TITLE PAGE

Title

The efficacy and duration of protection of pneumococcal conjugate vaccines against nasopharyngeal carriage: a meta-regression model

Running title

PCV efficacy against carriage over time

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FOOTNOTE PAGE

Conflict of Interest statement

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ABSTRACT (structured, 194 words (max 200 words))

Background

We aimed to estimate the vaccine efficacy (VE_C) and duration of protection of pneumococcal conjugate vaccines (PCVs) against *S.pneumoniae* carriage acquisition, through meta-regression models.

Methods

We identified intervention studies providing nasopharyngeal carriage estimates among vaccinated and unvaccinated children at any time after completion of the vaccination schedule. We calculated VE_C for PCV7 serotypes, grouped as well as individually, and explored cross protective serotype 6A using a Bayesian meta-logistic regression approach, with time since vaccination as a covariate.

Results

We used data from 22 carriage surveys (15 independent studies) from 5 to 64 months after the last PCV dose, including 14,298 children. The aggregate VE_C for all 7 serotypes 6 months after the last dose of a full schedule was 58% (95%CrI 50 – 65%), varying by serotype from 38% (19F) to 80% (9V). We found evidence of sustained protection through PCVs for several years, with an aggregate VE_C of 40% at 5 years, although the waning differed between serotypes.

Conclusion

Our results suggest that PCVs confer reasonable protection, against acquisition of pneumococcal carriage of the seven studies serotypes, for several years after vaccination, albeit with differences across serotypes.

KEYWORDS

Streptococcus pneumoniae, conjugate vaccines, efficacy, carriage, nasopharyngeal, meta-regression

MAIN TEXT

Introduction

Pneumococcal conjugate vaccines (PCVs) reduce disease largely through their impact on nasopharyngeal (NP) carriage acquisition of *Streptococcus pneumoniae* (the pneumococcus), a precondition for developing any form of pneumococcal disease [1]. The effect of PCV on carriage also drives the herd immunity effect of the vaccine in routine immunization, through a reduction in the transmission of vaccine serotypes (VT) in the community [2]. Recently, emphasis has been put on the importance of carriage as a proxy measure for PCV impact assessments, and for using carriage as an additional and essential biomarker in the licensure pathway of new pneumococcal vaccines [3, 4].

A recent systematic review of the direct impact of PCVs on dosing schedules [5] showed consistent reductions in carriage of the serotypes targeted by the vaccine, including a few years after vaccination, with evidence favouring 3-dose schedules over fewer doses. However, systematic estimates of the efficacy of PCVs against carriage and the duration of protection conferred are lacking. Such estimates will help improve predictions about the likely impact of introducing the vaccine in routine immunization under different epidemiological scenarios. Estimates of the rate of waning efficacy are important not only to quantify the level of individual protection over time, but also the degree to which vaccinated children contribute to reducing community transmission as they age. Efficacy against carriage estimates also provide a benchmark against which new vaccines and vaccines under development can be evaluated[3].

We studied the vaccine efficacy and duration of protection of pneumococcal vaccines against carriage, through meta-regression models.

Methods

Search strategy

We identified intervention studies reported by Fleming-Dutra et al. [5] in a recent systematic review of PCV vaccination schedules, which was based on data published between 1994 and September 2010, with post-hoc supplementation of studies published from 2011. We searched for any additional study published between 2011 and 31 May 2014 using a similar strategy as in [5], using EMBASE and MEDLINE databases. Details are provided in Appendix 1.

Inclusion criteria

We considered the following initial criteria for inclusion: (i) intervention studies (ii) providing nasopharyngeal carriage estimates in vaccinated and unvaccinated children, (iii) with children vaccinated as per routine schedule, including three primary doses ('3+0' schedule) or at least two primary doses with a booster dose ('2+1' and '3+1' schedules). We further restricted our analysis to studies of either 7-valent, 10-valent or 13-valent licensed vaccines (PCV7, PCV10 and PCV13) or unlicensed vaccines (e.g. PCV9 and PCV11) linked to similar carrier proteins as licensed vaccines, including the *Corynebacterium diphtheria* toxin mutant 197 (CRM197), meningococcal outer membrane protein complex (OMPC) or the non-typeable *Haemophilus Influenzae* derived protein D (NTHi). Studies based on vaccines conjugated to other proteins or for which immunological equivalence is unclear (such as tetra- and penta-valent vaccines [6-8]) were not included.

Given that PCVs are not known to affect carriage clearance [9, 10], that the average duration of vaccine serotype (VT) carriage in infants and young children is somewhere around two months, but may vary by setting and serotype [11-14], and that 2-4 weeks are required for the antibody response to peak after vaccination, we excluded any data collected earlier than four months after complete vaccination, when the prevalence and serotype distribution was considered non-stationary, as detailed elsewhere [15, 16].

Data extraction

All but four studies were PCV7 trials, with three other trials based on PCV9 and one on PCV10. We extracted data on the group of PCV7 serotypes, as well as each individual PCV7 serotype (4, 6B, 9V, 14, 18C, 19F, 23F). We also extracted data on serotypes 6A, one of the most common serotypes, which shares immunological traits with 6B but is notincluded in PCV7, PCV9 or PCV10, to explore possible cross-reactive protective efficacy. Other potential cross-reactive serotypes, such as 19A, were not studied, due to limited data.

Analysis

We defined the vaccine efficacy against carriage acquisition (VE_C) as the relative reduction in the rate of carriage acquisition among vaccinated compared to unvaccinated children. Although acquisition events cannot directly be observed, it is possible to obtain a robust estimate of VE_C from cross sectional data based on 1 - OR (odds ratio), under general assumptions, with the OR defined as the odds of vaccination among the (group of) VT serotype(s) (henceforth, the ‘target’ group) to the odds of vaccination among those not carrying any VT (henceforth the ‘reference’ group) [15-17]. Hence, in calculating the VE_C for each individual PCV7 serotype, we included in the target group all vaccinated and unvaccinated carriers of the particular serotype and in the reference group all non-vaccine serotype (NVT) carriers and non-carriers. Other VT were excluded from the serotype-specific analysis to account for vaccine-induced within-host changes in the pneumococcal flora, as explained elsewhere [15]. We also excluded all VT serotypes from the analysis of VE_C against 6A. Similarly, in trials based on vaccines with higher valency than PCV7 data on the additional VT serotypes were excluded. Further details about the methods and assumptions underpinning the estimation of VE_C from cross-sectional data are described elsewhere [15-17].

