Title

Predicting the impact of pneumococcal conjugate vaccine programme options in Vietnam: a dynamic transmission model

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ABSTRACT

Background

Catch-up campaigns (CCs) at the introduction of the pneumococcal conjugate vaccines (PCVs) may accelerate the impact of PCVs. However, limited vaccine supplies may delay vaccine introduction if additional doses are needed for such campaigns. We studied the relative impact of introducing PCV13 with and without catch-up campaign, and the implications of potential introduction delays.

Methods

We used a dynamic transmission model applied to the population of Nha Trang in Sout central Vietnam. Four strategies were considered: routine vaccination (RV) only, and RV alongside catch-up campaigns among <1y olds (CC1), <2y olds (CC2) and <5y olds (CC5). The model was parameterised with local data on human social contact rates, and was fitted to local carriage data. Post-PCV predictions were based on best estimates of parameters governing post-PCV dynamics, including serotype competition, vaccine efficacy and duration of protection.

Results

Our model predicts elimination of vaccine-type (VT) carriage across all age groups within 10 years of introduction in all scenarios with near-complete replacement by non-VT. Most of the benefit of CCs is predicted to occur within the first 3 years after introduction, with the highest impact in the first year, when IPD incidence is predicted to be 11% (95%CrI 9 – 14%)

lower than RV with CC1, 25% (21 – 30 %) lower with CC2 and 38% (32 – 46%) lower with CC5.

However, CCs would only prevent more cases of IPD insofar such campaigns do not delay introduction by more than 31 (95%CrI 30 – 32) weeks with CC1, 58 (53 – 63) weeks with CC2 and 89 (78 – 101) weeks for CC5.

Conclusion

CCs are predicted to offer a substantial additional reduction in pneumococcal disease burden over RV alone, if their implementation does not result in much introduction delay. Those findings are important to help guide vaccine introduction in countries that have not yet introduced PCV, particularly in Asia.

KEYWORDS

vaccine, pneumococcal, prediction, catch-up, model, transmission

Background

Disease due to *Streptococcus pneumoniae* (the pneumococcus) is a leading cause of morbidity and mortality worldwide, disproportionally so in resource-poor settings [1-3].

Ten- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13), which cover 10 and 13 of 94 known serotypes [4], are steadily being introduced into the routine immunisation programmes of many low and lower-middle income countries with the support from Gavi, the Vaccine Alliance [5]. In 2015, 50 out of 73 countries eligible for Gavi support had introduced the vaccine, and eight additional countries have been approved for introduction and are expected to introduce PCV within the next two years [5]. In 2012 Pakistan was the first Asian country to routinely introduce PCV, followed by Nepal, Cambodia and Lao PDR [5]. However, PCV has not been introduced in most of Asia, including Vietnam. Globally, the number of infants who had had 3-doses of PCV remains low [6].

The WHO recommends introducing PCV into childhood immunisation programmes alongside a catch-up campaign (CC) among older children [7], in order to provide direct protection to age groups at particular risk of pneumococcal disease, as well as to accelerate the population impact of the vaccine through herd protection [8].

However, the magnitude of the additional impact of different CCs over RV remains unclear. Moreover, Gavi has so far not been able to support CCs in eligible countries over concerns that they would increase vaccine introduction delays, given supply constraints [5].

The aim of our study was to explore the differential impact on carriage and invasive disease of catch-up campaigns targeting various age groups, through a dynamic compartmental model of disease transmission, and also explored the possible impact of delaying vaccine introduction to allow for CCs to be undertaken.

METHODS

The model was applied to the population of Nha Trang (~360,000 inhabitants), an urban and semi-rural area in south-central Vietnam.

Data

Nasopharyngeal carriage

Two surveys were conducted six month apart among children <5 years randomly drawn from two communes, with 350 children included in January 2008 [9] and another 350 children in July 2008 [10].

Samples were processed and cultured as per WHO recommendations [11]. Serotyping was done by PCR with 29 specific primer pairs which did not differentiate between serotypes 6A and 6B [9]. Given that both antigens are included in PCV13 but that PCV10 does not include 6A, we decided to implement our model for PCV13.

131 The carriage prevalence of VT and NVT among 5-17 year olds and adults (≥18 years) was
132 estimated based on the prevalence and serotype distribution in children <5 years of age,
133 using a meta-regression model [12].
134
135 *Social mixing patterns*
136 We derived the age-specific contact patterns from a survey conducted in the same area in
137 2010. The survey included a random sample of 2002 individuals drawn from the population
138 census, who completed a diary similar to the one used in the POLYMOD surveys [13], asking
139 about the frequency and characteristics of social encounters over 24 hours. The
140 corresponding mixing matrix was derived as in Melegaro et al. [14]. We parameterised our
141 model based on physical (i.e. skin-to-skin) contacts only, given that *S.pneumoniae* is
142 generally assumed to be transmitted through close interpersonal contact [15].
143
144 **Model structure**
145
146 We built an age-structured deterministic Susceptible-Infected-Susceptible transmission
147 model of carriage acquisition and clearance, in which we modelled VT jointly and separately
148 from NVT, but allowed for co-colonisation, as in previous models [16]. Details about the
149 model structure and model equations can be found in Supplementary File S1.
150
151 The model comprised of three levels of vaccine-induced immunity; (1) no protection, (2)
152 partial protection and (3) full protection. The latter refers to the efficacy and duration of
153 protection conferred after completion of the routine schedule (i.e. 2 infant doses and a
154 booster at 12 months ('2+1' schedule)) or the completion of a catch-up programme in older

children (2 doses in <18 months and 1 dose in ≥18 months). Partial protection was gained form two primary infant doses, or after the first catch-up dose in children aged 12 - 17 months. The difference between full and partial protection lied in the magnitude of vaccine efficacy against carriage (VE_C) and in the duration of protection.

We applied the model to a population of 81 annual age cohorts (0 to 80 years) divided into 52 weekly age bands of 100 individuals. In the calculation of the force of infection the population figure was adjusted to represent the actual population, based on census data.

Model fitting

We fitted the model to pre-vaccination nasopharyngeal prevalence data using a Markov Chain Monte-Carlo (MCMC) algorithm, and estimating the age-specific probability of effective transmission in the absence of PCV. For each posterior sample we simulated up to 15 years after vaccine introduction.

In the calculation of the log-likelihood for carriage, model estimates of VT carriage prevalence included VT carriers and VT-NVT co-colonization given the higher likelihood of our PCR assay to detect VT than NVT colonies in case of multiple colonization [9].

179 **Model parameters and outputs**

180

181 Table 1 displays the value assigned to the parameters governing transmission and
182 vaccination. Uncertainty around parameters was taken into account by sampling from their
183 posterior distribution in the MCMC process.

184

185 We obtained the vaccine efficacy against carriage conferring full protection (VE_C^F) from a
186 meta-regression model [17]. We estimated the partial efficacy against carriage (VE_C^P) as
187 0.78 (95% CI 0.64 – 0.92) that of VE_C^F through a meta-analysis of the relative risk of VT
188 carriage after full schedules (2+1 or 3+0) compared to partial schedules (2+0), which
189 included four trials [18-21]. Further details are provided in the Supplementary File S2.

190

191 We assumed an exponential decay function for the waning of VE_C^F, as in previous models
192 [16, 22]. We fixed the average duration of protection to 6 years, which best matched the
193 output of a meta-regression model of waning efficacy [17], and analysed the impact of
194 shorter (3 years) and longer (20 years) average protection in sensitivity analyses, based on
195 the uncertainty bounds of the same model [17]. The average duration of protection
196 following partial vaccination was assumed to be 0.78 (95%CI 0.64 – 0.92) that of a complete
197 schedule, as for efficacy. Details are provided in the Supplementary File S2.

198

199 In our base case model we set the vaccination coverage of both routine and catch-up
200 strategies at 90%, in accordance with coverage data from Vietnam [23].

201

Carriage estimates were translated into IPD estimates based on the propensity of VT and NVT serotypes to cause illness as a result of carriage, by age, using estimates from Choi et al. [24].

The impact of PCV on IPD was calculated based on VT and NVT disease propensity, as well as the efficacy against progression to invasive disease as a result of carriage (VE_{inv}). The latter was obtained from a function linking efficacy against IPD (VE_{IPD}) with VE_C and VE_{inv}, where $VE_{IPD} = 1 - (1 - VE_c) * (1 - VE_{inv})$ [25]. VE_{INV} was calculated based on estimates of VE_{IPD} from Lucero et al. [26] and estimates of VE_C derived from [17] (Table1), as detailed in the Supplementary File S2.

Given limited data on IPD from Nha Trang and Vietnam [27], our main analysis focused on the proportion reduction in IPD, rather than IPD incidence. However, we illustrated how the relative IPD change may translate into disease incidence based on a point estimate in <5y olds of 49 /100,000 as reported for Nha Trang [27]. We did not infer disease impact among ≥5 year olds.

To explore the impact of delayed vaccination, we assumed that for each additional week of delay the incidence of IPD during that time would be at its pre-PCV steady level.

Vaccination strategies

We explored four different strategies: (i) routine (2+1) vaccination only (RV), and routine vaccination with a catch-up campaign in (ii) <1y olds (CC1), (iii) <2y olds (CC2), and (iv) <5y olds (CC5).

WHO currently recommends introducing PCV either as a three primary infant dose schedule (3+0) or as two primary doses with a booster at 12 months of age (2+1 schedule), with the choice between schedules guided by setting-specific epidemiological characteristics [7]. We here present the predicted impact of a 2+1 programme, given the relatively low prevalence of carriage in young children in Nha Trang [27].

Sensitivity analyses

We also ran the model for coverage levels of 50% and 70% in both routine and catch-up programmes. We also explored the impact of duration of protection on our model outputs, based on lower values of 3 years and 20 years, which span across the range of likely values (Figure S3 in File S2).

