Predicting the impact of pneumococcal conjugate vaccine programme options in Vietnam

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Title

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Abstract

Although catch-up campaigns (CCs) at the introduction of pneumococcal conjugate vaccines (PCVs) may accelerate their impact, supply constraints may limit their benefit if the need for additional PCV doses results in introduction delay. We studied the impact of PCV13 introduction with and without CC in Nha Trang, Vietnam – a country that has not yet introduced PCV – through a dynamic transmission model. We modelled the impact on carriage and invasive pneumococcal disease (IPD) of routine vaccination (RV) only and that of RV with CCs targeting <1y olds (CC1), <2y olds (CC2) and <5y olds (CC5). The model was fitted to nasopharyngeal carriage data, and post-PCV predictions were based on best estimates of parameters governing post-PCV dynamics. With RV only, elimination in carriage of vaccine-type (VT) serotypes is predicted to occur across all age groups within 10 years after introduction, with near-complete replacement by non-VT. Most of the benefit of CCs is predicted to occur within the first 3 years with the highest impact at one 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 as such campaigns do not delay introduction by more than about 6, 12 and 18 months for CC1, CC2 and CC5. Those findings are important to help guide vaccine introduction in countries that have not yet introduced PCV, particularly in Asia.

Keywords: Asia; Viet Nam; Pneumococcus; vaccine; Campaign; Catch-up

Introduction

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 immunization programmes of most low and lower-middle income countries with the support from Gavi, the Vaccine Alliance. In 2017, 58 out of 73 countries eligible for Gavi support have introduced the vaccine, and seven 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 introduce PCV for routine use, followed by Nepal, Cambodia and Lao PDR [6]. However, PCV has not yet been introduced into the routine childhood immunisation programme in most of Asia, including Vietnam.

The WHO recommends introducing PCV into childhood immunisation programmes. It states that a catch-up campaign (CC) among older children can be used to accelerate PCV impact [7]. The aim of such campaign is 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 enhanced herd protection [8]. The WHO recommendation was recently reviewed and is due to be updated but remains unable to guide on the country specific expected impact and efficiency of alternative catch-up strategies [9, 10]. Moreover, CCs have so far not been conducted in most Gavi-supported countries over concerns that they would lead to vaccine introduction delays given limited vaccine supplies [6]. For routine vaccination, 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].

In this manuscript we explored 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 we explored the possible impact of vaccine introduction delay. More specifically, we explored four different strategies: (i) routine vaccination only (RV), with two infant doses and a booster dose at 12 months of age ('2+1'), and routine vaccination with a catch-up campaign in (ii) <1y olds (CC1), (iii) <2y olds (CC2), and (iv) <5y olds (CC5). A 2+1 routine programme was considered here, given the relatively low prevalence of carriage in young children in Nha Trang [11].

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 3% (95%CrI 0 – 7%) respectively, and that of NVT to be 15% (95%CrI 11 – 19%) and 3% (95%CrI 0 – 7%). The model fit to the carriage data is shown in Figure 1.

Nasopharyngeal carriage

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Our model predicts elimination of VT serotypes across all age groups within 10 years of PCV introduction in RV, with near-complete replacement by NVT serotypes, resulting in little or no change in the overall carriage prevalence (Figure 2 A&B), particularly in children aged >5 years and in adults. CCs are predicted to reduce VT carriage more quickly through combined direct and indirect (i.e. herd) effects (Figures 2 C&D).

In children under five years the VT carriage in children is predicted to decrease by >99% within 6 years and 7 months (95% CI 5y2m - 9 y6m) in RV, 5 years and 11 months (4y6m– 8 y10m) in CC1, 5 years and 1 month (3y9m – 7y10m) in CC2 and 3 yrs (2y2m–4y10m) in CC5. Similar trends are predicted in older children and adults (Figures 3C and 3D). And in all scenarios NVT would increase proportionally to the decrease in VT.