We explored whether the proportion of carried VT serotypes out of all VT serotypes differed between studies, based on data in unvaccinated children, and used I^2 values to quantify heterogeneity [18].

We used a Bayesian logistic meta-regression model to estimate the aggregate and serotype-specific VE_C and its waning. In the model, for each study i,

$$\log\left(\frac{P_{Vi}{}^{R}}{1-P_{Vi}{}^{R}}\right)=\alpha_i$$

$$\log\left(\frac{P_{Vi}{}^{T}}{1-P_{Vi}{}^{T}}\right)=\alpha_i+\theta_i+\beta_1*\log(t_i)$$

, where $P_{Vi}{}^{R}$ and $P_{Vi}{}^{T}$ are the proportion of vaccinated individuals in the reference and target groups respectively, θ_i is the study-specific natural logarithm of the OR and β_1 represents the coefficient by which the log(OR) changes for each increase in the natural logarithm of time t since the peak VE_C (i.e. 4 months after vaccination), such that $\log(OR_i)=\theta_i+\beta_1*\log(t_i)$, with time in months.

We used a random effect model taking the between-study heterogeneity into account by assuming that θ_i were independent and sampled from a normal distribution centred around the mean log(OR) of carriage (μ) with a precision τ, such that $\theta_i \sim N(\mu,\tau)$ and $\tau=1/\sigma^2$, where σ^2 is the between-study variance. A fixed effect was assumed for β_1.

The VE_C at time t can therefore be expressed as follows:

$$VEc_t=1-(e^{\mu}*t^{\beta_1})$$

We assigned uniform priors to α (unif (-10; 10)), μ (unif (-10, 0)), σ (unif (0,10)) and β_1 (unif (0,10)). The time coefficient β_1 was constrained to positive values, with the assumption that the efficacy should be declining.

Some studies provided more than one estimate. However, we did not adjust for the lack of independence due to the limited number of estimates from each study..

We explored the impact of schedule (booster (3+1 or 2+1) vs. non-booster (3+0)) by including schedule as a covariate in a multivariable model, and assigned a normal uninformed prior to its coefficient (β_2~N(0,10^3)). We used an interaction term between schedule and time to look for a difference in the waning by schedule, with a normal uninformed prior on the interaction coefficient (β_3~N(0,10^3)). Studies in which a 23-valent polysaccharide vaccine (PPV23) booster dose was provided after a primary schedule (as in [19, 20]) were considered part of the 3+0 group, given the lack of effect of PPV23 on carriage [19].

Finally, we conducted sensitivity analyses to explore the impact on our pooled VE_C estimates of omitting any one study. We also analysed two additional models of waning VE_C, including a model where time was included as a linear covariate and another model with an asymptotic function in which the VE_C of carriage approaches zero as time approaches infinity. Models were compared using the Deviance Information Criterion (DIC), a likelihood-based model fitting statistic for Bayesian models similar to the frequentist Akaike Information Criterion [21]. Further details are presented in Appendix 2.

Posterior distributions were obtained through a Markov Chain Monte Carlo (MCMC) Gibbs sampling algorithm based on 2 chains of 100,000 iterations running in parallel, after a burn-in of 5,000 iterations. The model was implemented in R using the jags package [22].

Results

Characteristics of the studies included

Of the eighteen intervention studies identified in [5], three were based on non-equivalent vaccines [6-8, 23] and one provided carriage data three months after the last dose [24], hence we ended up with thirteen studies. We identified two additional studies through our literature review, including a PCV7 trial with data six months after a 3+1 schedule[25], and another PCV10 trial with data collected in the first [26] as well the second year [27] after vaccination. Supplementary Figure S1 (Appendix 1) shows the results of the literature search. Our analysis therefore included 15 individual publications [7, 10, 19, 20, 26-36] providing estimates from 22 different surveys, spanning from 5 months to 64 months after vaccination, and including 7,485 samples from vaccinated children, and 6,813 from unvaccinated children. All but four studies were based on PCV7. Three were PCV9 trials [29, 32, 37] and one was a PCV10 trial [26, 27]. We were unable to restrict the latter to PCV7 serotypes only (as all data for PCV10 serotype were aggregated), and we explored the sensitivity of our model output to including (or not) data from that study. Nine data points were from surveys after booster vaccination (Table 1). Two studies [10, 33] were nested within a cluster randomized trial. The clustering was not adjusted for, and we explored the impact of those study estimates in the sensitivity analysis (see below). Serotype-specific data were obtained for 10 studies (7 PCV7 and 3 PCV9 studies), with 14 data points [10, 20, 25, 28, 29, 31-35].

Vaccine efficacy against carriage and its waning

We estimated a peak VE_C (i.e. 4 months after complete vaccination) of 62% (95%CrI 52 – 72%) against all VT serotypes, decreasing to 57% (95%CrI 50 – 65%) six months after vaccination, when the number of data points in the model is the highest, and 42% (95%CrI 19 – 54%) five years after vaccination (Figure 1, Table 2).

There was no evidence of a confounding effect of schedule on VE_C (with the coefficient β_2 centred around zero (-0.03 (95%CrI -0.32; 0.63)) or that the waning rate differed by schedule (interaction term β_3 0.01 (95%CrI -0.24; 0.13)). However, taken individually the median waning coefficient β_1 was smaller (i.e. 'flatter' slope) after a booster than after a 3+0 schedule (Figure 2 and Table 2).

The serotype distribution among the unvaccinated children was fairly stable across studies (Figure 3), with little or moderate statistical heterogeneity in the distribution of serotypes among PCV7 positive samples (serotype-specific I^2 values of heterogeneity ranging from 0% to 60%). Serotypes 6B, 23F and 19F were the VT serotypes most commonly found, contributing to 26%, 22%, 28% respectively of the isolated PCV7 serotypes overall among unvaccinated children. Serotype 14 was found in 11% and serotypes 4, 9V and 18C in 3%, 6% and 3% of PCV7 samples. Serotype 6A was found in about 9% of unvaccinated children, a little higher than the prevalence of 6B (8%, p=0.07).

Efficacy estimates differed across PCV7 serotypes. Six months after vaccination the highest VE_C was measured for serotypes 4 (80%) and 9V (79%), and the lowest for 19F (38%) (Figure 4 and Table 2).

The decline in the efficacy over time varied by serotype (Table 2), with the slowest decline for serotypes 23F and 19F (median β_1 0.09) and more rapid declines for rarer serotypes, although credible intervals overlapped for all serotypes (Table 1).

We found evidence of protection against 6A, with a peak VE_C of 48% (95%CrI 18% – 72%), decreasing to zero within five years post vaccination (Table 2, Figure 4).