RESULTS

The carriage prevalence in <5 year olds was 41% (95% CI 38 - 46%) overall, 27% (95%CI 23 - 32%) for VT serotypes and 14% (95%CI 11 - 18%) for NVT serotypes. We estimated the carriage prevalence of VT in 5 – 17 year olds and in adults to be 14% (95% CrI 10 – 18%) and

247 3% (95%CrI 0 – 7%) respectively, and that of NVT to be 15% (95%CrI 11 – 19%) and 3%
248 (95%CrI 0 – 7%). Figure 1 shows the model fit to the carriage data.
249
250 **Nasopharyngeal carriage**
251
252 Our model predicts elimination of VT serotypes across all age groups within 10 years of PCV
253 introduction in RV, with near-complete replacement by NVT serotypes, resulting in little or
254 no change in the overall carriage prevalence (Figure 2A&B), particularly in children >5 years
255 and in adults. CCs are predicted to reduce VT carriage more quickly through combined
256 direct and indirect (i.e. herd) effects (Figures 2C and D). In <5 year olds the VT carriage in
257 children is predicted to decrease by >99% within 6 years and 7 months (95% CI 5y2m - 9
258 y6m) in RV, 5 years and 11 months (4y6m– 8 y10m) in CC1, 5 years and 1 month (3y9m –
259 7y10m) in CC2 and 3 yrs (2y2m–4y10m) in CC5. Similar trends are predicted in older
260 children and adults (Figures 2C and 2D).
261
262 **Invasive Pneumococcal Disease (IPD)**
263
264 Our model predicts that the decline of IPD incidence will be proportionally highest among
265 <2 year olds, falling to about 45% (95%CrI 33% - 57%) of its pre-PCV level and would be
266 almost halved (57% (48 – 66%)) in children aged 2 – 4 years respectively (Figure 3A and 3B).
267
268 Most of the benefit of CCs over routine vaccination in children <5 years is predicted to occur
269 within the first three years after PCV introduction, with no noticeable difference at 5 years
270 (Fig 3C). Our model predicts that the relative risk of IPD after CCs compared to RV would be

lowest about 1 year after PCV introduction, with differences between strategies reducing thereafter until the new equilibrium is reached. Compared to RV, one year after vaccine introduction the number of cases of IPD is predicted to be 11% (95%CrI 9 – 14%) lower with CC1, 25% (21-30%) lower with CC2 and 38% (32 – 46%) lower with CC5 (Fig 3C).

The impact of each strategy on the cumulative proportion of cases averted in the first 3 years post PCV introduction, compared to no vaccination, is illustrated in Figure 3D.

Based on an average annual incidence risk of 49/100,000 children <5 years before PCV introduction [27], a routine introduction of PCV would result in a total of 74 cases (95%CrI 62 - 86) per 100,000 children <5 years averted over the first five years of programme implementation and catch-up campaigns would lead to the prevention of an additional 13 (95%CrI 11 – 16) cases with CC1, 25 (95%CrI 21 – 30) cases with CC2 and 39 (95%CrI 31 – 49) cases with RV5.

Delayed PCV introduction

We estimated the relative impact on IPD of catch-up campaigns for increasing delays. Our results suggest that, compared to RV, more IPD cases would be prevented in children <5 years insofar as PCV introduction is not delayed by more than 31 weeks (95%CI 30 – 32 weeks) for CC1, 58 weeks (53 – 63 weeks) for CC2 and 89 weeks (78 – 101 weeks) for CC5.

294 Vaccination delays would negatively impact <2 year olds more rapidly than 2 – 4 year old
295 (Figure 4).
296
297 **Sensitivity analyses**
298
299 *Vaccination coverage*
300 Our model predicts a lengthening of the time to near-elimination of VT serotypes (and
301 hence, the time to reach the new post-PCV disease equilibrium) as vaccination coverage
302 decreases but a similar differential impact of catch-up campaigns compared to routine
303 vaccination. Full details are provided in the Supplementary File S3.
304
305 *Duration of protection*
306 A duration of protection of 3 years would increase the time to elimination of VT carriage,
307 and thus prevent fewer IPD cases overall, while any average duration of protection longer
308 than 6 years would not change model outcomes. With a duration of 3 years the median
309 prevalence of VT in <5 year olds is predicted to reach near elimination about 2 years later in
310 RV and CC1, 1.5 years later with CC2 and about 1 year later with CC5. Similar differences
311 were predicted for the ≥5 year olds (Figure S5 in the Supplementary File S3). The relative
312 impact of one vaccination strategy over another was predicted to be similar than with a
313 duration of 6 years.
314
315 **DISCUSSION**
316

317 We explored the possible impact of introducing PCV13 with and without a catch-up
318 campaign in Vietnam through a dynamic transmission model. Our results feed into current
319 debates about introduction strategies, particularly in South-East Asia where pneumococcal
320 disease burden is high [28], where many countries have not yet introduced PCV [5], and
321 where epidemiological data to guide decision making remain scarce [28, 29]. Although
322 Vietnam is Gavi-eligible and is expected to introduce PCV in the coming years, it has not yet
323 applied [5]. Our results provide estimates about how much catch-up campaigns would
324 decrease disease burden compared to routine vaccine introduction without a campaign, for
325 different scenarios. Our study also shows that, although catch-up campaigns would
326 decrease disease burden more rapidly across age groups, their impact would only be
327 beneficial insofar as the additional supply and operational constraints of their
328 implementation does not delay PCV introduction by more than about 6 months to 2 years,
329 depending on the age cohorts targeted by those campaigns.
330
331 The availability of data on both social mixing patterns – which are central to transmission
332 models [13, 30] – and carriage in the same population allowed for thorough
333 parameterisation of a transmission model.
334
335 However, our study has a number of limitations. In the absence of post-PCV data,
336 predictions were based on the best available estimates of parameters governing vaccine
337 effects that were observed elsewhere [16, 17, 31], which may not fully capture the local
338 characteristics. Given that serotypes differ in their pathogenicity, fitness and transmissibility
339 [32, 33], and that vaccine efficacy and duration of protection differs by serotype [12], our
340 predictions based on homogeneous characteristics for the group of VT and NVT serotypes

341 may overlook local epidemiological characteristics. This uncertainty was nonetheless
342 captured to some extent by sampling from the known uncertainty around those parameters
343 [16]. Moreover, we were not able to assess the impact of PCV on pneumococcal
344 pneumonia, the burden of which is much higher than that of IPD [34], given the lack of
345 robust data and the challenges in the aetiological assessment of clinical pneumonia. Results
346 from ongoing studies in Gavi-eligible countries [35, 36] might help modelling work on the
347 impact of PCV on pneumonia in the future.
348
349 Our predictions are in line with the experience of PCV7 in Europe and North America [37-
350 44], as well with post-PCV trends observed in the few studies from low-income settings
351 [36]. In the region of Kilifi in Kenya, where a catch-up campaign was conducted at PCV
352 introduction, impact studies have shown a two third reduction in VT carriage prevalence
353 across all age groups within two years of PCV10 introduction with a catch-up campaign
354 among children <5 years [43].
355
356 The implementation of PCV in various settings has consistently resulted in little or no
357 change in overall carriage prevalence, due to replacement effects by NVT serotypes
358 colonising the space left vacant by VT in the nasopharynx, but a reduction in severe disease
359 given the lower pathogenicity of the latter, in accordance with our model output. Our
360 predictions were also robust to estimates of duration of protection of vaccination coverage,
361 and thus provide useful estimates of the impact of introducing PCV in a semi-urban
362 Southeast Asian setting.
363

364 While supply issues could also lead to other problems than just delay, such as incomplete
365 schedules once a programme has started, we here assumed that the planning of vaccine
366 introduction would be based on vaccine availability, full roll-out capacity and sustainability
367 at introduction. With supply constraints, and ignoring other supply side, staff and outreach
368 challenges that could potentially delay the implementation of CCs [5], our study can inform
369 whether delaying the introduction of the vaccine to allow for CCs would potentially be
370 beneficial, compared to a routine-only strategy. Moreover, this model also provides a
371 framework that could feed into economic evaluations to further guide decisions about
372 vaccine introduction with and without campaigns.
373
374 The generalisability to other settings of the differential impact of CCs needs to be
375 considered in light of the epidemiological and socio-demographic characteristics of Nha
376 Trang. In particular, the low prevalence of carriage and an ageing population - with only 5%
377 of children under the age of five years – impact on the speed with which herd effects are
378 established. Although similar epidemiological and demographic characteristics are observed
379 in many other South(east) Asian settings [45, 46], the differential impact of CCs and the
380 establishment of herd effects in settings with a younger population and a higher carriage
381 prevalence is likely to differ, and should be addressed with models applied to such settings.
382
383 In conclusion, our study offers insights into the current debate about vaccination strategies
384 when introducing PCV in South-East Asia. Our model suggests that catch-up campaigns have
385 the potential to rapidly decrease carriage and disease across age groups, but are only
386 offering added reduction in disease burden insofar their implementation results in little to
387 no implementation delay.

DECLARATIONS

Ethics approval

Ethical approval for the field surveys was granted by the institutional review board of the London School of Hygiene and Tropical Medicine and the Ethics Commission of National Institute of Hygiene and Epidemiology, Hanoi and the Nagasaki University.

Consent for publication

Availability of data and material

Other model outputs are available on request. Please contact the corresponding author at olivier.lepolain@gmail.com

Competing interests

- OLP: none
- WJE: WJE's partner works for GSK, who manufacture PCV10.
- KT: none
- KA: none
- EKM: Kim Mulholland has consulted for GSK on PCV vaccine use and nutritional strategies to improve vaccine effectiveness.

- DG: has served on ad-hoc advisory boards for Pfizer, GlaxoSmithKline and Merck, and the University College London Institute of Child Health Laboratory receives contract research funding from Pfizer, GlaxoSmithKline and Merck
- YHC: none
- DDA: none
- LMY: none
- SF: none

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Authors' contributions

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- Authors' information (optional)

LIST OF ABBREVIATIONS

CC: Catch-up campaign

CC1: CC in <1 year olds

CC2: CC in <2 year olds

CC5: CC in <5 year olds

IPD: Invasive Pneumococcal Disease

MCMC: Markov Chain Monte-Carlo

NVT: Non vaccine type

PCV: pneumococcal conjugate vaccine

PCV7: seven-valent PCV

PCV10: 10-valent PCV

PCV13, 13-valent PCV

RV: Routine vaccination

VE_C^F : vaccine efficacy against carriage conferring full protection

VE_C^P :vaccine efficacy against carriage conferring partial protection

VT: Vaccine Type

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453

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616 pneumococcal vaccine immunization schedule. Vaccine. 2011;29:2999-3007.