Invasive Pneumococcal Disease (IPD)

Our model predicts that the decline of IPD incidence will be proportionally highest among <2 year olds, falling to about 45% (95%CrI 33% - 57%) of its pre-PCV level and would be almost halved (57% (48 – 66%)) in children aged 2 – 4 years respectively (Figure 2A and 2B).

Most of the benefit of catch-up campaigns over routine vaccination in children <5 years is predicted to occur within the first three years after PCV introduction, with no noticeable difference at 5 years (Figure 2C). 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 then steadily 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 2C).

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 3.

Based on an average annual incidence risk of 49 cases per 100,000 children <5 years before PCV introduction [11], 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, considering all IPD (both VT and NVT), and catch-up campaigns would lead to the prevention of an

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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 CC5.

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. Vaccination delays would negatively impact under 2 year olds more rapidly than 2 – 4 year old (Figure 4).

Sensitivity analyses

Vaccination coverage

We explored model outputs with lower vaccination coverage in both cohort and catch-up immunization. Our model predicts a lengthening of the time to near-elimination of VT serotypes (and hence, the time reach the new post-PCV disease equilibrium) as vaccination coverage lowers but a similar differential impact of catch-up campaigns compared to routine vaccination. Full details are provided in the Supporting Information Part Three.

Duration of protection

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

Discussion

We explored the possible impact of introducing PCV13 with and without a catch-up campaign in Vietnam through a dynamic transmission model. Our results feed into current debates about introduction strategies, particularly in South-East Asia where pneumococcal disease burden is high [12], where many countries have not yet introduced PCV [6], and where epidemiological data to guide decision making remain scarce [12, 13]. Although Vietnam is Gavi-eligible and is expected to introduce PCV in the coming years, it has not yet been approved for introduction [6]. Our results provide estimates about how much catch-up campaigns would decrease disease burden compared

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to routine vaccine introduction without a campaign, for different scenarios. Our study also shows that, although catch-up campaigns would decrease disease burden more rapidly across age groups, their impact would only be beneficial insofar as the additional supply and operational constraints of their implementation does not delay PCV introduction by more than about 6 months to 2 years, depending on the age cohorts targeted by those campaigns.

The availability of data on both social mixing patterns – which are central to transmission models [14-16] – and carriage in the same population, allowed for thorough parameterisation of a transmission model.

Nevertheless, our study has a number of limitations. In the absence of post-PCV data, predictions were based on the best available estimates of parameters governing vaccine effects that were observed elsewhere [17-19], which may not fully capture the local characteristics. Given that serotypes differ in their pathogenicity, fitness and transmissibility [20, 21], and that vaccine efficacy and duration of protection differs by serotype [22], our predictions based on homogeneous characteristics for the group of VT and NVT serotypes may overlook local epidemiological characteristics. This uncertainty was nonetheless captured to some extent by sampling from the known uncertainty around those parameters [19]. Moreover, we were not able to assess the impact of PCV on pneumococcal pneumonia, the burden of which is much higher than that of IPD [23], given the lack of robust data and the challenges in the aetiological assessment of clinical pneumonia. Results from several large pneumonia aetiological studies [24] might help modelling work on the impact of PCV on pneumonia in the future.

Our predictions are in line with the experience of PCV7 in Europe and North America [25-32], as well with post-PCV trends observed in the few studies from resource-poor settings [33, 34].

The implementation of PCV in various settings has consistently shown little or no change in overall carriage prevalence, due to replacement effects by NVT serotypes colonising the space left vacant by VT in the nasopharynx, but a reduction in severe disease given the lower pathogenicity of the latter, in accordance with our model output. Our predictions were also robust to estimates of duration of protection of vaccination coverage, and thus provide useful estimates of the impact of introducing PCV in a semi-urban Southeast Asian setting.