Sensitivity analysis

Our sensitivity analysis showed no significant impact of any study estimate on the coefficients. Estimates were similar after excluding the cluster randomized trial [10, 33], with a VE_C of 62% (51 – 73%) at 4 months, decreasing to 40% (12 – 54%) at 5 years. Excluding the two estimates from Cheung et al. in the Gambia [29], which together accounted for about 28% of all children included in the analysis, did not affect model estimates (VE_C of 62% (50 – 74%) at 4 months and 39% (12 – 54%) at 5 years). Finally, overall and booster schedule VE_C estimates and respective model coefficients were similar with and without data from the PCV10 trial [26, 27].

We explored two other models of waning, in addition to the main model (Appendix 2). In all three models there was good evidence of protective efficacy in the first few years after vaccination. A similar DIC was obtained for all three models estimating the aggregate VE_C, as well as for serotype-specific models, except for serotypes 14 and 19F for which the model with the asymptotic time function was outperformed by the other two. Further information can be found in Appendix 2.

Discussion

We computed pooled aggregate and PCV7 serotype-specific vaccine efficacy against nasopharyngeal acquisition and its waning based on a meta-regression model of cross-sectional data. Our results suggest that PCVs confers reasonable protection against acquisition of pneumococcal carriage of the seven studies serotypes, for several years after vaccination, albeit with differences across serotypes.

Previous studies have explored PCV efficacy against carriage [16] and compared schedules [5], however, a pooled estimate was not previously calculated. We found that the distribution of VT serotypes was relatively stable across settings, making the pooling of aggregate estimates possible despite differences in the efficacy against individual serotypes.

Three serotypes (6B, 19F and 23F) accounted for about 75% of all PCV7 serotypes, but efficacy for each of those differed, with high efficacy against 6B and a weaker anti-19F efficacy. A possible reason for this divergence is the difference in the amount of antibody required for protection as well as differences in the vaccine-induced opsonophagocytic activity (i.e. the ingestion and killing of pathogens by phagocytes), despite similar antibody geometric mean concentrations (GMCs) following PCV7 vaccination [30, 38]. Interestingly, a recent study in the UK on the vaccine effectiveness and immune correlates of protection against IPD [39] showed that much less antibody is required for 6B and 23F protection than for 19F protection. The polysaccharide capsule of 19F is more resistant to complement deposition than 6B and requires higher levels of antibodies for opsonophagocytosis [38]. However, although trials [37, 40] have shown persistence of serum antibodies several years after vaccination, the exact mechanism underlying the protection against acquisition of carriage remains unclear. Such mechanisms may involve memory B cells residing in the nasopharyngeal compartment responding to carriage and secreting local IgG or IgA rather than pre-existing circulating serum IgG, with serological markers thus incompletely capturing the mucosal response.

While natural immunity to colonization in infancy is poor, conjugate vaccines stimulate B-cell responses and the generation of memory B-cells [41], which can be naturally boosted. If boosting does contribute to maintaining a protective efficacy then one might expect efficacy to wane faster for rarer serotypes and slower for the more prevalent ones. Our results support such a hypothesis to some extent, showing a slower VE_C decline for the most prevalent serotypes. This would also mean that efficacy may wane more rapidly after routine implementation of the vaccine than in trial conditions.

We also found evidence of cross-protective efficacy against 6A acquisition based on data from PCV7 and PCV9 trials. Such evidence is supported by trials and observational studies showing an impact of PCV7 on 6A disease [42], as well as immunological evidence with the vaccine eliciting functional antibody (i.e. antibodies inducing opsonophagocytosis) against 6A[44]. Efficacy estimates and their waning have several implications for vaccination programmes. Despite a stable distribution of serotypes across studies in this analysis, it is likely that some geographical variation occurs and serotype-specific efficacies are therefore important in predicting the impact of PCV in various epidemiological settings. Our results show good evidence of a direct protection against carriage in the first five years of life, when the pneumococcal burden is particularly high, and vaccinated children therefore also contribute to reducing transmission for several years. This may be particularly important in settings with low vaccine uptake or interrupted delivery.

The direct impact on disease is not solely conditioned on the VE_C, but also on the efficacy of the vaccine against progressing to disease following carriage [1]. This explains the higher efficacy of PCV against invasive disease, at around 80% [1, 3, 39] . In contrast, the efficacy on disease progression against mucosal forms of disease, such as acute otitis media (AOM), is small with most of the disease impact predicted by VE_C only [1, 3] Interestingly, the efficacy against pneumococcal AOM among Finnish children enrolled in a large PCV7 trial [30] was 62% (48 – 72%) in the year following the booster dose, and serotype-specific efficacies were lowest for serotype 19F, at about 37%, and high for 6B (79%) 4 (75%,) and 9V (82%). Those estimates are similar to our aggregate and serotype-specific efficacies, adding to the evidence that VE_C is a close measure of the efficacy against AOM.

An important question is the applicability of our results to 10- and 13-valent vaccines, given that many countries have introduced – or are planning to do so – those vaccines into their routine vaccination programmes. Data on immunological correlates of protection from trials suggest non–inferiority of PCV13 and PCV10 to PCV7 in the response against the serotypes included in PCV7 [44, 46]. However, a recent study comparing IgG concentration and functional antibodies in PCV7 and PCV13 vaccinated Navajo and White Mountains Apache children in the US [47] found higher functional antibody activity against 19F after PCV13 vaccination, compared to PCV7, which is explained by the inclusion of 19A in PCV13 and the additional activity of anti-19A antibodies against 19F.This could translate to differences in aggregate VE_C, particularly since 19F is amongst the most prevalent serotypes [48].

The estimation of the efficacy against carriage acquisition from cross sectional data relies on several assumptions, the most important being that of stationarity – i.e. that the relationship between carriage incidence and carriage prevalence is stable [15, 16]. Vaccination will introduce some temporary disturbance in the carriage rates of different serotypes, with the average prevalence estimates stabilising after some time [49]. Auranen et al. [17] suggest that stationary levels should not be considered before at least twice the duration of carriage since vaccination. We included studies from four months after vaccination to account for this, which we considered this to be a good trade-off between ensuring steady-state carriage levels and avoiding peak estimates to be affected by waning VE_C.

The assumption that PCV do not affect clearance is based on limited evidence [9, 10]. Similarly, studies have suggested that the vaccine may also impact carriage density [10]. In both scenarios (reduced duration and reduced density), VE_C could represent a combined efficacy estimate against acquisition and transmission under the assumption that a reduction in duration of carriage and/or carriage density is associated with both a reduction in the likelihood of detection and of transmission, as discussed elsewhere [15, 16].

