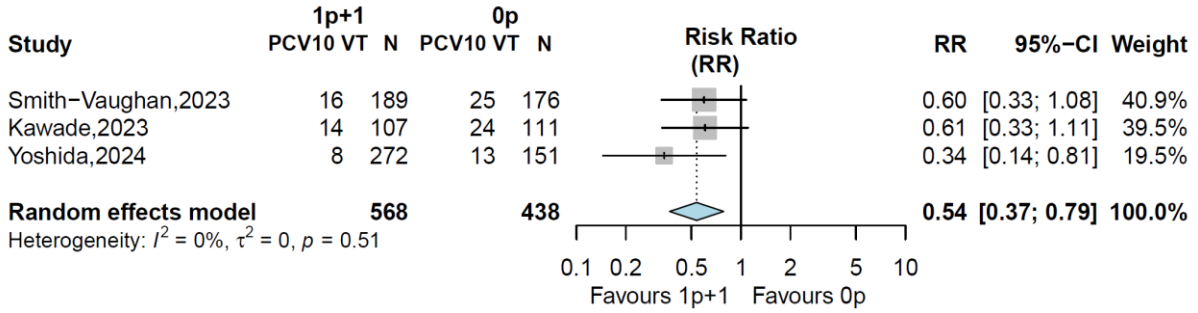


Figure 21 PCV10 vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 0p+0

For PCV10 NVT carriage, two RCTs from Vietnam compared 1p+1 and 0p+0 at 18 months of age (Figure 22). There was no evidence of statistical heterogeneity (I^2=0%, τ^2=0, *p*=0.36). Meta-analysis favoured neither 1p+1 nor 0p+0 (RR 1.23 [95% CI 0.87 to 1.73]). To determine the effect of trial design (individually randomised vs cRCT) on VT and NVT carriage, sensitivity analyses were not undertaken as there was only one individually randomised trial. Considering data from this individually randomised trial only, there was no evidence of a difference between 1p+1 and 0p+0 (RR 0.98 [95% CI 0.54 to 1.77]), and the overall conclusion remained consistent with the primary analysis.

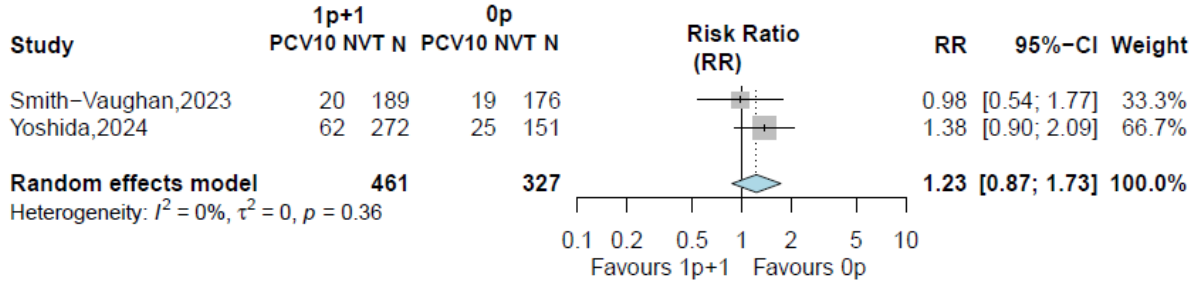


Figure 22 PCV10 non-vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 0p+0

For the comparison of PCV10 serotype-specific carriage between 1p+1 and 0p+0 post-final dose, only the cRCT from Vietnam provided data (Figure 23). For 6/10 serotypes (1, 4, 5, 9V, 14, and 18), no events occurred in either schedule, so RRs were not calculated. For serotypes 6B, 7F, and 23F, carriage was similar between 1p+1 and 0p+0. For serotype 19F, 1p+1 was associated with a lower prevalence than 0p+0 (RR 0.21 [95% CI 0.06 to 0.77]). Given the small numbers, caution should be taken in interpreting these results.

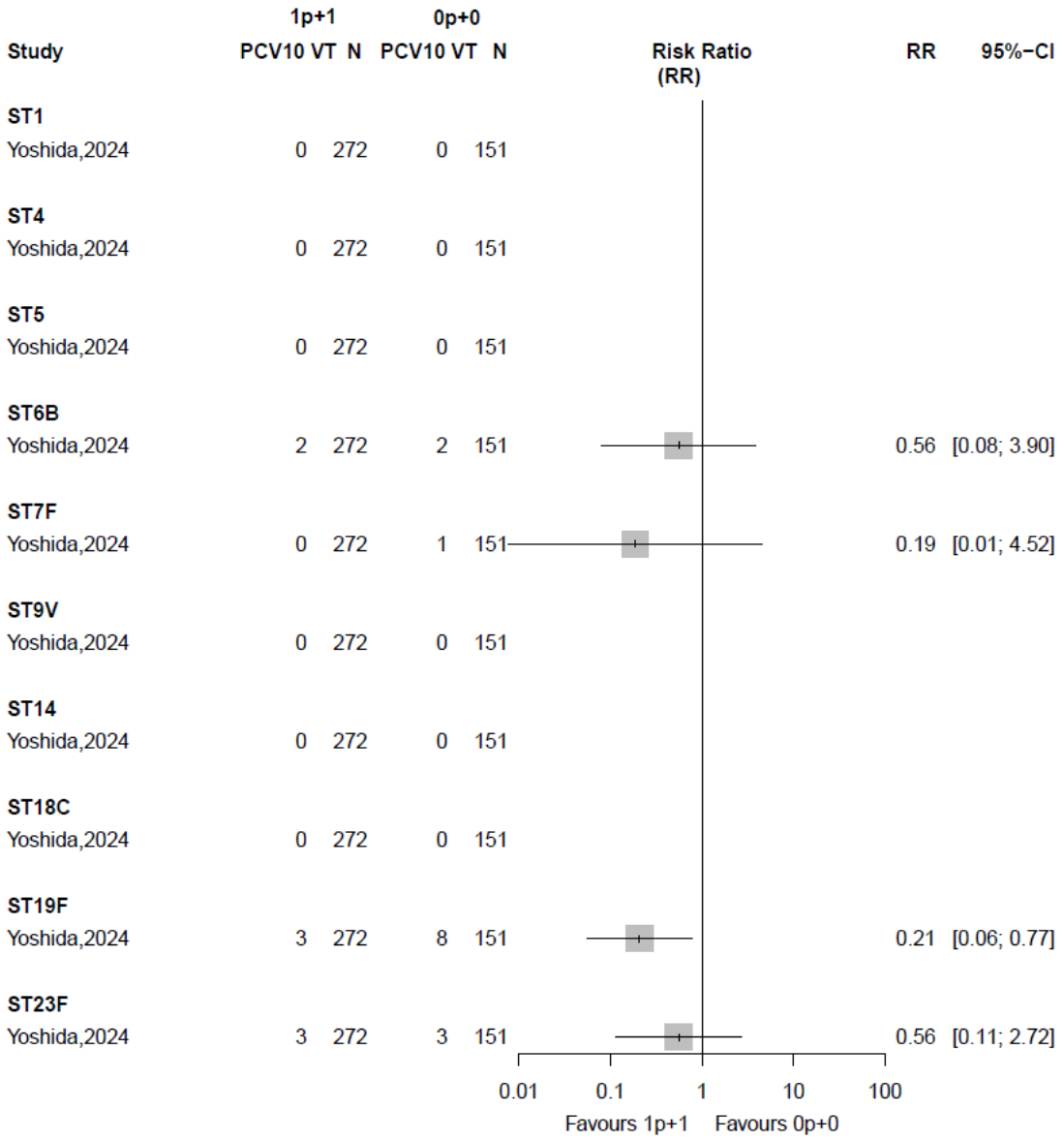


Figure 23 PCV10 serotype-specific carriage post-final dose and before two years of age, comparing 1p+1 and 0p+0

Serotype-specific IgG

For PCV10, one RCT from India provided serotype-specific IgG data one-month post-final dose comparing 1p+1 and 0p+0, so no meta-analysis was conducted. The estimated logGMRs indicate 1p+1 is associated with higher IgG levels than 0p+0 for serotypes 1, 4, 5, 6B, 7F, 9V, 14, and 19F. For serotypes 18C and 23F, the logGMRs were similar between 1p+1 and 0p+0 (Figure 24).

There were no data available for serotype-specific IgG $\geq$0.35 µg/mL.

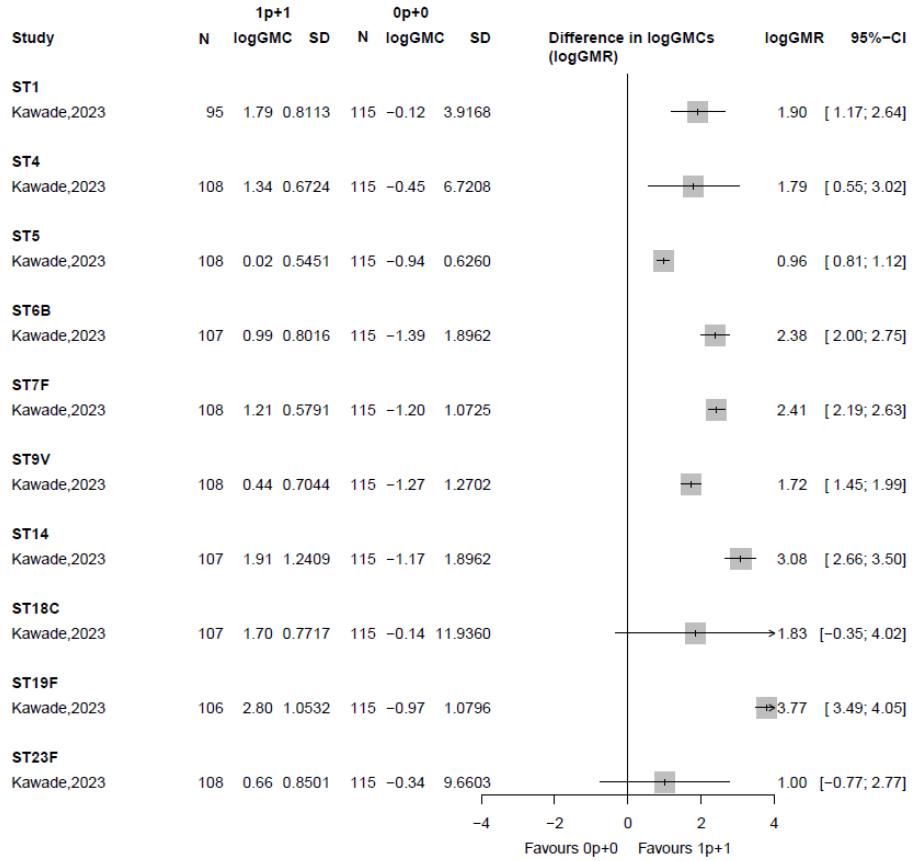


Figure 24 PCV10 serotype-specific IgG logGMR data one month post-final dose, comparing 1p+1 and 0p+0

Serotype-specific OPA

For PCV10 there were no serotype-specific OPA GMC or OI comparing 1p+1 and 0p+0, one-month post-final dose.

PCV13 1p+1 vs 2p+1

Carriage

For PCV13 VT carriage, four RCTs compared 1p+1 and 2p+1 (Figure 25). The studies were based in the UK, India, South Africa, and Canada, with data at 18 months of age, except for the Canadian study, which provided data at 13 months of age. There was little evidence of statistical heterogeneity (τ^2=0, χ^2 test *P*=0.87).

The meta-analysis results favoured neither 1p+1 or 2p+1.

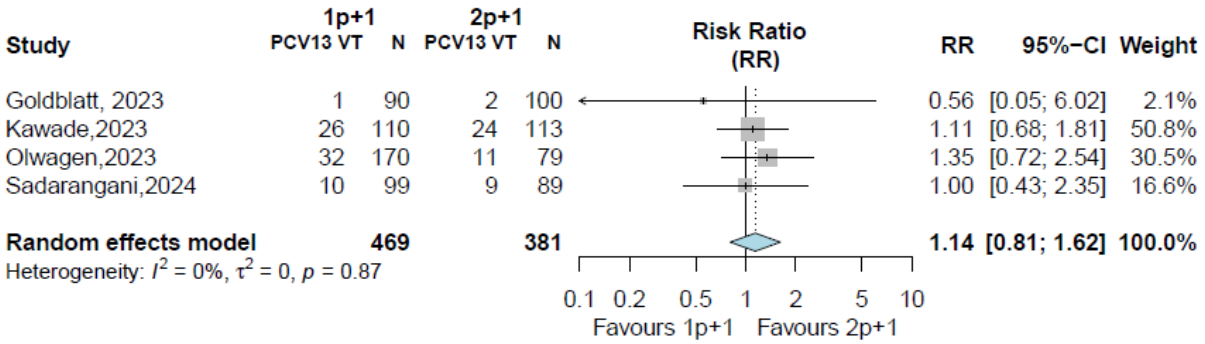


Figure 25 PCV13 vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 2p+1

For PCV13 NVT carriage, three RCTs from the UK, India, and Canada compared PCV13 1p+1 and 2p+1, each at 18 months of age, except for the Canadian study, which reported data from 13 months of age (Figure 26). There was little evidence of statistical heterogeneity (τ^2=0, χ^2 *P*=0.89).

The meta-analysis results favoured neither 1p+1 nor 2p+1.

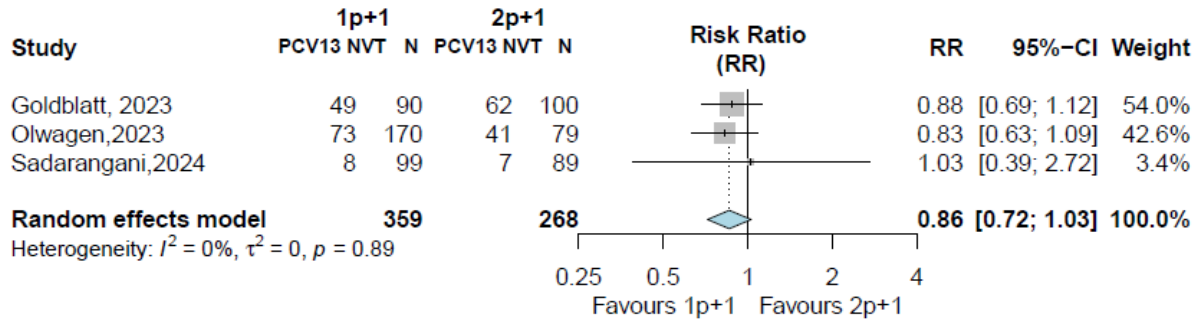


Figure 26 PCV13 non-vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 2p+1

Serotype-specific carriage

Only one RCT from Canada provided PCV13 serotype-specific carriage data comparing 1p+1 and 2p+1, so no meta-analysis was done. Results from available data are presented in Figure 27. There was no carriage event for 7/13 serotypes, and very low carriage for the other 6/13 serotypes. Results show similar serotype-specific carriage between 1p+1 and 2p+1. However, due to low carriage case numbers there was considerable uncertainty due to wide CIs.

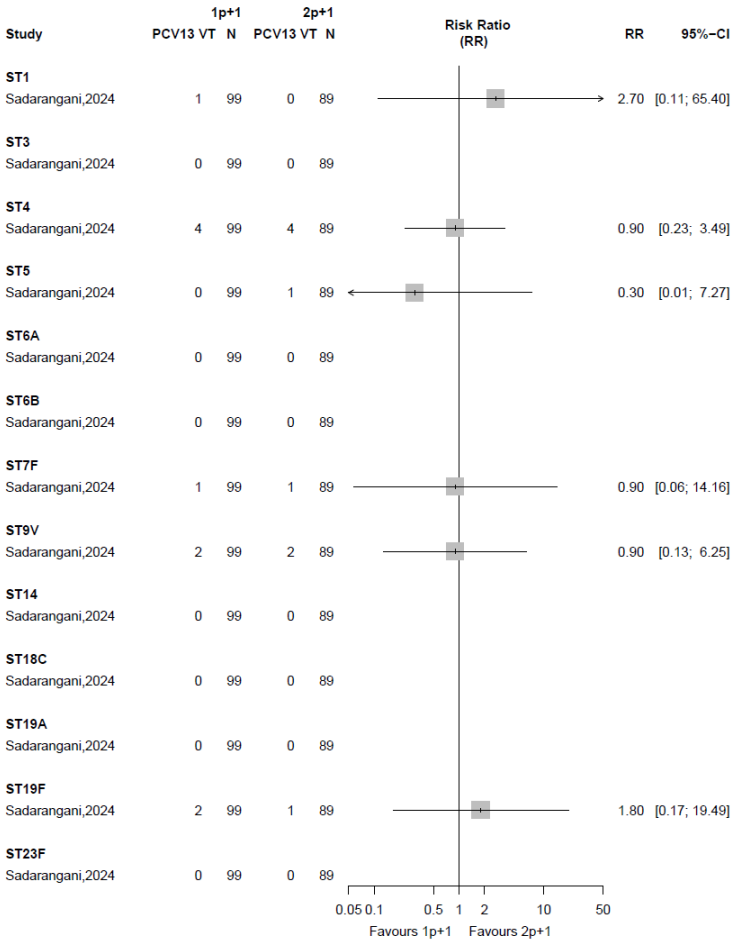


Figure 27 PCV13 serotype-specific carriage post-final dose at 13 months of age, comparing 1p+1 and 2p+1

Serotype-specific IgG

For PCV13 serotype-specific IgG GMC one-month post-final dose, three RCTs from the UK, South Africa and India compared 1p+1 and 2p+1 (Figure 28). There was statistical heterogeneity for most serotypes.

The meta-analysis results favoured 1p+1 for 5/13 serotypes (1, 4, 5, 19A, and 19F); 2p+1 for 5/13 serotypes (6A, 6B, 7F, 19C, and 23F); and neither 1p+1 nor 2p+1 for 3/13 serotypes (3, 9V, and 14).

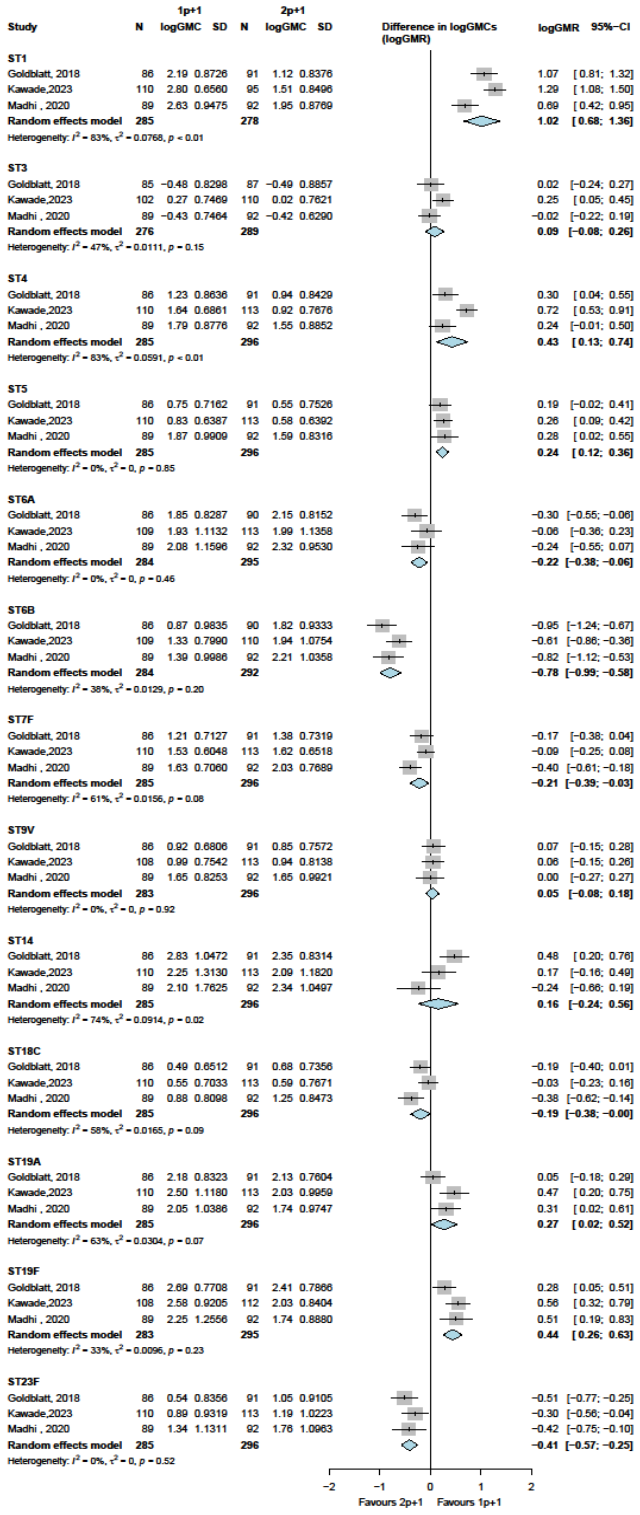


Figure 28 PCV13 serotype-specific IgG logGMR one month post-final dose, comparing 1p+1 and 2p+1

For PCV13 serotype-specific IgG ≥0.35 µg/mL one-month post-final dose, four RCTs from the UK, India, South Africa, and Canada compared 1p+1 and 2p+1 (Figure 29). Statistical heterogeneity was observed for most serotypes.

The meta-analysis results favoured neither 1p+1 nor 2p+1 for most serotypes, except 2p+1 for serotype 4, and 1p+1 for 6B.

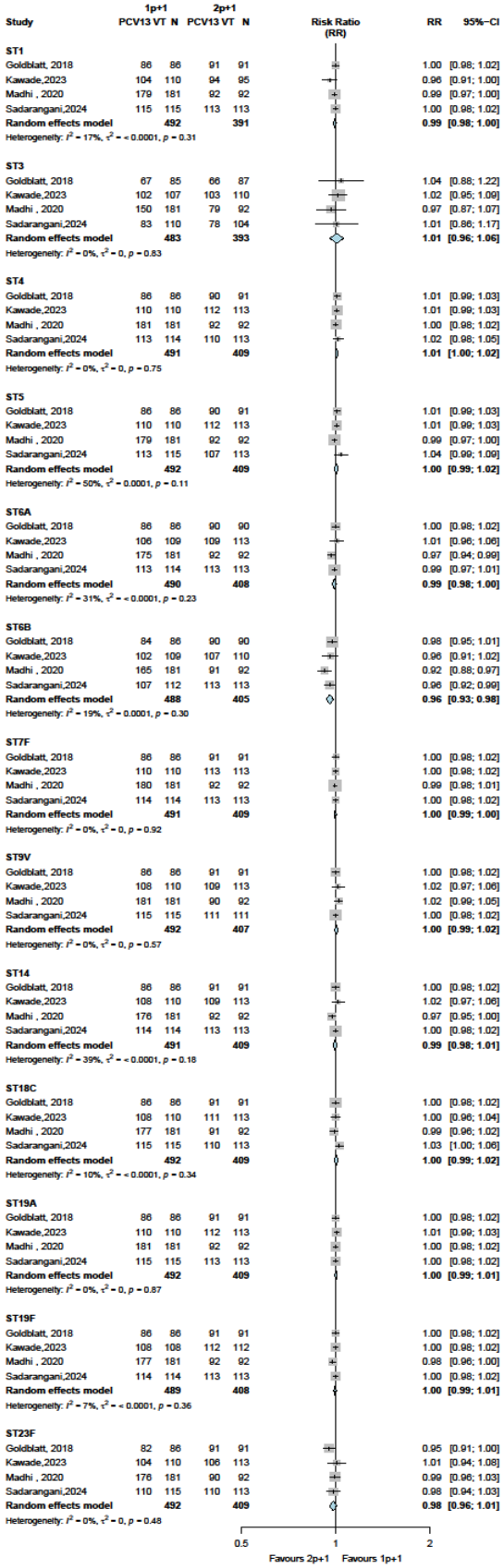


Figure 29 Proportion achieving PCV13 serotype-specific IgG ≥0.35µg/mL, one month post-final dose, comparing 1p+1 and 2p+1

Serotype-specific OPA

For PCV13 serotype-specific OPA GMT one-month post-final dose, three RCTs from the UK, India and South Africa compared 1p+1 and 2p+1 (Figure 30). There was little evidence of statistical heterogeneity for 7/13 serotypes (τ2 =0, I2 =0%).

The meta-analysis shows the OPA logGMR in favour of: 1p+1 for 2/13 serotypes (1, and 5); 2p+1 for 2/13 (6A and 9V); and neither 1p+1 nor 2p+1 for 9/13 serotypes (6B, 7F, 14, 19A, 19F, 18C, 23F, 3, and 4).

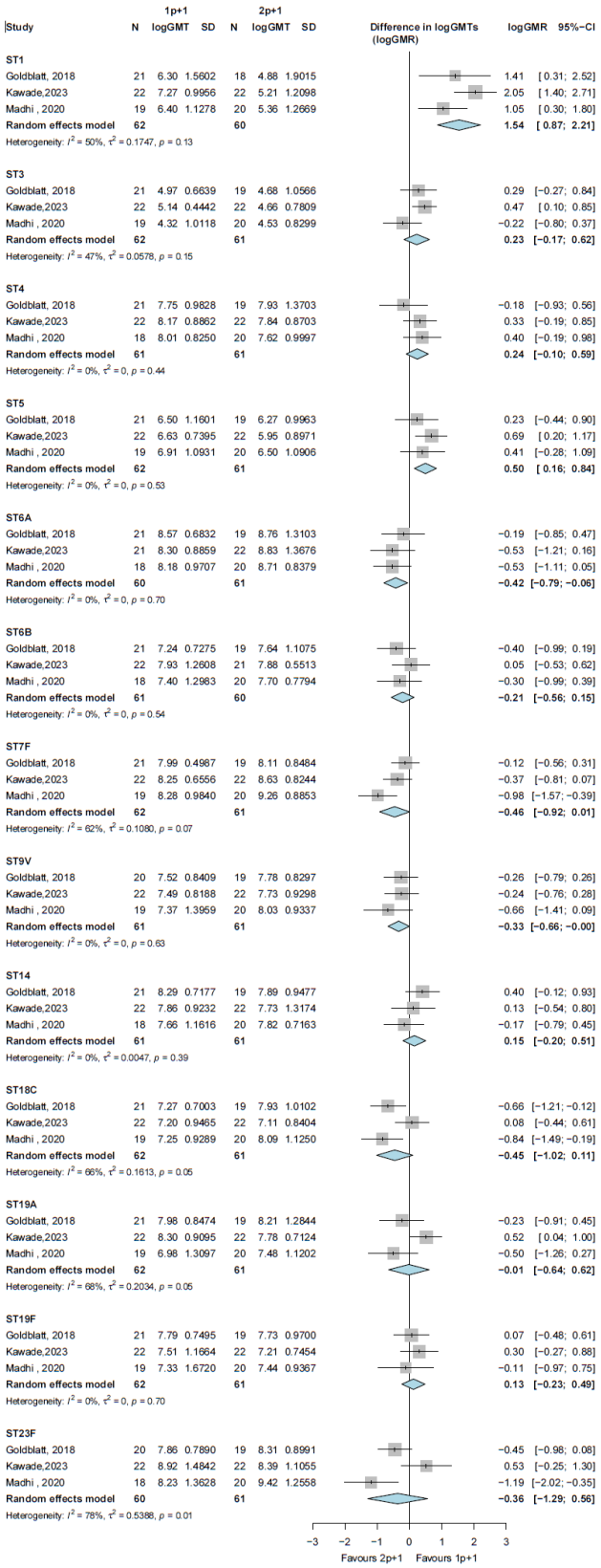


Figure 30 PCV13 serotype-specific OPA logGMR one-month post-final dose, comparing 1p+1 with 2p+1

For PCV13 serotype-specific OI ≥ 8 one-month post-final dose, two RCTs from India and South Africa compared 1p+1 and 2p+1 (Figure 31). There was no evidence of statistical heterogeneity for any of the 13 serotypes (τ^2=0, I^2=0%).

The meta-analysis findings favoured neither 1p+1 nor 2p+1 for any serotype.

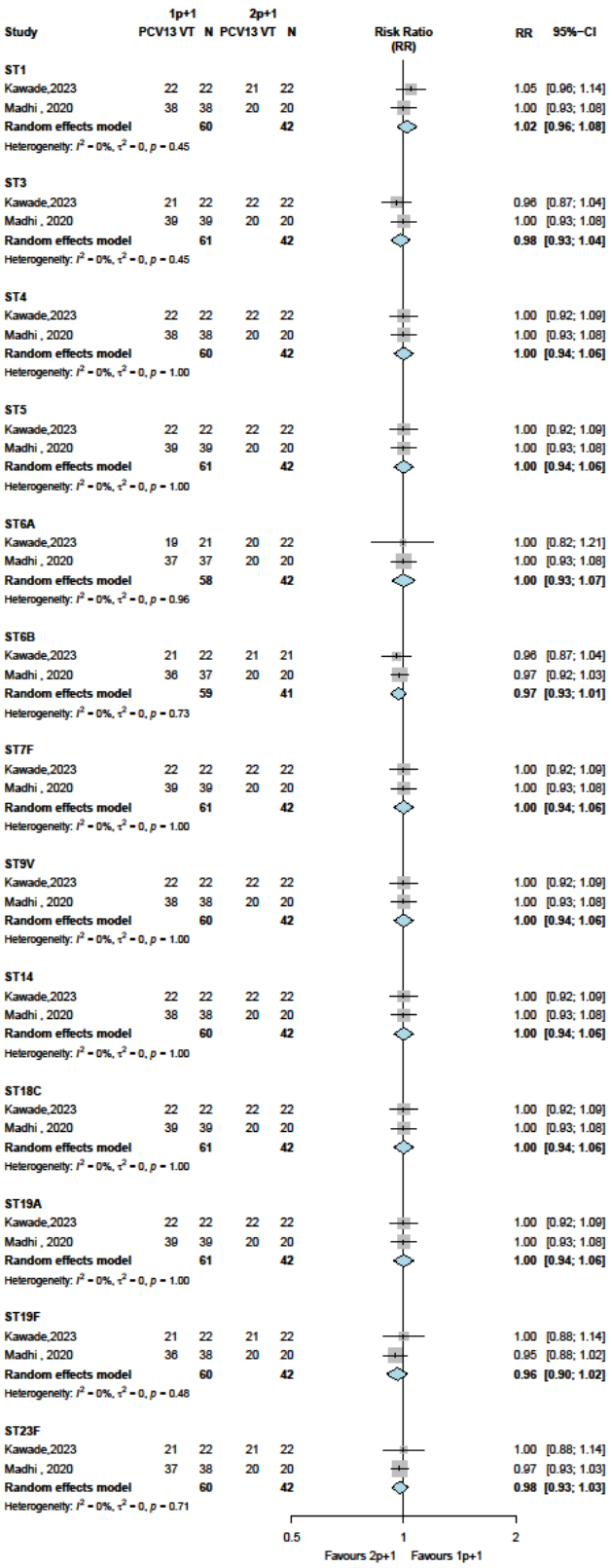


Figure 31 PCV13 serotype-specific OI ≥8 one month post-final dose, comparing 1p+1 and 2p+1

PCV10 1p+1 vs 2p+1

Carriage

For PCV10 VT carriage following the final dose, four RCTs compared 1p+1 and 2p+1 (Figure 32). Two RCTs were from Vietnam (including one by Yoshida, a cRCT) and two were based in India and South Africa. There was no evidence of statistical heterogeneity (τ^2=0, *p*=0.57). Findings from the sensitivity analysis excluding the cRCT were similar to the primary analysis (RR 1.06 [95% CI 0.74 to 1.53]).

The meta-analysis result favoured neither 1p+1 nor 2p+1.