The generalisability to other settings of the differential impact of CCs needs to be considered in light of the epidemiological and socio-demographic characteristics of Nha Trang. In particular, the low prevalence of carriage and an ageing population - with only 5% of children under the age of five years – likely contribute to the rapid predicted reduction of disease due to PCV under all scenarios. Although similar epidemiological and demographic characteristics are observed in many other South(east) Asian settings [35, 36], the differential impact of CCs and the establishment of herd

effects in settings with a younger population and a higher carriage prevalence is likely to differ, and should be addressed with models applied to such settings.

Results from our study are important to inform current debates around PCV introduction strategies in GAVI-eligible countries. Where the number of vaccine doses available is limited, and ignoring any other supply side, staffing and outreach challenges that could potentially delay the implementation of CCs, our study can inform whether delaying the introduction of the vaccine to allow for CCs would potentially be beneficial, compared to a routine-only strategy. Moreover, this model also provides a framework that could feed into economic evaluations to further guide decisions about vaccine introduction with and without campaigns, and evaluate strategies in the short and medium term.

In conclusion, our study offers insights into the current debate about PCV introduction strategies when particularly for South-East Asia. Our model suggests that catch-up campaigns have the potential to rapidly establish control of vaccine serotypes, potentially also aiding accelerated implementation of cost saving reduced dose schedules [37], but are only offering added reduction in disease burden insofar their implementation results in little to no implementation delay.

Materials and 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 among children aged 0 – 59 months randomly drawn from the population census, with 350 children included in January 2008 [38] and another 350 children in July 2008 [39].

Samples were processed and cultured as per WHO recommendations [40]. Serotyping was done using polymerase chain reaction with 29 specific primer pairs, and did not differentiate between 6A and 6B serotypes [38]. Given that both antigens are included in PCV13 but that PCV10 does not include 6A, we decided to implement our model for PCV13.

The carriage prevalence (and its uncertainty) of VT and NVT among 5-17 year olds and adults (≥18 years) was estimated based on the prevalence and serotype distribution in children <5 years of age, using a random effect meta-regression model [22].

Social mixing patterns

We derived the age-specific contact patterns from a survey conducted in the same area in 2010.

Study participants were interviewed about their contact on a given day, similarly to previous studies [41]. Participants were first asked to fill in some background information, and were then asked to remember their social encounter occurring in the following 24 hours, before being interviewed about those shortly after. As for other social contact studies, the questionnaire recorded information on the location and type of contacts, including whether or not contacts included physical (i.e. skin-to-skin touch).

In the study, household were randomly selected from all non-touristic urban and semi-rural areas of Nha Trang (i.e. matching the areas where the nasopharyngeal carriage was undertaken)., and one person per household was included in the study. The sample size was based on POLYMOD calculations [41]), but was higher to account for urban/rural differences.

The corresponding mixing matrix used in the model was derived as in Melegaro et al. [42]. We parameterised our model based on physical (skin-to-skin) contacts only, given that *S.pneumoniae* is generally assumed to be transmitted through close interpersonal contact [43].

A total of 2002 individuals were included in the study. The mean number of physical contacts per age group is shown in Figure 5. The manuscript is currently being written up for publication, and further results can be obtained on request.

Model structure

We built an age-structured deterministic Susceptible-Infected-Susceptible transmission model of carriage acquisition and clearance, in which we modelled VT jointly and separately from NVT, but allowed for co-colonisation, as in previous models [19]. Details about the model structure and model equations can be found in the Supporting Information (Part 1).

The model comprised of three levels of vaccine-induced immunity; (1) no protection, (2) partial protection and (3) full protection. The latter refers to the efficacy and duration of protection conferred after completion of the infant schedule (i.e. 2 infant doses and a 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 relied 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.

<u>Model fitting</u>

We fitted the model to pre-vaccination nasopharyngeal carriage 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 unique posterior sample we simulated up to 15 years after vaccine introduction.