Our study has a number of additional limitations.

First, our analysis was limited by the number of data points, with wider uncertainty as time since vaccination increases and the smaller study sizes for serotype specific analyses, with substantial uncertainty around model estimates for the least prevalent serotypes. The small number of data points in each schedule subgroup may have limited our ability to detect any difference between schedules

Second, studies were based on the identification of the dominant serotype in single colonies and multiple colonization was not taken into account. If the prevalence of multiple colonization is low and if there are no differences in the propensity of detecting one serotype over another, VE_C estimates based on single colonization would nonetheless adequately capture VE_C [15].

There are several other factors related to vaccine schedules and delivery that may impact on VE_C (and on the heterogeneity between studies) which we were unable to explore, including the timing and spacing of doses and the co-administration of PCV with different childhood vaccines [46]. For example, a recent systematic review of the impact of PCV vaccination schedules on immunological responses [46] suggests that immune responses to serotype 14 may be influenced by co-administration of PCV with DTP vaccines, with significantly higher GMCs observed with acellular pertussis compared to the whole cell pertussis vaccine.

In addition, although the description of the swabbing and sample processing techniques used in the studies included – although sometimes limited – seem to conform to WHO guidelines [50], we cannot rule out that some of the between-study heterogeneity may be due to differences in such techniques.

Finally, further research to obtain more precise estimates of VE_C after non-complete schedules, particularly single catch-up doses, is warranted. This is particularly relevant in the context of PCV roll out in low-income settings, as some countries may opt for catch-up campaigns at the introduction of the vaccine.

In conclusion, through this study we provide consistent evidence for a lasting efficacy of PCV in children during the first few years after completion of vaccination, although with differences in efficacy and duration of protection between serotypes.

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Table 1: Studies included in the analysis

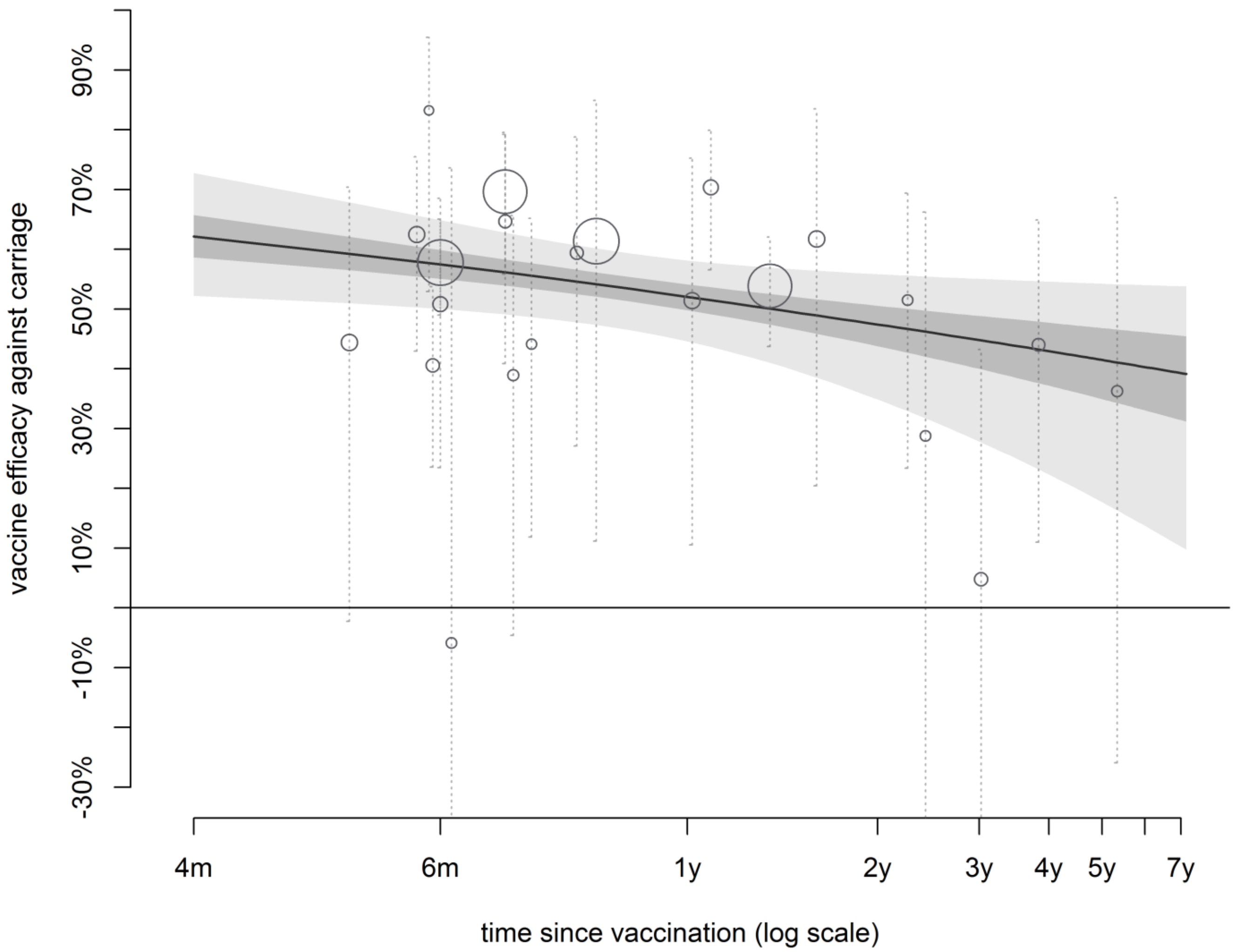
Study	Country	PCV valency	Schedule	NP swab collection: time since last PCV dose	Total number of children included	PCV7 VE_C (95CrI) at each sample collection in the survey
Cheung et al. (2009) [29]	The Gambia	PCV9	3+0	6 months, 16 months	2092,1847	58% (49%;65%), 54% (44%;62%)
Dagan et al. (2012) [28]	Israel	PCV7	3+0	6 months	499	51% (24%;68%)
Kilpi et al. (2001) [25]	Finland	PCV7	3+1	6 months	2403	41% (23%;54%)
Lakshman et al. (2003) [20]	UK	PCV7	3+1PPV23	29 months, 36 months	276, 331	29% (-49%;66%), 5% (-59%;43%)
Madhi et al. (2007) [31]	South Africa	PCV9	3+0	64 months	271	36% (-25%;68%)
Mbelle et al. (1999) [32]	South Africa	PCV9	3+0	6 months	481	62% (43%;76%)
Millar et al. (2006) [33]	USA	PCV7	3+1	27 months	197	45% (-2%;70%)
Obaro et al. (2000) [7]	The Gambia	PCV7	3+0	5 months	434	65% (40%;79%)
O'Brien et al. (2007) [10]	USA	PCV7	3+0, 3+1	7.5 months (3+0), 7.5 months (3+1)	458, 469	44% (11%;65%), (51% (23%;69%)
Palmu et al. (2002) [34]	Finland	PCV7	3+1	46 months	352	46% (-16%;76%)
Prymula et al. (2011) [26]	Czech Republic	PCV10*$	3+0, 3+1	8.5 months (3+0) ,	535,	59% (27%;79%)
				7 months (3+1), 12 months (3+1)	538, 541	39% (-5%;65%), 52% (12%;75%)
Prymula et al. (2013) [27]	Czech Republic	PCV10*$	3+1	19 months	316	62% (19%;83%)
Russell et al. (2010) [19]	Fiji	PCV7	3+1PPV23	6 months, 9 months	248, 269	83% (53%;95%), 70% (31%;79%)
van Gils et al. (2009) [35]	The Netherlands	PCV7	2+1	7 months, 13 months	646, 654	70% (56%;79%), 70% (57%;80%)
Yeh et al. (2003) [36]	USA	PCV7	3+0	6 months	69	-4% (-373%;74%)