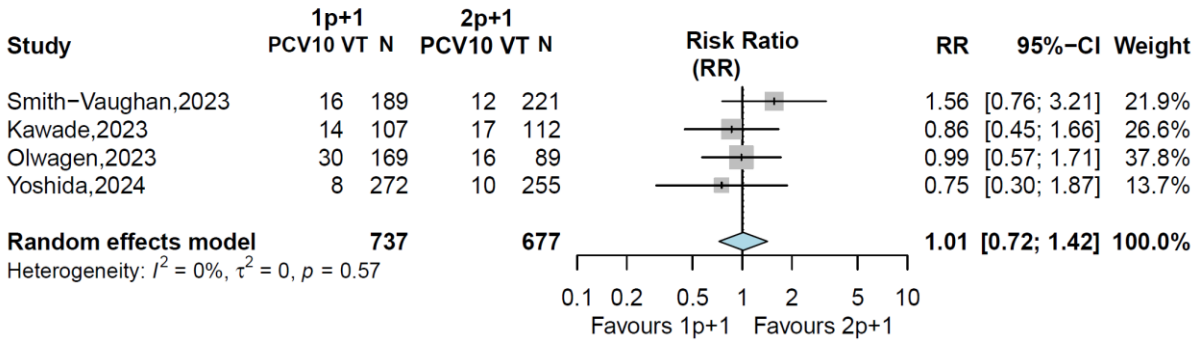


Figure 32 PCV10 vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 2p+1

For PCV10 NVT carriage, three RCTs compared 1p+1 and 2p+1, two in Vietnam (including one by Yoshida, a cRCT), and one in South Africa (Figure 33). There was little evidence of statistical heterogeneity (I^2= 25%, τ^2=0.0159, *p*=0.26).

The meta-analysis results favoured neither 1p+1 nor 2p+1.

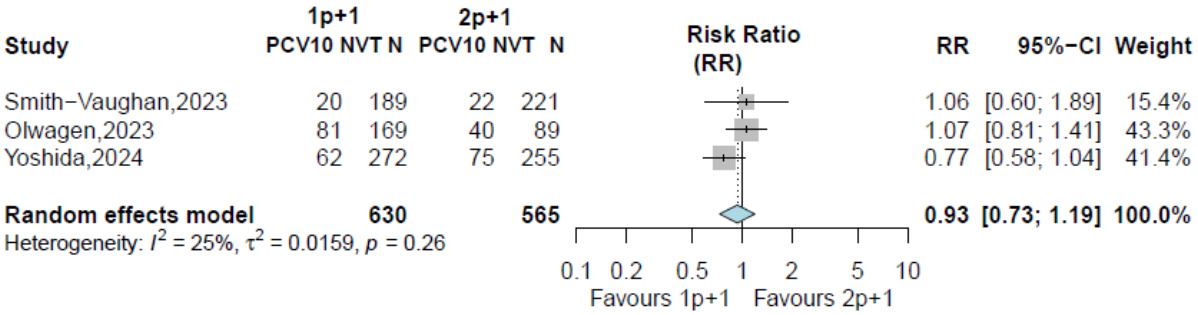


Figure 33 PCV10 non-vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 2p+1

To determine the effect of trial design (individually randomised vs cRCT), sensitivity analysis excluding the cRCT was undertaken and found similar findings to the primary analysis (RR 1.07 [0.83 to 1.37]).

For PCV10 serotype-specific carriage post-primary, one study from Vietnam provided data comparing 1p+1 and 2p+1 (Figure 34). There were no events for 7/10 serotypes (1, 4, 5, 7F, 9V, 14, and 18C). For 3/10 serotypes (6B, 19F, and 23F) results indicate similar RR between 1p+1 and 2p+1, but there were wide confidence intervals highlighting uncertainty in the estimates.

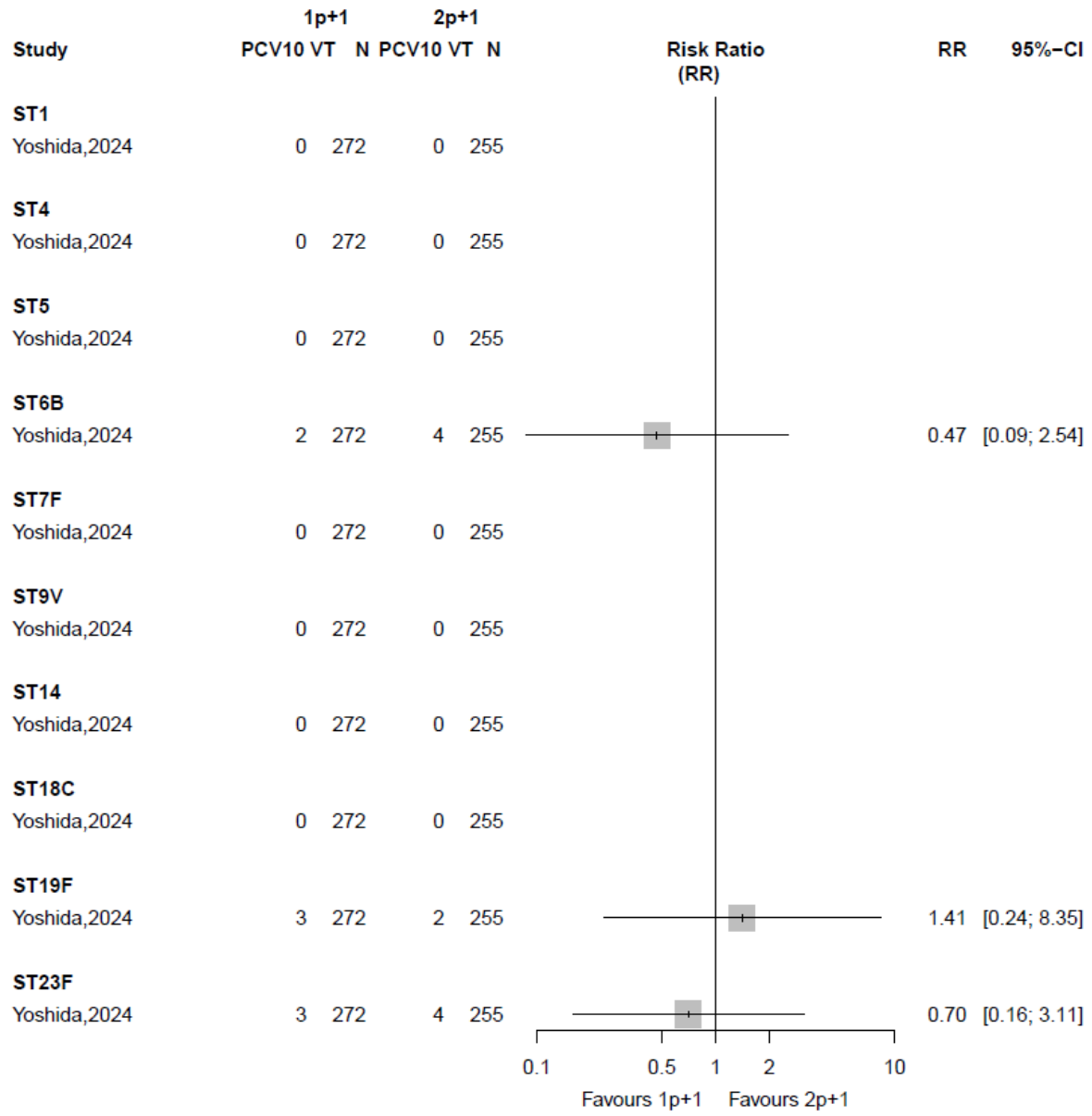


Figure 34 PCV10 serotype-specific carriage post-final dose and before two years of age, comparing 1p+1 and 2p+1

Serotype-specific IgG

For PCV10 serotype-specific IgG GMC, two eligible studies from India and South Africa that compared 2p+1 and 1p+1 at one-month post-final dose (Figure 35). There was little evidence of statistical heterogeneity for 7/10 serotypes ($\tau 2 = 0$, $I2 = 0\%$).

The meta-analysis shows the IgG logGMR favoured 1p+1 for serotype 4, and 2p+1 for 2/10 serotypes (6B and 18C). For the remaining serotypes (1, 5, 7F, 14, 19F, 9F, and 23F), meta-analysis results favoured neither 1p+1 nor 2p+1.

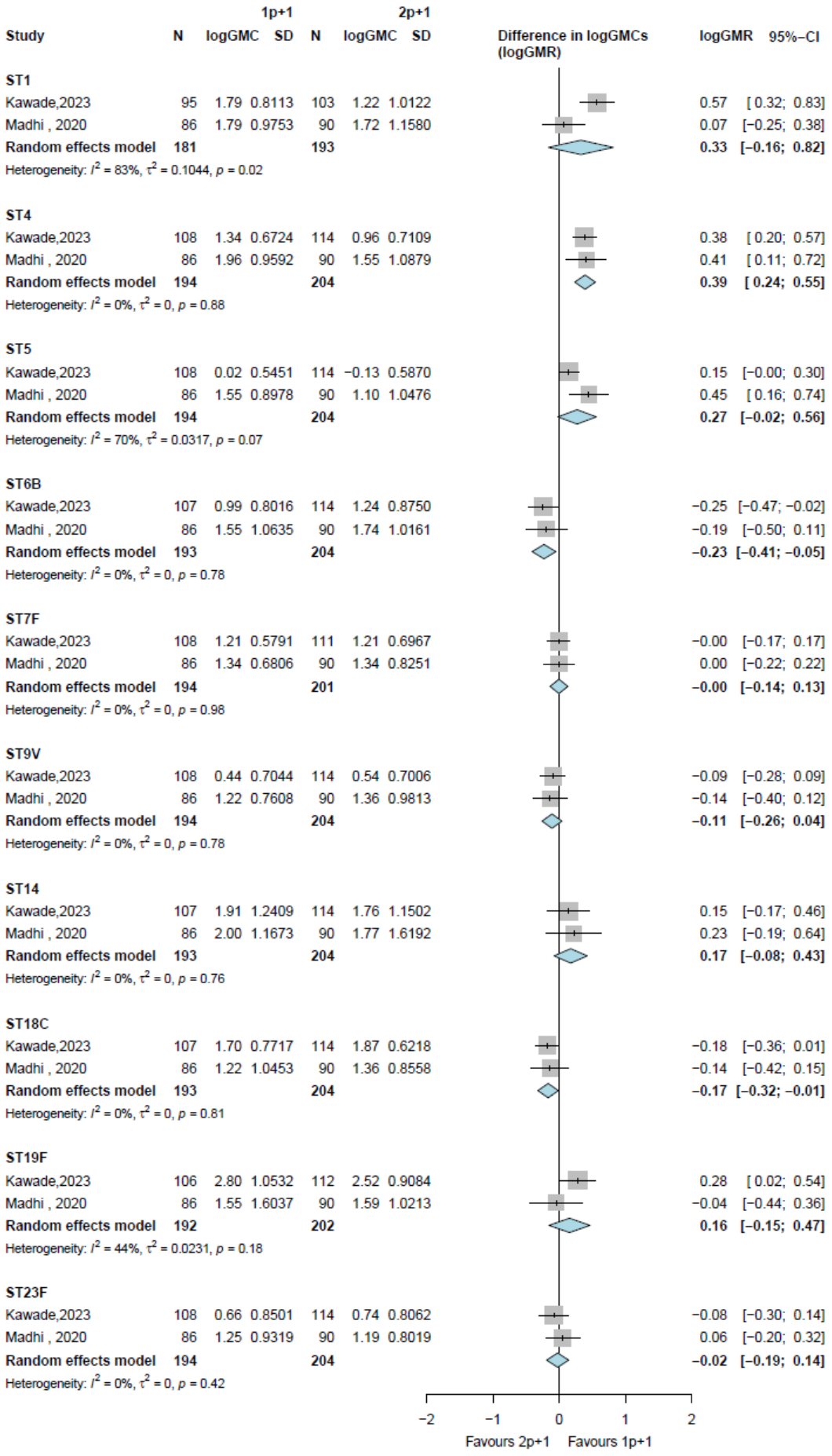


Figure 35 PCV10 serotype-specific IgG logGMR one-month post-final dose, comparing 1p+1 and 2p+1

For PCV10 serotype-specific IgG ≥0.35 µg/mL one-month post-final dose, two studies from India and South Africa compared 1p+1 and 2p+1 (Figure 36). Statistical heterogeneity was observed for serotype 19F.

The meta-analysis results indicate neither 1p+1 nor 2p+1 was favoured for any serotype.

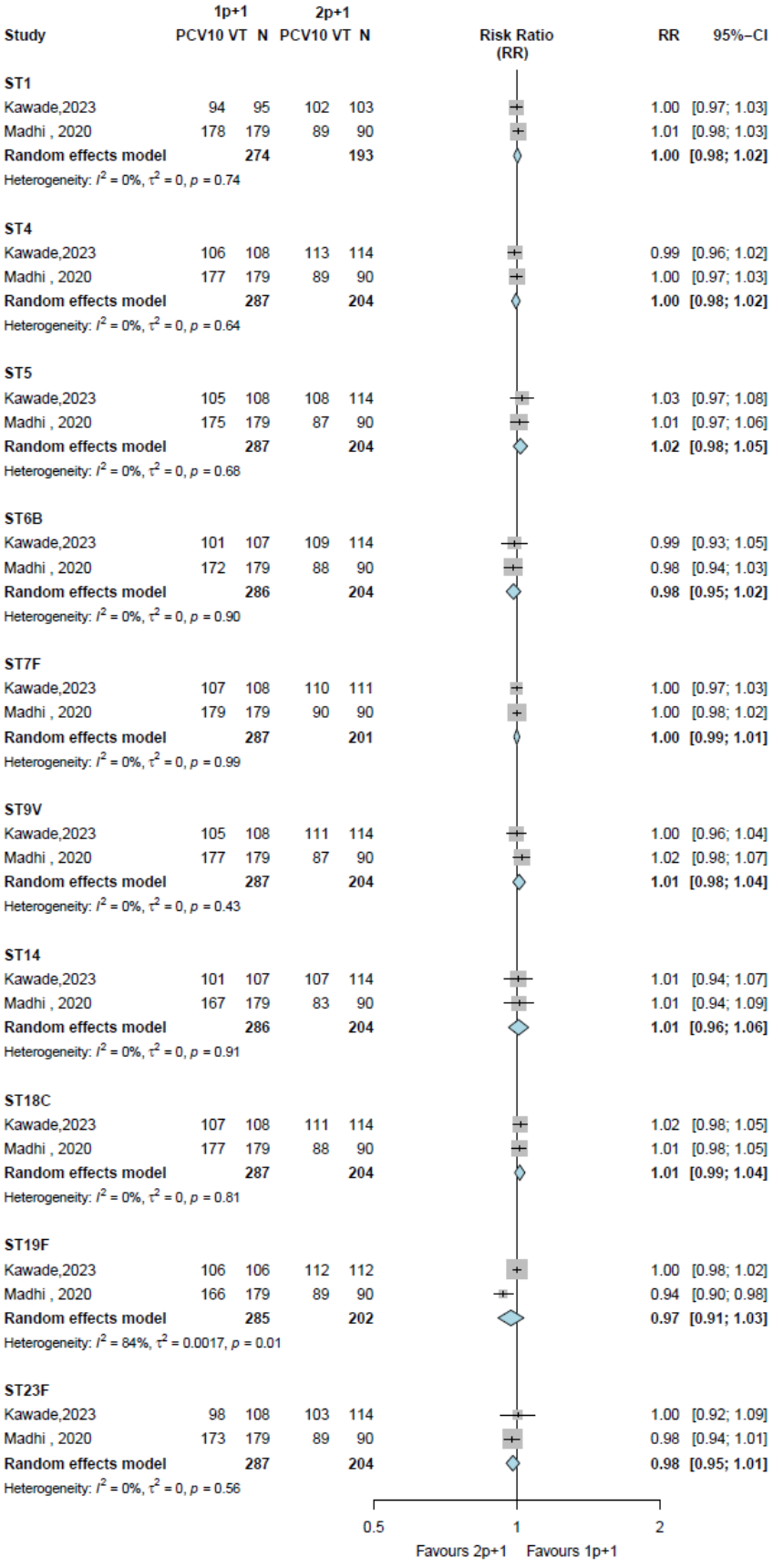


Figure 36 Proportion achieving PCV10 serotype-specific IgG >0.35µg/mL one month post-final dose, comparing 1p+1 and 2p+1

Serotype-specific OPA

For PCV10 serotype-specific OPA GMT one-month post-final dose, two studies from India and South Africa compared 1p+1 and 2p+1 (Figure 37). There was little evidence of statistical heterogeneity for 6/10 serotypes with τ2 =0, I2 =0%. The meta-analysis shows the point estimates of the OPA logGMR favouring 1p+1 for serotype 5 and neither 1p+1 nor 2p+1 for 9/10 serotypes (1, 4, 6B, 7F, 9V, 14, 18C, 19F, and 23F).

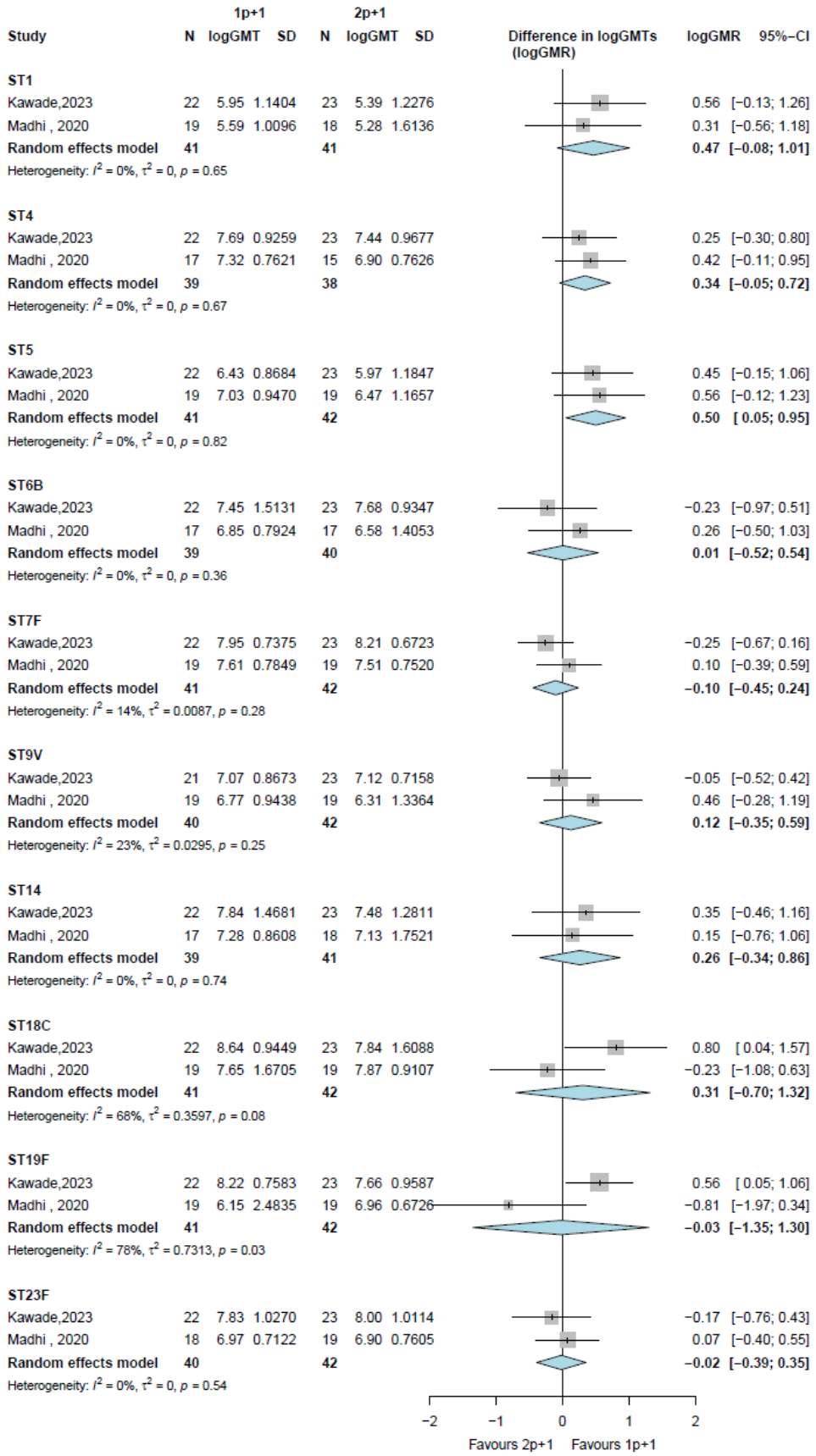


Figure 37 PCV10 serotype-specific OPA logGMR one month post-final dose, comparing 1p+1 and 2p+1

For PCV10 serotype-specific OI ≥8 RR one-month post-final dose, two studies from India and South Africa compared 1p+1 and 2p+1 (Figure 38). There was little statistical heterogeneity for 8/10 serotypes (τ2 =0, I2 =0%).

The meta-analysis shows the OI ≥8 RR favoured 2p+1 for serotype 19F. For all remaining serotypes, results were similar between 1p+1 and 2p+1.

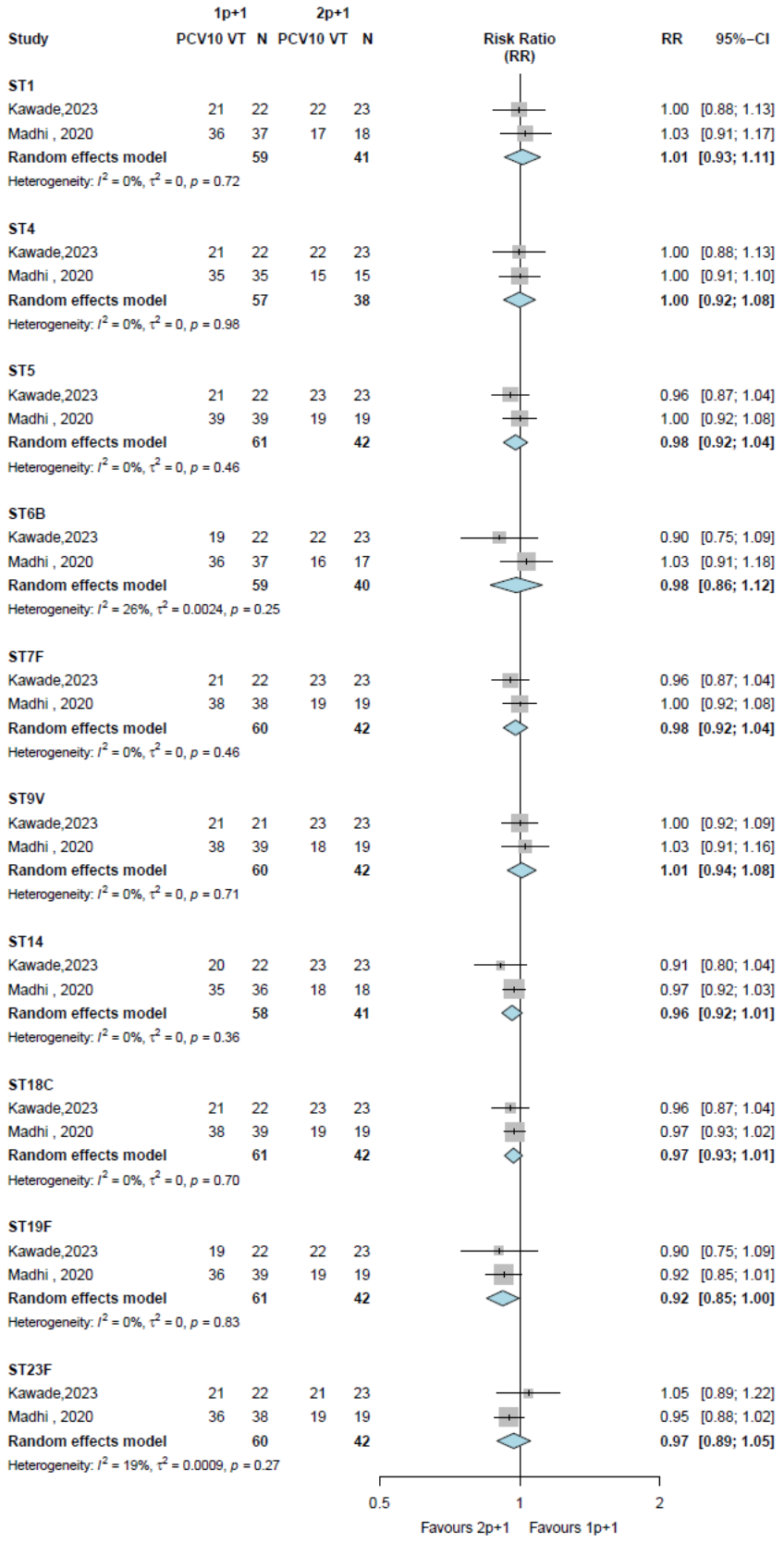


Figure 38 PCV10 serotype-specific OI ≥8 one month post-final dose, comparing 1p+1 and 2p+1

PCV13 1p+1 vs 3p+0

Carriage

For PCV13 VT carriage, there was one eligible RCT from India, and one cRCT from The Gambia that compared 1p+1 and 3p+0 post final dose and before the age of two years. Meta-analysis results favour neither schedule (Figure 39). There were no studies with PCV13 NVT or serotype-specific carriage for this comparison. Sensitivity analyses to determine the effect of trial design (individually randomised vs cRCT) on VT and NVT carriage, were not undertaken as there was only one individually randomised trial.

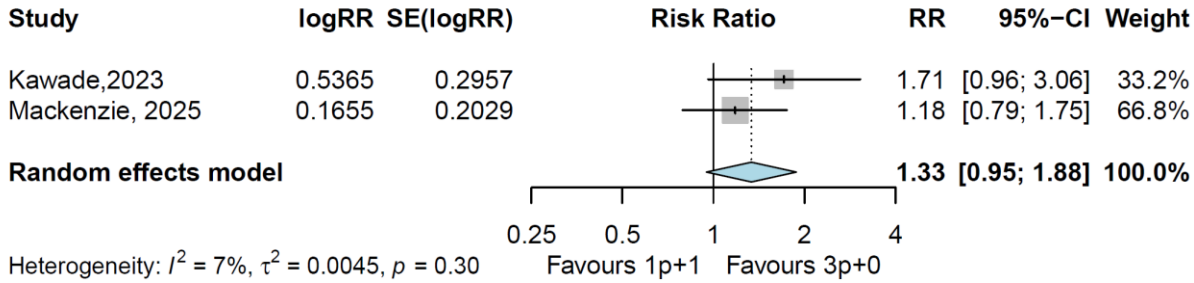


Figure 39 *PCV13 vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 3p+0*

Serotype-specific IgG

For PCV13 serotype-specific IgG GMC, one RCT from India compared 1p+1 and 3p+0 one-month post-final dose, so a meta-analysis was not performed. The estimated logGMRs from this study suggest that 1p+1 was associated with higher IgG levels for all serotypes compared with 3p+0 (Figure 40).

Figure 40 PCV13 serotype-specific IgG logGMR one-month post-final dose, comparing 1p+1 and 3p+0

Available data from one RCT in India indicate that the proportion of individuals who achieved PCV13 serotype-specific IgG ≥0.35 µg/mL one-month post-final dose was greater for 1p+1 compared with 3p+0 (Figure 41). As there was only one RCT, no meta-analysis was conducted, and these findings should be interpreted with caution.

Figure 41 Proportion achieving PCV13 serotype-specific IgG >0.35µg/mL one month post-final dose, comparing 1p+1 and 3p+0

Serotype-specific OPA

For PCV13 serotype-specific OPA GMT, one RCT from India compared 1p+1 and 3p+0 one-month post-final dose, so meta-analysis was not done. The estimated logGMRs indicate OPA GMTs were higher for 1p+1 for all 13 serotypes than 3p+0 (Figure 42).

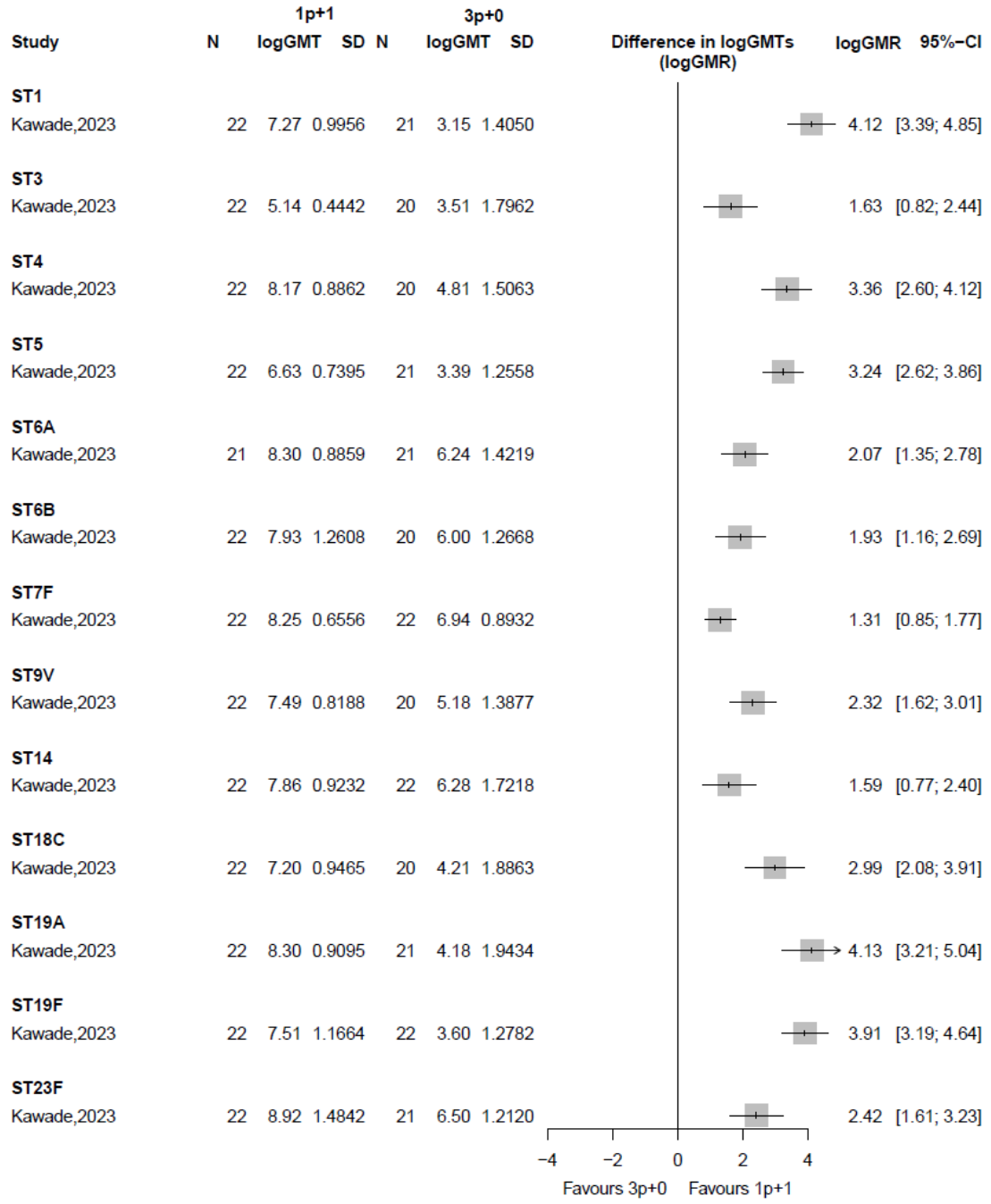


Figure 42 PCV13 serotype-specific OPA logGMR one month post-final dose, comparing 1p+1 and 3p+0

Serotype-specific OI ≥8

For PCV13 serotype-specific OI≥8, one study from India compared 1p+1 and 3p+0 one-month post-final dose. Therefore, a meta-analysis was not done. RR from this study indicate the proportion with OI ≥ 8 were greater for 1p+1 for 8/13 serotypes (1, 3, 4, 5, 6B, 14, 19A, and 23F). For the remaining 5/13 serotypes (6A, 7F, 9V, 18C, and 19F) the OI≥8 was similar between 1p+1 and 3p+0 (Figure 43).