The model was fitted the model to pre-vaccination nasopharyngeal carriage data using an MCMC algorithm. Estimates of the age-specific probability of effective transmission, which were obtained from the contact and carriage data were updated in the MCMC. Fitting was performed using a Poisson log likelihood, as follows:

$$\log L = \sum_{a=1,,n}^{n} (log(vt_a) \times VT_a - vt_a) + \sum_{a=1,,n}^{n} (\log(nvt_a) \times NVT_a - nvt_a) + constant$$

, where vt_a is the modelled number of VT carriers in age group a, VT_a is the observed number of VT carriers in age group a, nvt_a is the modelled number of NVT carriers in age group a, NVT_a is the observed number of NVT in age group a. The constant here is independent of the modelled number of cases.

The MCMC was run with 100,000 iterations of the chain and for each accepted set of parameters the post-vaccination simulation up to 15 years after vaccine introduction was computed, after a burn-in of 20,000 iterations.

Convergence of the log likelihood was first assessed visually and then with the Geweke test of convergence [49].

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 the PCR assay to detect VT than NVT colonies in case of multiple colonization [38].

Model parameters and input

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

We obtained the vaccine efficacy against carriage conferring full protection (VE_C^F) and its uncertainty from a meta-regression model [17]. We estimated the partial efficacy against carriage (VE_C^P) as 0.78 (95% CI 0.64 – 0.92) that of VE_C^F through a meta-analysis of the relative risk of VT carriage in 2+0 schedules compared to 3+0 or 2+1 schedules, which included four trials and eight entry points [44-47]. Further details are provided in the Supporting Information Part Two.

We assumed an exponential decay function for the waning of vaccine efficacy, as in previous models [19, 48]. We fixed the average duration of protection to 6 years, which best matched the output of an asymptomatic meta-regression model of waning efficacy [17], and analysed the impact of shorter (3 years) and longer (20 years) average protection in sensitivity analyses, based on the 95% credible intervals (CrI) of a model of waning efficacy [17]

The average duration of protection following particular vaccination was assumed to be 0.78 (95%CI 0.64 – 0.92) that of a complete schedule, as for vaccine efficacy. Details are provided in the Supporting Information (Part Two).

In our base case model we set the vaccination coverage of both routine and catch-up strategies at 90%, in accordance with coverage data from Vietnam for routine immunization programmes and supplementary immunization activities [49].

Sensitivity analyses

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We ran the model for coverage levels of 50% and 70% in both routine and catch-up programmes, and compared the results with that of the main model (coverage 90%). 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 (Supporting Information Part Three).

Ethics

Ethical approval for both the contact and nasopharyngeal 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.

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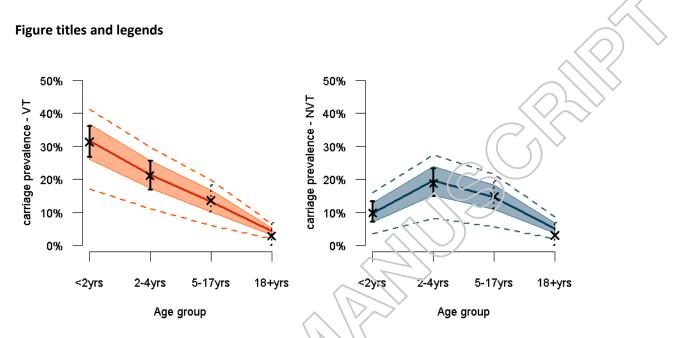**Figure titles and legends**