*In this trial two PCV10 arms were included, one receiving pre-vaccination paracetamol prophylaxis and one without prophylaxis. Only data from the latter and the placebo group were included. $Serotype –specific data were not available and VEC in this trial is against all PCV10 serotypes, not PCV7 serotypes as in other studies included.

Table 2: Aggregate and serotype-specific vaccine efficacy at different time points post vaccination, and model coefficient estimates

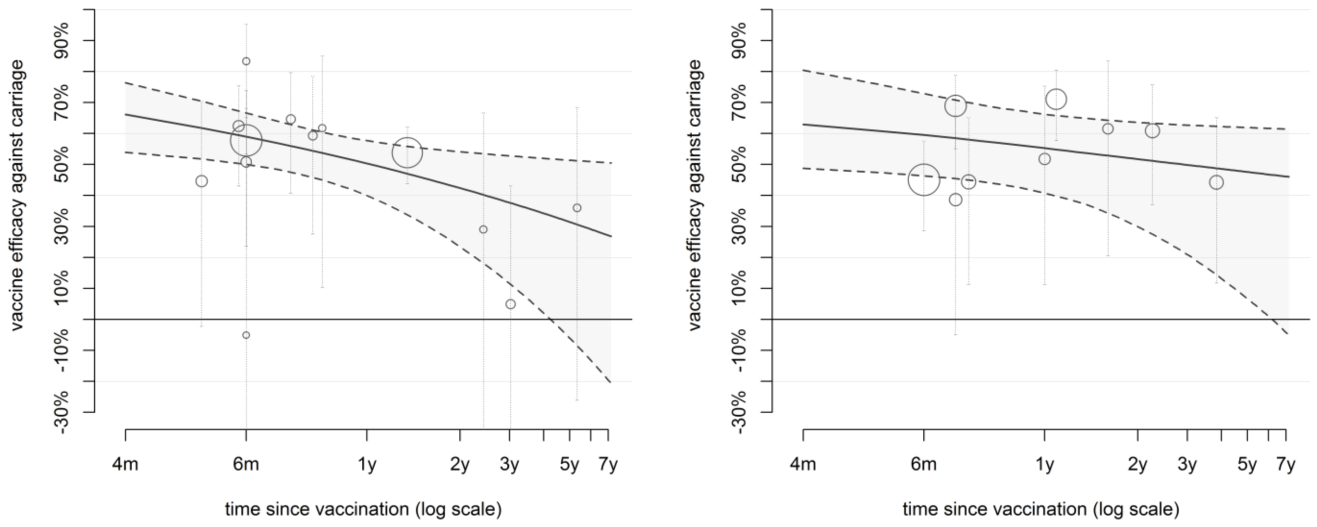
	VE_C (95%CrI) at several time points after vaccination				**Coefficient estimates (95%CrI)**	
	Peak (4 months)	**6 months**	**2 years**	**5 years**	**μ**	**β_1 (waning)**
PCV7 serotypes						
4	88% (62%;98%)	80% (54%;92%)	50% (-50%;78%)	18% (-328%;74%)	-2.11 (-3.75; -0.97)	0.46 (0.04; 1.21)
6B	77% (64%;89%)	72% (62%;83%)	62% (41%;72%)	54% (13%;71%)	-1.48 (-2.20; -1.03)	0.17 (0.01; 0.48)
9V	89% (71%;97%)	79% 64%;90%)	39% (-31%;69%)	-9% (-295%;62%)	-2.17 (-3.43; -1.24)	0.56 (0.11; 1.21)
14	64% (44%;81%)	57% (40%;71%)	40% (6%;58%)	29% (-44%;56%)	-1.01 (-1.65; -0.57)	0.16 (0.09; 0.47)
18C	59% (25%;82%)	52% (19%;73%)	34% (-14%;60%)	22% (-75%;58%)	-0.90 (-1.74; -0.29)	0.15 (0.01; 0.50)
19F	44% (28%;62%)	38% (24%;51%)	25% (3%;39%)	17% (-25%;37%)	-0.58 (-0.96; -0.33)	0.09 (0.01; 0.27)
23F	64% (49%;81%)	60% (46%;73%)	51% (25%;64%)	47% (3%;62%)	-1.02 (-1.64; -0.67)	0.09 (0.00; 0.36)
Cross reactive serotype						
6A	48% (18%%;72%)	39% (11%;58%)	16% (-33%%;41%)	0% (-95%;38%)	-0.65 (-1.28; -0.19)	0.15 (0.01; 0.43)
All PCV7 serotypes						
All schedules	62% (52%;72%)	57% (50%;65%)	47% (35%;56%)	42% (19%;54%)	-0.97 (-1.30;-0.72)	0.11 (0.01; 0.25)
Booster schedule	63% (49%;80%)	60% (47%;73%)	52% (30%;63%)	47% (6%;62%)	-1.00 (-1.64; -0.68)	0.08 (0.00; 0.36)
Primary dose schedule	66% (54%;77%)	59% (50%;67%)	42% (23%;54%)	31% (-7%;51%)	-1.10 (-1.49; -0.78)	0.18 (0.01; 0.37)

Figure 1: Plot of the model of VE_C over time and its 50% and 95% credible intervals, together with the individual study estimates



Legend: The plain line shows the model median, the dark grey shaded area the 50% credible interval (CrI) and the light grey shaded area the 95% CrI. The circles represent the point estimates of each individual study, with the size of the circle proportional to the study size, and the dotted vertical lines show the 95% confidence interval for each study

Figure 2: The vaccine efficacy and its waning, for schedules with a booster (right panel) and without a booster dose (left panel).