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631 **Tables and Figures**

632 **Table 1:** Parameters used in the model

Parameter	Value	Source*
Competition for carriage acquisition (C_N and C_V)$^{\$}$	0.1 (SD 0.01)	[16, 31]
Duration of carriage (δ_i)		
0 – 52 months	47.1 days	[47]
12 – 23 months	39.4 days	[47]
24 – 35 months	31.6 days	[47]
36 – 47 months	21.5 days	[47]
48 – 59 months	21.3 days	[47]
5 – 17 years	17.0 days	[22, 48]
18 years and over	18.0 days	[22, 48]
Vaccine efficacy against carriage		
Full protection (VE_C^F)	62% (95%CrI 52 – 72 %)	[17]
Partial protection (VE_C^P)	0.78 (95%CI 0.64 – 0.92) * VE_C^F	Meta-analysis of [18-21] (Supplementary File S2)
Mean duration of protection against carriage		
In fully protected (D_F)	6.0 years	[17](Supplementary File S2)
In partially protected (D_P)	0.78 (95%CI 0.64 – 0.92) * D_F	Supplementary File S2
Vaccine efficacy against IPD (VE_{IPD})	0.80 (95%CrI 0.61 – 0.90)	[49]

633 $^{\$}$Where 0.1 means a force of infection which is 10% that of a situation with no competition

Figure 1: Pre-PCV carriage estimates across age groups for VT (left panel) and NVT (right panel), based on survey (plain vertical lines) and meta-regression model (dotted vertical lines) estimates, and estimates from the corresponding transmission model. **Legend:** Dots and bars correspond to the point and 95% confidence interval for the carriage estimates from the survey data (plain dot and plain lines) and the meta-regression model (cross and dotted lines). The dark red and dark blue plain lines represent the median transmission model estimate for VT and NVT respectively, the shaded areas the 50% credible interval (CrI) around the median and the dotted red and blue lines the 95%CrI

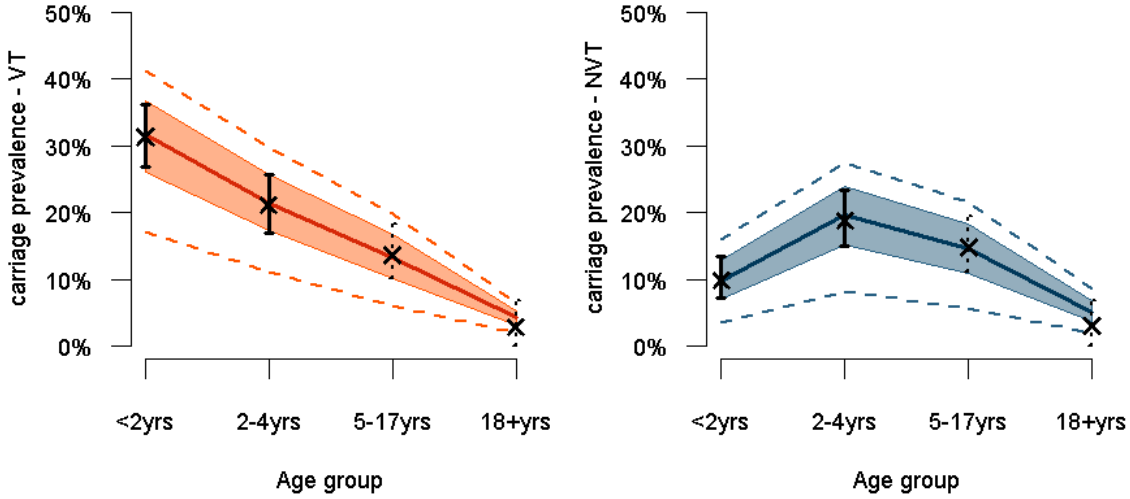
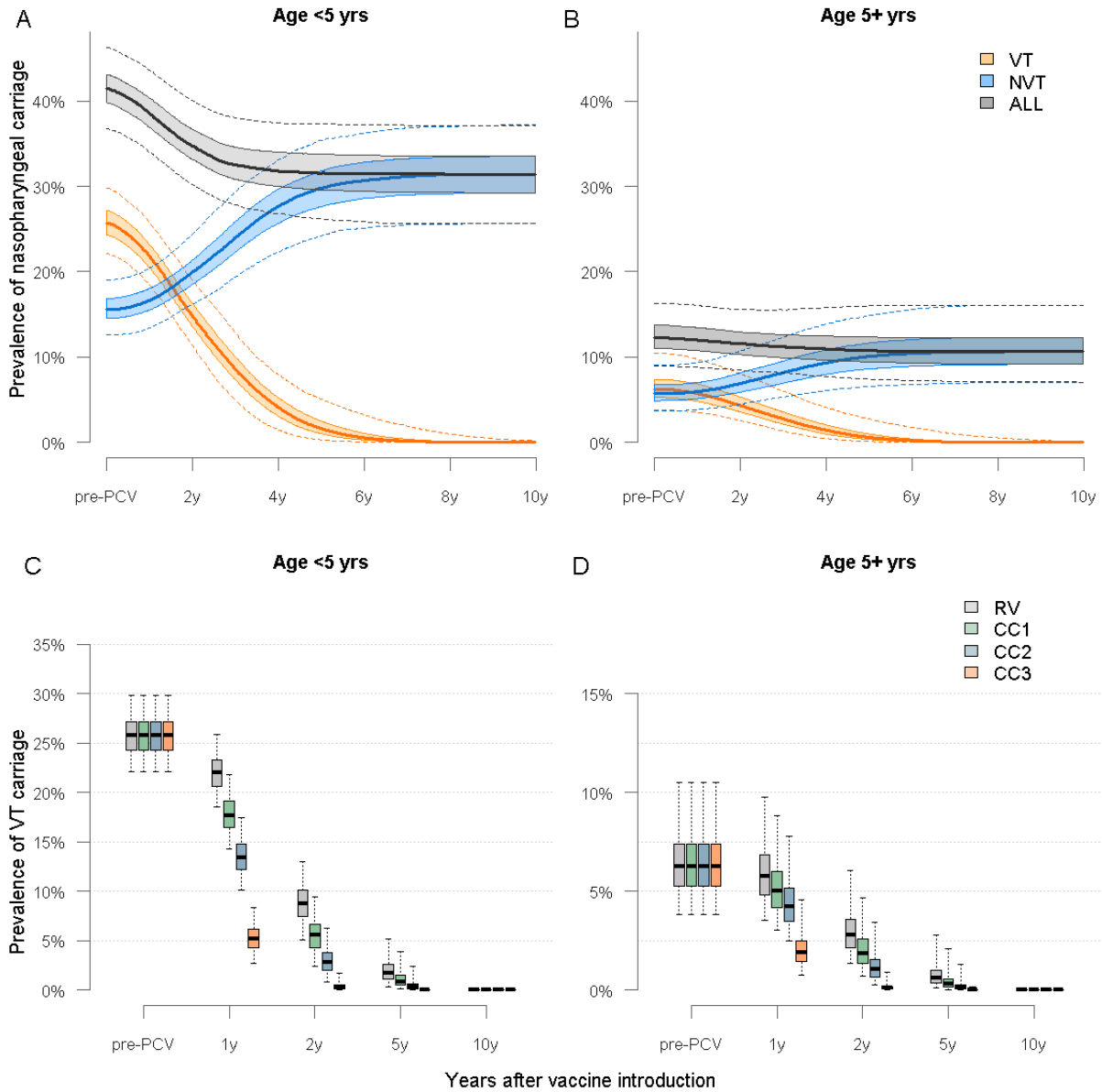


Figure 2: Predicted trends in nasopharyngeal carriage following PCV13 introduction in Nha Trang. **Legend:** A: Predicted trends in VT, NVT and overall carriage in <5 year olds without a catch-up campaign. B: Predicted trends in VT, NVT, and overall carriage in ≥5 year olds without a catch-up campaign. C: Predicted prevalence of VT carriage in <5 year olds for each vaccination strategy. D: Predicted prevalence of VT carriage in ≥5 year olds for each vaccination strategy. In all four panels: plain line= median, shaded areas= 50% credible intervals and dotted line or whiskers= 95% credible interval



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670 **Figure 3:** Trends in IPD following PCV introduction in children under five years of age in Nha
671 Trang **Legend:** A: Predicted trends the cumulative annual incidence of IPD in children <2
672 years for each vaccination strategy considered, at a 90% vaccination coverage B: Predicted
673 trends the cumulative annual incidence of IPD in children aged 2-4 years for each
674 vaccination strategy considered, at a 90% vaccination coverage C: Cumulative number of IPD
675 cases saved for each catch up strategy compared to RV, in children <5 years of age. D:
676 Overall cumulative number of cases saved for each vaccination strategy, compared to no
677 vaccination, in the first 3 years post PCV introduction. In all four panels: plain line= median,
678 shaded areas= 50% credible intervals and dotted line or whiskers= 95% credible interval
679