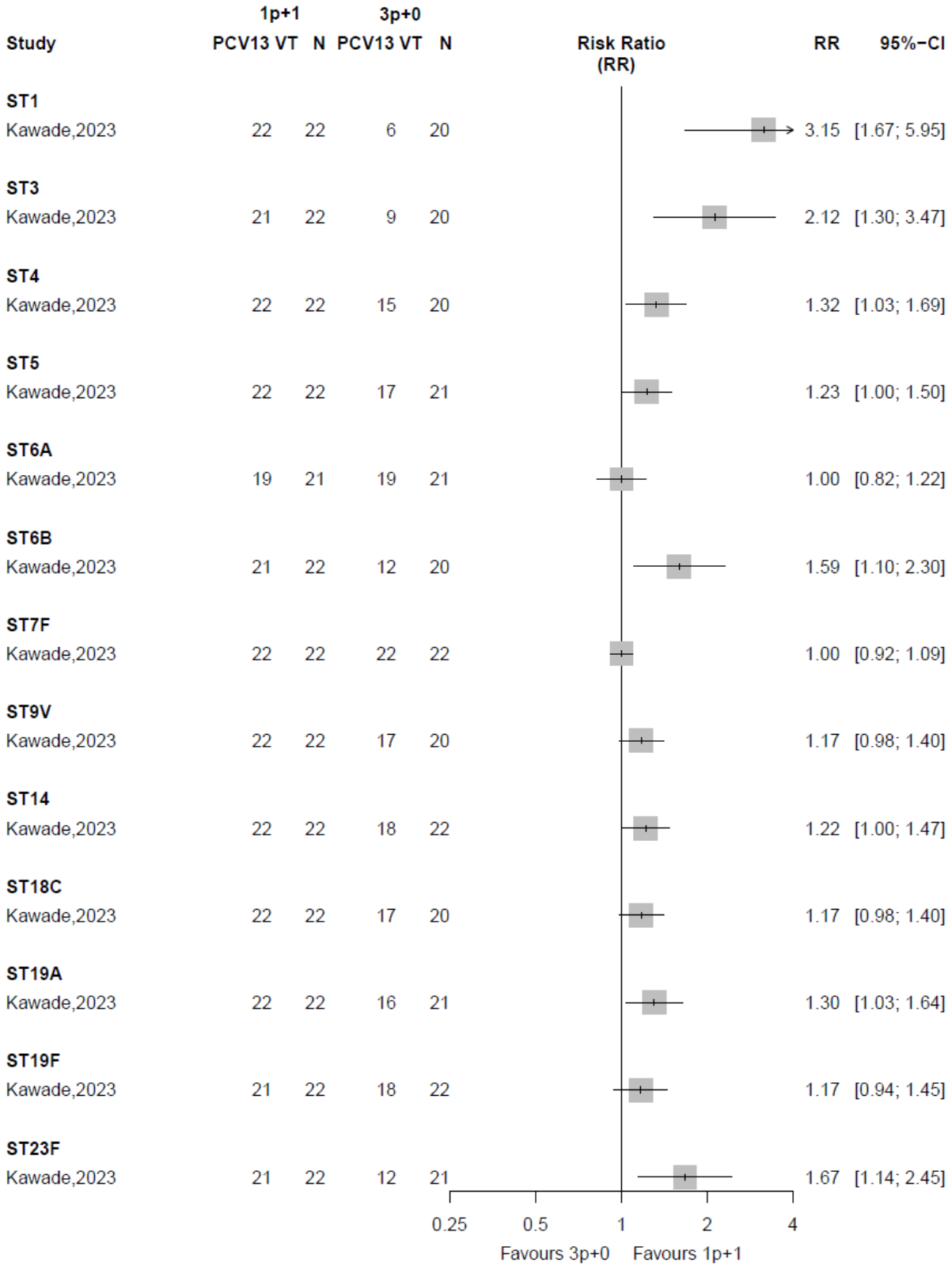


Figure 43 PCV13 serotype-specific OI ≥8, one month post-final dose, comparing 1p+1 and 3p+0

PCV10 1p+1 vs 3p+0

Carriage

For PCV10 VT carriage, three eligible studies compared 1p+1 and 3p+0 at 18 months (Figure 44). Two studies were from Vietnam (including one by Yoshida, a cRCT), and one was from India. There was little evidence of statistical heterogeneity (I^2=0%, $\tau^2 < 0.0001$, p=0.46). The meta-analysis results favoured neither 1p+1 nor 3p+0. To determine the effect of trial design (individually randomised vs cRCT), sensitivity analysis excluding the cRCT was undertaken and found similar findings to the primary analysis (RR 0.93 [95% CI 0.57 to 1.52]).

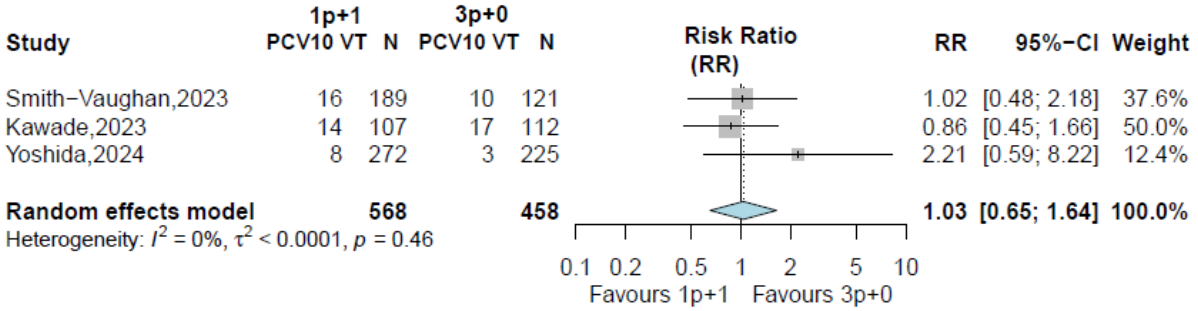


Figure 44 PCV10 vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 3p+0

For PCV10 NVT carriage, two studies, both from Vietnam compared 1p+1 and 3p+0 at 18 months of age (Figure 44). There was little evidence of statistical heterogeneity (I^2=0%, τ^2=0, p=0.72).

The meta-analysis results favoured neither 1p+1 nor 3p+0.

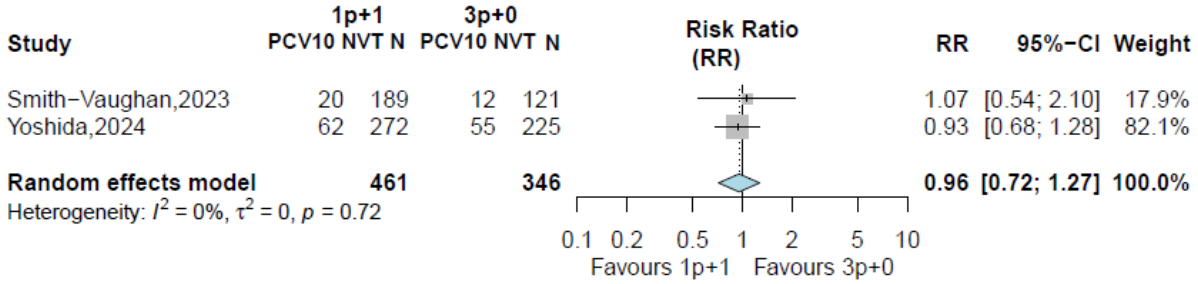


Figure 45 PCV10 non-vaccine-type carriage post-final dose and before two years of age, comparing 1p+1 and 3p+0

To determine the effect of trial design (individually randomised vs cRCT), sensitivity analysis excluding the cRCT was not undertaken as there was only one individually randomised trial.

Only one cRCT from Vietnam reported PCV10 serotype-specific carriage following the final dose for 1p+1 and 3p+0. There were no events in the 1p+1 group for 6/10 serotypes (1, 4, 5, 7F, 9V, and 18C). For the other four serotypes (6B, 14, 19F, and 23F) the RR were similar between 1p+1 and 3p+0, however the wide confidence intervals for some serotypes suggest uncertainty in the findings (Figure 46).

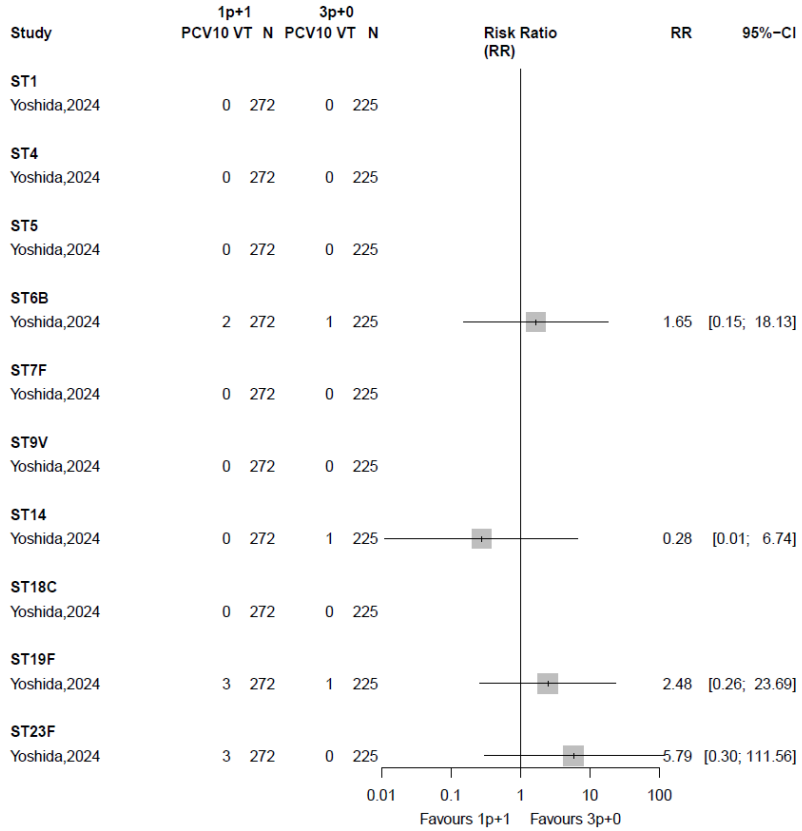


Figure 46 PCV10 serotype-specific carriage post-final dose and before two years of age, comparing 1p+1 and 3p+0

Serotype-specific IgG

For PCV10 serotype-specific IgG GMC and IgG ≥0.35 µg/mL, only one study from India compared 1p+1 and 3p+0 one-month post-final dose. Therefore, meta-analyses were not done. The estimated logGMRs and RR from this study for each serotype comparing 1p+1 to 3p+0 are shown in Figure 47 and 48, respectively.

The IgG GMC and proportion achieving IgG ≥0.35 µg/mL were greater for 1p+1 compared with 3p+0 for all 10 serotypes.

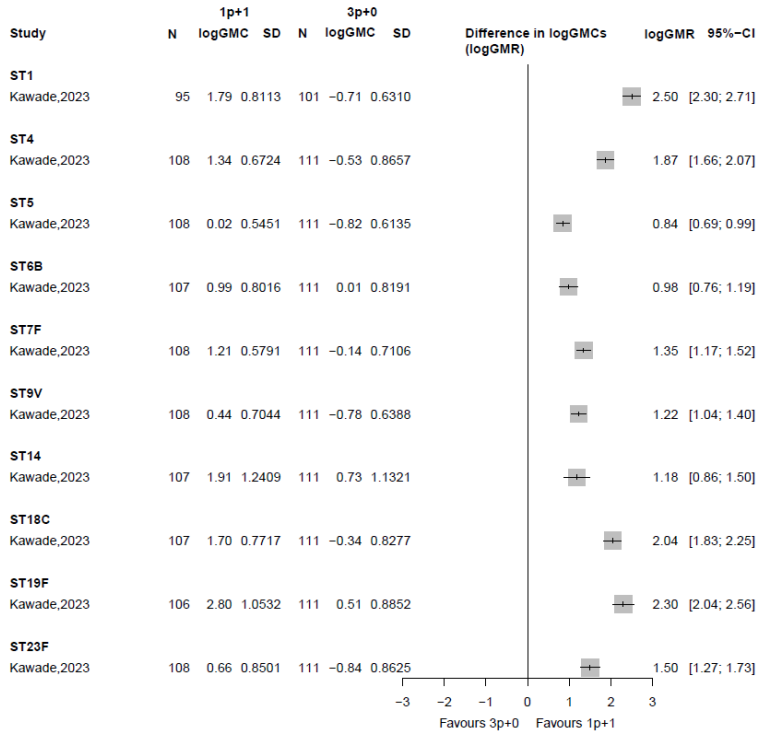


Figure 47 PCV10 serotype-specific IgG logGMR one-month post-final dose, comparing 1p+1 and 3p+0

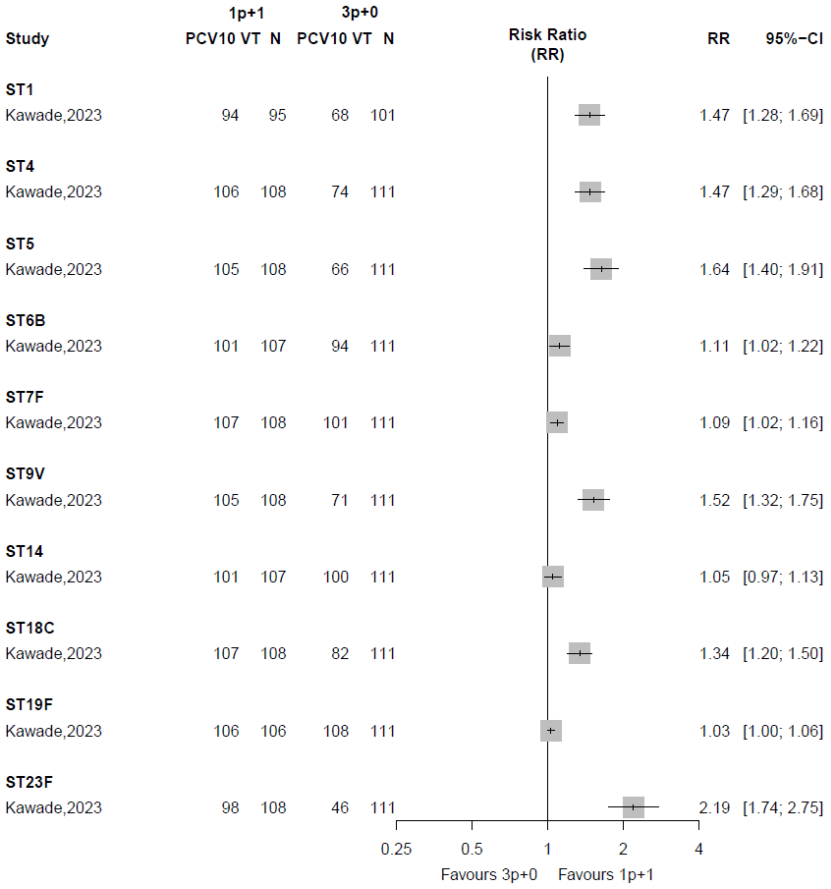


Figure 48 Proportion achieving PCV10 serotype-specific IgG ≥ 0.35 one-month post-final dose, comparing 1p+1 and 3p+0

Serotype-specific OPA

For PCV10 serotype-specific OPA GMT, only one study from India compared 1p+1 and 3p+0 one-month post-final dose so a meta-analysis was not done. The estimated logGMRs for 1p+1 vs 3p+0 indicate 1p+1 was associated with higher OPA GMTs for all serotypes, except for serotype 1, for which there was no difference between 1p+1 and 3p+0 (Figure 49).

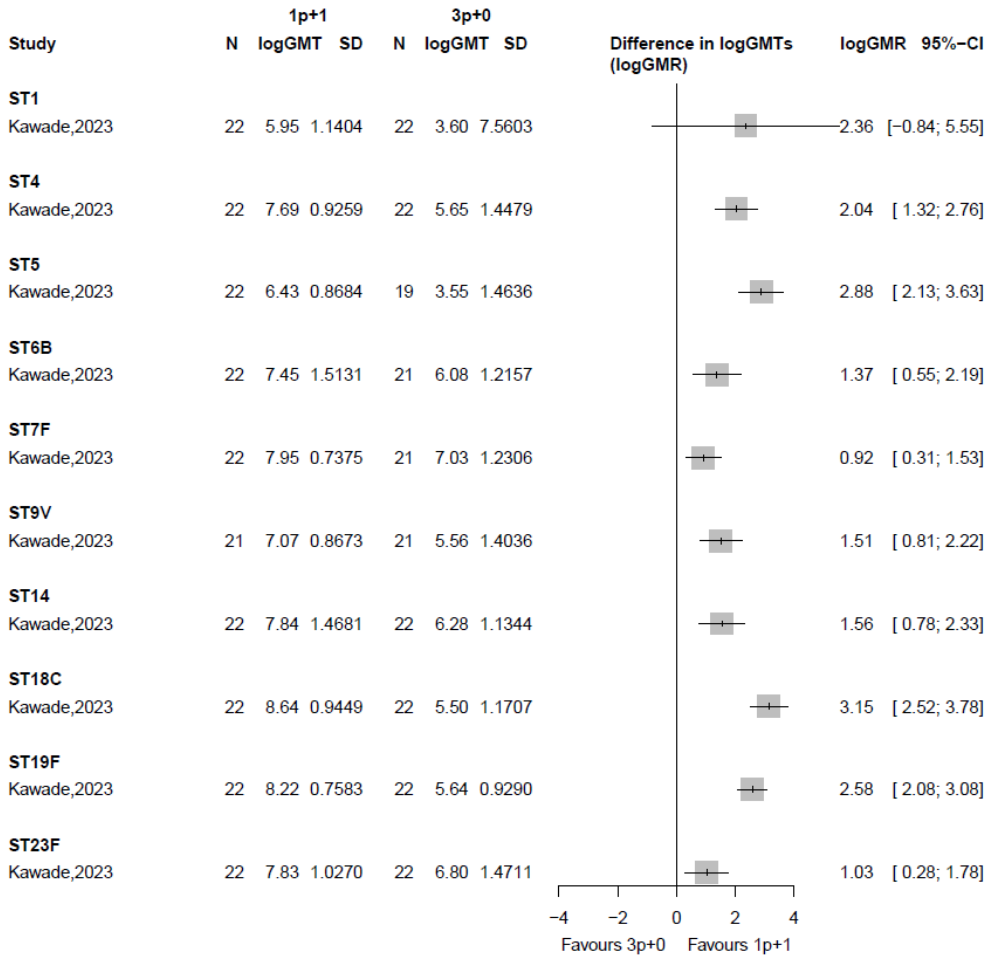


Figure 49 PCV10 serotype-specific OPA logGMR one month post-final dose, comparing 1p+1 and 3p+0

For PCV10 serotype-specific OI≥8, only one study from India compared 1p+1 and 3p+0 one-month post-final dose, so a meta-analysis was not done. The estimated RR from this study found that for 3/10 serotypes (1, 9V, 23F) 1p+1 was associated with a greater proportion of OI ≥ 8 than 3p+0 , but for all other serotypes, there was no difference (Figure 50).

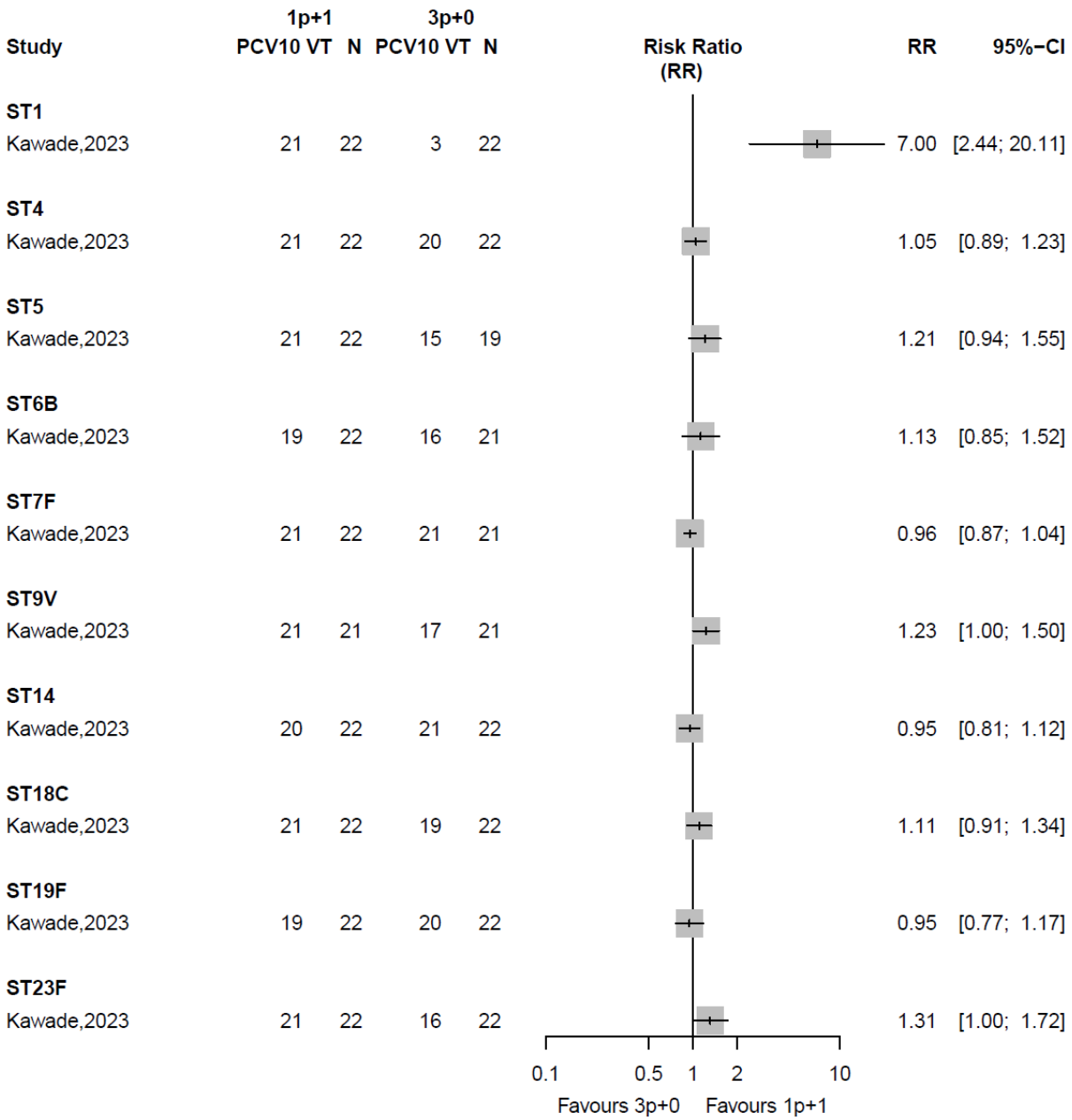


Figure 50 PCV10 serotype-specific OI ≥8 one month post-final dose, comparing 1p+1 and 3p+0

PCV13 and PCV10 1p+1 vs 3p+1

Carriage

For PCV13 VT carriage, there were no studies comparing 1p+1 and 3p+1 post-final dose at 18 months of age.

For PCV10 VT and NVT carriage, there was only one eligible study from Vietnam, so no meta-analyses were conducted. Available data indicate no difference between 1p+1 and 3p+1 for PCV10 VT (RR 1.13 [95% CI 0.53 to 2.42]) and PCV10 NVT (RR 1.09 [95% CI 0.56 to 2.12]. No serotype-specific carriage data were available.

Serotype-specific IgG and OPA

For PCV13 and PCV10, there were no data for this outcome.

Post-final PCV dose between two and five years of age

This section presents the comparison of different schedules on PCV13 and PCV10 VT and NVT carriage for children aged two to five years, post-final dose.

PCV13 1p+1 vs 2p+1

Carriage

One study, conducted in South Africa, compared PCV13 1p+1 and 2p+1 between two and five years of age, with results reported at three different ages: 36, 48, and 60 months. For PCV13 NVT carriage, the RR at 36 months was 0.38 (95% CI 0.18 to 0.80), 0.77 (95% CI 0.35 to 1.69) at 48 months, and 0.94 (95% CI 0.39 to 2.26) at 60 months. For PVC13 NVT carriage, the RR at 36 months was 0.86 (95% CI 0.50 to 1.48), 0.56 (95% CI 0.34 to 0.91) at 48 months, and 0.90 (95% CI 0.56 to 1.43) at 60 months.

No data were available for PCV13 serotype-specific carriage.

Serotype-specific IgG and OPA

For PCV13, no data were available for both outcomes.

PCV10 1p+1 vs 2p+1

Carriage

The study conducted in South Africa also evaluated PCV10 VT and NVT carriage at three different ages (36, 48, and 60 months) for 1p+1 vs 2p+1 between two and five years of age.

For PCV10 VT carriage, the RR at 36 months was 1.26 (95% CI 0.54 to 2.92), 0.90 (95% CI 0.34 to 2.41) at 48 months, and 1.37 (95% CI 0.56 to 3.37) at 60 months. For PCV10 NVT carriage, the RR at 36 months was 1.06 (95% CI 0.67 to 1.66), 0.67 (95% CI 0.44 to 1.01) at 48 months, and 1.23 (95% CI 0.83 to 1.81) at 60 months

No data were available for serotype-specific carriage.

Serotype-specific IgG and OPA

For PCV10, no data were available for these outcomes.

PCV13 and PCV10 1p+1 vs 3p+0

Carriage and serotype-specific IgG and OPA

For both PCV13 and PCV10, there were no data available.

PCV13 and PCV10 1p+1 vs 3p+1

Carriage, serotype-specific IgG and OPA

For PCV13 and PCV10, there were no carriage or immunogenicity data available.

PCV13 1p+1 vs 0p+0

Carriage, serotype-specific IgG and OPA

For PCV13 and PCV10, there were no carriage or immunogenicity data available.

Sub-analyses of carriage and immunogenicity outcomes by time point and vaccine formulation

Sub-analyses can be found in Appendix 12. Overall, the findings did not differ from the main analysis.

Serotype-specific sub-analyses have been conducted, focusing on the serotypes shared across PCV7, PCV9, PCV10, and PCV13. These include serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F from PCV7, and serotypes 1 and 5, which are additional to PCV9. The analyses compare outcomes for serotype-specific carriage, IgG GMC, and OPA following a different number of doses (single dose vs. no dose, 1p vs. 2p, 1p vs. 3p), as data allowed. Overall, the sub-analyses reinforced the findings in the main analyses, showing that while carriage outcomes were similar between schedules, IgG responses were higher with 2p and 3p compared with 1p.

Additionally, the timing of the final 1p+1 dose was examined by comparing the logGMRs of 1p+1 with the final dose at six months versus 2p+1, with those of 1p+1 with the final dose at nine months versus 2p+1. This sub-analysis focuses on IgG and OPA outcomes, with no carriage data available for the timing comparison. Results of this sub-analysis showed that with a six-month final dose, 1p+1 generally produced higher IgG responses (despite some OPA advantages for 2p+1), whereas with a nine-month final dose the immunogenicity differences between 1p+1 and 2p+1 were minimal.

RoB and GRADE

RoB tables can be found in Appendix 13. The risk of bias assessments across the included randomised trials varied, with most studies showing concerns or low risk across multiple domains. Most studies consistently showed low risk in most domains, though some concerns about reporting were noted (13-16). A few studies had higher risk of bias, particularly related to domain 2 (confounding) and domain 5 (reporting)(17-22).

GRADE (Appendix 14) was used to assess the certainty of evidence for PCV 1+1 schedules compared with 2p+0 and 3p+0 across key outcomes, including IPD, pneumonia, VT carriage, and immunogenicity.

For IPD, confidence was low due to reliance on a single PCV13 observational study from England, which, while relevant, had wide confidence intervals leading to imprecision. For radiologic pneumonia, confidence was moderate based on a PCV13 cluster-randomised trial from The Gambia. No studies were available for PCV10 for IPD or pneumonia.

For post-primary VT carriage, confidence in the evidence for the effect of differing PCV13 and PCV10 dosing schedules was high. RCTs and cRCTs provided consistent results with low statistical heterogeneity, and no downgrades were applied for risk of bias, indirectness, or imprecision.

Confidence in the evidence for the effect of differing PCV13 and PCV10 dosing schedules on serotype-specific IgG ≥0.35 µg/mL post-primary series was moderate to low. PCV13 evidence was rated as moderate, with downgrades for inconsistency and imprecision but an upgrade for dose response due to higher IgG levels with increasing doses. PCV10 evidence was rated as low due to similar concerns but without a dose-response upgrade.

For VT carriage post-final dose to <2 years, confidence in the evidence was moderate to low. For PCV13 confidence was moderate – while RCTs and cRCTs provided relevant data, confidence was downgraded for imprecision. For PCV10, confidence was low due to both imprecision and inconsistency.

Confidence in the evidence for the effect of differing PCV13 and PCV10 dosing schedules on serotype-specific IgG logGMR post-final dose to <2 years was moderate to low. PCV13 evidence was rated as low due to study limitations and high heterogeneity for some serotypes. PCV10 evidence was rated as moderate, with a downgrade for study limitations.

CONCLUSION

For IPD, one study on VT IPD in under five-year-olds from England found no difference between PCV13 1p+1 nor 2p+1. For pneumonia, one cRCT in The Gambia among children aged two weeks to < 5 years found a similar risk of radiological pneumonia between PCV10 1p+1 and 3p+0.

Post-primary series, compared with zero doses, 1p PCV10 reduced VT carriage, whereas no difference was observed for PCV13. When comparing 1p to 2p or 3p post-primary series, there were no differences in VT carriage for either vaccine, but there were no pre-final carriage data, so the duration of this effect is unknown. However, 2p and 3p were more immunogenic than 1p for both vaccines, a trend also seen for shared PCV7 and PCV9 serotypes and persisting until the pre-final dose. Substantial differences in immunogenicity were observed for 1p+1 vs 2p+1 when the final 1p+1 dose was administered at six or nine months.

Following the final dose, before two years of age, 1p+1 resulted in a greater reduction in VT carriage compared to no dose. No differences in VT carriage were found between 1p+1 and 2p+1 or 3p+0. Serotype replacement was lower with 1p+1 vs 2p+1 for both vaccines at different time points. For 1p+1 vs 3p+1, no PCV13 data were available, and PCV10 data showed no difference in VT carriage by schedule.

Analyses were limited by the small number of carriage events at all time points, reducing statistical power. Furthermore, the meta-analyses included both individual and cRCTs, which may be assessing different vaccine effects, with cRCTs additionally measuring indirect effects. However, sensitivity analyses excluding the cRCTs were consistent with results from the primary analyses.

Summary

Available data indicate no difference in the incidence of VT IPD between 1p+1 and 2p+1 among children under five years in England, three years after the schedule change. The findings from The Gambia found no difference between radiological pneumonia incidence comparing 3+0 vs 1p+1 four years after the schedule change.