Legend: Left panel: model for 3+0 schedules. Left panel: 2+1 or 3+1 schedules.

The plain dark regression line shows the model median, the grey shaded area the 95% credible interval (CrI) and the dotted lines the upper and lower bounds of the 95%CrI. The circles represent the point estimates of each individual study, with the size of the circle proportional to the study size, and the dotted vertical lines show the 95% confidence interval.

Figure 3: Distribution of the serotypes contained in PCV7, in each of the studies included in the serotype-specific model of vaccine efficacy

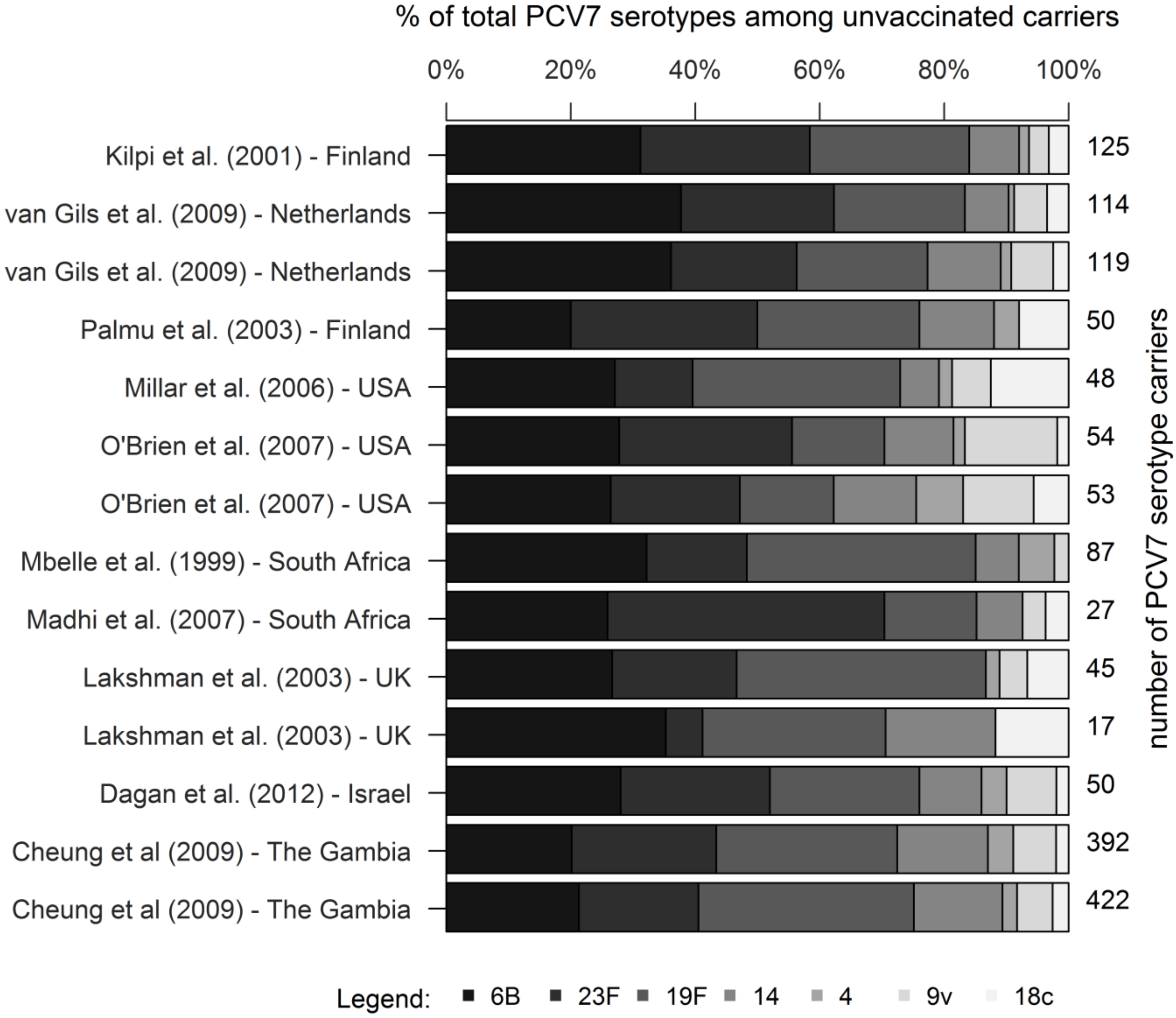
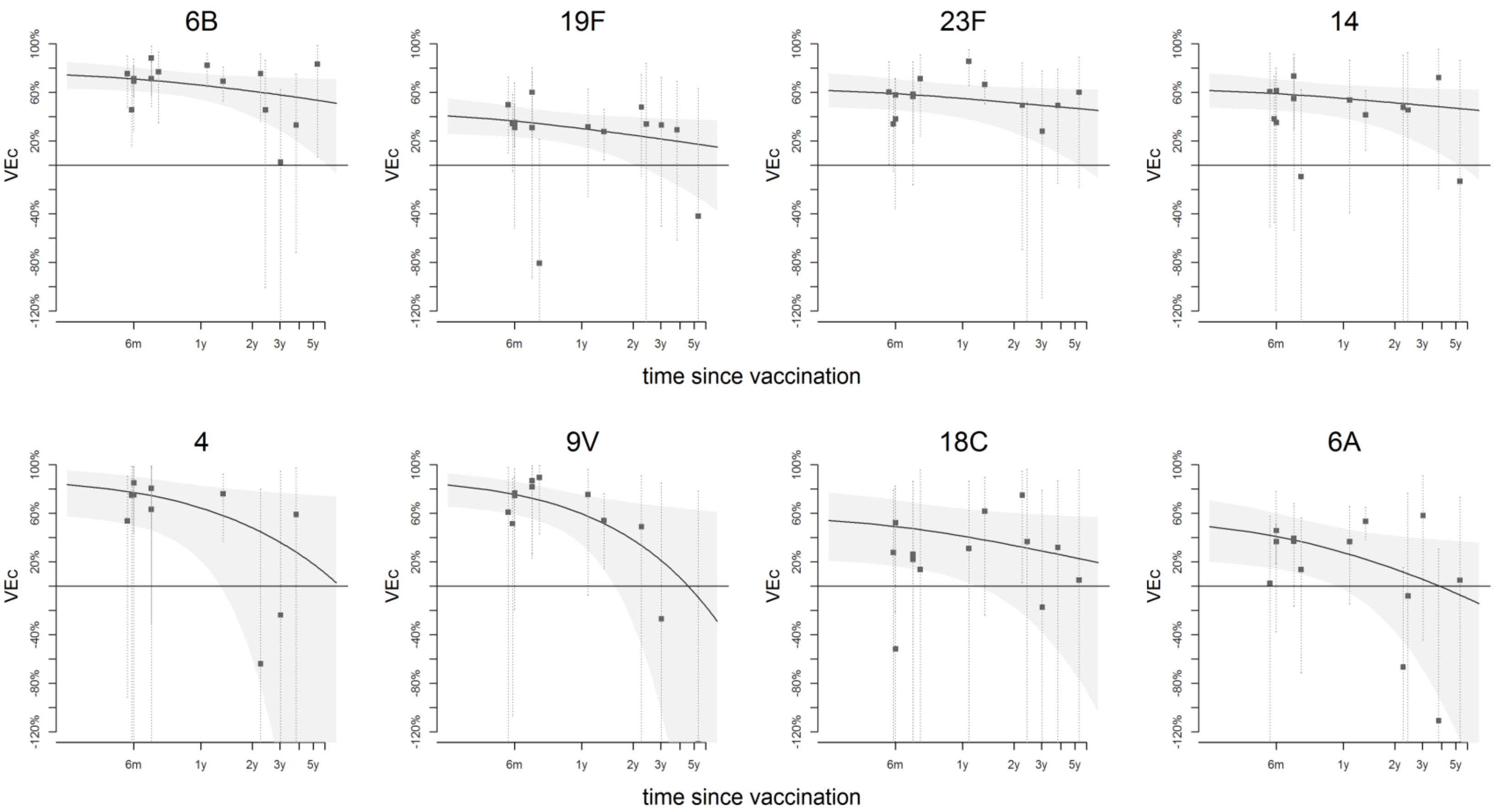