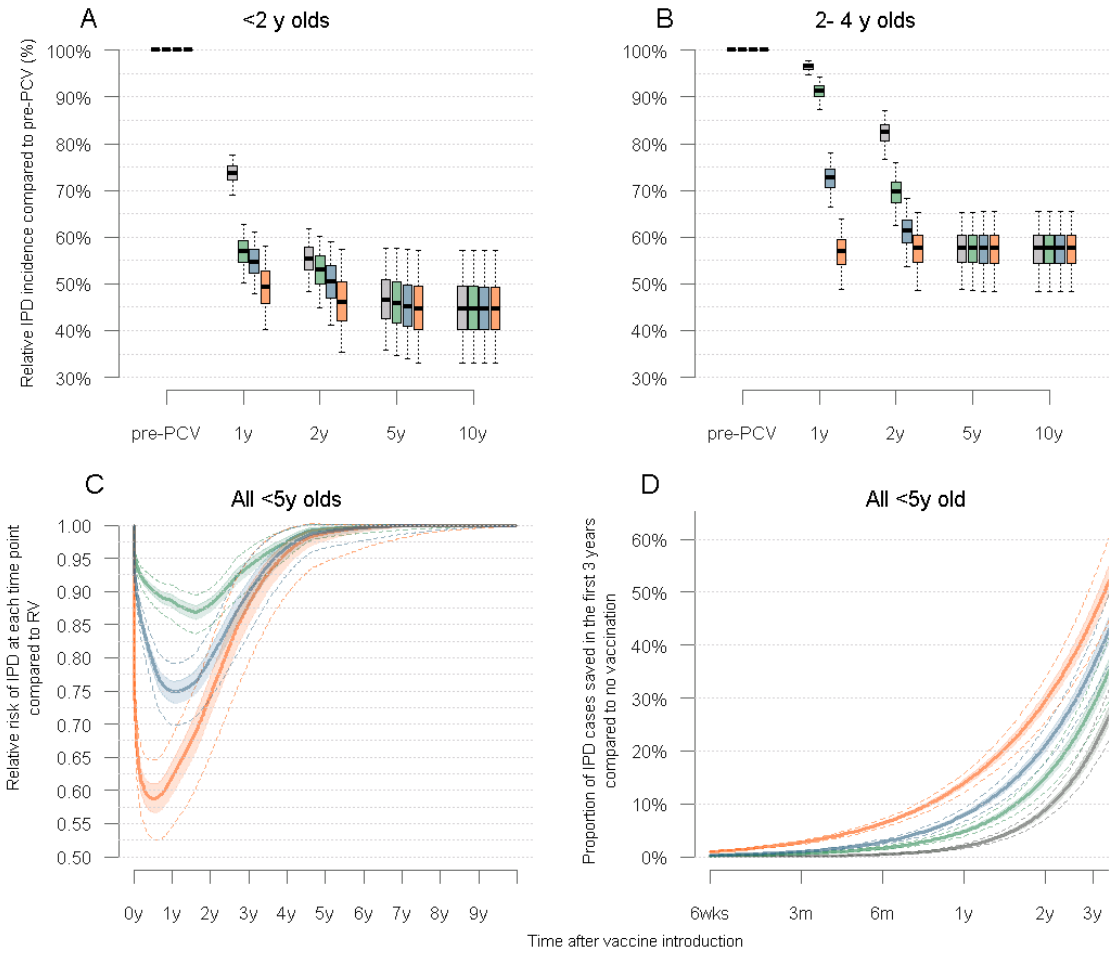

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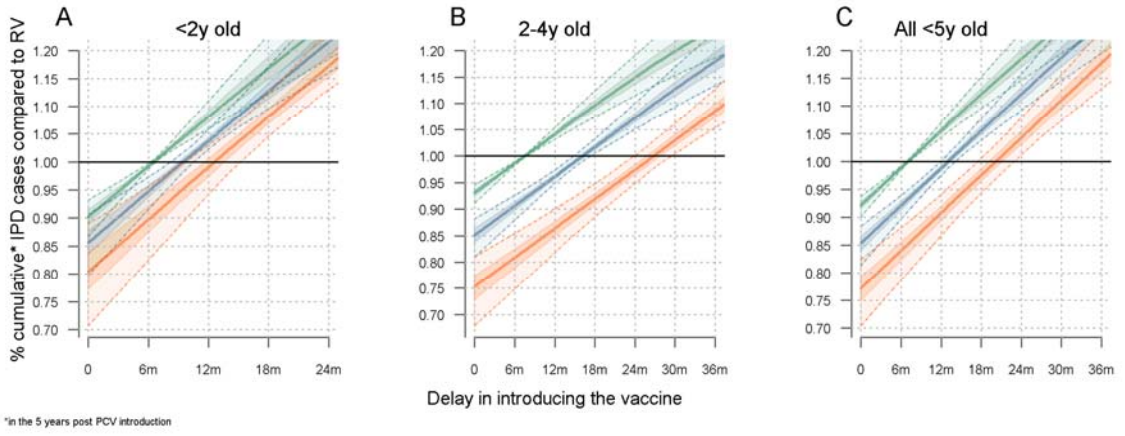
Figure 4: Impact of delayed PCV introduction with a catch-up campaign on VT carriage (panel A) and on IPD cases saved (panel B) in children under five years of age. **Legend:** A: <2 year olds. B: 2 – 4 year olds C: <5 years olds. The middle plain trend line corresponds to the median estimate (Green=CC1, Blue=CC2, Red=CC5), the dark shaded areas the 50% CrI and the light shaded areas the 95%CrI. The plain horizontal line at 1.00 represents the point below which interventions will be more favourable than a timely RV.



707

708 **Supplementary File S1**: **Model structure**

709

710 We built a realistic age-structured deterministic Susceptible-Infected-Susceptible (SIS)
711 transmission model of carriage acquisition and clearance, similar to Choi et al. [16].
712 The model considers all VT serotypes jointly and separately from the group of NVT
713 serotypes, but allows for VT-NVT co-colonization, thus resulting in four compartments of
714 carriage states, namely susceptible, VT carriers, NVT carriers and VT-NVT co-colonized as in
715 Choi et al. [16]. In this model movements from the susceptible to the VT or NVT
716 compartments are determined by age-specific forces of infection for VT (λ_{Vi}) and NVT (λ_{Ni})
717 respectively, and co-colonization is determined by competition parameters (C_N and C_V),
718 which represent the degree with which prior colonization reduces the likelihood of co-
719 colonization. Age-specific recovery rates (r_i) determine the speed with which individuals
720 revert back from the co-colonized to either VT or NVT compartments, and from colonization
721 to susceptible compartments, assuming no natural immunity to carriage.

722

723 The model comprised of three levels of vaccine-induced immunity; (1) no protection, (2)
724 partial protection and (3) full protection (Figure S1). The latter means the efficacy and
725 duration of protection conferred after completion of the infant schedule (i.e. 2 infant doses
726 and a booster at 12 months ('2+1' schedule)) or the completion of a catch-up programme in
727 older children (2 doses in <18 months and 1 dose in ≥18 months). Partial protection was
728 gained form two primary infant doses, or after the first catch-up dose in children aged 12 -
729 17 months. The difference between full and partial protection lied in the magnitude of
730 vaccine efficacy against carriage (VE_C) and in the duration of protection.

731

732 We applied the model to a population of 81 annual age cohorts (0 to 80 years) divided into
733 52 weekly age bands of 100 individuals. In the calculation of the force of infection the
734 population figure was adjusted to represent the actual population, based on census data.

735

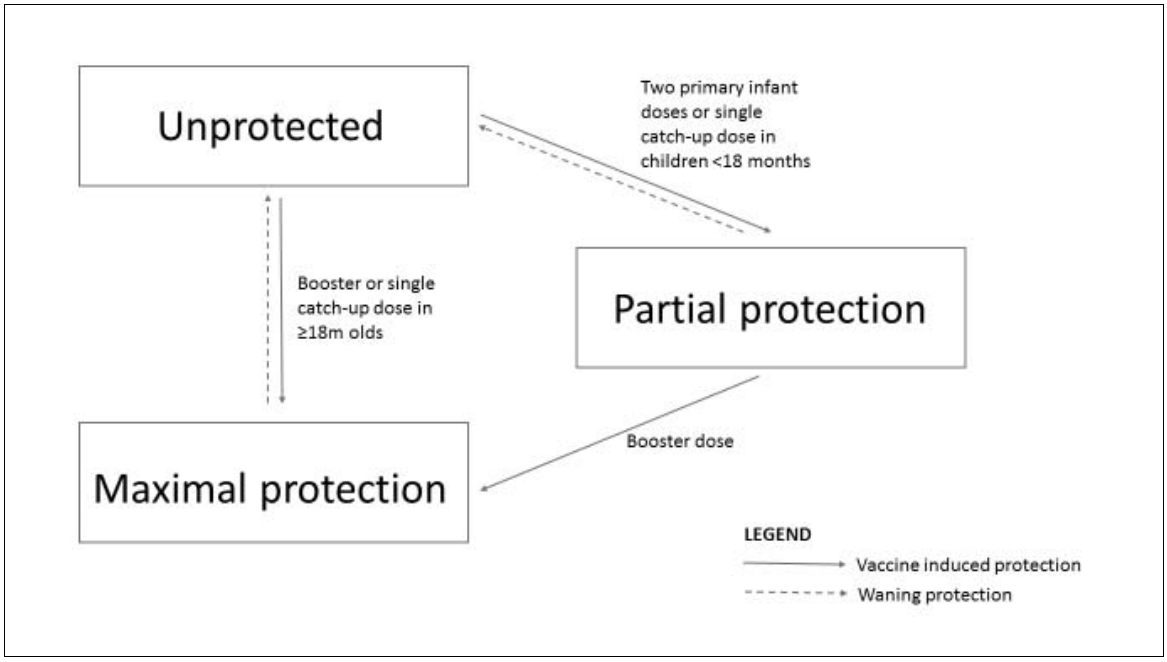
736 We inferred the impact on IPD based posterior estimates of carriage at each time step,
737 case:carrier ratios for VT and NVT by age group [16], the vaccine efficacy against
738 invasiveness and the vaccination coverage of each weekly age cohort at each time step.
739 Details about parameters of vaccine efficacy are provided in the Supplementary File S2.