Post-primary, there was no difference in PCV13 VT carriage between 1p and 0p. PCV10 1p was favoured for VT carriage compared with 0p, but there was little difference for NVT or serotype-specific carriage between 1p and 0p. For PCV13 and PCV10, there was little difference between 2p and 3p compared with 1p for VT, NVT, and serotype-specific carriage, however, data were limited. For both PCV13 and PCV10, 2p was favoured over 1p for serotype-specific IgG levels and the proportions of individuals achieving $\geq$ 0.35 µg/mL across all serotypes, except for serotype 3 in PCV13, where no clear preference was observed. Available data suggest PCV13 3p achieved higher serotype-specific IgG levels and proportions of IgG ≥0.35 µg/mL than 1p for all PCV13 serotypes, except serotype 3 for which results were similar between 1p and 3p. For PCV10, data suggest 3p achieved higher serotype-specific IgG levels and proportions of individuals achieving IgG ≥0.35 µg/mL compared with 1p for all serotypes. No OPA data were available for either vaccine.

There were no available data comparing pre-final dose immunogenicity between 1p and 0p for PCV13 or PCV10. For the 1p vs 2p comparison, 2p was favoured over 1p for several serotypes in both vaccines, with mixed results for PCV13 and limited data for PCV10. For the 1p vs 3p comparison, 3p generally resulted in higher IgG GMCs for multiple serotypes in both vaccines, although results were similar for some serotypes. No OPA data were available for these comparisons.

Following the final dose to two years, 1p+1 was associated with lower VT carriage compared with zero doses for PCV13 and PCV10. Neither 1p+1 nor 0p+0 was favoured for non-vaccine type carriage for PCV10 and there were PCV13 non-vaccine type carriage data to compare 1p+1 with zero doses. Results indicated neither 2p+1 or 3p+1 was associated with lower VT or NVT carriage compared with 1p+1 for PCV13 or PCV10 post-final dose to < 2 years. For most serotypes, 1p+1 had higher serotype-specific IgG levels compared with zero doses for PCV13 and PCV10. No data were available for serotype-specific IgG $\geq$0.35 µg/mL, OPA, or OI post-final dose. The immunogenicity of 1p+1 versus 2p+1 varied by serotype for both PCV13 and PCV10, with no consistent favouring of 1p+1 or 2p+1. For PCV10, differences between schedules were minimal, with neither favoured for proportions achieving IgG ≥0.35 µg/mL. In contrast, 1p+1 elicited higher IgG levels and a greater proportion achieving IgG ≥0.35 µg/mL than 3p+0 for all serotypes in both PCV13 and PCV10. These findings suggest that while 1p+1 performs similarly to 2p+1, it generates a stronger immune response than 3p+0, highlighting the importance of a booster dose.

For longer term protection between two and five years of age, 1p+1 showed VT carriage was lower at 36 months for PCV13 compared with 2p+1, but did not differ by schedule at later time points. PCV13 1p+1 showed less serotype replacement at 48 months compared with 2p+1, but this effect was not observed at 36 or 60 months. This indicates that 1p+1 may offer some initial benefit in limiting serotype replacement compared with 2p+1. No data were available for IgG or OPA outcomes.

APPENDICES

Appendix 1. Administrative Information

Registration

The protocol for this systematic review has been prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) Checklist (see Appendix 2)(24). The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42024560160, see Appendix 3).

Sources, Sponsor, and Roles

WHO's role includes financial support (WHO 2023/103/HQ/PCV) and reviewing the protocol to ensure it aligns with global health priorities and standards. All decisions regarding the methodology, data interpretation, and publication of findings are made by the research team. MCRI has supported the research infrastructure and provided resources necessary for the systematic review but has not been involved in the protocol's conceptualisation or development.

Appendix 2. PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) Checklist

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1.1	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritisation	13	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

Appendix 3. PROSPERO PROTOCOL REGISTRATION

The detailed protocol for this systematic review has been registered with PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=560160. This registration ensures transparency and allows for tracking of any updates or changes to the review process.

Appendix 4. ELIGIBILITY CRITERIA

Eligibility criteria

Studies published in languages other than English were excluded to maintain consistency and manageability in data synthesis and analysis. The review excluded animal studies, laboratory studies, dose-finding studies, case reports, letters, and editorials due to their limited contribution to evidence synthesis. Appendix Table 1 outlines eligibility criteria by PICO element

Appendix Table 1 Eligibility criteria as defined by PICO elements

Include	Exclude
Population	
• Children younger than five years • Children scheduled to receive their first PCV dose before six months and final PCV dose before 18 months	• Children are not in this age range. • First PCV dose not before six months or final PCV dose after 18 months
Intervention – main analyses	
• 1p+1 schedule of PCV7, PCV10, and PCV13 (for main analyses) • First dose scheduled at the same time a dose of DTP-containing vaccine offered • Final PCV dose scheduled from six to < 18 months • PCV7 or PCV9 with post-first dose outcome data and where the first dose was administered before six months of age (sub-analyses only)	• PCV schedule other than 1p+1 (for main analyses) • First PCV dose not scheduled at the same time as DTP-containing vaccines • Final PCV dose not scheduled from six to < 18 months • Studies using PCV7 and PCV9 without post-first dose data (excluded from main analyses but included in sub-analyses)
Comparator	
• 2p+1, 3p+0, 3p+1 schedule of PCV7, PCV10 or PCV13 as per current WHO recommendations • Zero doses of PCV	• Where PCV received, the schedule differs from current WHO recommendations
Outcomes	
• Serotype-specific immunoglobulin G (IgG) Geometric Mean Concentration (GMC), measured in µg/mL • Serotype-specific Correlate of Protection (CoP) for IgG – the percentage of vaccinated individuals who achieve an IgG antibody level considered protective against pneumococcal disease, > 0.35µg/mL. • Serotype-specific Opsonophagocytic Activity (OPA) Geometric Mean Titre (GMT). • Percentage of participants achieving the specified level of OPA for each serotype (OI of ≥8). • Vaccine-serotype carriage, number and rates of children carrying vaccine-included serotypes, by vaccination schedule. • Non-vaccine serotype carriage, number and rates of children carrying non-vaccine serotypes, by vaccination schedule. • Serotype-specific carriage, number and rates of children carrying specific serotypes, by vaccination schedule. • The incidence rate – rates of pneumonia, by pneumonia definition and vaccination	• Outcomes are not represented by vaccination schedules

schedule. • IPD– number of IPD cases reported by vaccination schedule. • IPD – case counts for vaccine-serotype (PCV7, PCV9, PCV10, PCV13) IPD, as the percentage reduction of case counts or incidence by vaccination schedule. • IPD – case counts for serotype-specific IPD, as the percentage reduction of cases or incidence, by vaccination schedule. • Breakthrough vaccine serotype IPD and vaccine failures - number of vaccine serotype IPD cases despite vaccination, measured in case counts.	
Others	
• Published in English • Published after 1st Jan 2000. • Randomised controlled trials (RCTs), cohort studies, case-control studies, and population-based surveillance studies	• Studies published only in languages other than English • Published before 1st Jan 2000. • Case reports, letters, editorials, animal, laboratory, and dose-finding studies.

Appendix 5. SEARCH STRATEGIES

EMBASE via Ovid

Embase Classic+Embase <1947 to 2024 Week 25>

1 exp pneumonia/ 442383

2 ((lower-respiratory adj3 infection*) or pneumonia or pneumonias or lung-inflammation* or lobitis or nonspecific-inflammatory-lung-disease* or peripneumonia or pleuropneumonia or pleuropneumonitis or pneumonic-lung* or pneumonic-pleurisy or pneumonic-pleuritis or pneumonitides or pneumonitis or pulmonal-inflammation* or pulmonary-inflammation* or pulmonic-inflammation* or invasive-pneumococcal).tw,kf,dq. 321816

3 pneumococcal infection/ or pneumococcal pneumonia/ 12097

4 Streptococcus pneumoniae/ 55367

5 vaccine immunogenicity/ 8017

6 conjugate vaccine/ 700

7 (antigenicit* or immunogenicit* or vaccine-efficac*).tw,kf,dq. 95764

8 bacterium antibody/ 22710

9 opsonin/3213

10 phagocytosis/ 94971

11 opsonization/ 5351

12 (Opsonophagocyt* or Opsonin-Protein* or phagocyt* or opsonization or opsonisation).tw,kf,dq. 124377

13 outcome*.tw,kf,hw,dq. 4734343

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 5432506

15 Pneumococcus vaccine/ 24637

16 (pnu-im?une or pnuim?une or pcv7 or pcv-7 or pcv10 or pcv-10 or pcv13 or pcv-13 or prevenar7 or prevenar-7 or prevenar10 or prevenar-10 or prevnar13 or prevnar-13).tw,kf,dq. 5229

17 ((7-valent or seven-valent or 10-valent or ten-valent or 13-valent or thirteen-valent) and (pneumococcal adj5 vaccine*)).tw,kf,dq. 4004

18 15 or 16 or 17 25369

19 (2-month? or 3-month? or 4-month? or 5-month? or 6-month? or 7-month? or 8-month? or 9-month? or 10-month? or 11-month? or 12-month? or 13-month? or 14-month? or 15-month? or 16-month? or 17-month? or 18-month? or 19-month? or 20-month? or 21-month? or 22-month? or 23-month? or 24-month? or two-month? or three-month? or four-month? or five-month? or six-month? or seven-month? or eight-month? or nine-month? or ten-month? or eleven-month? or twelve-month? or thirteen-month? or fourteen-month? or fifteen-month? or sixteen-month? or seventeen-month? or eighteen-month? or nineteen-month? or twenty-month? or twenty-one-month? or Under-2-year? or Below-2-year? or Less-than-2-year? or Under-two-year? or Below-two-year? or Less-than two-year? or newborn* or new-born* or baby or babies or neonat* or neo-nat* or infan* or toddler* or pre-school* or preschool* or one-year-old* or one-years-old* or two-year-old* or two-years-old* or three-year-old* or three-years-old* or four-year-old* or four-years-old* or five-year-old* or five-years-old* or 1-year-old* or 1-years-old* or 2-year-old* or 2-years-old* or 3-year-old* or 3-years-old* or 4-year-old* or 4-years-old* or 5-year-old* or 5-years-old* or aged-one or aged-1 or aged-two or aged-2 or aged-three or aged-3 or aged-four or aged-4 or aged-five or aged-5 or less-than-5-years or less-than-five-years or younger-than-5-years or younger-than-five-years).tw,kf,hw,dq. 4544516

20 (schedule or dose or dosing or doses).tw,kf,hw,dq. 3083841

21 drug dose/ 31216

22 20 or 21 3083841

23 pharynx/ or exp nasopharynx/ or exp oropharynx/ 78249

24 (Pharyn* or nasopharyn* or oropharyn*).tw,kf,dq. 179805

25 23 or 24 213335

26 disease carrier/ 37816

27 (carriage or density or densities or load or bacterial-load or biome or microbiome or coloni#ation or carrier-state or CFU or colony-forming or colony-formation or heterozygo* or genome-equivalent* or genomic-equivalent* or GE or CT or Cq).tw,kf,dq. 2580115

28 26 or 27 2613231

29 18 and 19 and 22 and 25 and 28 253

30 14 and 18 and 19 and 22 2012

31 29 or 30 2020
32 case report/ 3113281
33 limit 31 to (conference abstract or conference paper or "conference review" or editorial or letter or "preprint (unpublished, non-peer reviewed)") 294
34 31 not (32 or 33) 1666
35 limit 34 to (english language and yr="2000 -Current") 1532

MEDLINE via Ovid

Ovid MEDLINE(R) ALL <1946 to June 21, 2024>
1 exp *Pneumonia/ 332401
2 ((lower-respiratory adj3 infection*) or pneumonia or pneumonias or lung-inflammation* or lobitis or nonspecific-inflammatory-lung-disease* or peripneumonia or pleuropneumonia or pleuropneumonitis or pneumonic-lung* or pneumonic-pleurisy or pneumonic-pleuritis or pneumonitides or pneumonitis or pulmonal-inflammation* or pulmonary-inflammation* or pulmonic-inflammation* or invasive-pneumococcal).tw,kf. 204206
3 *pneumococcal infections/ 11780
4 *Streptococcus pneumoniae/ 16065
5 immunogenicity, vaccine/ or vaccine efficacy/ 4529
6 (antigenicit* or immunogenicit* or vaccine-efficac*).tw,kf. 72506
7 *Antibodies, Bacterial/bl or *Opsonin Proteins/bl or *phagocytosis/ or *opsonization/ 27363
8 (Opsonophagocyt* or Opsonin-Protein* or phagocyt* or opsonization or opsonisation).tw,kf. 95366
9 outcome*.tw,kf,hw. 3395859
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 3952024
11 exp *Pneumococcal Vaccines/ 5684
12 (pnu-im?une or pnuim?une or pcv7 or pcv-7 or pcv10 or pcv-10 or pcv13 or pcv-13 or prevenar7 or prevenar-7 or prevenar10 or prevenar-10 or prevnar13 or prevnar-13).tw,kf. 3420
13 ((7-valent or seven-valent or 10-valent or ten-valent or 13-valent or thirteen-valent) and (pneumococcal adj5 vaccine*)).tw,kf. 3077
14 11 or 12 or 13 7774
15 (2-month? or 3-month? or 4-month? or 5-month? or 6-month? or 7-month? or 8-month? or 9-month? or 10-month? or 11-month? or 12-month? or 13-month? or 14-month? or 15-month? or 16-month? or 17-month? or 18-month? or 19-month? or 20-month? or 21-month? or 22-month? or 23-month? or 24-month? or two-month? or three-month? or four-month? or five-month? or six-month? or seven-month? or eight-month? or nine-month? or ten-month? or eleven-month? or twelve-month? or thirteen-month? or fourteen-month? or fifteen-month? or sixteen-month? or seventeen-month? or eighteen-month? or nineteen-month? or twenty-month? or twenty-one-month? or Under-2-year? or Below-2-year? or Less-than-2-year? or Under-two-year? or Below-two-year? or Less-than two-year? or newborn* or new-born* or baby or babies or neonat* or neo-nat* or infan* or toddler* or pre-school* or preschool* or one-year-old* or one-years-old* or two-year-old* or two-years-old* or three-year-old* or three-years-old* or four-year-old* or four-years-old* or five-year-old* or five-years-old* or 1-year-old* or 1-years-old* or 2-year-old* or 2-years-old* or 3-year-old* or 3-years-old* or 4-year-old* or 4-years-old* or 5-year-old* or 5-years-old* or aged-one or aged-1 or aged-two or aged-2 or aged-three or aged-3 or aged-four or aged-4 or aged-five or aged-5 or less-than-5-years or less-than-five-years or younger-than-5-years or younger-than-five-years).tw,kf,hw. 3484160
16 (schedule or dose or dosing or doses).tw,kf,hw. 1981357
17 *pharynx/ or exp *nasopharynx/ or exp *oropharynx/ 25473
18 (Pharyn* or nasopharyn* or oropharyn*).tw,kf. 125341
19 17 or 18 136163
20 *Carrier State/ 11891
21 (carriage or density or densities or load or bacterial-load or biome or microbiome or coloni#ation or carrier-state or CFU or colony-forming or colony-formation or heterozygo* or genome-equivalent* or genomic-equivalent* or GE or CT or Cq).tw,kf. 1935740
22 20 or 21 1941653
23 14 and 15 and 16 and 19 and 22 223
24 10 and 14 and 15 and 16 1241
25 23 or 24 1263

26 limit 25 to (case reports or comment or editorial or letter or preprint) 26
27 25 not 26 1237
28 limit 27 to (english language and yr="2000 -Current") 1184

PubMed

#1 "lower-respiratory infection"[tiab:~2]
#2 title/abstract
"pneumonia" OR "pneumonias" OR "lung-inflammation*" OR "lobitis" OR "nonspecific-inflammatory-lung-disease*" OR "peripneumonia" OR "pleuropneumonia" OR "pleuropneumonitis" OR "pneumonic-lung*" OR "pneumonic-pleurisy" OR "pneumonic-pleuritis" OR "pneumonitides" OR "pneumonitis" OR "pulmonal-inflammation*" OR "pulmonary-inflammation*" OR "pulmonic-inflammation*" OR "invasive-pneumococcal" OR "pneumococcal-infection*" OR "Streptococcus-pneumoniae"
#3 title/abstract
"antigenicit*" OR "immunogenicit*" OR "vaccine-efficac*" OR "antibod*" OR "Opsonophagocyt*" OR "Opsonin-Protein*" OR "phagocyt*" OR "opsonization" OR "opsonization" OR "outcome*"
#4 #1 OR #2 OR #3
#5 title/abstract
"pnu-imune" OR "pnu-immune" OR "pnuimune" OR "pnuimmune" OR "pcv7" OR "pcv-7" OR "pcv10" OR "pcv-10" OR "pcv13" OR "pcv-13" OR "prevenar7" OR "prevenar-7" OR "prevenar10" OR "prevenar-10" OR "prevnar13" OR "prevnar-13"
#6 title/abstract
("7-valent" OR "seven-valent" OR "10-valent" OR "ten-valent" OR "13-valent" OR "thirteen-valent") AND "pneumococcal" AND "vaccine*"
#7 #5 OR #6
#8 title/abstract
"2-month*" OR "3-month*" OR "4-month*" OR "5-month*" OR "6-month*" OR "7-month*" OR "8-month*" OR "9-month*" OR "10-month*" OR "11-month*" OR "12-month*" OR "13-month*" OR "14-month*" OR "15-month*" OR "16-month*" OR "17-month*" OR "18-month*" OR "19-month*" OR "20-month*" OR "21-month*" OR "22-month*" OR "23-month*" OR "24-month*" OR "two-month*" OR "three-month*" OR "four-month*" OR "five-month*" OR "six-month*" OR "seven-month*" OR "eight-month*" OR "nine-month*" OR "ten-month*" OR "eleven-month*" OR "twelve-month*" OR "thirteen-month*" OR "fourteen-month*" OR "fifteen-month*" OR "sixteen-month*" OR "seventeen-month*" OR "eighteen-month*" OR "nineteen-month*" OR "twenty-month*" OR "twenty-one-month*" OR "Under-2-year*" OR "Below-2-year*" OR "Less-than-2-year*" OR "Under-two-year*" OR "Below-two-year*" OR "Less-than two-year*" OR "newborn*" OR "new-born*" OR "baby" OR "babies" OR "neonat*" OR "neo-nat*" OR "infan*" OR "toddler*" OR "pre-school*" OR "preschool*" OR "one-year-old*" OR "one-years-old*" OR "two-year-old*" OR "two-years-old*" OR "three-year-old*" OR "three-years-old*" OR "four-year-old*" OR "four-years-old*" OR "five-year-old*" OR "five-years-old*" OR "1-year-old*" OR "1-years-old*" OR "2-year-old*" OR "2-years-old*" OR "3-year-old*" OR "3-years-old*" OR "4-year-old*" OR "4-years-old*" OR "5-year-old*" OR "5-years-old*" OR "aged-one" OR "aged-1" OR "aged-two" OR "aged-2" OR "aged-three" OR "aged-3" OR "aged-four" OR "aged-4" OR "aged-five" OR "aged-5" OR "less-than-5-years" OR "less-than-five-years" OR "younger-than-5-years" OR "younger-than-five-years"
#9 title/abstract
"schedule" OR "dose" OR "dosing" OR "doses"
#10 title/abstract
"Pharyn*" OR "nasopharyn*" OR "oropharyn*"
#11 title/abstract
"carriage" OR "density" OR "densities" OR "load" OR "bacterial-load" OR "biome" OR "microbiome" OR "coloni*ation" OR "carrier-state" OR "CFU" OR "colony-forming" OR "colony-formation" OR "heterozygo*" OR "genome-equivalent*" OR "genomic-equivalent*" OR "GE" OR "CT" OR "Cq"
#12 All fields NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint
#13 #7 AND #8 AND #9 AND #10 AND #11 AND #12
#14 #4 AND #7 AND #8 AND #9 AND #12
#14 #13 OR #14

Appendix 6. STUDY RECORDS

Data management

All articles obtained from the search strategy were imported into COVIDENCE(25). Following deduplication, records that met eligibility criteria (as outlined in Appendix Table 1) were retrieved for full-text screening. Two reviewers (QL and MB-H) independently screened full-text reports. A third reviewer (FR or EN) arbitrated discrepancies.

Data extraction

Study details extracted included publication year, study design, setting, country or countries of study conduct, participant demographics such as age and health status, and the types and schedules of PCV administered.

Outcome measures were extracted according to predefined criteria in the studies, covering the incidence and incidence rates of IPD, the incidence and incidence rates of pneumonia, the rates of VT and NVT nasopharyngeal carriage, and immunogenicity indices such as IgG and OPAs. There is no gold standard definition of pneumonia sufficiently sensitive and specific to capture all cases of pneumococcal pneumonia. Therefore, the following categories of pneumonia were used as defined by each study: pneumococcal pneumonia, hospitalised pneumonia, clinical pneumonia, and radiological (X-ray-confirmed) pneumonia. Whenever necessary, authors were contacted to acquire data.

Data extraction was conducted independently by two investigators per included study, with any discrepancies resolved through discussion with a third reviewer, as necessary. In cases where essential data were missing or incomplete, efforts were made to contact study authors to obtain necessary information. If data could not be obtained despite these efforts, the study was noted as having missing data.

We contacted several researchers for data contributions. Dr Courtney Olwagen and Dr Anand Kawade shared data that were not extractable directly from their published studies (20, 26). Manish Sadarangani provided additional unpublished data from his trial (23). Furthermore, Prof Grant Mackenzie and Prof Yoshida Lay Mint, whose studies meet the PICO but are not yet published, have expressed interest in sharing their data for our review when available (12, 27).

Data were extracted from articles in prepared Excel templates. Data were imported into Stata 18.0 and for cleaning and description analysis (28). Data were exported to R for meta-analyses using the meta-package (29-31).

Appendix 7. DESCRIPTIVE AND META-ANALYSES METHODS

Descriptive analysis

Study characteristics were summarised, including study design, location, and participant demographics. Data were grouped by outcome domain (i.e. IPD, pneumonia, immunogenicity, carriage). Key outcome measures were outlined, including rates of invasive IPD, pneumonia, and nasopharyngeal carriage rates of vaccine and non-vaccine serotypes. Immunogenicity data (GMCs and OPA) were summarised.

Our primary objective was to evaluate the effectiveness of PCV 1p+1 PCV, with the final dose given at or after nine months, compared to 3p+0, 2p+1, and 3p+1. We analysed PCV dose schedules, comparing two doses (1p+1) against three (2p+1, 3p+0) and four doses (3p+1). Additionally, we assessed the efficacy/effectiveness of the 1p+1 schedule compared with receiving zero doses of PCV.

Meta-analyses were conducted separately for each comparison, outcome, and time point. We analysed data from RCTs and non-randomised studies separately. Random-effects meta-analysis models were fitted due to expected clinical and methodological differences. We used the restricted maximum likelihood (REML) estimator for heterogeneity variance and the Hartung-Knapp-Sidik-Jonkman method for confidence intervals. Heterogeneity was tested using the $\chi 2$ test (significance level of 0.10) and assessed with the I2 statistic. Sufficient studies allowed for calculating a prediction interval to summarise the spread of underlying true intervention effects.

For cluster RCTs, we used reported effect measures and standard errors accounting for intra-cluster correlation (ICC). We have indicated where adjustment for clustering had not been performed for cRCTs. For multi-arm trials, we combined groups to create a single pair-wise comparison. If a study reported data across multiple years, we considered data from the most recent year in the primary analysis due to the potential impact of herd immunity effects.

Analyses were conducted on available data without using imputation methods for missing data. Subgroup analyses were conducted based on the PCV formulation (PCV7, PCV9, PCV10, and PCV13) and study type (randomised vs. non-randomised). Meta-analyses within each subgroup assessed the impact on IPD, pneumonia, nasopharyngeal carriage, and immunogenicity. Comparisons between 1p+1 and zero doses were included to examine the baseline effects of PCV vaccination in a reduced dose schedule. We used random-effects meta-regression to account for differences and potential biases between studies.

Post-first dose data from studies using PCV7 and PCV9, where the first dose was administered before six months of age, have been included in sub-analyses but have not contributed to the main analysis. This is because earlier PCVs may generate a higher immunogenic response, which could potentially skew the main analyses if they were included.

Data included in the syntheses were checked for consistency with original study results. Results are presented in GRADE tables, adhering to GRADE methodology to evaluate the certainty of evidence across studies.

The timing/age of outcome measurements have been provided in Table 1. For IPD and pneumonia outcomes, analyses included age groups under five years. For nasopharyngeal carriage, outcomes were assessed at least four weeks post-primary and before any booster dose, post-final dose to less than two years of age, and post-final dose from two years of age to less than five years of age, as data allows. For immunogenicity outcomes, IgG assessment was assessed one-month post-primary, pre-final dose, and one-month post-final dose. OPAs were assessed at one-month post-primary series and final dose (as defined below):

- One-month post-primary (this assessment acknowledges age-related confounding, yet the main effect is attributed to the primary course)
    - For 1p+1, one-month after the first dose
    - For 2p+1, one-month after the second dose
    - For 3p+0 & 3p+1, one-month after the third dose
- Pre-final dose
    - For 1p+1, immediately before booster dose
    - For 2p+1, immediately before booster dose

    - For 3p+0, at the same age as the booster dose is given in the 1p+1 group
    - 3p+1, immediately before booster dose
- One-month post-final dose
    - For 1p+1, one-month post-booster dose
    - For 2p+1, one-month post-booster dose
    - For 3p+0, one-month-post-final
    - 3p+1, one-month post-booster dose

Planned meta-analyses

Appendix Table 2 List of planned analyses

	Outcome measure	Summary measure	Effect measure	Comparison	Timing	Data available for synthesis (Y/N)
OUTCOME DOMAIN: INVASIVE PNEUMOCOCCAL DISEASE						
1.1	Invasive pneumococcal disease	Incidence rate	IRR	1p+1 vs 2p+1	Age < five years	Yes
1.2	Invasive pneumococcal disease	Incidence rate	IRR	1p+1 vs 3p+0	Age < five years	No
1.3	Invasive pneumococcal disease	Incidence rate	IRR	1p+1 vs 3p+1	Age < five years	No
1.4	Invasive pneumococcal disease	Incidence rate	IRR	1p+1 vs 0p+0	Age < five years	No
2.1	Vaccine-type IPD	Incidence rate	IRR	1p+1 vs 2p+1	Age < five years	No
2.2	Vaccine-type IPD	Incidence rate	IRR	1p+1 vs 3p+0	Age < five years	No
2.3	Vaccine-type IPD	Incidence rate	IRR	1p+1 vs 3p+1	Age < five years	No
2.4	Vaccine-type IPD	Incidence rate	IRR	1p+1 vs 0p+0	Age < five years	No
3.1	Serotype-specific IPD	Incidence rate	IRR	1p+1 vs 2p+1	Age < five years	No
3.2	Serotype-specific IPD	Incidence rate	IRR	1p+1 vs 3p+0	Age < five years	No
3.3	Serotype-specific IPD	Incidence rate	IRR	1p+1 vs 3p+1	Age < five years	No
3.4	Serotype-specific IPD	Incidence rate	IRR	1p+1 vs 0p+0	Age < five years	No
OUTCOME DOMAIN: PNEUMONIA						
4.1	Pneumococcal pneumonia	Incidence rate	IRR	1p+1 vs 2p+1	Age < five years	No
4.2	Pneumococcal pneumonia	Incidence rate	IRR	1p+1 vs 3p+0	Age < five years	No
4.3	Pneumococcal pneumonia	Incidence rate	IRR	1p+1 vs 3p+1	Age < five years	No
4.4	Pneumococcal pneumonia	Incidence rate	IRR	1p+1 vs 0p+0	Age < five years	No
5.1	Clinical pneumonia	Incidence rate	IRR	1p+1 vs 2p+1	Age < five years	No
5.2	Clinical pneumonia	Incidence rate	IRR	1p+1 vs 3p+0	Age < five years	No
5.3	Clinical pneumonia	Incidence rate	IRR	1p+1 vs 3p+1	Age < five years	No
5.4	Clinical pneumonia	Incidence rate	IRR	1p+1 vs 0p+0	Age < five years	No
6.1	Radiologic pneumonia	Incidence rate	IRR	1p+1 vs 2p+1	Age < five years	No
6.2	Radiologic pneumonia	Incidence rate	IRR	1p+1 vs 3p+0	Age < five years	Yes
6.3	Radiologic pneumonia	Incidence rate	IRR	1p+1 vs 3p+1	Age < five years	No
6.4	Radiologic pneumonia	Incidence rate	IRR	1p+1 vs 0p+0	Age < five years	No
7.1	Hospitalised pneumonia	Incidence rate	IRR	1p+1 vs 2p+1	Age < five years	No
7.2	Hospitalised pneumonia	Incidence rate	IRR	1p+1 vs 3p+0	Age < five years	No
7.3	Hospitalised pneumonia	Incidence rate	IRR	1p+1 vs 3p+1	Age < five years	No
7.4	Hospitalised pneumonia	Incidence rate	IRR	1p+1 vs 0p+0	Age < five years	No
OUTCOME DOMAIN: NASOPHARYNGEAL CARRIAGE						
8.1	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-primary series	PCV13- No PCV10- Yes PCV9- No PCV7- Yes (sub-analyses)

8.2	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-primary series	PCV13- No PCV10- Yes PCV9- No PCV7- Yes (sub-analyses)
8.3	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-primary series	PCV13- No PCV10- No PCV9- No PCV7- No
8.4	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-primary series	PCV13- No PCV10- Yes PCV9- No PCV7- Yes (sub-analyses)
9.1	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-primary series	PCV13- No PCV10- Yes PCV9- No PCV7- Yes (sub-analyses)
9.2	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-primary series	PCV13- No PCV10- Yes PCV9- No PCV7- Yes (sub-analyses)
9.3	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-primary series	PCV13- No PCV10- No PCV9- No PCV7- No
9.4	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-primary series	PCV13- No PCV10- Yes PCV9- No PCV7- Yes (sub-analyses)
10.1	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-primary series	PCV13- No PCV10- Yes
10.2	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-primary series	PCV13- No PCV10- Yes
10.3	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-primary series	PCV13- No PCV10- No
10.4	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-primary series	PCV13- No PCV10- No
11.1	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-final to $\leq$ 2 years	PCV13- Yes PCV10- Yes
11.2	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-final to $\leq$2 years	PCV13- No PCV10- Yes

11.3	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-final to ≤2 years	PCV13- No PCV10- No
11.4	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-final to ≤2 years	PCV13- No PCV10- Yes
12.1	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-final to ≤2 years	PCV13- Yes PCV10- Yes
12.2	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-final to ≤2 years	PCV13- No PCV10- Yes
12.3	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-final to ≤2 years	PCV13- No PCV10- No
12.4	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-final to ≤2 years	PCV13- No PCV10- Yes
13.1	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-final to ≤2 years	PCV13- No PCV10- Yes
13.2	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-final to ≤2 years	PCV13- No PCV10- Yes
13.3	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-final to ≤2 years	PCV13- No PCV10- No
13.4	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-final to ≤2 years	PCV13- No PCV10- Yes
14.1	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-final to < five years	PCV13- Yes PCV10- Yes
14.2	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-final to < five years	PCV13- No PCV10- No
14.3	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-final to < five years	PCV13- No PCV10- No
14.4	Vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-final to < five years	PCV13- No PCV10- No
15.1	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-final to < five years	PCV13- Yes PCV10- Yes
15.2	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-final to < five years	PCV13- No PCV10- No
15.3	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-final to < five years	PCV13- No PCV10- No
15.4	Non-vaccine-serotype carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-final to < five years	PCV13- No PCV10- No
16.1	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 2p+1	Post-final to < five years	PCV13- No PCV10- No
16.2	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 3p+0	Post-final to < five years	PCV13- No PCV10- No