Figure 4: Serotype-specific models of vaccine efficacy against carriage, for each of the PCV7 serotypes as well as for serotype 6A



Legend: The black plain lines represent the model median and the grey shaded areas the model 95% credible interval. The squares and vertical dotted bars represent the study-specific point VE$_C$ estimates and their 95% confidence interval.

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Appendix 1: Literature search to complement the existing systematic review

Search strategy

We searched for any additional study published between 2011 and 31 May 2014 using MEDLINE and EMBASE databases, and the same search strategy as in [5], but restricted to nasopharyngeal carriage as outcome.

We used the following keywords [all fields] :

Search #1: pathogen

"Streptococcus pneumoniae" OR ("Diplococcus" AND "pneumoniae") OR ("micrococcus" AND "pneumoniae") OR "Pneumococcus" OR "pneumococcal" OR "s.pneumoniae" OR "pneumococci" OR "streptococcus" OR "streptococcal" OR "Pneumococc"

Search #2: outcome

("Nasopharyngeal" AND "carriage") OR ("Nasopharyngeal" AND "colonization") OR ("Nasopharyngeal" AND "colonisation")

Search #3: vaccine

"Vaccine" OR "vaccines" OR "vaccination" OR "vaccinated" OR "immunization" OR "immunisation" OR "immunized" OR "immunised" OR "PCV" OR "Prevenar" OR "PCV7" OR "PCV-7" OR "PNCRM7" OR "PNCRM-7" OR "PCV10" OR "PCV-10" OR "PCV9" OR "PCV-9" OR "PCV11" OR "PCV-11".

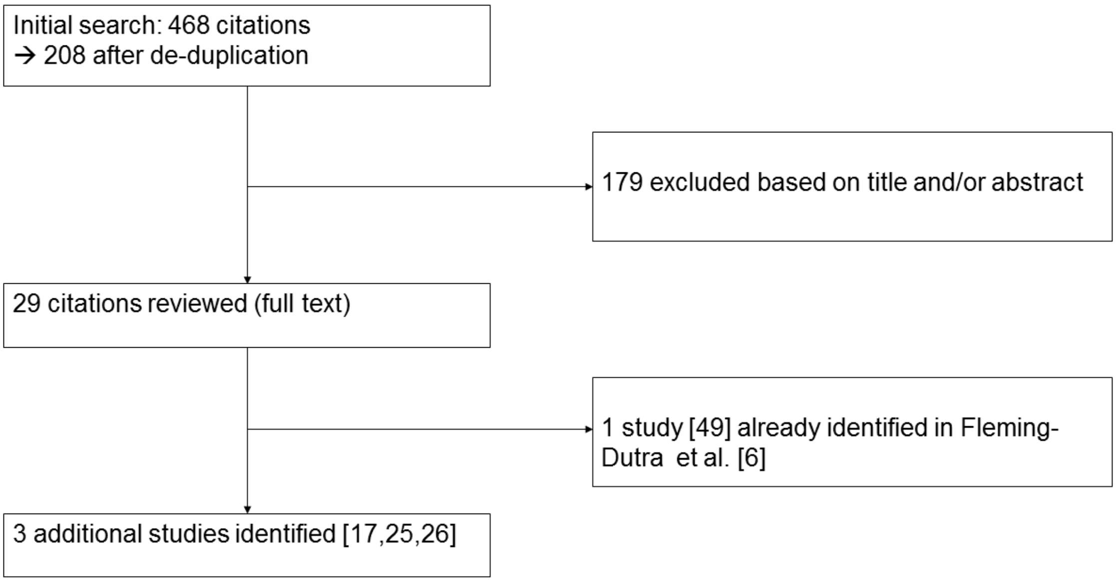
Results

Combining those three searches yielded 468 citations. After automatic and manual de-duplication, we ended up with 208 citations to screen.

Of those, 179 were excluded based on the title or the abstract. The full text of 29 references were screened. Of those, three were from trials meeting our inclusion criteria, including a PCV7 trial from Israel [28] and a PCV10 trial from the Czech Republic, with two different publications [26, 27] (Figure S1 below). Additionally, we also retreived data from a large

Finnish trial presented at a conference in 2001 [25], and used illustratively by Auranen et al.[15]

Supplementary Figure S1: Flow diagram of the literature search



Appendix 2: Comparing models of waning VE_C

Three models of waning VE_C were considered.