740

741 The model equations are provided in Text S1 below.

742

743 **Figure S1**: The three groups of vaccine protection states defined in the model and
744 movement between groups



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748 **Text S1:** Model equations

$$\frac{dS_i(t)}{dt} = r_{Vi} * V_i(t) + r_{Ni} * N_i(t) - (\lambda_{Vi}(t) + \lambda_{Ni}(t)) * (\gamma_{i(\text{inf})} + \gamma_{i(catch-up)}) * S_i(t) + \omega_p * Sp_i(t) + \omega_f * Sf_i(t)$$

$$\frac{dV_i(t)}{dt} = \lambda_{Vi}(t) * S_i(t) + r_{Ni} * B_i(t) - (C_N * \lambda_{Ni}(t) + r_{Vi}) * V_i(t) - \gamma_{i(\text{inf})} + \gamma_{i(catch-up)}) * V_i(t) + \omega_p * Vp_i(t) + \omega_f * Vf_i(t)$$

$$\frac{dN_i(t)}{dt} = \lambda_{Ni}(t) * S_i(t) + r_{Vi} * B_i(t) - (C_V * \lambda_{Vi}(t) + r_{Ni}) * N_i(t) - \gamma_{i(\text{inf})} + \gamma_{i(\text{catch-up})}) * N_i(t) + \omega_p * Np_i(t) + \omega_f * Nf_i(t)$$

$$\frac{dB_i(t)}{dt} = (C_V * \lambda_{Vi}(t) * N_i(t) + C_N * \lambda_{Ni}(t) * V_i(t) - (r_{Ni} + r_{Vi}) * B_i(t) - (\gamma_{i(\text{inf})} + \gamma_{i(\text{catch-up})}) * B_i(t) + \omega_p * Bp_i(t) + \omega_f * Bf_i(t)$$

$$\frac{dSp_i(t)}{dt} = r_{Vi} * Vp_i(t) + r_{Ni} * Np_i(t) - ((1 - VE_{pc}) * \lambda_{Vi}(t) + \lambda_{Ni}(t) + \gamma_{i(\text{booster})} + \omega_p) * Sp_i(t) + \gamma_{i(\text{inf})} * S_i(t)$$

$$\frac{dVp_i(t)}{dt} = (1 - VE_{pc}) * \lambda_{Vi}(t) * Sp_i(t) + r_{Ni} * Bp_i(t) - (C_N * \lambda_{Ni}(t) + \gamma_{i(\text{booster})} + \omega_p) * Vp_i(t) + \gamma_{i(\text{inf})} * V_i(t)$$

$$\frac{dNp_i(t)}{dt} = \lambda_{Ni}(t) * Sp_i(t) + r_{Vi} * Bp_i(t) - (C_V * (1 - VE_{pc}) * \lambda_{Ni}(t) + \gamma_{i(\text{booster})} + \omega_p) * Np_i(t) + \gamma_{i(\text{inf})} * N_i(t)$$

$$\frac{dBp_i(t)}{dt} = (C_V * (1 - VE_{pc}) * \lambda_{Vi}(t) * Np_i(t) + C_N * \lambda_{Ni}(t) * V_i(t) - (r_{Ni} + r_{Vi} + \gamma_{i(\text{booster})} + \omega_p) * Bp_i(t) + \gamma_{i(\text{inf})} * B_i(t)$$

$$\frac{dSf_i(t)}{dt} = r_{Vi} * Vf_i(t) + r_{Ni} * Nf_i(t) - ((1 - VE_{fc}) * \lambda_{Vi}(t) + \lambda_{Ni}(t) + \omega_f) * Sf_i(t) + \gamma_{i(\text{booster})} * Sp_i(t) + \gamma_{i(\text{catch-up})} * Sp_i(t)$$

749

$$\frac{dVf_i(t)}{dt} = (1 - VE_{fc}) * \lambda_{Vi}(t) * Sf_i(t) + r_{Ni} * Bf_i(t) - (C_N * \lambda_{Ni}(t) + \omega_f) * Vf_i(t) + \gamma_{i(\text{booster})} * Vp_i(t) + \gamma_{i(\text{catch-up})} * Vp_i(t)$$

$$\frac{dNf_i(t)}{dt} = \lambda_{Ni}(t) * Sf_i(t) + r_{Vi} * Bf_i(t) - (C_V * (1 - VE_{fc}) * \lambda_{Ni}(t) + \omega_f) * Nf_i(t) + \gamma_{i(\text{booster})} * Np_i(t) + \gamma_{i(\text{catch-up})} * Np_i(t)$$

$$\frac{dBf_i(t)}{dt} = (C_V * (1 - VE_{fc}) * \lambda_{Vi}(t) * Nf_i(t) + C_N * \lambda_{Ni}(t) * V_i(t) - (r_{Ni} + r_{Vi} + \omega_f) * Bf_i(t) + \gamma_{i(\text{booster})} * Bp_i(t) + \gamma_{i(\text{catch-up})} * Bp_i(t)$$

750

751 *i* represent the weekly age groups. ? is the vaccination coverage for infant doses (inf), the

752 booster dose (boost) and the catch-up dose (catch-up). VEf_C and VEp_C is the vaccine efficacy

753 against carriage acquisition after full and partial vaccination respectively. ω_P and ω_f

754 represent the rate of waning immunity after partial and full vaccination.

755

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760 **Supplementary File S2: Vaccine efficacy and duration of protection**

761

762 **Vaccine efficacy against carriage**

763

764 *Full vaccination*

765 We obtained the vaccine efficacy against carriage after full protection (VE_C^F) and its
766 uncertainty from a Bayesian meta-regression model based on estimates from 22
767 intervention studies. The details have been published elsewhere [17]. The model of vaccine
768 efficacy was run for as many iterations as in our transmission model, so that we could
769 sample one estimate of VE_C^F at each iteration of the post-vaccination simulations.

770

771 *Partial vaccination*

772 A systematic review of the impact of pneumococcal conjugate vaccines on carriage [50]
773 provided information on intervention studies with 2 primary-dose arms where compared
774 with either 2+1 schedules or 3+0 schedules.

775

776 We included individual randomized controlled trials providing nasopharyngeal carriage
777 estimates within 3 – 20 months after a 2-dose infant schedule (2+0 arm) and after a
778 complete schedule (either 3+0 or 2+1 arm). We excluded studies providing carriage
779 estimates within 3 months after vaccination to account for the delay in producing an
780 immune response, and time to carriage clearance under the assumption that existing
781 carriage at the time of vaccination is not affected by PCV [17].

We extracted data on the number of carriers of VT and total number of individuals swabbed in each study arm before and after vaccination. We then computed the relative risk of VT carriage among fully vaccinated compared to partially vaccinated children. The pooled estimates were obtained through a random effects meta-regression model.

We pooled estimates from four studies, including trials in Fiji [19], Israel[18], The Gambia [51] and The Netherlands [20], providing together eight different survey points, into a simple random effects meta-analysis, not taking into account within-study dependence given the limited number of data points per study. The details of the studies are provided in Table S1 below.

Table S1: Studies included in the meta-analysis

Study	Country	Schedule	Age (months)	Time since last dose (months)	Carriers /total	Relative Risk (95%I)
Dagan (2012)[18]*	Israel	3+0	9.5m	3.5m	58/327	0.83 (0.57 – 1.20)
Dagan (2012)[18]*	Israel	2+0	9.5m	3.5m	36/169	ref
Ota (2011)[51]	Gambia	3+0	11m	7m	20/200	0.59 (0.36 – 1.00)
Ota (2011)[51]	Gambia	2+0	11m	8m	33/198	ref
Ota (2011)[51]	Gambia	3+0	15m	11m	24/193	0.80 (0.49 – 1.32)
Ota (2011)[51]	Gambia	2+0	15m	12m	30/196	ref
Russell (2010)[19]	Fiji	3+0	6m	3m	13/127	0.95 (0.47 – 1.89)
Russell (2010)[19]	Fiji	2+0	6m	3m	16/148	ref
Russell (2010)[19]	Fiji	3+0	9m	6m	4/122	0.32 (0.11 – 0.93)
Russell (2010)[19]	Fiji	2+0	9m	6m	15/146	ref
Russell (2010)[19]	Fiji	3+0	12m	9m	8/114	1.25 (0.49 – 3.23)
Russell (2010)[19]	Fiji	2+0	12m	9m	9/143	ref
van Gils (2009)[20]	Netherlands	2+1	18m	7m	51/329	0.64 (0.47 – 0.88)
van Gils (2009)[20]	Netherlands	2+0	18m	14m	79/327	ref
van Gils (2009)[20]	Netherlands	2+1	24m	13m	47/333	0.96 (0.66 -1.39)
van Gils (2009)[20]	Netherlands	2+0	24m	20m	49/332	ref

*In this study pooled results were provided for samples taken at 7 months and 12 months of age, and we therefore considered the age and time since the last dose as the average between the two

797 The pooled relative risk of carriage among children with a full schedule was 78% (95%CI 64

798 – 92%) that of a partial schedule (Figure S2), with no evidence of heterogeneity (I^2=3%).

799

800 At each iteration of the MCMC, we sampled a value from the relative risk 78% (95%CI 64 –

801 92%) multiplied by a value of the full vaccine efficacy against carriage acquisition (VE_C^F), to

802 obtain a measure of the partial efficacy (VE_C^P).

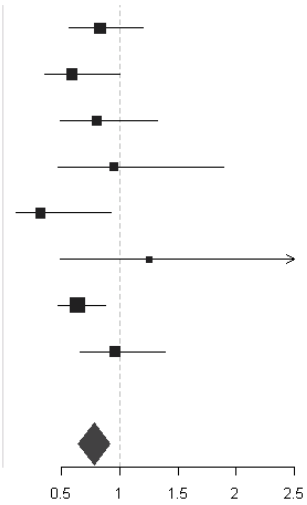
803

804 **Figure S2**: Forest plot of the relative risk of VT carriage of 3 primary doses (2+1 or 3+0), for

805 four different individual randomized controlled trials (RCTs), at eight different time points

806 [18-20, 51].