16.3	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 3p+1	Post-final to < five years	PCV13- No PCV10- No
16.4	Serotype-specific carriage	Proportion	Risk ratio	1p+1 vs 0p+0	Post-final to < five years	PCV13- No PCV10- No
OUTCOME DOMAIN: IMMUNOGENICITY						
17.1	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 2p+1	Post-primary series	PCV13- Yes PCV10- Yes
17.2	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 3p+0	Post-primary series	PCV13- Yes PCV10- Yes
17.3	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 3p+1	Post-primary series	PCV13- No PCV10- No
17.4	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 0p+0	Post-primary series	PCV13- No PCV10- No
18.1	Serotype-specific IgG ≥0.35µg/mL	Proportion	Risk ratio	1p+1 vs 2p+1	Post-primary series	PCV13- Yes PCV10- Yes
18.2	Serotype-specific IgG ≥0.35µg/mL	Proportion	Risk ratio	1p+1 vs 3p+0	Post-primary series	PCV13- Yes PCV10- Yes
18.3	Serotype-specific IgG ≥0.35µg/mL	Proportion	Risk ratio	1p+1 vs 3p+1	Post-primary series	PCV13- No PCV10- No
18.4	Serotype-specific IgG ≥0.35µg/mL	Proportion	Risk ratio	1p+1 vs 0p+0	Post-primary series	PCV13- No PCV10- Yes
19.1	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 2p+1	Pre-final	PCV13- Yes PCV10- Yes
19.2	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 3p+0	Pre-final	PCV13- Yes PCV10- Yes
19.3	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 3p+1	Pre-final	PCV13- No PCV10- No
19.4	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 0p+0	Pre-final	PCV13- No PCV10- No
20.1	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 2p+1	Post-final	PCV13- Yes PCV10- Yes
20.2	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 3p+0	Post-final	PCV13- Yes PCV10- Yes
20.3	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 3p+1	Post-final	PCV13- No PCV10- Yes
20.4	Serotype-specific IgG	Geometric mean	GMR	1p+1 vs 0p+0	Post-final	PCV13- Yes PCV10- Yes
21.1	Serotype-specific OPA	Geometric mean	GMR	1p+1 vs 2p+1	Pre-final	PCV13- No PCV10- No
21.2	Serotype-specific OPA	Geometric mean	GMR	1p+1 vs 3p+0	Pre-final	PCV13- No

						PCV10- No
21.3	Serotype-specific OPA	Geometric mean	GMR	1p+1 vs 3p+1	Pre-final	PCV13- No PCV10- No
21.4	Serotype-specific OPA	Geometric mean	GMR	1p+1 vs 0p+0	Pre-final	PCV13- No PCV10- No
22.1	Serotype-specific OI ≥8	Proportion	Risk ratio	1p+1 vs 2p+1	Pre-final	PCV13- No PCV10- No
22.2	Serotype-specific OI ≥8	Proportion	Risk ratio	1p+1 vs 3p+0	Pre-final	PCV13- No PCV10- No
22.3	Serotype-specific OI ≥8	Proportion	Risk ratio	1p+1 vs 3p+1	Pre-final	PCV13- No PCV10- No
22.4	Serotype-specific OI ≥8	Proportion	Risk ratio	1p+1 vs 0p+0	Pre-final	PCV13- No PCV10- No
23.1	Serotype-specific OPA	Geometric mean	GMR	1p+1 vs 2p+1	Post-final	PCV13- Yes PCV10- Yes
23.2	Serotype-specific OPA	Geometric mean	GMR	1p+1 vs 3p+0	Post-final	PCV13- Yes PCV10- Yes
23.3	Serotype-specific OPA	Geometric mean	GMR	1p+1 vs 3p+1	Post-final	PCV13- No PCV10- No
23.4	Serotype-specific OPA	Geometric mean	GMR	1p+1 vs 0p+0	Post-final	PCV13- No PCV10- No
24.1	Serotype-specific OI ≥8	Proportion	Risk ratio	1p+1 vs 2p+1	Post-final	PCV13- Yes PCV10- Yes
24.2	Serotype-specific OI ≥8	Proportion	Risk ratio	1p+1 vs 3p+0	Post-final	PCV13- Yes PCV10- Yes
24.3	Serotype-specific OI ≥8	Proportion	Risk ratio	1p+1 vs 3p+1	Post-final	PCV13- No PCV10- No
24.4	Serotype-specific OI ≥8	Proportion	Risk ratio	1p+1 vs 0p+0	Post-final	PCV13- No PCV10- No

Notes: GMR=Geometric mean ratio. GMRs will be synthesised on the logarithmic scale; IRR =incidence rate ratio; Vaccine-type serotype carriage and non-vaccine serotype carriage will be repeated for PCV7, PCV9, PCV10 and PCV13; Vaccine-type IPD will be repeated for PCV7, PCV9, PCV10 and PCV13

SYNTHESIS METHODS

Continuous outcomes

The continuous outcomes (IgG and OPA values) were expected to be skewed. The data required for synthesis included the geometric mean, 95% confidence intervals and sample sizes. Data were analysed on the log-scale as follows:

1. The natural logarithm of the geometric means and the upper and lower limits of the 95% confidence intervals were calculated for each group.
2. The standard deviations of the log-transformed data were computed using the sample size (N) and upper and lower limits of the 95% CI, using the formula (see Cochrane handbook 6.5.2.2): $SD = \sqrt{N} * (upper\ limit - lower\ limit)/3.92$
3. Meta-analyses were performed on the scale of the natural log data, where the effect measure was a difference in log-transformed geometric means.
4. Results were exponentiated for presentation

Binary outcomes

Binary outcomes included nasopharyngeal carriage outcomes and dichotomised immunogenicity measures (e.g., the proportion of participants with IgG>0.35µg/ml or OI≥8). For all binary outcomes, the effect measure was the risk ratio (i.e., the ratio of risk/proportion in the intervention group divided by risk/proportion in the comparator group).

Where possible, binary outcomes were extracted directly as raw numbers (i.e. numbers of events and sample sizes in the intervention and comparator groups) for analysis. If raw numbers were not available, then the risk ratios and standard errors were extracted (or calculated). We calculated SE for a risk ratio from a confidence interval as follows, (see Cochrane Section 3.1.2):

1. Calculated the natural logarithm (ln) of the reported lower limit of the RR, i.e. $lower\ limit = ln(lower\ confidence\ limit\ given\ for\ RR)$
2. Calculated $upper\ limit = ln(upper\ confidence\ limit\ given\ for\ RR)$
3. Calculated $Intervention\ effect\ estimate = lnRR$
4. If it was a 95% confidence interval, then the SE was calculated as: $SE = (upper\ limit - lower\ limit)/3.92$
5. Synthesis was performed on the log-scale.

If there were no events in one or more arms, then a continuity correction was applied.

Synthesis of summary and effect measures

If summary measures by group (e.g., number of events and non-events for carriage outcomes, geometric mean concentrations and 95% confidence intervals for IgG data) were available for all studies in a specific meta-analysis, these data were used in the meta-analysis. If some studies only provided effect measures (e.g., risk ratio or geometric mean ratio with 95% confidence intervals), the effect measures and standard errors were pooled in the meta-analysis. This approach allowed us to synthesise both types of available data, ensuring that the maximum amount of information was used in the meta-analysis.

Incidence outcomes

The incidence outcomes included the disease outcomes (IPD and pneumonia), with the effect measure being the incidence rate ratio. Where possible, the number of events and person-time at risk were extracted for each group and synthesised using the raw values. If the raw data were not available, then incidence rate ratios and standard errors were combined (using methods described in the section above on binary outcomes).

Appendix 8. STUDY CONDUCT AND DISSEMINATION

Study conduct and protocol

This review has been conducted and reported in line with the PRISMA guidelines (32) (see Appendix 9, PRISMA 2020 Statement) and the protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42024560160). Any changes to the protocol that has affected the scientific intent or study design has been considered an amendment. All such amendments were documented and submitted to PROSPERO before being implemented.

Financial disclosure and conflicts of interest

The technical lead (FR) has given talks on this topic at workshops, seminars, and conferences for which the conference organisers have paid for travel and accommodation. FR was co-PI of one of the included clinical trials.

CN is a study statistician on trials of reduced-dose PCV schedules in Vietnam and Gambia. She is a co-investigator/biostatistician on a Merck Investigator Studies Program grant funded by MSD on pneumococcal serotype epidemiology in children with empyema. She is also a co-investigator/biostatistician on a clinical research collaboration with Pfizer on PCV vaccination in Mongolia.

The other authors declare that they have no known conflicts of interest.

Dissemination and translation plan

In addition to this report for WHO, a paper will be submitted to a leading journal in this field. The PI (Prof Russell) holds the primary responsibility for publication of the results of the study.

Appendix 9. PRISMA 2020 STATEMENT

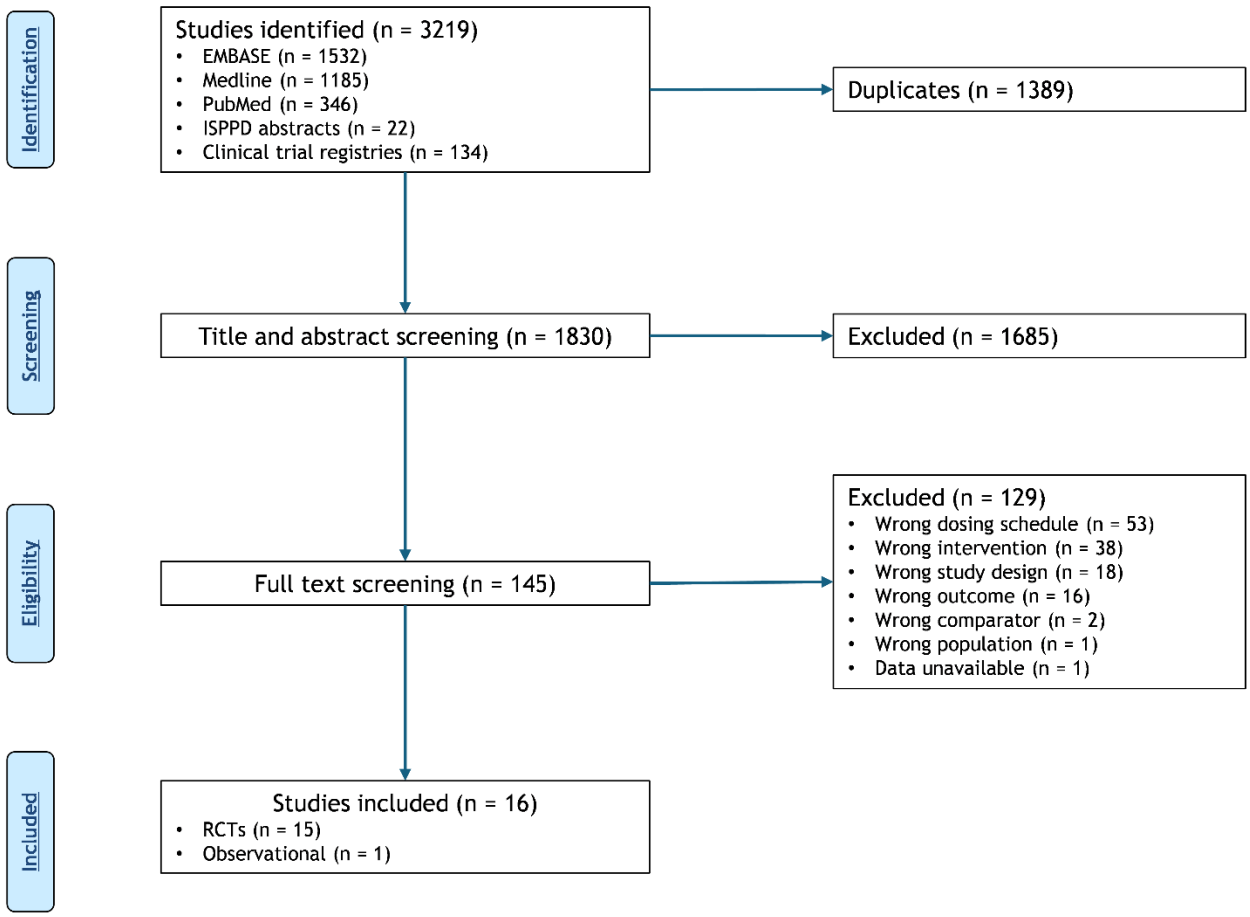
Appendix Table 3 PRISMA 2020 statement checklist(33)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix 10. PRISMA FLOW DIAGRAM



Appendix Figure 1 Flow diagram of selection of studies into the systematic review

Appendix 11. STUDY CHARACTERISTICS

Appendix Table 4 Characteristics of nine randomised controlled trials with 15 articles, and one observational study, included in the systematic review including main PICO elements

First Author, year (ref)	Location	PCV formulation	Study design	PCV schedule	Age at each dose		Number randomised	Outcomes & outcome definition	Age at measurement	Outcome measure	Funding	WHO methods for outcome measurement[a]
					Intended	Actual						
Randomised controlled trials												
Russell, 2009(13)	Suva, Fiji	PCV7, Wyeth	Single-blind, open-label RCT	1p+0 2p+0 3p+0 0p	6w 6w, 10w, 6w, 10w, 14w NA	NR	128 156 136 132	PCV7 serotype-specific IgG GMC	18w	GMC in µg/mL (95%CI)	NIAID, NHMRC	Y
								Seropositivity of PCV7 serotype-specific IgG		% achieving IgG≥0.35µg/mL		Y
Russell, 2010(14)	Suva, Fiji	PCV7, Wyeth	Single-blind, open-label RCT	1p+0 2p+0 3p+0 0p	6w 6w, 10w, 6w, 10w, 14w NA	NR	128 156 136 132	PCV7 serotype-specific IgG GMC	12m	GMC in µg/mL (95%CI)		Y
								Seropositivity of PCV7 serotype-specific IgG		% achieving IgG≥0.35µg/mL		Y
Russell, 2010(15)	Suva, Fiji	PCV7, Wyeth	Single-blind, open-label RCT	1p+0 2p+0 3p+0 0p	6w 6w, 10w, 6w, 10w, 14w NA	NR	128 156 136 132	PCV7 VT & NVT carriage	6m	n/N (%, 95% CI) with PCV7 VT & NVT detected in nasopharyngeal swabs		Y
								PCV7 VT & NVT carriage	9m	n/N (%, 95% CI) with PCV7 VT & NVT detected in nasopharyngeal swabs		Y
								PCV7 VT & NVT carriage	12m	n/N (%, 95% CI) with PCV7 VT & NVT detected in nasopharyngeal swabs		Y
Russell, 2011(16)	Suva, Fiji	PCV7, Wyeth	Single-blind, open-label RCT	1p+0 2p+0 3p+0 0p	6w 6w, 10w, 6w, 10w, 14w NA	NR	128 156 136 132	PCV7 serotype-specific OPA GMT	12m	GMT in µg/mL (95%CI)		Y
								OI		% (95%CI) with OI≥8		Y

Ota, 2011(34)	Upper & Central River Regions, The Gambia	PCV7, Wyeth	RCT	1p+0 2p+0 3p+0	2m 2m, 3m 2m, 3m, 4m	NR	228 228 227	PCV7 serotype-specific IgG GMC	5m	GMC in µg/mL (95%CI)	WHO and UK Medical Research Council	Y
								Seropositivity of PCV7 serotype-specific IgG		% achieving IgG≥0.35µg/mL		Y
								PCV7 VT & NVT carriage		n/N (%, 95% CI) with PCV7 VT & NVT detected in nasopharyngeal swabs		Y
Goldblatt, 2018(18)	Oxfordshire, England	PCV13, Pfizer	Multicentre, open label, RCT	2p+1 1p+1	2m, 4m, 12m 3m, 12m	2m, 4.1m, 12.4m 3m, 12.4m	106 107	PCV13 serotype-specific IgG GMC	5m, 13m	GMC in µg/mL (95%CI)	NIHR, BMGF	Y
								Seropositivity of PCV13 serotype-specific IgG		% (95% CI) achieving IgG≥0.35µg/mL		Y
								PCV13 serotype-specific OPA GMT	13m	GMT in µg/mL (95%CI)		Y
Madhi, 2020(19)	Soweto, South Africa	PCV10, GSK PCV13, Pfizer	Single-centre, open-label, RCT	2p+1 1p+1 1p+1 2p+1 1p+1 1p+1	6w, 14w, 9m 6w, 9m 14w, 9m 6w, 14w, 9m 6w, 9m 14w, 9m	6.37w, 14.5w, 9m 6.39w, 8.96m 14.43 w, 9.03m 6.37w, 14.5w, 9m 6.36w, 8.98m 14.58 w, 8.98m	100 100 100 100 100 100	PCV10 & PCV13 serotype-specific IgG GMC	10w 18w 9m 10m	GMC in µg/mL (96%CI)	BMGF	Y
								Seropositivity of PCV10 & PCV13 serotype-specific IgG		% (95% CI) achieving IgG≥0.35µg/mL		Y
								PCV10 and PCV13 serotype-specific OPA GMT	10m	GMT in µg/mL (96%CI)		Y
								OI		% (96%CI) with OI≥8		Y
Licciardi, 2021(21)	Ho Chi Minh City, Vietnam	PCV10, GSK	Single-blind, parallel-group, open-label RCT	3p+1 3p+0 2p+1 1p+1 0p	2m, 3m, 4m, 9m 2m, 3m, 4m 2m, 4m, 9.5m 2m, 6m NA	NR	152 149 250 202	PCV10 serotype-specific GMC	5m	GMC in µg/mL (95%CI)	NIHR, BMGF	Y
								Seropositivity of PCV10 serotype-specific IgG		% (95%CI) achieving IgG ≥0.35µg/mL		Y
								PCV10 serotype-specific OPA GMT	7m 10m	GMT in µg/mL (95%CI)		Y
								OI		% (95%CI) with OI≥8		Y

Kawade, 2023(26)[b]	Pune, India	PCV10, GSK PCV13, Pfizer	Single-centre, open-label, parallel-arm RCT	3p+0 2p+1 1p+1 3p+0 2p+1 1p+1 0p	6w, 10w, 14w 6w, 10w, 9m 6w, 9m 6w, 10w, 14w 6w, 10w, 9m 6w ,9m NA	NR	115 115 115 115 115 114 115	PCV10 & PCV13 VT & NVT carriage	18w 9m 10m 15m 18m	n/N (%, 95% CI) with PCV10 & PCV13 VT & NVT detected in nasopharyngeal swabs	KEM Hospital Research Centre, BMGF	Y
								PCV10 & PCV13 serotype-specific IgG GMC	18w 9m 10m 18m	GMC in µg/mL (95%CI)		Y
								Seropositivity of PCV10 & PCV13 serotype-specific IgG		% (95%CI) achieving IgG ≥0.35µg/mL		Y
								PCV10 & PCV13 serotype-specific OPA GMT	10m	GMT in µg/mL (95%CI)		Y
								OI		% (95%CI) with OI≥8		Y
Olwagen, 2023(20)[b]	Soweto, South Africa	PCV10, GSK PCV13, Pfizer	Single-centre, open-label, RCT	2p+1 1p+1 1p+1 2p+1 1p+1 1p+1	6w, 14w, 9m 6w, 9m 14w, 9m 6w, 14w, 9m 6w, 9m 14w, 9m	6.37w, 14.5w, 9m 6.39w, 8.96m 14.43 w, 9.03m 6.37w, 14.5w, 9m 6.36w, 8.98m 14.58 w, 8.98m	100 100 100 100 100 100	PCV10 & PCV13 VT & NVT carriage	15m 18m	n/N (%, 95% CI) with PCV10 & PCV13 VT & NVT detected in nasopharyngeal swabs	BMGF	Y
Smith-Vaughan, 2023(22)	Ho Chi Minh City, Vietnam	PCV10, GSK	Single-blind, parallel-group, open-label RCT	3p+1 3p+0 2p+1 1p+1 0p	2m, 3m, 4m, 9m 2m, 3m, 4m 2m, 4m, 9.5m 2m, 6m 24m	NR	152 149 250 202 199	PCV10 VT & NVT carriage	12m 18m 24m	n/N (%, 95% CI) with PCV10 VT & NVT detected in nasopharyngeal swabs	NIHR, BMGF	Y
Goldblatt, 2023(35)	Oxfordshire, England	PCV13, Pfizer	Multicentre, open	2p+1 1p+1	2m, 4m, 12m 3m, 12m	2m, 4.1m, 12.4m	106 107	PCV13 VT & NVT carriage	12m 18m	n/N (%, 95% CI) with PCV13 VT & NVT detected in	NIHR, BMGF	Y

			label, RCT			3m, 12.4m				nasopharyngeal swabs		
Yoshida, 2024(27)[b]	Nha Trang, Vietnam	PCV10, GSK	Open-label, cluster RCT	3p+0 2p+1 1p+1	2m, 3m, 4m 2m, 4m, 12m 2m, 12m	NR	5335 2676 3355	PCV10 VT & NVT carriage	October 2018, 2019 2020	n/N (%, 95% CI) with PCV10 VT & NVT detected in nasopharyngeal swabs	BMGF	Y
Sadarangani, NYP (23)[b, c]	Vancouver, Canada	PCV13, Pfizer	RCT	2p+1 1p+1	2m, 4m, 12m 2m, 12m	NR	125 123	PCV13 serotype-specific IgG GMC	5m 13m	GMC in µg/mL (95%CI)	NR	Y
								Seropositivity of PCV13 serotype-specific IgG		% (95%CI) achieving IgG ≥0.35µg/mL		Y
Mackenzie, NYP(12)[d]	The Gambia	PCV13, Pfizer	Cluster RCT	3p+0 1p+1	6w, 10w, 14w 6w, 9m	NR	NR	PCV13 VT & NVT carriage	2y, 4y	n/N (%, 95% CI) with PCV13 VT & NVT detected in nasopharyngeal swabs	BMGF; JGHTS	Y
								Clinical pneumonia and radiological pneumonia	Throughout study period	Incidence		Y
								IPD		Serotype-specific IPD incidence		Y
Non-Randomised Controlled Trials												
First Author, year (ref)	Location	PCV formulation	Study design	PCV schedule	Age range	Study population	Observation period or ages at observation	Outcomes and outcome definition	Outcome measure		Funding	WHO methods for outcome measurement[a]
Bertran, 2024(36)	England	PCV13, Pfizer	Prospective national observational surveillance	2p+ 1p+1	<12m 1-4 y	Cases of IPD living in England	01 Apr 2017 - 31 Mar 2023 1p+1 started on 01 Jan 2020	Laboratory confirmed IPD	IPD cases, IR & IRR (95% CI) in 2022-2023 compared with 2019-2020.		None	Y
								Breakthrough infections defined as VT IPD diagnosed ≥ 14 days post ≥ one dose PCV13 before 12m	IPD cases & incidence rate			Y
								Vaccine failure: VT IPD ≥ seven days post ≥ one dose PCV13 before 12m	IPD cases & incidence rate			Y

Abbreviations: 95% CI - 95% confidence interval; BMGF – Bill & Melinda Gates Foundation; GMC – Geometric mean concentration; GMT-Geometric mean titre; IgG – Immunoglobulin G; IPD – invasive pneumococcal disease; IR – incidence rate; IRR – incidence rate ratio; m – months; JGHTS – Joint Global Health Trials Scheme; KEM-King Edward Memorial; NHMRC – National Health and Medical Research Council; NIAID – National Institute of Allergy and Infectious Disease; NIHR – National Institute for Health and Care Research; NR – not reported; NYP – not yet published; NVT – non-vaccine-serotype; OI-Opsonisation indices; OPA-Opsonophagocytic activity; PCV- pneumococcal conjugate vaccine; PCV7 – 7-valent pneumococcal conjugate vaccine; PCV9 – 9-valent pneumococcal conjugate vaccine; PCV10 – 10-valent pneumococcal conjugate vaccine; PCV13 – 13-valent pneumococcal conjugate vaccine; RCT – randomised controlled trial; ref – reference; UK – United Kingdom; VT – vaccine-serotype; w – weeks; WHO – World Health Organisation; y – years; Y – Yes. **Footnotes**: [a] WHO guidelines for the assessment of immune response and carriage(37, 38); [b] Data was provided by authors that was not extractable directly from published studies(20, 26); [c] Not yet published studies that met the PICO, and for which authors shared data(23); [d] Not yet published studies that meet the PICO, and for which authors have indicated data will be shared in the future(12, 27).

Appendix Table 5 Descriptive characteristics of nine randomised controlled trials reporting on relevant outcomes in 15 studies, and one observational study included in the systematic review by study design

Characteristics, n (%)	**Study design**	
	Randomised controlled trial articles (N =15[a])	**Non-randomised articles (N=1)**
Publication status		
Published	13 (87)	1 (100)
Unpublished, data shared	2 (13)	0 (0)
Included 1p	5 (33)	0 (0)
Included 1p+1	10 (67)	1 (100)
1p	N=5	
Age at first dose		
6 weeks	4 (80)	0 (0)
2 months	1 (20)	0 (0)
1p+1	N=10	
Age at first dose		
6 weeks	4 (40)	0 (0)
12 weeks	0 (0)	1 (100)
14 weeks	2 (20)	0 (0)
2 months	6 (60)	0 (0)
3 months	2 (20)	0 (0)
Age at booster dose		
6 months	2 (20)	0 (0)
9 months	4 (40)	0 (0)
12 months	4 (40)	1 (100)
Comparator		
2p+1	9 (60)	1 (100)
3p+0	10 (67)	0 (0)
3p+1	2 (13)	0 (0)
Zero doses	7 (47)	0 (0)
PCV product		
PCV7	5 (33)	0 (0)
PCV9	0 (0)	0 (0)
PCV10 GSK	6 (40)	0 (0)
PCV10 PNEUMOSIL	0 (0)	0 (0)
PCV13	7 (47)	1 (100)
WHO region		
AFR	4 (27)	0 (0)
AMR	1 (7)	0 (0)
SEAR	1 (7)	0 (0)
EUR	2 (13)	1 (100)
EMR	0 (0)	0 (0)
WPR	7 (47)	0 (0)
World Bank income classification[b]		
Low	2 (13)	0 (0)
Lower-middle	4 (27)	0 (0)
Upper-middle	6 (40)	0 (0)
High	3 (20)	1 (100)
Outcome		
IPD	1 (7)	1 (100)
Pneumonia	1 (7)	0 (0)
Nasopharyngeal carriage	8 (53)	0 (0)
Immunogenicity	9 (60)	0 (0)

Abbreviations: ref – WHO – World Health Organization; AFR – African Region; AMR – Region of the Americas; SEAR – South-East Asian Region; EUR – European Region; EMR – Eastern Mediterranean Region; WPR – Western Pacific Region; IPD - invasive pneumococcal disease. Footnotes: [a] Unless otherwise indicated; [a] As defined by the World Bank at the time the study was conducted(39).

Appendix 12. SUB-ANALYSES

Sub-analyses of carriage and immunogenicity outcomes, by time point and formulation

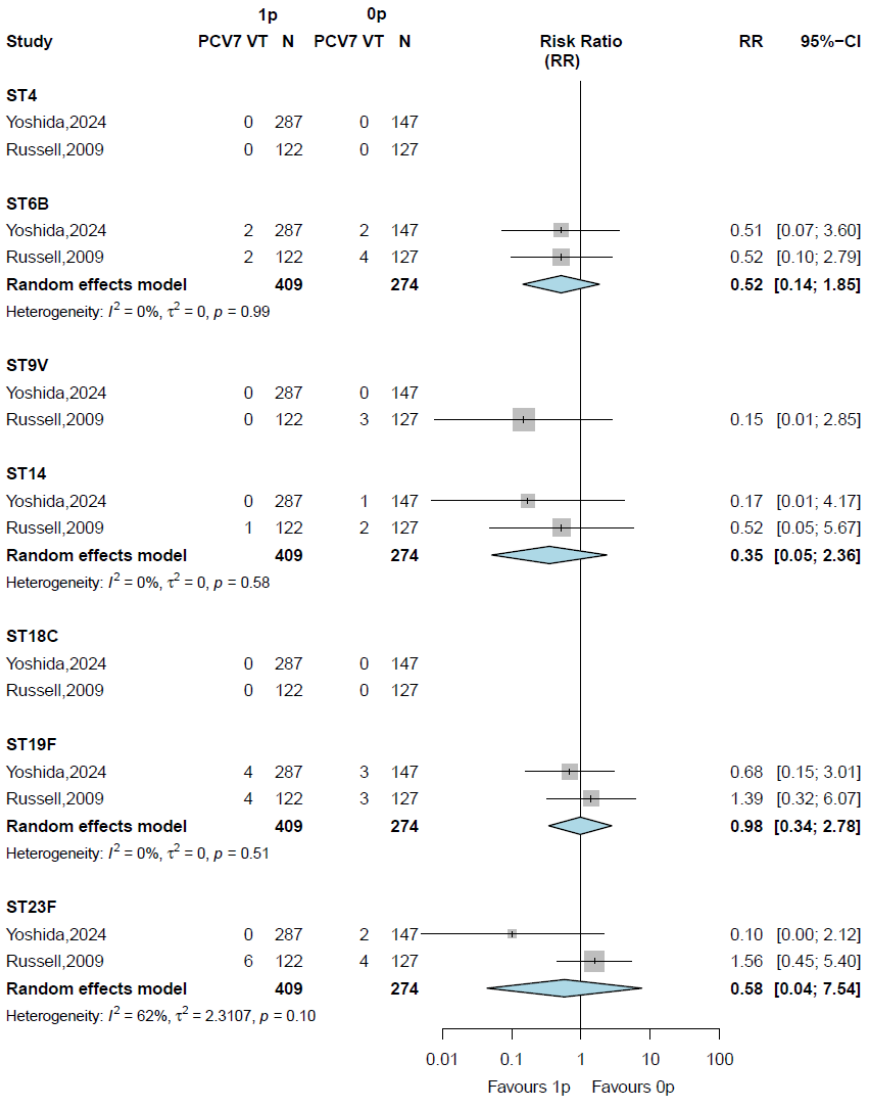
Post-primary PCV dose for the seven shared serotypes in PCV7, PCV9, PCV10, PCV13

These sub-analyses are for the serotypes shared between PCV7, PCV9, PCV10 and PCV13 – serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

PCV7 shared serotypes 1p vs 0p

Carriage

In the main analysis, no meta-analysis was conducted for serotype-specific carriage of 6B, 14, 19F, and 23F comparing 1p and 0p, as only one study (using PCV10) provided data. The sub-analysis, which included an additional PCV7 study from Fiji, allowed for a meta-analysis of serotypes 6B, 14, 19F, and 23F comparing 1p and 0p post-primary (Appendix Figure 2). For serotypes 4 and 18C, there were no carriage events in either RCT. For serotype 9V meta-analysis was not done, as there were no carriage events in Vietnam. In Fiji, there was no difference in carriage of 9V between 1p and 0p. For the remaining serotypes (6B, 14, 19F, and 23F), meta-analysis results favoured neither 1p nor 0p. The sub-analysis changed point estimates of the RR slightly and increased precision, as reflected in a narrower 95% CI, but did not change the overall findings from the primary analysis.