For each study i ,

$$\log\left(\frac{P_{Vi}^{R}}{1-P_{Vi}^{R}}\right)=\alpha_i$$ # In all models

$$\log\left(\frac{P_{Vi}^{T}}{1-P_{Vi}^{T}}\right)=\alpha_i+\theta_i+\beta_1 * \log(t_i)$$ # In model 1 (main model presented)

$$\log\left(\frac{P_{Vi}^{T}}{1-P_{Vi}^{T}}\right)=\alpha_i+\theta_i+\beta_1 * t_i$$ # In model 2

$$\log\left(\frac{P_{Vi}^{T}}{1-P_{Vi}^{T}}\right)=\alpha_i+\theta_i * \beta_1^{t_i}$$ # In model 3

, where P_{Vi}^{R} and P_{Vi}^{T} are the proportion of vaccinated individuals in the reference and target groups respectively, θ_i is the study-specific natural logarithm of the OR

We used a random effect model taking the between-study heterogeneity into account by assuming that θ_i were independent and sampled from a normal distribution centred around the mean log(OR) of carriage (μ) with a precision τ , such that $\theta_i \sim N(\mu,\tau)$ and $\tau = 1/\sigma^2$, where σ^2 is the between-study variance. A fixed effect was assumed for β_1 .

Therefore, the vaccine efficacy at time *t* (VE_{Ct}) is as follows;

$$VE_{Ct}=1-(e^{\mu} * t^{\beta_1})$$ # In model 1

$$VE_{Ct}=1-e^{(\mu+\beta_1 * t)}$$ # In model 2

$$VEc_t = 1 - e^{(\mu + \beta_1 t)}$$ # In model 3

We used the same priors in all three models.

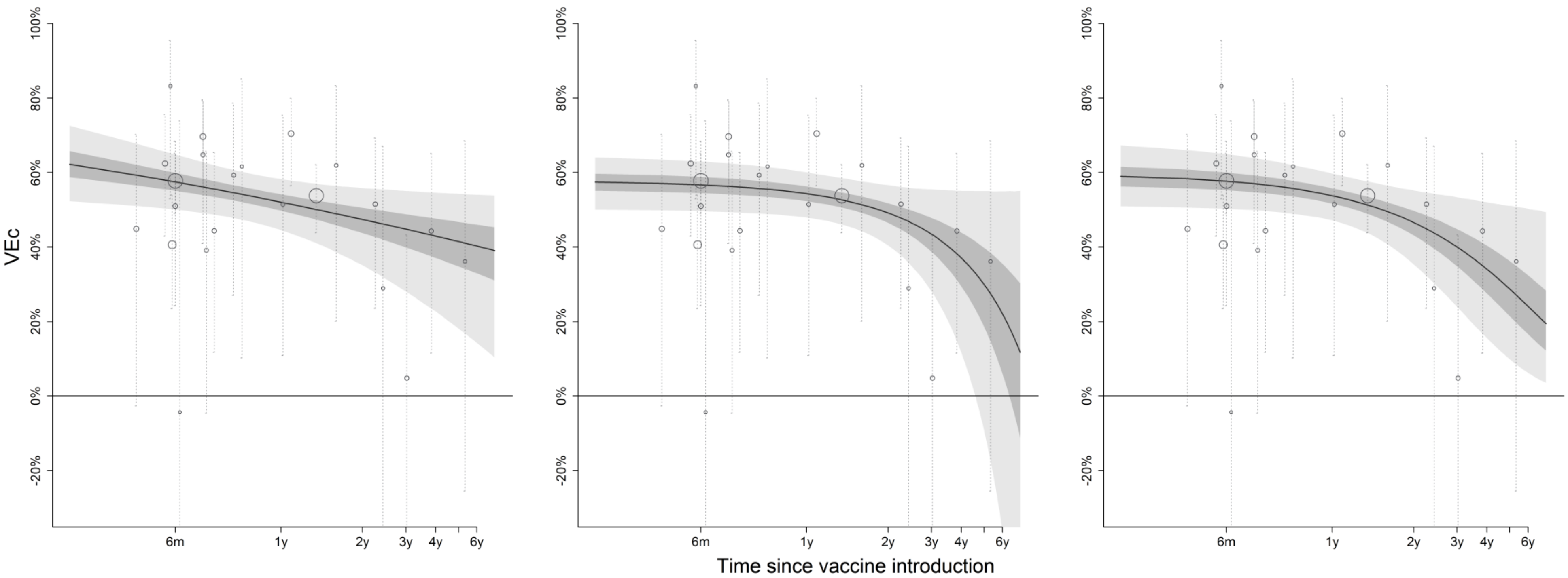
The models outputs were compared visually (Figure S1) as well as through the Deviance Information Criterion (DIC), with the smallest DIC suggesting the best model fit.

In the models of vaccine efficacy against carriage acquisition of all VT serotypes, the DIC was the same at 307.7, 307.4 and 307.0 for models 1, 2 and 3 respectively. Differences in DIC smaller than 5 are not considered meaningful in random effects meta-regression models.

The DIC for the modelling of each individual serotype and each model considered are shown in Table S1.

The smallest DIC values were consistently seen for model 1 (the main model presented) – with the exception of serotype 9V -, but the difference in DIC values between models was not considered significant, except for 19F for which model 3 was outperformed by the two other models.

Supplementary Figure S2: Model 1 (left panel), model 2 (middle panel) and model 3 (right panel)



Legend: Left panel: model 1. Middle panel: Model 2. Right panel: Model 3.

The plain line shows the model median, the dark grey shaded area the 50% credible interval (CrI) and the light grey shaded area the 95% CrI. The circles represent the point estimates of each individual study, with the size of the circle proportional to the study size, and the dotted vertical lines show the 95% confidence interval for each study

Supplementary Table S1: Deviance Information Criterion (DIC) values for ST-specific models, comparing each of the three models considered

Serotype	Deviance Information Criterion for each model		
	MODEL 1	**MODEL 2**	**MODEL3**
4	116.7	117.0	119.0
6B	193.2	193.2	193.5
9V	142.9	142.0	143.5
14	174.4	175.3	178.4
18C	151.9	151.9	153.6
19F	193.4	193.4	199.5
23F	192.8	193.3	193.7
6A	192.7	192.8	193.5

Hence, model 1 was presented as the main model in this paper based on a priori assumptions about the waning of vaccine efficacy, rather than on strong statistical grounds when comparing model 1 to the two other models.