Study	Relative efficacy mean	[2 vs 3 doses] (95%CI)
Dagan (2012)	0.83	(0.57-1.20)
Ota (2011)	0.59	(0.36-1.00)
Ota (2011)	0.80	(0.49-1.32)
Russell (2010)	0.95	(0.47-1.89)
Russell (2010)	0.32	(0.11-0.93)
Russell (2010)	1.25	(0.49-3.23)
van Gils (2009)	0.64	(0.47-0.88)
van Gils (2009)	0.96	(0.66-1.39)
Summary	**0.78**	**(0.64-0.92)**



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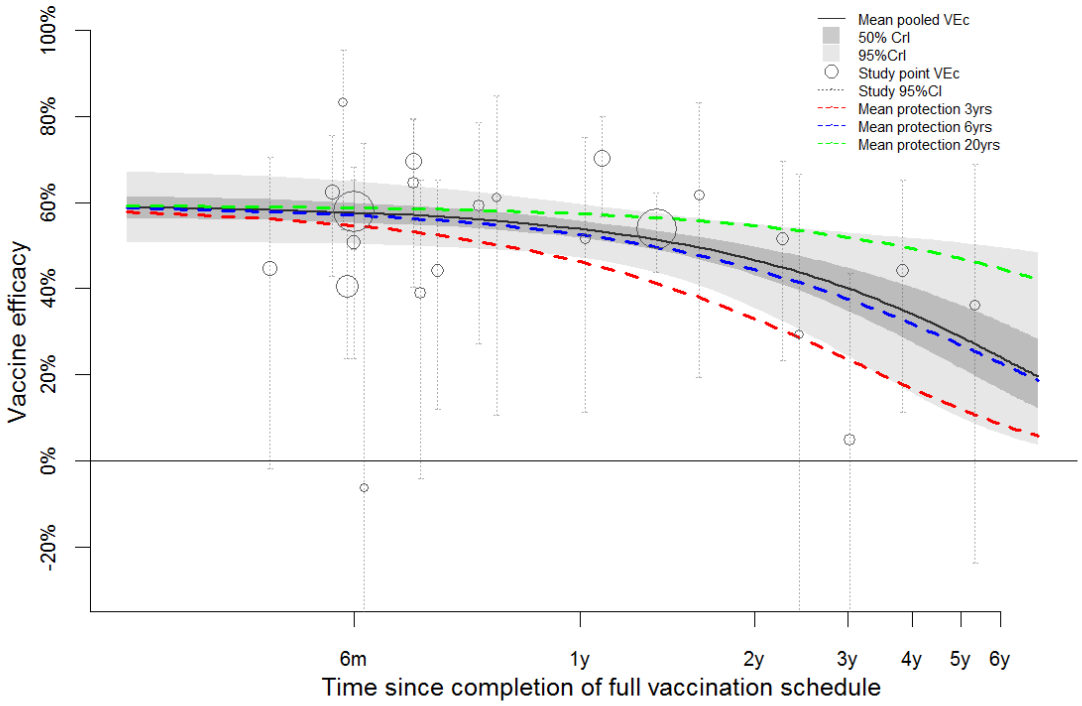
812 **Duration of protection**

813

814 The duration of protection against carriage acquisition was obtained from le Polain et al
815 [17]. The median estimate of a model of waning efficacy, using an asymptomatic function,
816 closely matched that of an exponential decay with a mean duration of protection of 6 years
817 (Figure S3). Hence, this estimate was taken as the average duration of protection in the
818 main model. For sensitivity analyses, we considered mean durations of 3 years and 20 years
819 as the lower and higher values, as shown in Figure S3.

820

821 **Figure S3:** Duration of protection of PCV against carriage acquisition



822
823 **Legend** : Each circle represents the mean vaccine efficacy estimate for each study included
824 in the analysis – see [17]. The size of the circle is proportional to the study size. The whiskers
825 on either side of each circle represent the 95%CrI around the point estimate. The dark grey

826 area corresponds to the 50% CrI around the main model estimate of vaccine efficacy and its
827 waning (plain black line), and the lighter grey area to the 95% CrI. The blue, red and green
828 dotted lines show the waning with an exponential decay function for a mean duration of
829 protection of 6 years, 3 years and 20 years respectively. Figure adapted from le Polain de
830 Waroux et al. [17], with permission from PIDJ
831

832 In the absence of estimates on the duration of protection of partial vaccination, we assumed
833 that the duration of protection of a partial vaccination was 0.78 (0.64 – 0.92) that of a full
834 vaccination, as for VE_C.
835

836 **Vaccine efficacy against Invasive Pneumococcal Disease**
837

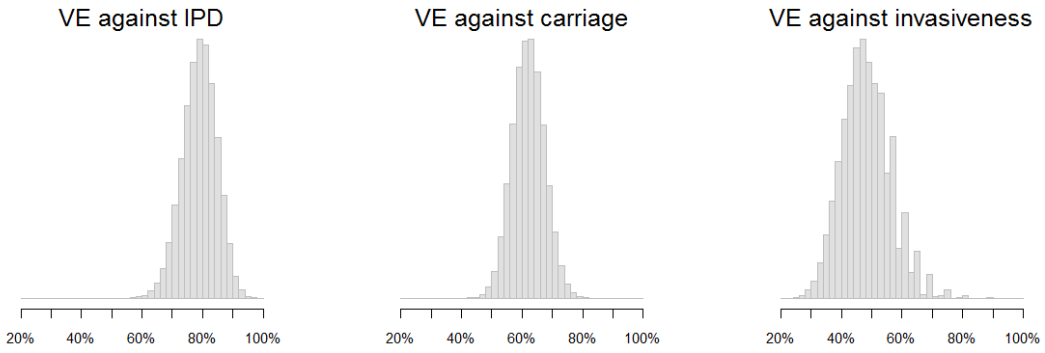
838 The vaccine efficacy against invasive pneumococcal disease (VE_{IPD}) can be expressed as a
839 function of the vaccine efficacy against carriage acquisition (VE_C) and the efficacy against
840 progression to disease as a result of carriage, which we here term the vaccine efficacy
841 against invasiveness (VE_{inv}) [25], where $VE_{IPD} = 1 - (1-VE_C)(1-VE_{inv})$.
842

843 Based on estimates from a large systematic review by Lucero et al. [26], we assumed VE_{IPD}
844 to be 80% (95%CI 58 – 90%) and generated a binomial distribution that closely matched
845 those estimates . Hence, we calculated VE_{inv} based on the distribution of VE_{IPD} and that of
846 VE_C, and obtained a value of VE_{inv} at each iteration in our MCMC process.
847

848 The mean VE_{INV} was 80% (95%CrI 67 – 90%), the mean VE_C was 62% (95%CrI 52 – 73%) and
849 mean VE_{inv} was 48% (95%CrI 34 – 65%). The distributions are shown in Figure S4 below.
850

851

852 **Figure S4**: Estimates of vaccine efficacy



853

854 **Legend:** density plot of the vaccine efficacy against IPD (left panel), carriage (medium panel)
855 and invasiveness (right panel). The x axis displays the vaccine efficacy.
856
857

858 In the model, was assumed no waning of VE_{inv}, and that VE_{inv} would be conferred after 2
859 primary doses, or any catch-up dose. Although there is evidence that VE_C after partial
860 vaccination differs from that after complete vaccination (see earlier), evidence that the
861 efficacy against progression to invasiveness differs between two and three primary doses is
862 scarce.

863

864 Although it is likely that VE_{inv} wanes over time, we did not consider waning in the main
865 model, given that most of the direct impact of PCV on IPD occurs in the first few years of
866 life, before establishment of the herd immunity effect (see results), and given the lack of
867 estimates of waning of VE_{INV}.

868

869

870

871

872

873 **Supplementary File S3: Sensitivity analysis (coverage and duration of vaccine protection)**

874

875 **Vaccination coverage**

876

877 We explored model outputs with lower vaccination coverage in both cohort and catch-up
878 immunization. Our model predicted a lengthening of the time to near-elimination of VT
879 serotypes (and hence, the time reach the new post-PCV disease equilibrium) as vaccination
880 coverage lowers but a similar differential impact of catch-up campaigns compared to
881 routine vaccination.

882

883 Figure S4 compares predictions of trends in VT carriage for all four strategies and
884 vaccination coverage levels of 90%, 70% and 50%.