Appendix Figure 2 Serotype-specific carriage of PCV7 shared serotypes, post-primary series, comparing 1p and 0p

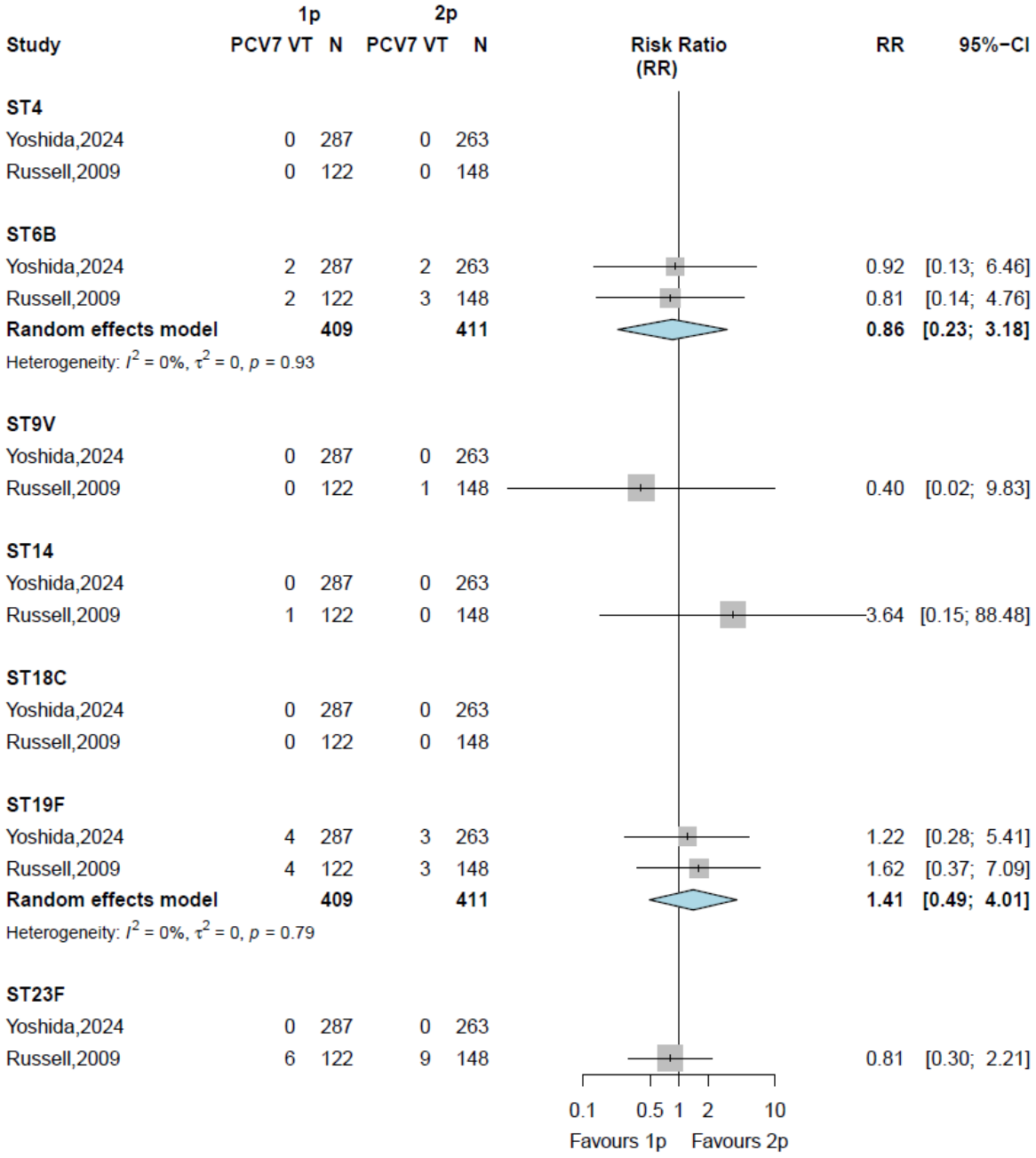
Serotype-specific IgG and OPA

No data were available for serotype-specific IgG or OPA post-primary 1p vs 0p.

PCV 7 shared serotypes 1p vs 2p

Carriage

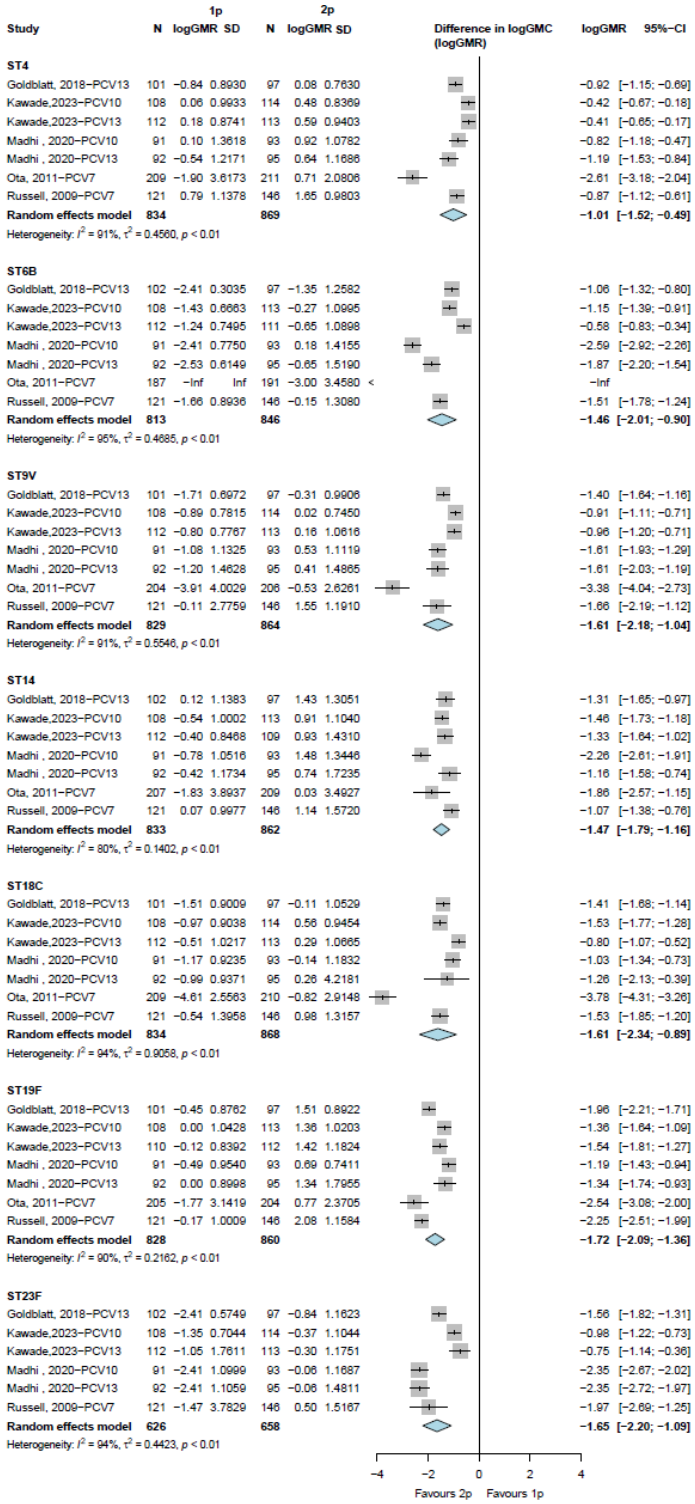
In the main analysis, no meta-analysis was conducted for serotype-specific carriage of 6B and 19F comparing 1p and 2p, as only one study (using PCV10) provided data. This sub-analysis incorporates PCV7 data from Fiji, comparing 1p and 2p post-primary (Appendix Figure 3). For serotypes 4 and 18C, there were no carriage events in either RCT. No meta-analyses were done for serotypes 9V, 14, and 23F because there were only carriage events in Fiji. For those serotypes, we calculated RR for Fiji only and found no difference between 1p vs 2p. For serotypes 6B and 19F, meta-analyses show no difference in carriage between 1p and 2p, but the analysis increased the precision of data reported in the primary analysis as the bounds of the 95% CI were narrower.



Appendix Figure 3 Serotype-specific carriage of PCV7 shared serotypes, post-primary series, comparing 1p and 2p

Serotype-specific IgG

In the main analysis, meta-analysis of IgG GMC for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F favoured PCV13 and PCV10 2p for all serotypes compared with PCV13 and PCV10 1p. In this sub-analysis, we incorporated serotype-specific IgG GMC data for PCV7 shared serotypes from five trials in the UK, India, South Africa, The Gambia, and Fiji, comparing 1p and 2p (Appendix Figure 4). Statistical heterogeneity was observed for most serotypes. Through sub-analysis, the precision of logGMRs for shared PCV7 serotypes were increased and the findings favoured 2p compared with 1p for all PCV7 shared serotypes were reinforced.



Appendix Figure 4 Serotype-specific IgG logGMR of PCV7 shared serotypes, post-primary series, comparing 1p and 2p

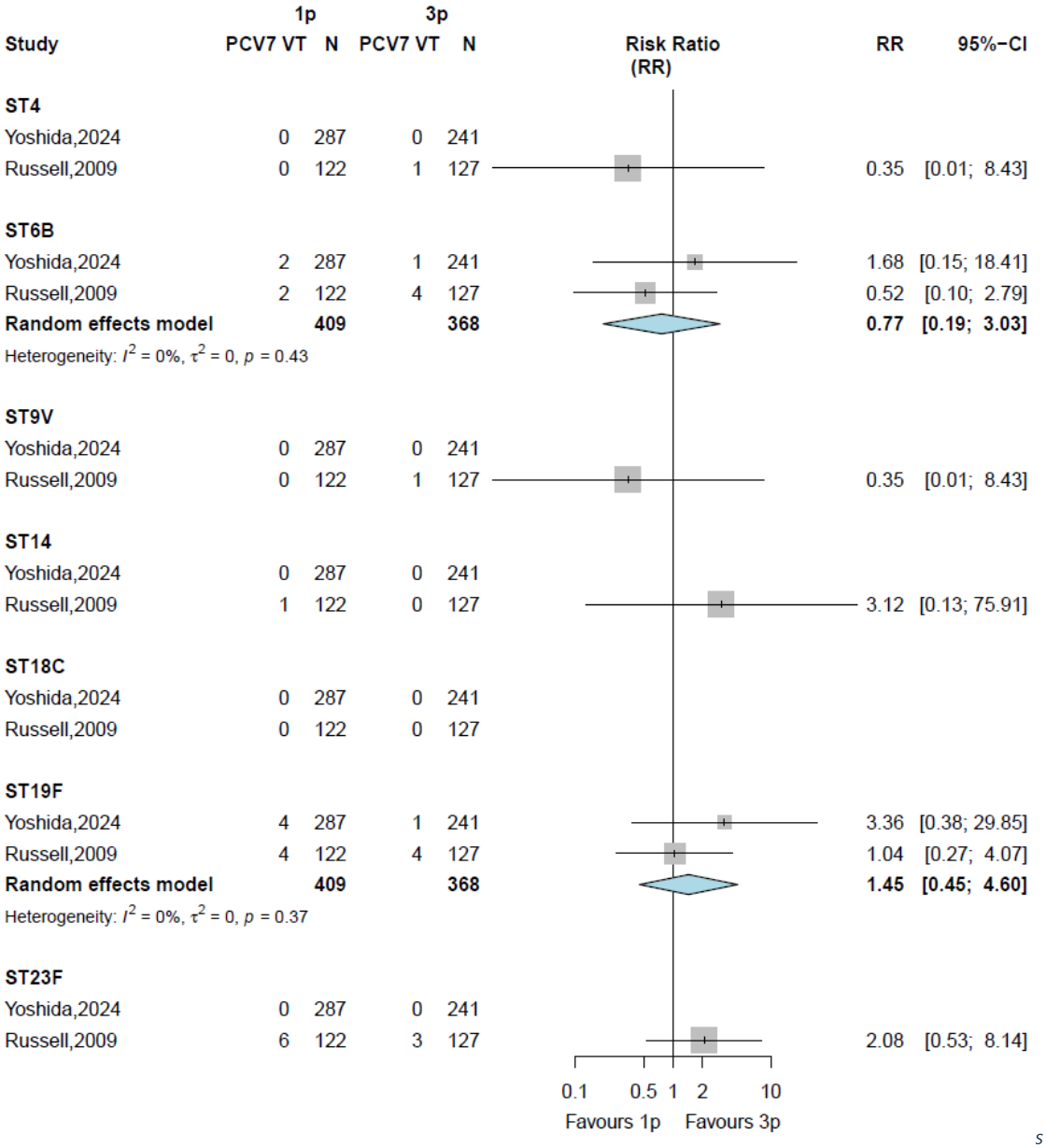
Serotype-specific OPA

No data were available for serotype-specific OPA post-primary 1p vs 2p.

PCV7 shared serotypes 1p vs 3p

Carriage

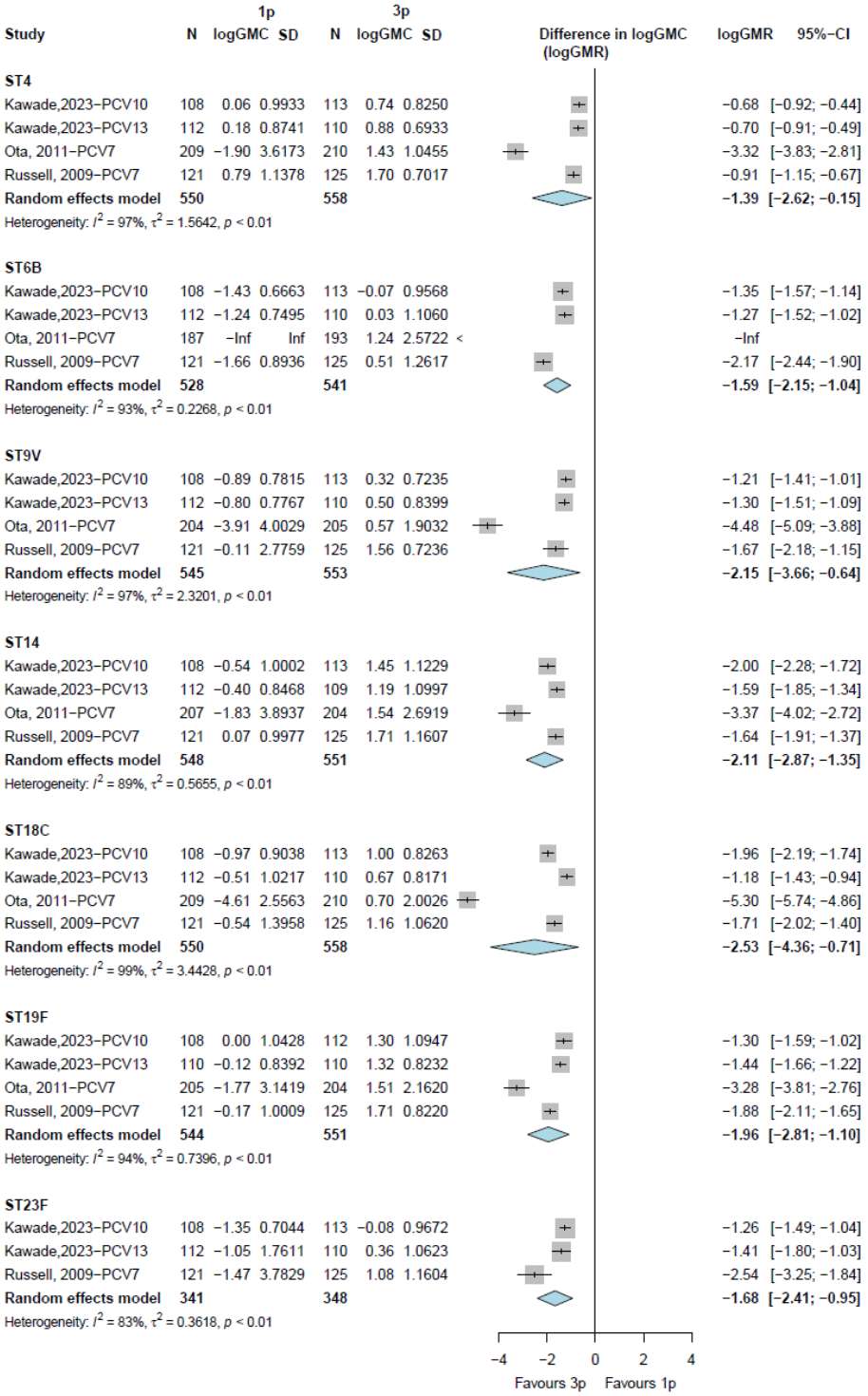
In the main analysis, no meta-analysis was conducted for serotype-specific carriage of 6B and 19F comparing 1p and 3p, as only one study (using PCV10) provided data. In this sub-analysis, we incorporated PCV7 data from Fiji, comparing 1p and 3p post-primary (Appendix Figure 5). For serotype 18C there were no carriage events in either RCT. No meta-analyses were done for serotypes 4, 9V, 14, and 23F, as carriage events only occurred in the Fiji RCT. For those serotypes, we calculated RRs and found similar rates by 1p and 3p. For carriage of serotypes 6B and 19F, for which there were carriage events in both RCTs, meta-analyses changed point estimates of the RR slightly and increased the precision of data reported in the main analysis, as the bounds of the 95% CI were narrower, and reiterate the findings of neither 1p nor 3p being favoured.



Appendix Figure 5 Serotype specific carriage of PCV7 shared serotypes, post-primary series, comparing 1p and 3p

Serotype-specific IgG

In the main analysis, meta-analyses for serotype-specific IgG GMCs comparing 1p vs 3p were not possible for PCV10 or PCV13 separately, as only one study had data for each formulation. By incorporating serotype-specific IgG GMC data from post-PCV7 studies in Fiji and The Gambia, along with PCV13 and PCV10 3p and 1p data from India, we were able to conduct a meta-analysis (Appendix Figure 6). In this sub-analysis, the precision of logGMRs for shared PCV7 serotypes was improved, reinforcing the findings favoured 3p over 1p for all shared PCV7 serotypes.



Appendix Figure 6 Serotype specific IgG logGMR post-primary series for PCV7 shared serotypes, comparing 1p and 3p

Serotype-specific OPA

No data were available for serotype-specific OPA post-primary 1p vs 3p.

Post-primary PCV dose for the additional two shared serotypes (1, 5) including PCV9, PCV10, PCV13

These sub-analyses are for the additional two serotypes, 1 and 5, shared between PCV9, PCV10 and PCV13.

PCV9 shared serotypes 1p vs 0p

Carriage

One study provided serotype-specific carriage data post-primary for 1p vs 0p, however, there were no carriage events for serotypes 1 and 5, preventing comparisons.

Serotype-specific IgG and OPA

No data were available for serotype-specific IgG or OPA post-primary 1p vs 0p for the two additional serotypes (serotypes 1 and 5).

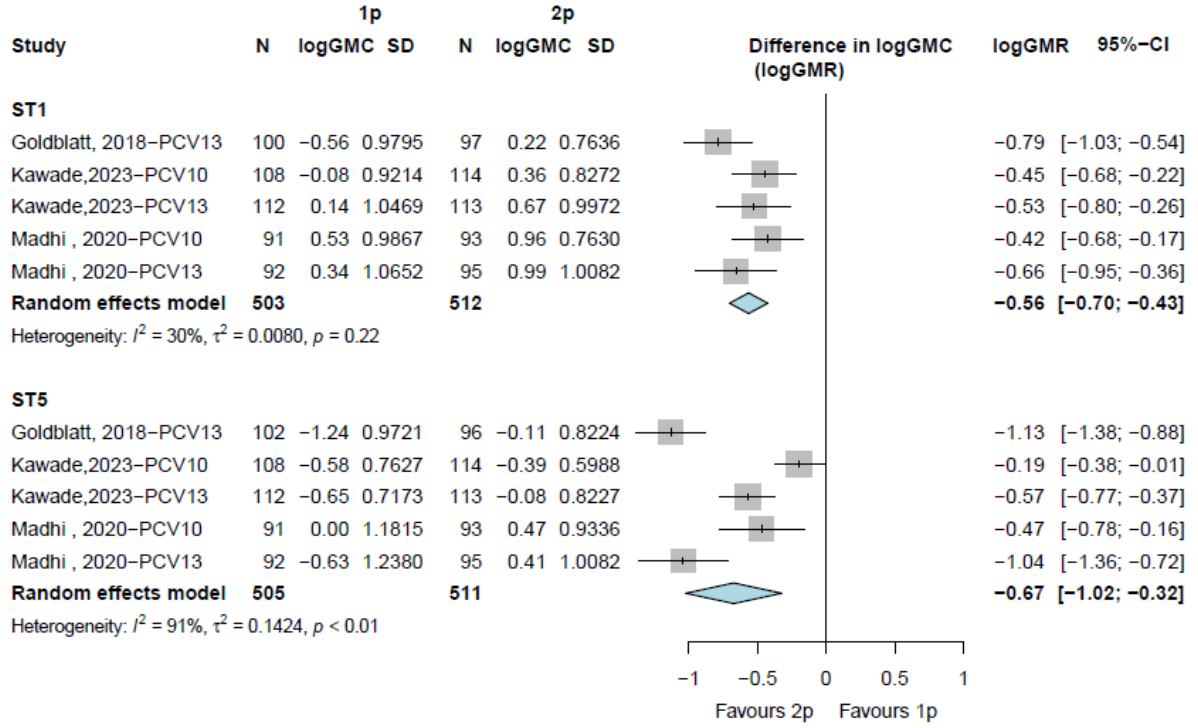
PCV9 shared serotypes 1p vs 2p

Carriage

One study provided serotype-specific carriage data post-primary for 1p vs 0p, however there were no carriage events for serotypes 1 and 5 in the 1p group, preventing comparisons.

Serotype-specific IgG

In the main analysis, meta-analysis of IgG GMC for serotypes 1 and 5 favoured PCV13 and PCV10 2p for both serotypes compared with PCV13 and PCV10 1p. In this sub-analysis, we incorporated serotype 1 and 5 IgG GMC data from three trials based in the UK, India, and South Africa comparing 1p and 2p (Appendix Figure 7). The precision of logGMRs for serotypes 1 and 5 were increased compared with the main analysis, as indicated by the narrower bounds of the 95% CI, and the findings favoured 2p compared with 1p for both serotypes strengthened.



Appendix Figure 7 Serotypes 1 and 5 IgG logGMR post-primary series, comparing 1p and 2p

Serotype-specific OPA

No data were available for serotype-specific OPA post-primary 1p vs 2p for the serotypes 1 and 5.

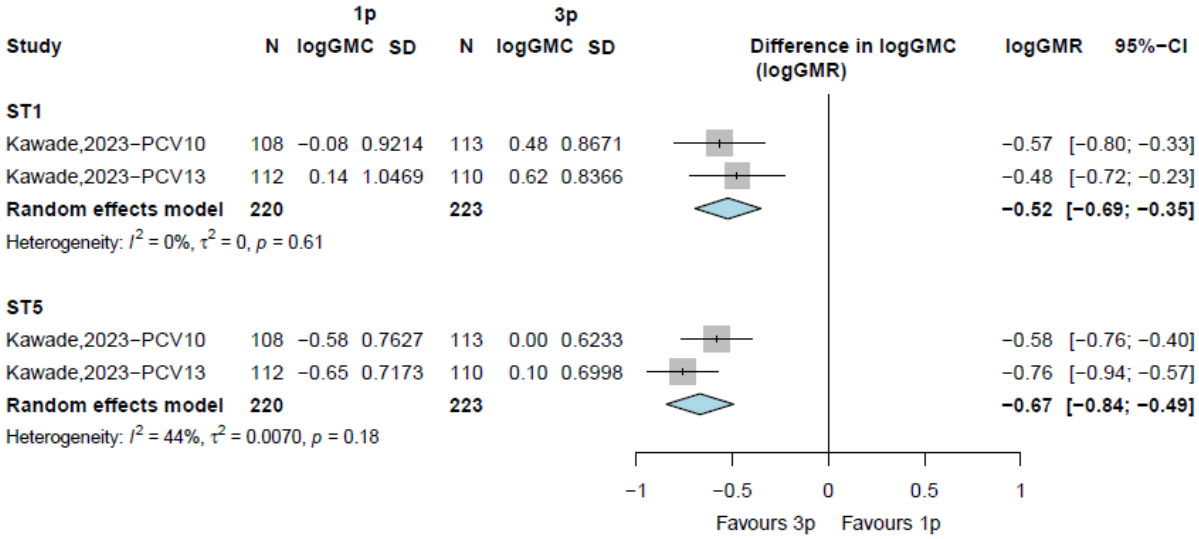
PCV9 shared serotypes 1p vs 3p

Carriage

One study provided serotype-specific carriage data post primary for 1p vs 3p, however there were no carriage events for serotypes 1 and 5 in the 1p group, preventing comparisons.

Serotype-specific IgG

In the main analysis, meta-analyses of IgG GMC for serotypes 1 and 5 could not be done for 1p vs. 3p, as only one study had data for PCV13 and PCV10 each. Available data indicated 3p was associated with higher IgG GMCs for both serotypes compared 1p. In this sub-analysis, we used serotype 1 and 5 IgG GMC data from both PCV13 and PCV10 arms of an RCT in India, comparing 1p and 3p (Appendix Figure 8). Compared with the reported results in the main analysis, the precision of logGMRs for serotypes 1 and 5 were increased, as indicated by narrower bounds for the 95% CI, and the findings favoured 3p compared with 1p for both serotypes were reiterated.



Appendix Figure 8 Serotypes 1 and 5 IgG logGMR post-primary series, comparing 1p and 3p

Serotype-specific OPA

No data were available for serotype-specific OPA post-primary 1p vs 3p for the serotypes 1 and 5.

Effect of the timing of the final 1p+1 dose (six or nine months)

All studies administered the final 1p+1 dose at nine months of age. One study from Vietnam had an additional arm which gave the final 1p+1 dose at six months of age. The following sub-analysis compares the available serotype-specific IgG and OPA logGMRs of 1p+1 with the final dose at six months vs 2p+1 with the serotype-specific IgG and OPA logGMRs of 1p+1 with the final dose at nine months vs 2p+1. There were no carriage data available.

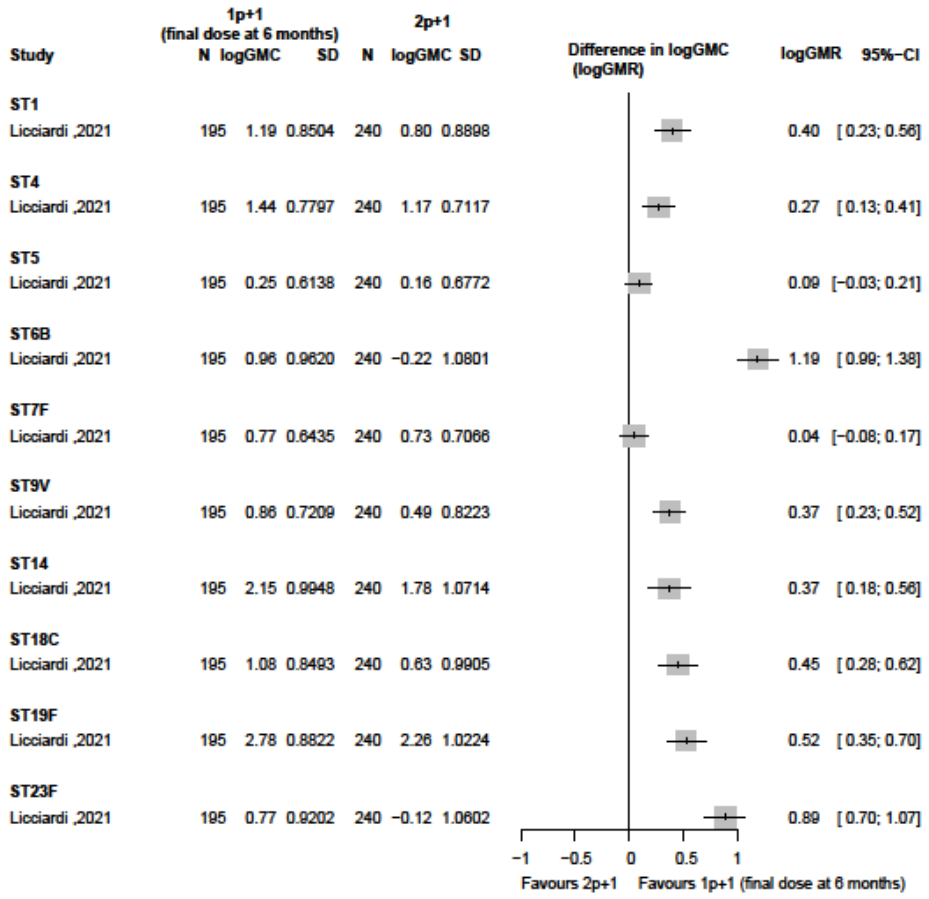
PCV10 1p+1 vs 2p+1

Serotype-specific IgG

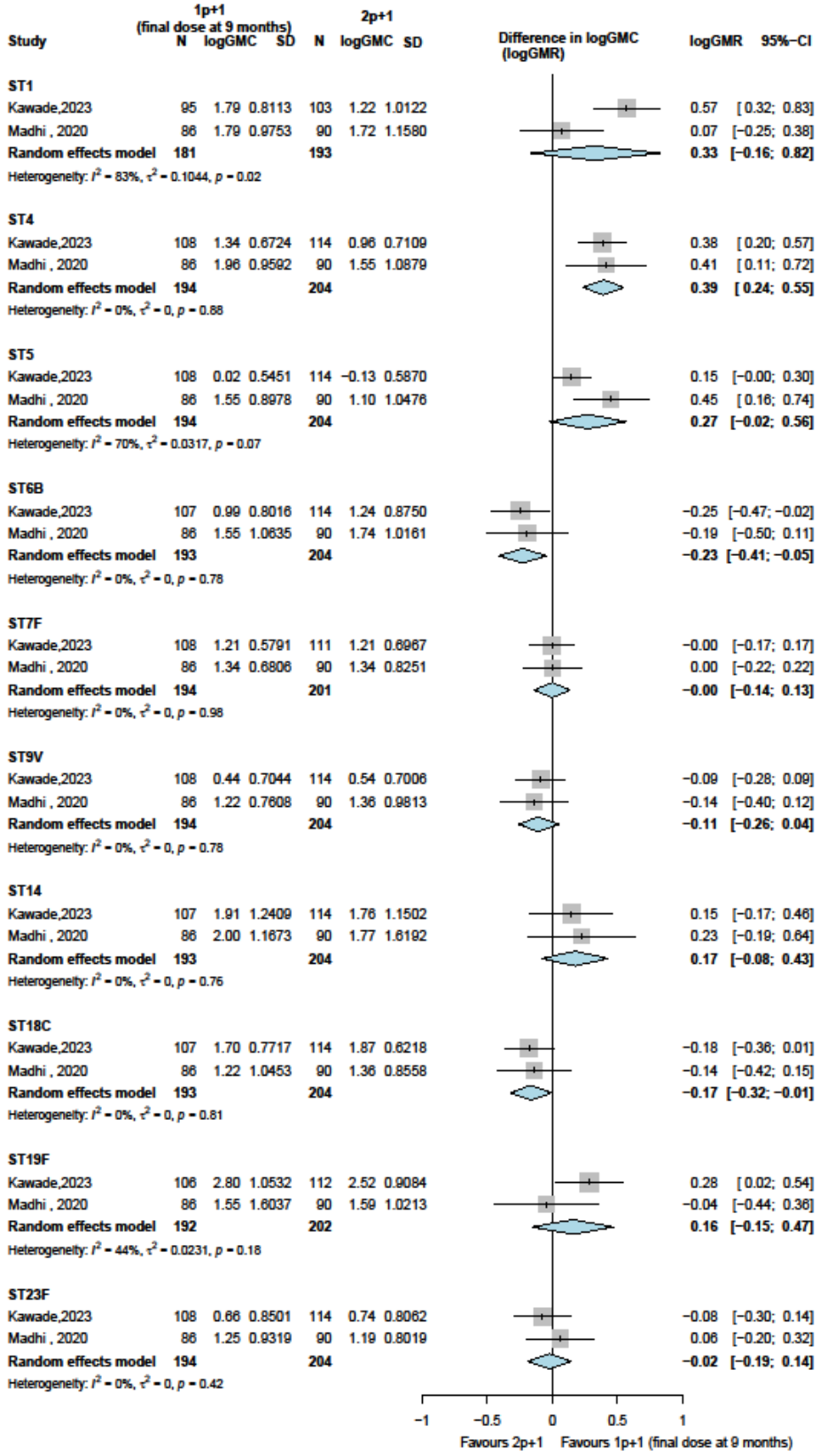
A sub-analysis of PCV10 serotype-specific IgG GMC data from RCTs in Vietnam (where the final 1p+1 dose was given at six months) and in India and South Africa (where it was given at nine months) compared 1p+1 and 2p+1 (Appendix Table 6). With the final dose at six months, IgG GMCs were higher for 1p+1 than 2p+1 for serotypes 1, 4, 6B, 9V, 14, 18C, 19F, and 23F, while neither 1p+1 nor 2p+1 was favoured for serotypes 5 and 7F. When the final dose was at nine months, results were less consistent—1p+1 was favoured for serotype 4, 2p+1 for 6B and 18C, and neither 1p+1 nor 2p+1 for the remaining serotypes (1, 5, 7F, 9V, 14, 19F, and 23F). Notably, for serotypes 6B and 18C, 1p+1 was favoured when the final dose was given at six months but favoured 2p+1 when the final 1p+1 dose was given at nine months. Serotype-specific IgG GMC results from a single study in Vietnam comparing PCV10 1p+1 with the final dose at six months with 2p+1 are shown in Appendix Figure 9. Meta-analysis results from the two RCTs with the final 1p+1 dose at nine months compared with 2p+1 are shown in Appendix Figure 10.