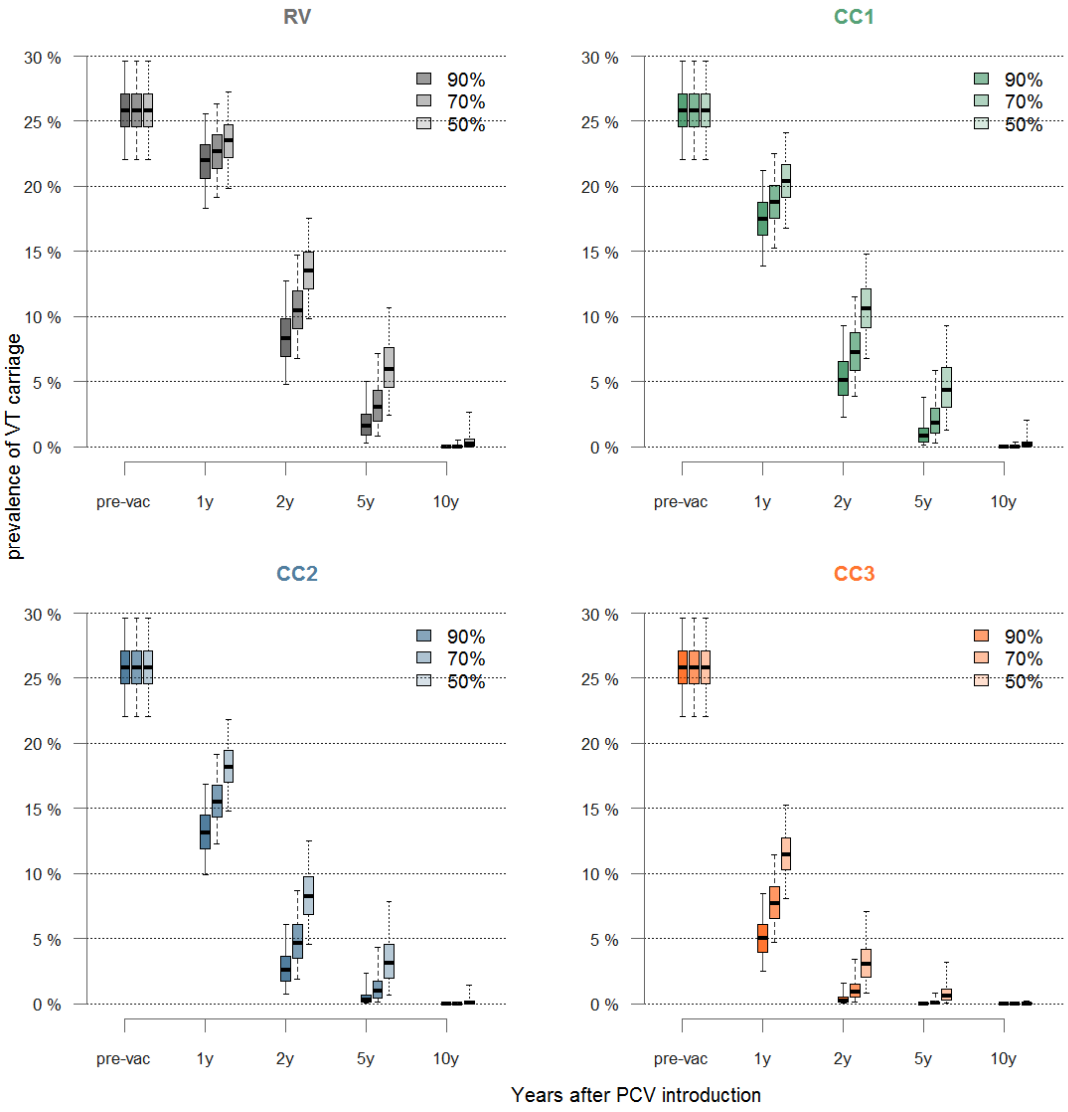
885

886 **Duration of protection**

887

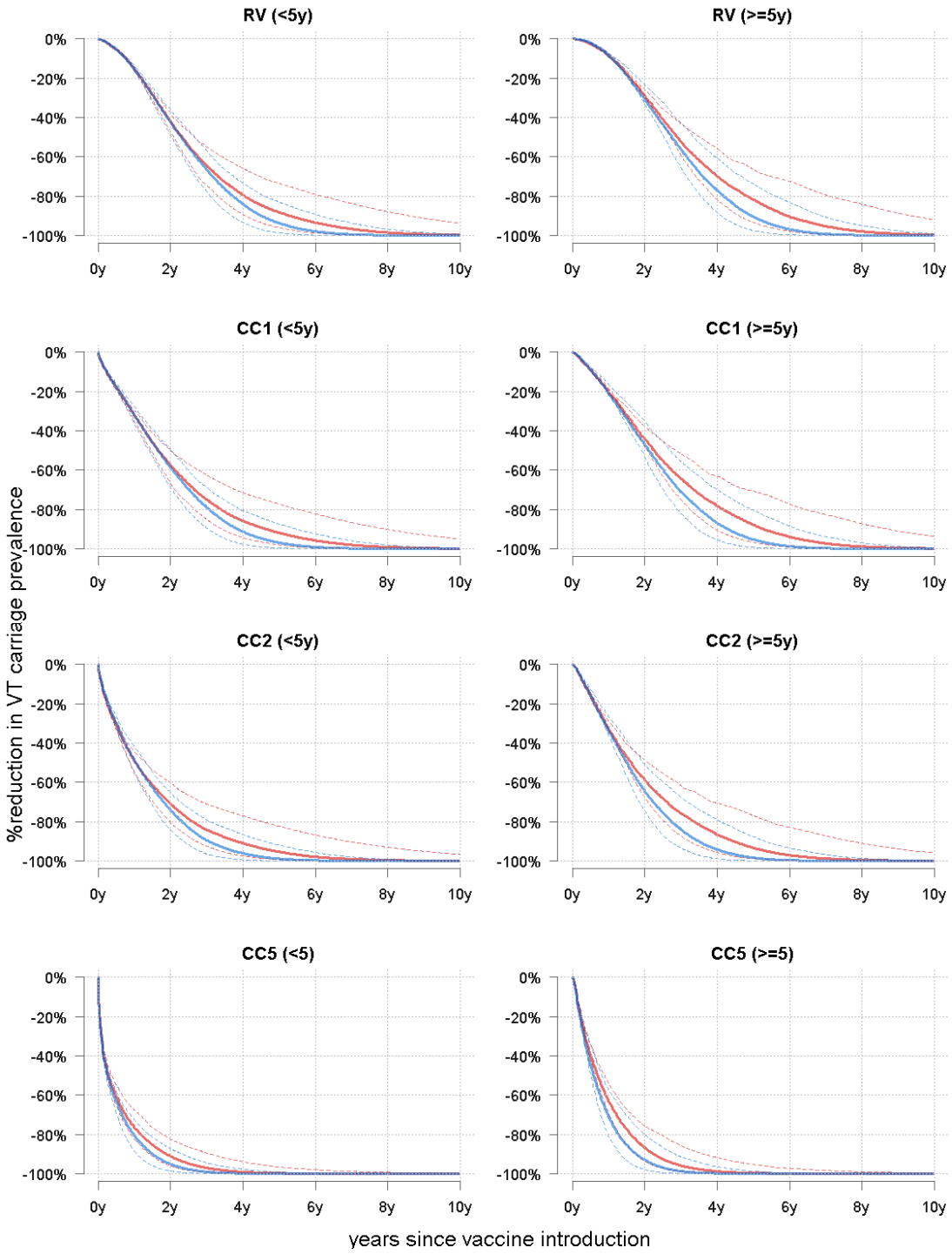
888 A duration of protection of 3 years would increase the time to elimination of VT carriage,
889 and thus prevent fewer IPD cases overall, while any average duration of protection longer
890 than 6 years would not change model outcomes. With a duration of 3 years the median
891 prevalence of VT in <5 year olds is predicted to reach near elimination about 2 years later in
892 RV and CC1, 1.5 years later with CC2 and about 1 year later with CC5. Similar differences
893 were predicted for the ≥5 year olds (Figure S5). The relative impact of one vaccination
894 strategy over another was predicted to be similar than with a duration of 6 years.

Figure S4: Impact of vaccination coverage on VT carriage for each strategy considered, and comparing 90%, 70% and 50% homogeneous coverage for each of the four strategies, in children aged 0 – 59 months

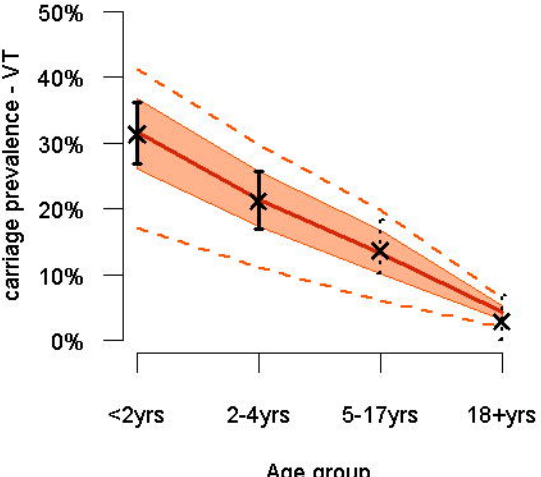


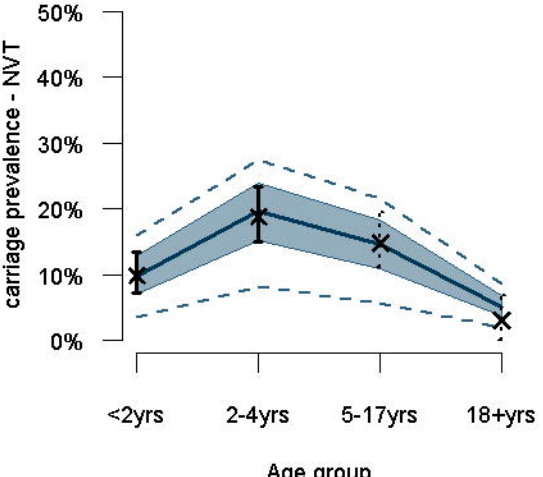
Legend: In all four panels: plain horizontal line= median, boxes= 50% credible intervals and whiskers= 95% credible interval, for each of the three levels of vaccination coverage (90%, 70%, 50%) and for all four vaccination strategies.

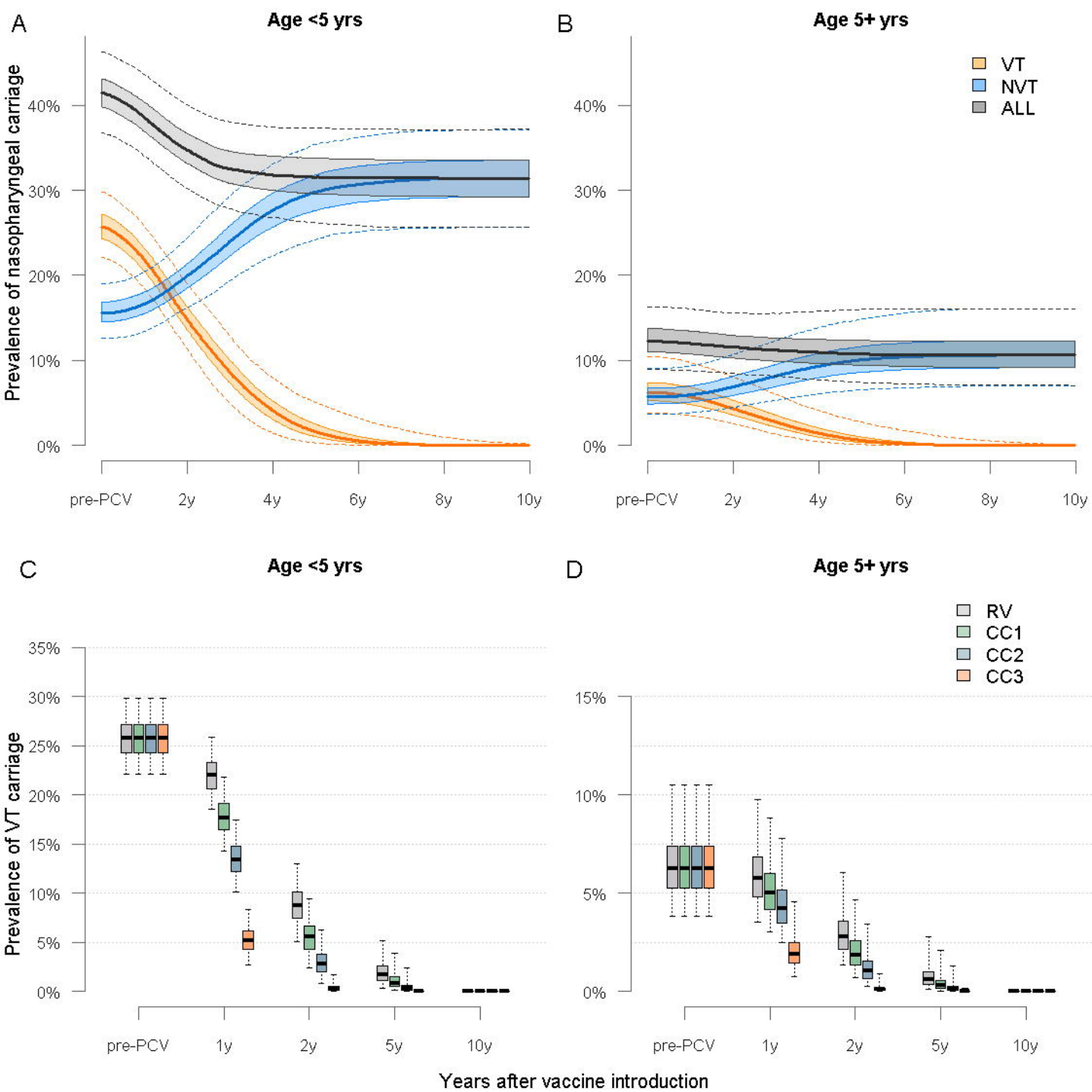
Figure S5: Comparing model estimates with an average duration of protection of 6 years (blue) and of 3 years (red) for each of the vaccination scenarios considered and by age group

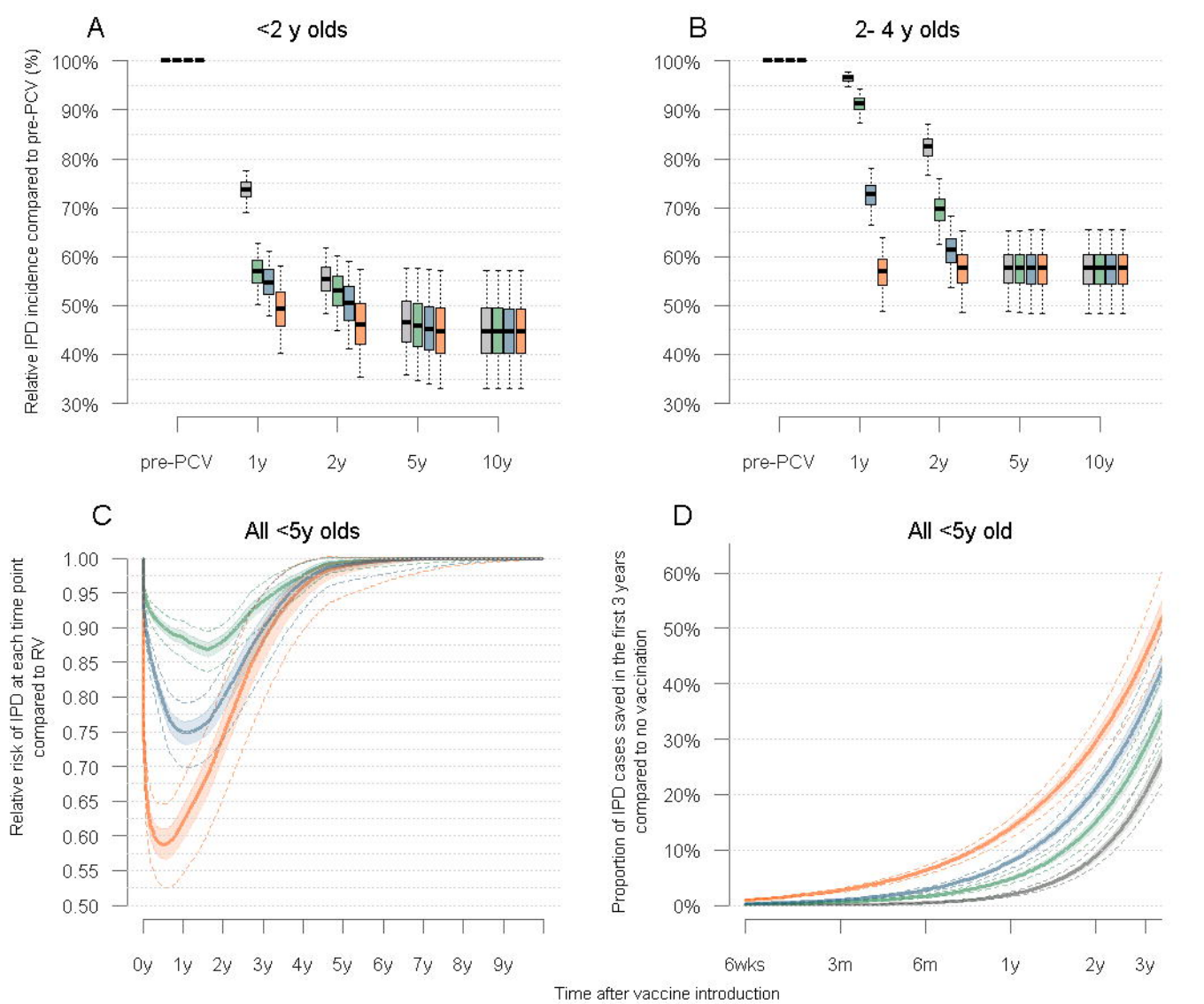


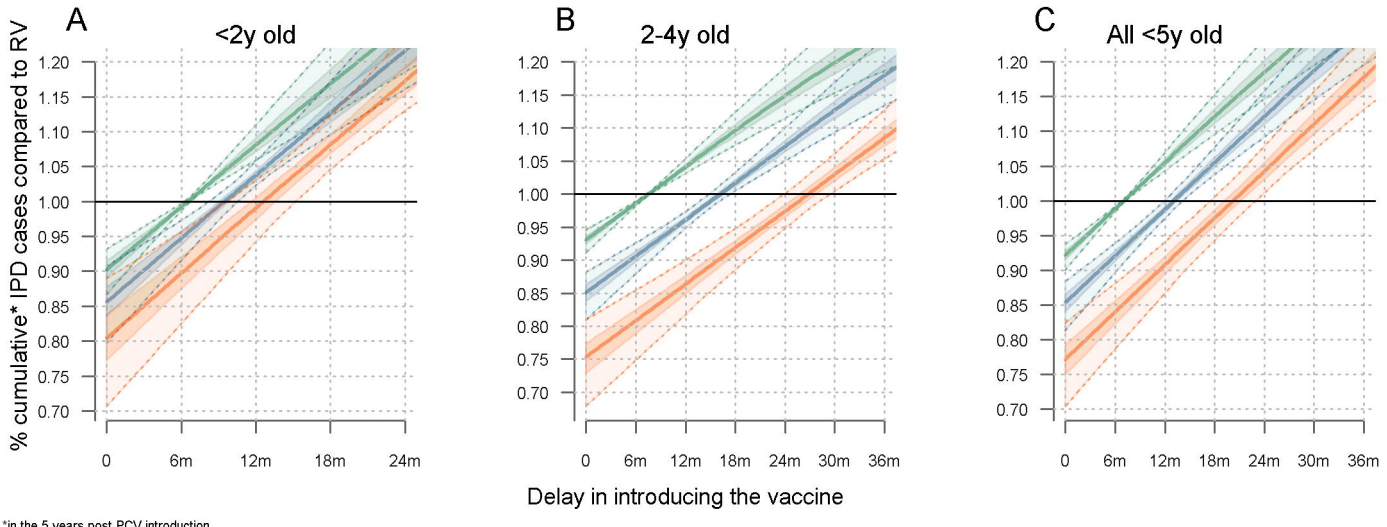
Legend: Percentage reduction in VT carriage in children <5 years (left) and ≥ 5 years old. In blue is are estimates of the main model (average duration of protection of 6 years) and in red are estimates considering a mean duration of protection of 3 years. The plain lines represent the median and the dotted lines the 95% credible interval


50%
40%
30%
20%
10%
0%
carriage prevalence - VT
<2yrs
2-4yrs
5-17yrs
18+yrs
Age group


50%
40%
30%
20%
10%
0%
carriage prevalence - NVT
<2yrs
2-4yrs
5-17yrs
18+yrs
Age group


A
Age <5 yrs
B
Age 5+ yrs
VT
NVT
ALL
Prevalence of nasopharyngeal carriage
40%
30%
20%
10%
0%
pre-PCV
2y
4y
6y
8y
10y
C
Age <5 yrs
D
Age 5+ yrs
RV
CC1
CC2
CC3
Prevalence of VT carriage
35%
30%
25%
20%
15%
10%
5%
0%
pre-PCV
1y
2y
5y
10y
Years after vaccine introduction


A
<2 y olds
Relative IPD incidence compared to pre-PCV (%)
100%
90%
80%
70%
60%
50%
40%
30%
pre-PCV
1y
2y
5y
10y
B
2- 4 y olds
100%
90%
80%
70%
60%
50%
40%
30%
pre-PCV
1y
2y
5y
10y
C
All <5y olds
Relative risk of IPD at each time point compared to RV
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0y
1y
2y
3y
4y
5y
6y
7y
8y
9y
D
All <5y old
Proportion of IPD cases saved in the first 3 years compared to no vaccination
60%
50%
40%
30%
20%
10%
0%
6wks
3m
6m
1y
2y
3y
Time after vaccine introduction



*in the 5 years post PCV introduction