Appendix Table 6 Serotype-specific IgG logGMR of PCV10 1p+1 (final dose at six months) vs 2p+1 compared with IgG GMC of 1p+1 (final dose at nine months) vs 2p+1

Serotype	IgG logGMR comparing 1p+1 (final dose at six months) vs 2p+1	IgG logGMR comparing 1p+1 (final dose at nine months) vs 2p+1
1	0.40 (95% CI 0.23 to 0.56)	0.33 (-0.16 to 0.02)
4	0.27 (95% CI 0.13 to 0.41)	0.39 (0.24 to 0.55)
5	0.09 (95% CI-0.03 to 0.41)	0.27 (-0.02 to 0.56)
6B	1.19 (95% CI 0.99 to 1.38)	-0.23 (-0.41 to-0.05)
7F	0.04 (95% CI-0.08 to 0.17)	-0.00 (-0.14 to 0.13)
9V	0.37 95% CI (0.23 to 0.52)	-0.11 (-0.26 to 0.04)
14	0.37 (95% CI 0.18 to 0.56)	0.17 (-0.08 to 0.43)
18C	0.45 (95% CI 0.28 to 0.62)	-0.17 (-0.32 to-0.01)
19F	0.52 (95% CI 0.35 to 0.70)	0.16 (-0.15 to 0.47)
23F	0.89 (95% CI 0.70 to 1.07)	-0.02 (-0.19 to 0.14)



Appendix Figure 9 PCV10 serotype-specific IgG logGMR one month post-final dose, comparing 1p+1 with final dose at six months and 2p+1



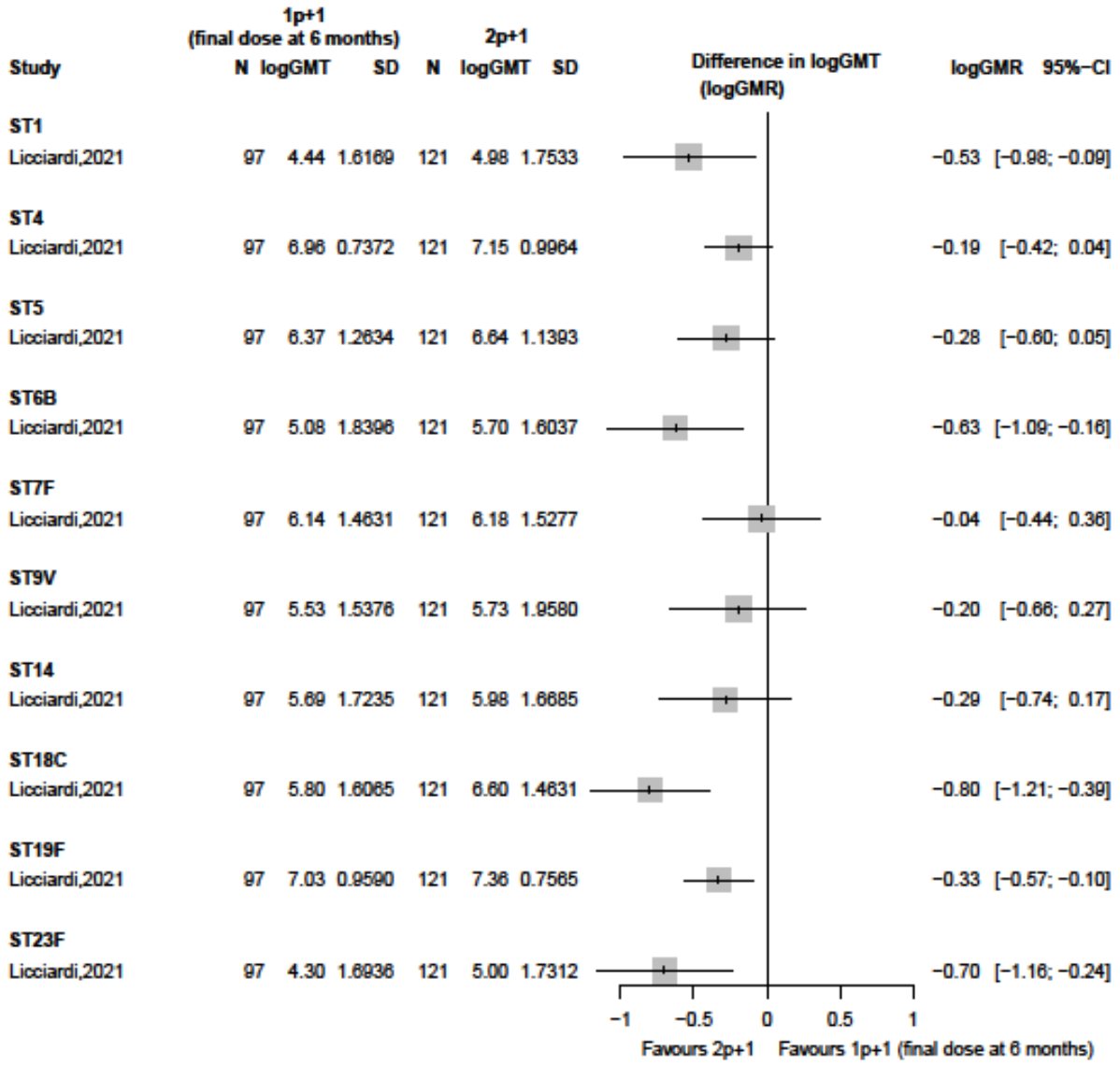
Appendix Figure 10 PCV10 serotype-specific IgG GMC one month post-final dose, comparing 1p+1 with final dose at 9 months and 2p+1

Serotype-specific OPA

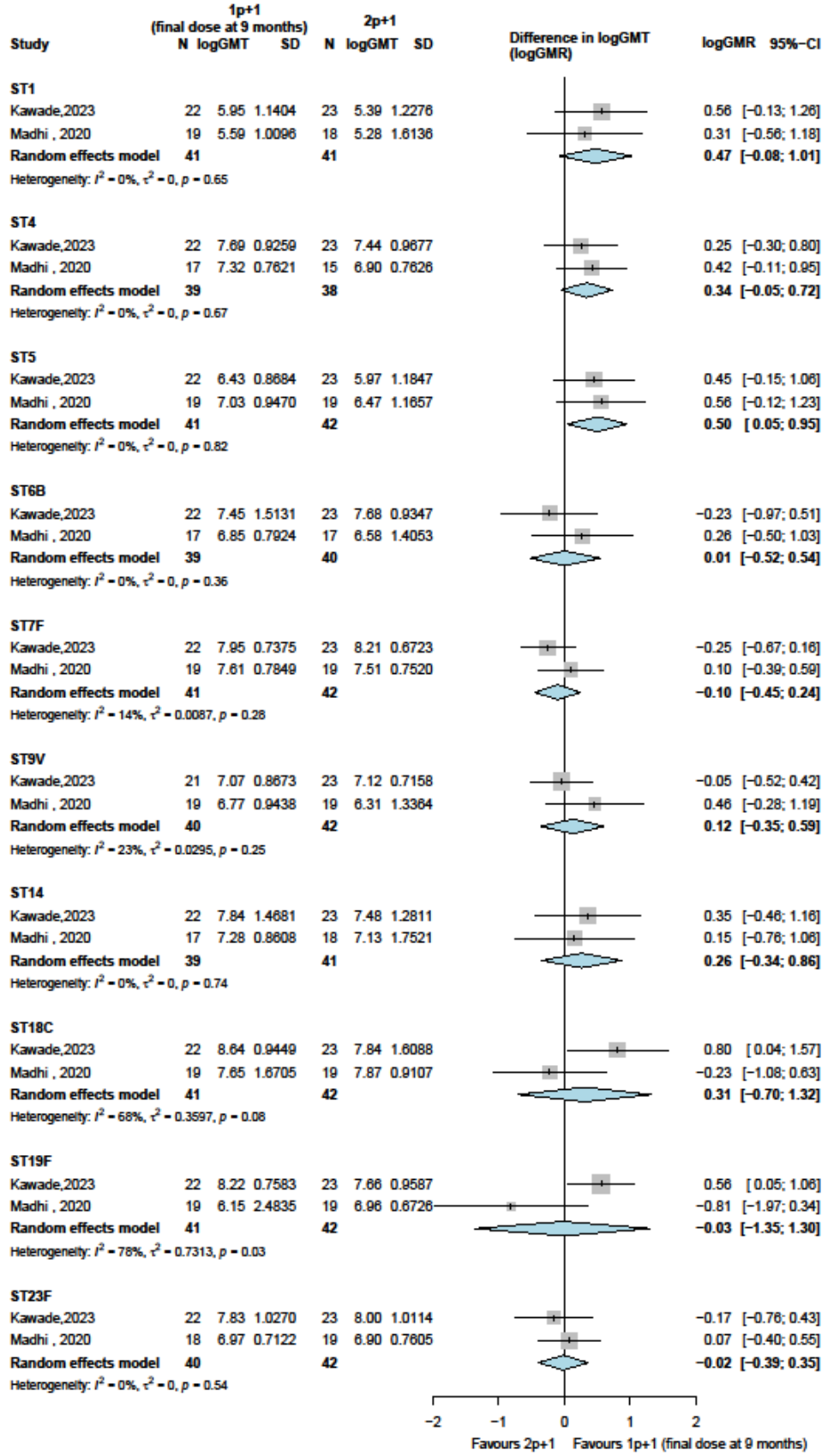
A sub-analysis of PCV10 serotype-specific OPA data from RCTs in Vietnam (where the final 1p+1 dose was given at six months) and in India and South Africa (where it was given at nine months) compared 1p+1 and 2p+1 (Appendix Table 7). When the final dose was given at six months, 2p+1 was favoured for serotypes 1, 6B, 18C, 19F, and 23F, while neither 1p+1 nor 2p+1 was favoured for serotypes 4, 5, 7F, 9V, or 14. While 2p+1 may elicit stronger functional antibody responses than 1p+1 for these serotypes at six months, this was not evident when the 1p+1 booster dose was administered at nine months. Serotype-specific OPA results from the single study in Vietnam comparing PCV10 1p+1 (final dose at six months) with 2p+1 are shown in Appendix Figure 11. Meta-analysis results from the two RCTs comparing PCV10 1p+1 with the final dose at nine months compared with 2p+1 are shown in Appendix Figure 12.

Appendix Table 7 Serotype-specific OPA logGMR of PCV10 1p+1 (final dose at six months) vs 2p+1 compared with logGMR of 1p+1 (final dose at nine months) vs 2p+1

Serotype	OPA logGMR comparing 1p+1 (final dose at six months) vs 2p+1	OPA logGMR comparing 1p+1 (final dose at nine months) vs 2p+1
1	-0.53 (95% CI-0.98 to-0.09)	0.47 (95% CI-0.06 to 1.01)
4	-0.19 (95% CI-0.42 to 0.04)	0.34 (95% CI-0.05 to 0.72)
5	-0.28 (95% CI-0.60 to 0.05)	0.50 (95% CI 0.05 to 0.95)
6B	-0.63 (95% CI-1.09 to-0.16)	0.01 (95% CI-0.52 to 0.54)
7F	-0.04 (95% CI-0.44 to 0.36)	-0.10 (95% CI-0.45 to 0.24)
9V	-0.20 (95% CI-0.66 to 0.27)	0.12 (95% CI-0.35 to 0.59)
14	-0.29 (95% CI-0.74 to 0.17)	0.26 (95% CI-0.34 to 0.86)
18C	-0.80 (95% CI-1.21 to-0.39)	0.31 (95% CI-0.70 to 1.32)
19F	-0.33 (95% CI-0.57 to-0.10)	-0.03 (95% CI-1.35 to 1.30)
23F	-0.70 (95% CI-1.16 to-0.24)	-0.02 (95% CI-0.39 to 0.35)



Appendix Figure 11 PCV10 serotype-specific OPA logGMR one month post-final dose, comparing 1p+1 with final dose at six months with 2p+1



Appendix Figure 12 PCV10 serotype-specific OPA logGMR one month post-final dose, comparing 1p+1 with final dose at nine months with 2p+1

PCV10 1p+1 vs 3p+0, 1p+1 vs 3p+1, and 1p+1 vs 0p+0

There were no post-final carriage or serotype-specific IgG and OPA data where the final dose was given at six months.

Post-final PCV dose, including PCV7 and PCV9

PCV7 and PCV9 1p+1 vs 2p+1, 1p+1 vs 3p+0, 1p+1 vs 3p+1, and 1p+1 vs 0p+0

There were no post-final dose to < 2 years of age carriage or serotype-specific IgG and OPA data where PCV7 or PCV9 had been given.

Appendix 13. RISK OF BIAS

The overall risk of bias for each study was determined using algorithms presented in the guidance for each tool where available (https://www.riskofbias.info/). Studies judged to be at critical risk of bias did not contribute to the synthesis (applies to NRSIs only).

Assessment of Bias due to missing results from each synthesis

We assessed the risk of bias from incomplete reporting of outcomes or studies using the Risk of Bias due to Missing Evidence (ROB-ME) tool.

The risk of bias across included RCTs was generally low or raised some concerns, with no studies at high risk. Most trials had low risk in randomisation, adherence, and missing data, but some concerns in reporting (domain 5) and, in some cases, outcome measurement (domain 4) due to unclear assessor blinding (Appendix Table 8). .

Appendix Table 8 Risk of bias assessments for randomised trials

First Author, year (ref)	Outcome	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall risk of bias
Russell, 2009(13)	PCV7 serotype-specific IgG GMC	Low	Low	Low	Low	Some concerns	Some concerns
	Seropositivity of PCV7 serotype-specific IgG	Low	Low	Low	Low	Some concerns	Some concerns
Russell, 2010(14)	PCV7 serotype-specific IgG GMC	Low	Low	Low	Low	Some concerns	Some concerns
	Seropositivity of PCV7 serotype-specific IgG	Low	Low	Low	Low	Some concerns	Some concerns
Russell, 2010(15)	PCV7 VT & NVT carriage	Low	Low	Low	Low	Some concerns	Some concerns
Russell, 2011(16)	PCV7 serotype-specific OPA GMT & proportion of infants with OI ≥8	Low	Low	Low	Low	Some concerns	Some concerns
Ota, 2011(34)	PCV7 serotype-specific IgG GMC	Low	Low	Low	Low	Low	Low
	Seropositivity of PCV7 serotype-specific IgG	Low	Low	Low	Low	Low	Low
Goldblatt, 2018 (18)	Serotype-specific IgG at 13 months	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
	Proportions achieving serotype-specific IgG ≥ 0·35 µg/mL at 13 months	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns

	Serotype-specific OPA at 13 months	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
	Serotype-specific IgG at five months	Some concerns	Some concerns	Low	High	Low	High
	Proportions achieving serotype-specific IgG ≥ 0·35 µg/mL at five months	Some concerns	Some concerns	Low	High	Low	High
Madhi, 2020 (19)	PCV10 & PCV13 serotype-specific IgG GMC	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
	Seropositivity of PCV10 & PCV13 serotype-specific IgG	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
	PCV10 and PCV13 serotype-specific OPA GMT	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
	OI	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Licciardi, 2021(21)	PCV10 serotype-specific GMC	Low	Some concerns	Some concerns	Low	Low	Some concerns
	Seropositivity of PCV10 serotype-specific IgG	Low	Some concerns	Some concerns	Low	Low	Some concerns
	PCV10 serotype-specific OPA GMT	Low	Some concerns	Some concerns	Low	Low	Some concerns
	OI	Low	Some concerns	Some concerns	Low	Low	Some concerns
Kawade, 2023(26)[a]	PCV10 & PCV13 VT & NVT carriage	Low	Low	Low	Low	Low	Low
	PCV10 & PCV13 serotype-specific IgG GMC	Low	Low	Some concerns	Low	Low	Some concerns
	Seropositivity of PCV10 & PCV13 serotype-specific IgG	Low	Low	Some concerns	Low	Low	Some concerns
	PCV10 & PCV13 serotype-specific OPA GMT	Low	Low	Some concerns	Low	Some concerns	Some concerns

	OI	Low	Low	Some concerns	Low	Some concerns	Some concerns
Olwagen, 2023(20)[a]	VT & NVT carriage post PCV booster dose of PCV (6- and 9-months post-booster, i.e., 15 and 18 months of age).	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
	VT & NVT carriage post PCV booster dose of PCV immediately prior booster (9 months of age).	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
	Serotype-specific IgG responses in relation to putative thresholds associated with a risk reduction of homologous-serotype colonisation, one-month post-booster.	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Smith-Vaughan, 2023(22)	PCV10 VT & NVT carriage carriage at 2, 6, 9, 12, and 18 months	Low	Some concerns	Low	Low	Low	Some concerns
	PCV10 VT & NVT carriage carriage at 24 months	Low	Some concerns	Some concerns	Low	Low	Some concerns
Goldblatt, 2023(35)	VT & NVT carriage (prior to booster & six months following booster)	Low	Low	Low	Low	Low	Low
Yoshida, 2024(27)[a]	PCV10 VT & NVT carriage	Low	Low	Some concerns	Low	Low	Some concerns
Sadarangani, NYP (23)[b]	PCV13 serotype-specific IgG GMC	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
	Seropositivity of PCV13 serotype-specific IgG	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
	PCV13 VT, NVT, &	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns

	serotype-specific carriage						
Mackenzie, NYP(12)[c]	PCV13 VT & NVT carriage	Low	Low	Low	Low	Low	Low
	Radiological pneumonia	Low	Low	Some concerns	Some concerns	Low	Some concerns

Abbreviations: GMC – Geometric mean concentration; GMT-Geometric mean titre; IgG – Immunoglobulin G; IPD – invasive pneumococcal disease; NVT – non-vaccine-serotype; OI-Opsonisation indices; OPA- Opsonophagocytic activity; PCV-pneumococcal conjugate vaccine; PCV7 – 7-valent pneumococcal conjugate vaccine; PCV9 – 9-valent pneumococcal conjugate vaccine; PCV10 – 10-valent pneumococcal conjugate vaccine; PCV13 – 13-valent pneumococcal conjugate vaccine; ref – reference; VT – vaccine-serotype; **Footnotes**: [a] Data was provided by authors that was not extractable directly from published studies(20, 26); [b] Not yet published studies that met the PICO, and for which authors shared data(23); [c] Not yet published studies that meet the PICO, and for which authors have indicated data will be shared in the future(12, 27).

Appendix Table 9 Risk of bias assessments for non-randomised studies of interventions

First Author, year (ref)		Domain							
	Outcome	1	2	3	4	5	6	7	Overall risk of bias
Bertran, 2024(36)	IPD	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

Appendix 14. CERTAINTY OF EVIDENCE USING GRADE

This section summarises the certainty of evidence using GRADE, following SAGE methods, for comparisons of 1p+1 versus 2p+1 and 1p+1 versus 3p+0 schedules. The certainty of evidence for the effectiveness and impact of different PCV13 and PCV10 schedules has been assessed based on available data for IPD, radiological pneumonia, VT carriage, and the proportion achieving the serotype-specific IgG protective threshold post-primary, as well as VT carriage and serotype-specific IgG levels post-final dose up to two years of age.

Appendix Table 10 GRADE: Effectiveness and impact of different schedules of PCV13 on IPD among children < 5 years

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age

VS:

Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.

Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.

Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and post-final dose to < 2 years.

Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and logGMR post-final dose to < 2 years.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		1 observational study[1]	2
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	NA[3]	0
		Indirectness	None serious[4]	0
		Imprecision	Serious[5]	-1
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			1

Summary of Findings	Statement on quality of evidence	Evidence supports a low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion	We have a low level of confidence in the ability of the available evidence to detect any differences in the overall effectiveness of a 1+1 dosing schedule compared to a 2+1 dosing schedule in children under five years.

[1] One population-level surveillance study from England (Ladhani et al., 2024) comparing IPD incidence between children eligible for the PCV13 2+1 schedule (2017–2020) and those eligible for the 1+1 schedule (2020–2023). No difference in incidence among children aged 1-<5 years in 2022-23 versus 2019-20 (IRR 1.54 [95% CI 0.66 – 3.60] *p*=0.32) and for infants (IRR 2.46 [95% CI 0.84 – 7.21] *p*=0.10).

[2] Not downgraded for limitation in study design, as this has already been considered in the starting rating of 2, based on being an observational study.

[3] Not applicable, as only one study was available.

[4] No downgrade for indirectness, as the study directly measures IPD incidence in a relevant population, and intervention and comparator align with the research question.

[5] Downgraded by one level for imprecision, as confidence intervals are wide.

[6] Not downgraded for publication bias as there is no evidence of selective reporting or missing relevant studies.

[7] No upgrade for dose-response, as the study compared pre-defined schedules rather than assessing a true-dose response gradient, and pandemic related differences complicate interpretation of any potential dose effect.

[8] Not applicable, as the study compared different dosing schedules rather than evaluating vaccine efficacy against disease

[9] Not applicable as this was an observational surveillance study where confounding was a concern, rather than a mitigated factor.

References

Observational study

1. Bertran M, D'Aeth JC, Abdullahi F, Eletu S, Andrews NJ, Ramsay ME, Litt DJ, Ladhani SN. Invasive pneumococcal disease 3 years after introduction of a reduced 1+1 infant 13-valent pneumococcal conjugate vaccine immunisation schedule in England: a prospective national observational surveillance study. Lancet Infect Dis. 2024 May;24(5):546-556. doi: 10.1016/S1473-3099(23)00706-5. Epub 2024 Feb 1. Erratum in: Lancet Infect Dis. 2024 Jun;24(6):e356. doi: 10.1016/S1473-3099(24)00224-X. PMID: 38310905.

Appendix Table 11 GRADE: Effectiveness and impact of different schedules of PCV10 on IPD among children < 5 years

No studies were identified reporting on the effectiveness or impact of different PCV10 schedules on IPD in children under five years.

Appendix Table 12 GRADE: Effectiveness and impact of different schedules of PCV13 on radiologic pneumonia among children < 5 years

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age

VS:

Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.

Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.

Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and post-final dose to < 2 years.

Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and logGMR post-final dose to < 2 years.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		1 cluster RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	NA[3]	0
		Indirectness	None serious[4]	0
		Imprecision	Serious[5]	-1
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			3
Summary of Findings	**Statement on quality of evidence**			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a moderate level of confidence in the ability of the available evidence to detect any differences in the overall effectiveness of a 1+1 dosing schedule compared to a 3+0 dosing schedule in children under five years.

[1] One cRCT conducted in The Gambia (Mackenzie et al., 2023) comparing radiologic pneumonia incidence between PCV13 1p+1 and 3p+0 schedules. No significant difference in incidence was observed (adjusted incidence proportion ratio: 1.06, 95% CI: 0.81–1.39). This GRADE assessment was conducted using the published trial protocol, the shared CONSORT diagram, shared baseline characteristics, and additional unpublished data provided through personal communication with the trialist.

[2] No downgrade for limitation in study design, as all domains were rated low in risk of bias

[3] Not applicable as only one study was available for this comparison, preventing an assessment of heterogeneity.

[4] No downgrade for indirectness, as the study directly measured radiologic pneumonia incidence in children < 5 years, using a relevant clinical endpoint and a directly comparable intervention.

[5] Downgraded for imprecision by one level as per WHO SAGE methods, imprecision is ideally assessed using pooled estimates from meta-analysis. However, only one study was available.

[6] No downgrade for publication bias, as the trial protocol was published, and the CONSORT diagram, baseline characteristics, and unpublished data were available directly from the trialist

[7] Not applicable, as the study compared two PCV13 dosing schedules (1p+1 vs 3p+0) rather than evaluating the overall effectiveness of PCV13 itself in preventing radiologic pneumonia.

[8] No upgrade for dose response, as the study compared two fixed dose schedules rather than evaluating a continuous dose-response gradient.

[9] No upgrade for mitigated bias, as the trial was randomised and adjusted for clustering, minimising the impact of major confounders.

References

Protocol for cluster RCT

1. Mackenzie GA, Palmu AA, Jokinen J, Osei I, Flasche S, Greenwood B, Mulholland K, Nguyen C. Pneumococcal vaccine schedules (PVS) study: a cluster-randomised, non-inferiority trial of an alternative versus standard schedule for pneumococcal conjugate vaccination-statistical analysis plan. Trials. 2022 Dec 28;23(1):1058. doi: 10.1186/s13063-022-06900-x. PMID: 36578030; PMCID: PMC9798555.

Appendix Table 13 GRADE: Effectiveness and impact of different schedules of PCV10 on radiologic pneumonia among children < 5 years

No studies were identified reporting on the effectiveness or impact of different PCV10 schedules on radiological pneumonia in children under five years.

Appendix Table 14 GRADE: Effectiveness and impact of different schedules of PCV13 on vaccine-type carriage post-primary series

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age

VS:

Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.

Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.

Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and post-final dose to < 2 years.

Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and logGMR post-final dose to < 2 years.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		1 RCT and 1 cRCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	None serious[3]	0
		Indirectness	None serious[4]	0
		Imprecision	None serious[5]	0
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			4
Summary of Findings	**Statement on quality of evidence**			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a high level of confidence in the ability of the available evidence to detect any differences in the overall effectiveness of a 1+1 dosing schedule compared to a 2+1 and 3+0 dosing schedule in children under five years.

[1] The cRCT conducted in The Gambia (Mackenzie et al., 2023) is unpublished, and it assessed vaccine-type carriage in children aged 4 – 9 months through cross-sectional surveys, which aligns with the post-primary series. This GRADE assessment was conducted using the published trial protocol cRCT conduced in The Gambia (Mackenzie et al., 2023), and the shared CONSORT diagrams, shared baseline characteristics, and unpublished data provided through personal communication with the trialist. The other RCT (Kawade et al, 2024) has been published.
[2] No downgrade as both studies were low risk.
[3] No downgrade for inconsistency as heterogeneity was low for 1p vs 3p ($I^2 = 0\%$, $I^2 = 0$, $p = 0.87$), and for 1p vs 2p, there was only one study
[4] No downgrade for indirectness, as study populations and outcomes were relevant. While the cRCT used cross-sectional design rather than specific timepoints, this does not substantially affect the certainty of evidence.
[5] No downgrade for imprecision, as confidence intervals are within acceptable range for carriage studies.
[6] No downgrade as unpublished data from the cRCT (Mackenzie et al., 2023) were obtained directly from trialists and supplemented with published trial protocols and shared study materials. The other RCT has been published.
[7] Not applicable, as the study compared different dosing schedules rather than evaluating the overall impact of PCV13 on vaccine-type carriage.
[8] No upgrade for dose response, as no gradient in VT carriage reduction was observed with increasing doses.
[9] No upgrade for bias mitigation as all studies were randomised and the cRCT adjusted for clustering, minimising residual confounding.

References

RCTs

1. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79

Protocol for cRCT

2. Mackenzie GA, Palmu AA, Jokinen J, Osei I, Flasche S, Greenwood B, Mulholland K, Nguyen C. Pneumococcal vaccine schedules (PVS) study: a cluster-randomised, non-inferiority trial of an alternative versus standard schedule for pneumococcal conjugate vaccination-statistical analysis plan. Trials. 2022 Dec 28;23(1):1058. doi: 10.1186/s13063-022-06900-x. PMID: 36578030; PMCID: PMC9798555.

Appendix Table 15 GRADE: Effectiveness and impact of different schedules of PCV10 on vaccine-type carriage post-primary series

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age

VS:

Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.

Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.

Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and post-final dose to < 2 years.

Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and logGMR post-final dose to < 2 years.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		1 RCT and 1 cRCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	None serious[3]	0
		Indirectness	None serious[4]	0
		Imprecision	None serious[5]	0
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			4
Summary of Findings	**Statement on quality of evidence**			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a high level of confidence in the ability of the available evidence to detect any differences in the overall effectiveness of a 1+1 dosing schedule compared to a 2+1 and 3+0 dosing schedule in children under five years.

[1] The cRCT conducted in Vietnam (Yoshida et al, 2024) assessed vaccine-type carriage in children aged 4 – 11 months, which aligns with the post-primary series and individual level vaccination status was unknown. The cRCT (Yoshida et al, 2024) and the RCT (Kawade et al, 2024) have both been published.
[2] No downgrade for risk of bias, as the trial in India (Kawade et al, 2023) and was low risk of bias, and the study with some concerns (Yoshida et al, 2024) had low weight in the pooled estimates.
[3] No downgrade for inconsistency as heterogeneity was low (I^2 = 0%) across both comparisons.
[4] No downgrade for indirectness, as study populations and outcomes were relevant. While cRCTs used cross-sectional sampling rather than time point swabs, this does not substantially affect the certainty of evidence.
[5] No downgrade for imprecision as statistical heterogeneity was low (I^2 = 0%).
[6] No downgrade for publication bias data that were not easily extractable from the published cRCT (Yoshida et al, 2024) were obtained directly from the trialist. Data from the RCT was published (Kawade et al, 2023)
[7] Not applicable, as the study compared different dosing schedules rather than evaluating the overall impact of PCV10 on vaccine-type carriage.
[8] No upgrade for dose response, as no gradient in VT carriage reduction was observed with increasing doses.
[9] No upgrade for bias mitigation, as all trials were randomised. The cRCT in Vietnam (Yoshida et al, 2024) did not account for clustering, and while the statistical analysis plan for the cRCT in Vietnam described valid reasoning behind not accounting for clustering, there is still a small potential for some residual confounding. As a result, no upgrade was applied.

References

RCT

1. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79

cRCT

2. Yoshida LM, Toizumi M, Nguyen HAT, Quilty BJ, Lien LT, Hoang LH, Iwasaki C, Takegata M, Kitamura N, Nation ML, Hinds J, van Zandvoort K, Ortika BD, Dunne EM, Satzke C, Do HT, Mulholland K, Flasche S, Dang DA. Effect of a Reduced PCV10 Dose Schedule on Pneumococcal Carriage in Vietnam. N Engl J Med. 2024 Nov 28;391(21):1992-2002. doi: 10.1056/NEJMoa2400007. PMID: 39602629; PMCID: PMC11661757.

Appendix Table 16 GRADE: Effectiveness and impact of different schedules of PCV13 on vaccine-type carriage post-final dose to < 2 years

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age

VS:

Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.

Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.

Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and **post-final dose to < 2 years**.

Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and logGMR post-final dose to < 2 years.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		4 RCTs and 1 cRCTs[1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	None serious[3]	0
		Indirectness	None serious[4]	0
		Imprecision	Serious[5]	-1
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			3
Summary of Findings	**Statement on quality of evidence**			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We are moderately confident in the ability of the available evidence to detect any differences in the overall effectiveness of a 1+1 dosing schedule compared to a 2+1 and 3+0 dosing schedule in children under five years.

[1] The cRCT conducted in The Gambia (Mackenzie et al., 2023) is unpublished, and it assessed vaccine-type carriage in children aged 12 – 23 months through cross-sectional surveys, which aligns with the post-final dose to less than two years series. The RCT conducted in Canada

(Sadarangani et al., 2024) is unpublished and assessed vaccine type carriage in children aged 13 months. This GRADE assessment was conducted using the published trial protocol cRCT conduced in The Gambia (Mackenzie et al., 2023), and the shared CONSORT diagrams, shared baseline characteristics, and additional unpublished data provided through personal communication with the trialists for the cluster RCT conduced in The Gambia (Mackenzie et al., 2023) and the RCT in Canada (Sadarangani et al, 2024). The RCTs in the UK, India, and South Africa (Goldblatt et al, 2023; Kawade et al, 2024; Olwagen et al., 2023; and Yoshida et al., 2024) have been published.

[2] No downgrade for risk of bias, as most studies were low risk, and those with some concerns were not severe enough to affect the overall certainty of evidence

[3] No downgrade for inconsistency as statistical heterogeneity was low for both comparisons (I^2 = 0% for 1p+1 vs 2p+1, I^2 = 7% for 1p+1 vs 3p+0).

[4] No downgrade for indirectness, as studies directly assessed PCV13 VT carriage in children < 2 years with relevant interventions and comparators. The cRCTs assessed carriage at predefined age groups rather than specific post-vaccine time points, but this was not considered a serious limitation.

[5] Downgraded by one level for imprecision, as the confidence intervals are wide across comparisons, indicating uncertainty in the true effect size of different dosing schedules on vaccine-type carriage. The broad range of possible effects limits the precision of the estimates and reduces confidence in their reliability

[6] No downgrade as unpublished data from two studies (Mackenzie et al., 2023 and Sadarangani et al, 2024) were obtained directly from trialist and supplemented with publsihed trial protocols and shared study materials. All other RCTs and cRCTs have been published.

[7] Not applicable, as the study compared different dosing schedules rather than evaluating the overall impact of PCV13 on vaccine-type carriage.

[8] No upgrade for dose response, as no gradient in VT carriage reduction was observed with increasing doses.

[9] No upgrade for bias mitigation, as all trials were randomised. The cRCT in The Gambia (Mackenzie et al, 2024) accounted for clustering, reducing confounding risk. The cRCT in Vietnam (Yoshida et al., 2024) did not account for clustering. While the statistical analysis plan for the cRCT in Vietnam described valid reasoning behind not accounting for clustering, there is still a small potential for some residual confounding. As a result, no upgrade was applied.

References

RCTs

1. Goldblatt D, Andrews NJ, Sheppard CL, Rose S, Aley PK, Roalfe L, et al. Pneumococcal carriage following PCV13 delivered as one primary and one booster dose (1 + 1) compared to two primary doses and a booster (2 + 1) in UK infants. Vaccine. 2023;41(19):3019-23
2. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79
3. Olwagen CP, Izu A, Mutsaerts E, Jose L, Koen A, Downs SL, et al. Single priming and booster dose of ten-valent and 13-valent pneumococcal conjugate vaccines and Streptococcus pneumoniae colonisation in children in South Africa: a single-centre, open-label, randomised trial. Lancet Child Adolesc Health. 2023;7(5):326-35.

Protocol for cRCT

4. Mackenzie GA, Palmu AA, Jokinen J, Osei I, Flasche S, Greenwood B, Mulholland K, Nguyen C. Pneumococcal vaccine schedules (PVS) study: a cluster-randomised, non-inferiority trial of an alternative versus standard schedule for pneumococcal conjugate vaccination-statistical analysis plan. Trials. 2022 Dec 28;23(1):1058. doi: 10.1186/s13063-022-06900-x. PMID: 36578030; PMCID: PMC9798555.

Clinical trial registration for RCT

5. Sadarangani M. A randomized controlled trial to compare a 1-dose vs. 2-dose priming schedule of 13-valent pneumococcal conjugate vaccine in Canadian infants; a Canadian Immunization Research Network (CIRN) study [Internet]. 2017 [updated 2024 Mar 04; cited 2024 Sep 16]. Available from: https://www.clinicaltrials.gov/study/NCT03384589#study-record-dates.

Appendix Table 17 GRADE: Effectiveness and impact of different schedules of PCV10 on vaccine-type carriage post-final dose to < 2 years

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age
VS:
Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.
Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.
Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and **post-final dose to < 2 years**.
Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and logGMR post-final dose to < 2 years.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		3 RCTs and 1 cRCTs[1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	Serious[3]	-1
		Indirectness	None serious[4]	0
		Imprecision	Serious[5]	-1
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			2
Summary of Findings	**Statement on quality of evidence**			Evidence supports a low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a low level of confidence in the ability of the available evidence to detect differences in the overall effectiveness and impact of differing dosing schedules of PCV10 on vaccine-type carriage post-final dose to < 2 years.

[1] The RCTs in Vietnam (Smith -Vaughan et al., 2023), India (Kawade et al., 2023), and South Africa (Olwagen et al., 2024) and the cRCT in Vietnam (Yoshida et al., 2024) have all been published.
[2] No downgrade for risk of bias, as most studies were low risk, and those with some concerns were not severe enough to affect the overall certainty of evidence. The highest weighted studies had minimal bias, aiding confidence in the pooled estimates.
[3] Downgraded by one level for inconsistency as results for PCV10 1p+1 vs 2p+1 and PCV10 1p+1 vs 3p+0 were in different directions, despite low statistical heterogeneity for both comparisons (I^2 = 0% for 1p+1 vs 2p+1 and 1p+1 vs 3p+0). .
[4] No downgrade for indirectness, as studies directly assessed PCV10 VT carriage in children < 2 years with relevant interventions and comparators. The cRCT assessed carriage at predefined age groups rather than specific post-vaccine time points, but this was not considered a serious limitation.
[5] Downgraded by one level for imprecision, as the confidence intervals are wide across comparisons, indicating uncertainty in the true effect size of different dosing schedules on vaccine-type carriage. The broad range of possible effects limits the precision of the estimates and reduces confidence in their reliability.
[6] No downgrade for publication bias as all included studies were published, and no strong evidence of selective reporting was identified.
[7] Not applicable, as the study compared different PCV10 dosing schedules rather than evaluating the overall impact of PCV10 on vaccine-type carriage.
[8] No upgrade for dose response, as no clear trend was observed indicating a stepwise reduction in carriage with increasing vaccine doses.
[9] No upgrade for bias mitigation, as all trials were randomised. The cRCT in Vietnam (Yoshida et al., 2024) did not account for clustering. While the statistical analysis plan for the cRCT in Vietnam (Yoshida et al., 2024) described the reasoning behind not accounting for clustering, and was valid, there is still a small potential for some residual confounding. As a result, no upgrade was applied.

References

RCTs

1. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79
2. Olwagen CP, Izu A, Mutsaerts E, Jose L, Koen A, Downs SL, et al. Single priming and booster dose of ten-valent and 13-valent pneumococcal conjugate vaccines and Streptococcus pneumoniae colonisation in children in South Africa: a single-centre, open-label, randomised trial. Lancet Child Adolesc Health. 2023;7(5):326-35.
3. Smith-Vaughan H, Temple B, Trang Dai VT, Hoan PT, Loc Thuy HN, Phan TV, Bright K, Toan NT, Uyen DY, Nguyen CD, Beissbarth J, Ortika BD, Nation ML, Dunne EM, Hinds J, Lai J, Satzke C, Huu TN, Mulholland K. Effect of different schedules of ten-valent pneumococcal conjugate vaccine on pneumococcal carriage in Vietnamese infants: results from a randomised controlled trial. Lancet Reg Health West Pac. 2022 Dec 3;32:100651. doi: 10.1016/j.lanwpc.2022.100651. PMID: 36785850; PMCID: PMC9918756.

cRCT

4. Yoshida LM, Toizumi M, Nguyen HAT, Quilty BJ, Lien LT, Hoang LH, Iwasaki C, Takegata M, Kitamura N, Nation ML, Hinds J, van Zandvoort K, Ortika BD, Dunne EM, Satzke C, Do HT, Mulholland K, Flasche S, Dang DA. Effect of a Reduced PCV10 Dose Schedule on Pneumococcal Carriage in Vietnam. N Engl J Med. 2024 Nov 28;391(21):1992-2002. doi: 10.1056/NEJMoa2400007. PMID: 39602629; PMCID: PMC11661757.

Appendix Table 18 GRADE: Effectiveness and impact of different schedules of PCV13 on serotype-specific IgG ≥ 0.35µg/mL post-primary series

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age
VS:
Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.
Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.
Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and post-final dose to < 2 years.
Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and logGMR post-final dose to < 2 years.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		4 RCTs [1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	Serious[3]	-1
		Indirectness	None serious[4]	0
		Imprecision	Serious[5]	-1
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	Upgrade[8]	1
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			3
Summary of Findings	**Statement on quality of evidence**			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a moderate level of confidence in the ability of the

		available evidence to detect differences in the overall effectiveness and impact of differing dosing schedules of PCV10 on vaccine-type carriage post-final dose to < 2 years.

[1] The RCTs in India (Kawade et al., 2023), South Africa (Madhi et al., 2020), the UK (Goldblatt et al., 2018) are published. The RCT is Canada (Sadarangani et al, 2024) is unpublished. This GRADE assessment was conducted using the publications and the shared trial data, protocol, CONSORT diagrams, baseline characteristics, provided through personal communication with the trialist for the RCT in Canada (Sadarangani et al, 2024).
[2] No downgrade for risk of bias, as all studies were RCTs and while some had "some concerns", none had high risk of bias.
[3] Downgraded one level for inconsistency due to high heterogeneity ($I^2 > 75\%$) for most serotypes for 1p vs 2p. There was only one study with data for 1p vs 3p.
[4] No downgrade for indirectness, as all studies measured serotype-specific IgG $\geq$0.35 µg/mL post-primary series.
[5] Downgraded by one level for imprecision, as wide confidence intervals introduce uncertainty in the true effect size of different dosing schedules for some serotypes.
[6] No downgrade as unpublished data from one study (Sadarangani et al, 2024) were obtained directly from the trialist and supplemented with trial protocols and shared study materials. All other RCTs have been published.
[7] Not applicable, as the study compared different PCV13 dosing schedules rather than evaluating the overall impact of PCV13 on vaccine-type carriage.
[8] Upgraded one level for dose response, as there was a clear pattern of increased IgG response with additional doses, consistent across serotypes.
[9] No upgrade for bias mitigation, as all trials were randomised.

References

RCTs

1. Goldblatt D, Southern J, Andrews NJ, Burbidge P, Partington J, Roalfe L, Valente Pinto M, Thalasselis V, Plested E, Richardson H, Snape MD, Miller E. Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial. Lancet Infect Dis. 2018 Feb;18(2):171-179. doi: 10.1016/S1473-3099(17)30654-0. Epub 2017 Nov 22. PMID: 29174323; PMCID: PMC5805912.
2. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79
3. Madhi SA, Mutsaerts EA, Izu A, Boyce W, Bhikha S, Ikulinda BT, Jose L, Koen A, Nana AJ, Moultrie A, Roalfe L, Hunt A, Goldblatt D, Cutland CL, Dorfman JR. Immunogenicity of a single-dose compared with a two-dose primary series followed by a booster dose of ten-valent or 13-valent pneumococcal conjugate vaccine in South African children: an open-label, randomised, non-inferiority trial. Lancet Infect Dis. 2020 Dec;20(12):1426-1436. doi: 10.1016/S1473-3099(20)30289-9. Epub 2020 Aug 25. Erratum in: Lancet Infect Dis. 2020 Nov;20(11):e275. doi: 10.1016/S1473-3099(20)30741-6. PMID: 32857992; PMCID: PMC7689288.

Clinical trial registration for RCT

4. Sadarangani M. A randomized controlled trial to compare a 1-dose vs. 2-dose priming schedule of 13-valent pneumococcal conjugate vaccine in Canadian infants; a Canadian Immunization Research Network (CIRN) study [Internet]. 2017 [updated 2024 Mar 04; cited 2024 Sep 16]. Available from: https://www.clinicaltrials.gov/study/NCT03384589#study-record-dates.

Appendix Table 19 GRADE: Effectiveness and impact of different schedules of PCV10 on serotype-specific IgG $\geq$ 0.35µg/mL post-primary series

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age

VS:

Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.

Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.

Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and post-final dose to < 2 years.

Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and logGMR post-final dose to < 2 years.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		2 RCTs [1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	Serious[3]	-1
		Indirectness	None serious[4]	0
		Imprecision	Serious[5]	-1
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			2
Summary of Findings	**Statement on quality of evidence**			Evidence supports a low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a low level of confidence in the ability of the available evidence to detect differences in the overall effectiveness and impact of differing dosing schedules of PCV10 on vaccine-type carriage post-final dose to < 2 years.

[1] The RCTs in India (Kawade et al., 2023) and South Africa (Madhi et al., 2020) are published.

[2] No downgrade for risk of bias, as all studies were RCTs and while some had "some concerns", none had high risk of bias.

[3] Downgraded one level for inconsistency due to high heterogeneity ($I^2 > 75\%$) for some serotypes for 1p vs 2p. There was only one study with data for 1p vs 3p.

[4] No downgrade for indirectness, as all studies measured serotype-specific IgG ≥0.35 µg/mL post-primary series.

[5] Downgraded by one level for imprecision, as wide confidence intervals introduce uncertainty in the true effect size of different dosing schedules for some serotypes.

[6] No downgrade as unpublished data from one study (Sadarangani et al, 2024) were obtained directly from the trialist and supplemented with trial protocols and shared study materials. All other RCTs have been published.
[7] Not applicable, as the study compared different PCV10 dosing schedules rather than evaluating the overall impact of PCV10 on serotype-specific IgG ≥0.35 µg/mL post-primary series.
[8] No upgrade for dose response, as while there was a general trend of increasing IgG levels with more doses, the inconsistency across serotypes reduces confidence in applying this criterion.
[9] No upgrade for bias mitigation, as all trials were randomised.

References

RCTs

1. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79
2. Madhi SA, Mutsaerts EA, Izu A, Boyce W, Bhikha S, Ikulinda BT, Jose L, Koen A, Nana AJ, Moultrie A, Roalfe L, Hunt A, Goldblatt D, Cutland CL, Dorfman JR. Immunogenicity of a single-dose compared with a two-dose primary series followed by a booster dose of ten-valent or 13-valent pneumococcal conjugate vaccine in South African children: an open-label, randomised, non-inferiority trial. Lancet Infect Dis. 2020 Dec;20(12):1426-1436. doi: 10.1016/S1473-3099(20)30289-9. Epub 2020 Aug 25. Erratum in: Lancet Infect Dis. 2020 Nov;20(11):e275. doi: 10.1016/S1473-3099(20)30741-6. PMID: 32857992; PMCID: PMC7689288.

Appendix Table 20 GRADE: Effectiveness and impact of different schedules of PCV13 on serotype-specific IgG logGMR post-final dose to < 2 years

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age
VS:
Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.
Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.
Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and post-final dose to < 2 years.
Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and **logGMR post-final dose to < 2 years**.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		3 RCTs [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	Serious[3]	-1
		Indirectness	None serious[4]	0
		Imprecision	None serious[5]	0
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			2
Summary of Findings	**Statement on quality of evidence**			Evidence supports a low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a low level of confidence in the ability of the available evidence to detect differences in the overall effectiveness and impact of differing

		dosing schedules of PCV10 on vaccine-type carriage post-final dose to < 2 years.

[1] The RCTs in the UK (Goldblatt et al., 2018), India (Kawade et al., 2023) and South Africa (Madhi et al., 2020) are published.
[2] Downgraded one level as all RCTs had some concerns in at least two domains for risk of bias, however none had high risk of bias.
[3] Downgraded one level for inconsistency due to high heterogeneity ($I^2 > 50\%$) for some serotypes for 1p+1 vs 2p+1. This indicates that the effect of different PCV13 dosing schedules on IgG GMCs may vary across populations and serotypes. There was only one study with data for 1p+1 vs 3p+0.
[4] No downgrade for indirectness, as all studies measured serotype-specific IgG µg/mL post-final dose to < 2 years.
[5] No downgrade for imprecision as confidence intervals were not sufficiently wide across serotypes to introduce substantial uncertainty in the true effect size of different dosing schedules.
[6] No downgrade as al RCTs have been published, and no evidence of selecting reporting was identified.
[7] Not applicable, as the study compared different PCV13 dosing schedules rather than evaluating the overall impact of PCV13 on serotype-specific IgG GMC.
[8] No upgrade for dose response, as there was no clear pattern indicating a stepwise increase in IgG GMCs with increasing doses.
[9] No upgrade for bias mitigation, as all trials were randomised.

References

RCTs

1. Goldblatt D, Southern J, Andrews NJ, Burbidge P, Partington J, Roalfe L, Valente Pinto M, Thalasselis V, Plested E, Richardson H, Snape MD, Miller E. Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial. Lancet Infect Dis. 2018 Feb;18(2):171-179. doi: 10.1016/S1473-3099(17)30654-0. Epub 2017 Nov 22. PMID: 29174323; PMCID: PMC5805912.
2. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79
3. Madhi SA, Mutsaerts EA, Izu A, Boyce W, Bhikha S, Ikulinda BT, Jose L, Koen A, Nana AJ, Moultrie A, Roalfe L, Hunt A, Goldblatt D, Cutland CL, Dorfman JR. Immunogenicity of a single-dose compared with a two-dose primary series followed by a booster dose of ten-valent or 13-valent pneumococcal conjugate vaccine in South African children: an open-label, randomised, non-inferiority trial. Lancet Infect Dis. 2020 Dec;20(12):1426-1436. doi: 10.1016/S1473-3099(20)30289-9. Epub 2020 Aug 25. Erratum in: Lancet Infect Dis. 2020 Nov;20(11):e275. doi: 10.1016/S1473-3099(20)30741-6. PMID: 32857992; PMCID: PMC7689288.

Appendix Table 21 GRADE: Effectiveness and impact of different schedules of PCV10 on serotype-specific IgG logGMR post-final dose to < 2 years

Population

Children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6 – 18 months of age

Interventions compared

Two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between six and 18 months of age
VS:
Three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) and three primary doses and no booster (3p+0).

Outcomes

Invasive Pneumococcal Disease: Difference in incidence of vaccine-serotype, serotype-specific, and all-cause IPD in under five year olds between different schedules.
Pneumonia - difference in incidence rates for radiologic pneumonia in under five year olds between different schedules.
Nasopharyngeal carriage - difference in the prevalence of VT carriage between different schedules post primary series and post-final dose to < 2 years.
Immunogenicity - Difference in vaccine serotype-specific immune responses measured by the percentage achieving protective IgG levels (≥0.35 µg/mL) between different schedules post primary series and **logGMR post-final dose to < 2 years**.

PICO Question: In children under five years of age scheduled to receive their first PCV dose before six months of age and their final PCV dose between 6-18 months of age, what are the effects on IPD, pneumonia, pneumococcal carriage, and immunogenicity of administering two doses of PCV (7-valent PCV, 9-valent PCV, 10-valent PCV and 13-valent PCV), with the first dose scheduled at the same time point a dose of a DTP-containing vaccine would be offered, followed by a booster dose given between 6-18 months of age, compared with children who received three doses of PCV (PCV7, PCV9, PCV10, or PCV13) in one of the following schedules: two primary doses and one booster (2p+1) or three primary doses and no booster (3p+0).

			Rating	Adjustment to rating
Quality assessment	No of studies/started rating		2 RCTs [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious[3]	0
		Indirectness	None serious[4]	0
		Imprecision	None serious[5]	0
		Publication bias	None serious[6]	0
	Factors increasing confidence	Strength of association/large effect	NA[7]	0
		Dose-response	No upgrade[8]	0
		Antagonistic/mitigated bias and confounding	No upgrade[9]	0
	Final numerical rating of quality of evidence			3
Summary of Findings	**Statement on quality of evidence**			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have a moderate level of confidence in the ability of the available evidence to detect

		differences in the overall effectiveness and impact of differing dosing schedules of PCV10 on vaccine-type carriage post-final dose to < 2 years.

[1] The RCTs in India (Kawade et al., 2023) and South Africa (Madhi et al., 2020) are published.
[2] Downgraded one level as both RCTs had some concerns in at least two domains for risk of bias impacting confidence, however, none had high risk of bias.
[3] No downgrade for inconsistency as statistical heterogeneity was generally low (I^2 < 50%) for most serotypes for 1p+1 vs 2p+1, except for serotype 1 (I^2 = 83%, p = 0.02) and serotype 5 (I^2 = 70%, p = 0.07). However, effect estimates were generally in the same direction. There was only one study with data for 1p+1 vs 3p+0.
[4] No downgrade for indirectness, as all studies measured serotype-specific IgG µg/mL post-final dose to < 2 years.
[5] No downgrade for imprecision as confidence intervals were not sufficiently wide across serotypes to introduce substantial uncertainty in the true effect size of different dosing schedules.

[6] No downgrade as al RCTs have been published, and no evidence of selecting reporting was identified.
[7] Not applicable, as the study compared different PCV10 dosing schedules rather than evaluating the overall impact of PCV10 on serotype-specific IgG GMC.
[8] No upgrade for dose response, as there was no clear pattern indicating a stepwise increase in IgG GMCs with increasing doses.
[9] No upgrade for bias mitigation, as all trials were randomised.

References

RCTs

1. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79
2. Madhi SA, Mutsaerts EA, Izu A, Boyce W, Bhikha S, Ikulinda BT, Jose L, Koen A, Nana AJ, Moultrie A, Roalfe L, Hunt A, Goldblatt D, Cutland CL, Dorfman JR. Immunogenicity of a single-dose compared with a two-dose primary series followed by a booster dose of ten-valent or 13-valent pneumococcal conjugate vaccine in South African children: an open-label, randomised, non-inferiority trial. Lancet Infect Dis. 2020 Dec;20(12):1426-1436. doi: 10.1016/S1473-3099(20)30289-9. Epub 2020 Aug 25. Erratum in: Lancet Infect Dis. 2020 Nov;20(11):e275. doi: 10.1016/S1473-3099(20)30741-6. PMID: 32857992; PMCID: PMC7689288.

REFERENCES

1. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health. 2018;6(7):e744-e57.
2. Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet Child Adolesc Health. 2022;6(2):106-15.

3. Simell B, Auranen K, Kayhty H, Goldblatt D, Dagan R, O'Brien KL, Pneumococcal Carriage G. The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines. 2012;11(7):841-55.
4. Haasis MA, Ceria JA, Kulpeng W, Teerawattananon Y, Alejandria M. Do pneumococcal conjugate vaccines represent good value for money in a lower-middle income country? A cost-utility analysis in the Philippines. PloS One. 2015;10(7):e0131156.
5. Guillaume D, Meyer D, Waheed DE, Schlieff M, Muralidharan K, Chou VB, Limaye R. Factors influencing the prioritization of vaccines by policymakers in low and middle income countries: A scoping review. Health Policy Plan. 2022.
6. Tricarico S, McNeil HC, Cleary DW, Head MG, Lim V, Yap IKS, et al. Pneumococcal conjugate vaccine implementation in middle-income countries. Pneumonia. 2017;9:6.
7. Lucero MG, Dulalia VE, Nillos LT, Williams G, Parreno RA, Nohynek H, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. The Cochrane database of systematic reviews. 2009;2009(4):CD004977.
8. International Vaccine Access Center (IVAC). Pneumococcal conjugate vaccine (PCV) Introduction & use [Internet]. Johns Hopkins Bloomberg School of Public Health.; 2024 [cited 2024 Aug 21]. Available from: https://view-hub.org/vaccine/pcv.
9. World Health Organization. Pneumococcal conjugate vaccine for childhood immunization—WHO position paper. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 2007;82(12):93-104.
10. Publication W. Pneumococcal vaccines WHO position paper–2012–Recommendations. Vaccine. 2012;30(32):4717-8.
11. International Vaccine Access Center (IVAC). PCV: vaccine coverage: WUENIC Coverage [Internet]. Johns Hopkins Bloomberg School of Public Health; 2022 [updated 2022; cited 2022 Oct 14]. Available from: https://view-hub.org/map/?set=wuenic-coverage&group=vaccine-coverage&category=pcv.
12. Mackenzie GA, Osei I, Salaudeen R, Hossain I, Young B, Secka O, et al. A cluster-randomised, non-inferiority trial of the impact of a two-dose compared to three-dose schedule of pneumococcal conjugate vaccination in rural Gambia: the PVS trial. Trials. 2022;23(1):71.
13. Russell FM, Balloch A, Tang ML, Carapetis JR, Licciardi P, Nelson J, et al. Immunogenicity following one, two, or three doses of the 7-valent pneumococcal conjugate vaccine. Vaccine. 2009;27(41):5685-91.
14. Russell FM, Licciardi PV, Balloch A, Biaukula V, Tikoduadua L, Carapetis JR, et al. Safety and immunogenicity of the 23-valent pneumococcal polysaccharide vaccine at 12 months of age, following one, two, or three doses of the 7-valent pneumococcal conjugate vaccine in infancy. Vaccine. 2010;28(18):3086-94.
15. Russell FM, Carapetis JR, Satzke C, Tikoduadua L, Waqatakirewa L, Chandra R, et al. Pneumococcal nasopharyngeal carriage following reduced doses of a 7-valent pneumococcal conjugate vaccine and a 23-valent pneumococcal polysaccharide vaccine booster. Clin Vaccine Immunol. 2010;17(12):1970-6.
16. Russell FM, Carapetis JR, Burton RL, Lin J, Licciardi PV, Balloch A, et al. Opsonophagocytic activity following a reduced dose 7-valent pneumococcal conjugate vaccine infant primary series and 23-valent pneumococcal polysaccharide vaccine at 12 months of age. Vaccine. 2011;29(3):535-44.
17. Huebner RE, Mbelle N, Forrest B, Madore DV, Klugman KP. Immunogenicity after one, two or three doses and impact on the antibody response to coadministered antigens of a nonavalent pneumococcal conjugate vaccine in infants of Soweto, South Africa. Pediatr Infect Dis J. 2002;21(11):1004-7.
18. Goldblatt D, Southern J, Andrews NJ, Burbidge P, Partington J, Roalfe L, et al. Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1 + 1) compared with two primary doses and a booster (2 + 1) in UK infants: a multicentre, parallel group randomised controlled trial. Lancet Infect Dis. 2018;18(2):171-9.
19. Madhi SA, Mutsaerts EA, Izu A, Boyce W, Bhikha S, Ikulinda BT, et al. Immunogenicity of a single-dose compared with a two-dose primary series followed by a booster dose of ten-valent or 13-valent pneumococcal conjugate vaccine in South African children: an open-label, randomised, non-inferiority trial. Lancet Infect Dis. 2020;20(12):1426-36.
20. Olwagen CP, Izu A, Mutsaerts E, Jose L, Koen A, Downs SL, et al. Single priming and booster dose of ten-valent and 13-valent pneumococcal conjugate vaccines and Streptococcus pneumoniae colonisation in children in South Africa: a single-centre, open-label, randomised trial. Lancet Child Adolesc Health. 2023;7(5):326-35.
21. Licciardi PV, Temple B, Dai VTT, Toan NT, Uyen D, Nguyen CD, et al. Immunogenicity of alternative ten-valent pneumococcal conjugate vaccine schedules in infants in Ho Chi Minh City, Vietnam: results from a single-blind, parallel-group, open-label, randomised, controlled trial. Lancet Infect Dis. 2021;21(10):1415-28.
22. Smith-Vaughan H, Temple B, Trang Dai VT, Hoan PT, Loc Thuy HN, Phan TV, et al. Effect of different schedules of ten-valent pneumococcal conjugate vaccine on pneumococcal carriage in Vietnamese infants: results from a randomised controlled trial. Lancet Reg Health West Pac. 2023;32:100651.

23. Sadarangani M. A randomized controlled trial to compare a 1-dose vs. 2-dose priming schedule of 13-valent pneumococcal conjugate vaccine in Canadian infants; a Canadian Immunization Research Network (CIRN) study [Internet]. 2017 [updated 2024 Mar 04; cited 2024 Sep 16]. Available from: https://www.clinicaltrials.gov/study/NCT03384589#study-record-dates.
24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4:1-9.
25. Veritas Health Innovation. Covidence systematic review software [Internet]. Melbourne, Australia. 2024 [updated 2024; cited 2024 July 22]. Available from: www.covidence.org.
26. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix(TM) and Prevenar13(TM))) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066-79.
27. Yoshida LM, Flasche S, Mulholland K, Nguyen HA, Nguyen C, Toizumi M, Dang DA. Evaluation of the effect of reduced-dose pneumococcal conjugate vaccine schedules on vaccine serotype carriage in children and their caretakers in a naïve population in Vietnam: Protocol for a cluster randomized non-inferiority trial. Gates Open Res. 2023;7:110.
28. StataCorp. Stata Statistical Software. Release 18. ed: College Station, TX: StataCorp LLC.; 2023.
29. R Core Team. R: A language and environment for statistical computing.: R Foundation for Statistical Computing, Vienna, Austria.; 2021.
30. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. BMJ Ment Health. 2019;22(4):153-60.
31. Schwarzer G. meta: An R package for meta-analysis. R news. 2007;7(3):40-5.
32. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
33. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj. 2021;372.
34. Ota MO, Akinsola A, Townend J, Antonio M, Enwere G, Nsekpong D, et al. The immunogenicity and impact on nasopharyngeal carriage of fewer doses of conjugate pneumococcal vaccine immunization schedule. Vaccine. 2011;29(16):2999-3007.
35. Goldblatt D, Andrews NJ, Sheppard CL, Rose S, Aley PK, Roalfe L, et al. Pneumococcal carriage following PCV13 delivered as one primary and one booster dose (1 + 1) compared to two primary doses and a booster (2 + 1) in UK infants. Vaccine. 2023;41(19):3019-23.
36. Bertran M, D'Aeth JC, Abdullahi F, Eletu S, Andrews NJ, Ramsay ME, et al. Invasive pneumococcal disease 3 years after introduction of a reduced 1+1 infant 13-valent pneumococcal conjugate vaccine immunisation schedule in England: a prospective national observational surveillance study. Lancet Infect Dis. 2024;24(5):546-56.
37. Satzke C, Turner P, Virolainen-Julkunen A, Adrian PV, Antonio M, Hare KM, et al. Standard method for detecting upper respiratory carriage of Streptococcus pneumoniae: updated recommendations from the World Health Organization Pneumococcal Carriage Working Group. Vaccine. 2013;32(1):165-79.
38. World Health Organization. Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines, Annex 3, [Internet]. Geneva2013 [cited 2024 Sep 16]. No. 977:[Available from: https://www.who.int/publications/m/item/pneumococcal-conjugate-vaccines-annex3-trs-977.
39. The World Bank. World Bank Country and Lending Groups [Internet]. [cited 2024 July 19]. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.