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
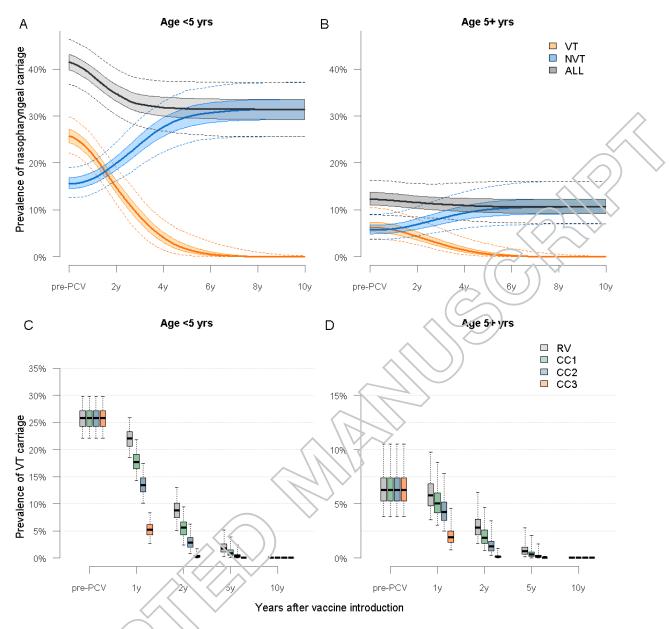
Figure 2: Predicted trends in nasopharyngeal carriage following PCV13 introduction in Nha Trang.

Legend: 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 in RV. C: Predicted prevalence of VT carriage in <5 year olds for each vaccination strategy. D: Predicted prevalence of VT carriage in ≥5 year olds. In all four panels: plain line= median, shaded areas= 50% CrI and dotted line or whiskers= 95% CrI
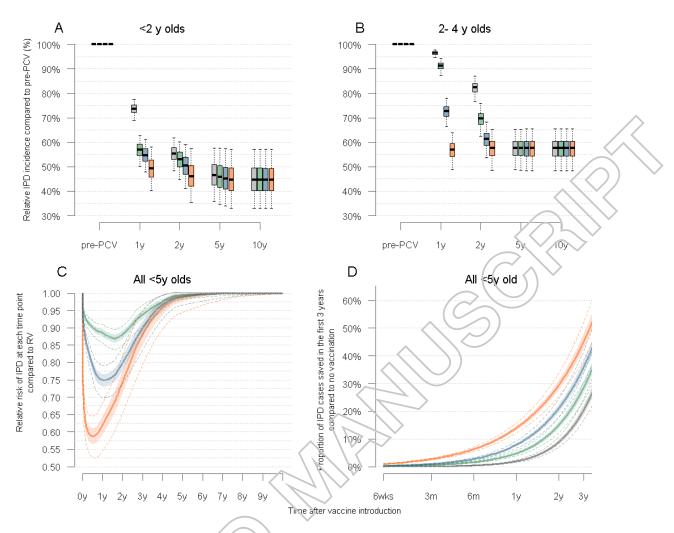
Figure 3: Trends in IPD following PCV introduction in children under five years of age in Nha Trang

Legend: A: Predicted trends the cumulative annual incidence of IPD in children <2 years for each vaccination strategy considered, at a 90% vaccination coverage B: Predicted trends the cumulative annual incidence of IPD in children aged 2-4 years for each vaccination strategy considered, at a 90% vaccination coverage C: Cumulative number of IPD cases saved for each catch up strategy compared to RV, in children <5 years of age. D: Overall cumulative number of cases saved for each vaccination strategy, compared to no vaccination, in the first 3 years post PCV introduction. In all four panels: plain line= median, shaded areas= 50% credible intervals and dotted line or whiskers= 95% credible interval
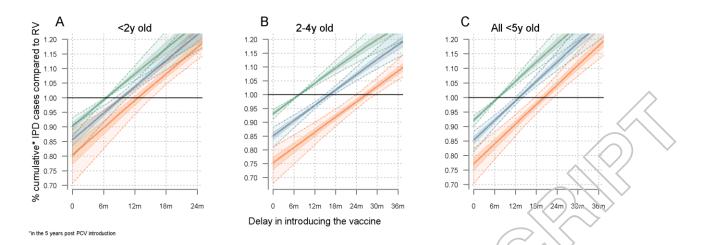
Figure 4: Impact of delayed PCV introduction with a catch-up campaign on VT carriage (panel A) and on IPD cases saved (panel B) in children under five years of age.

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
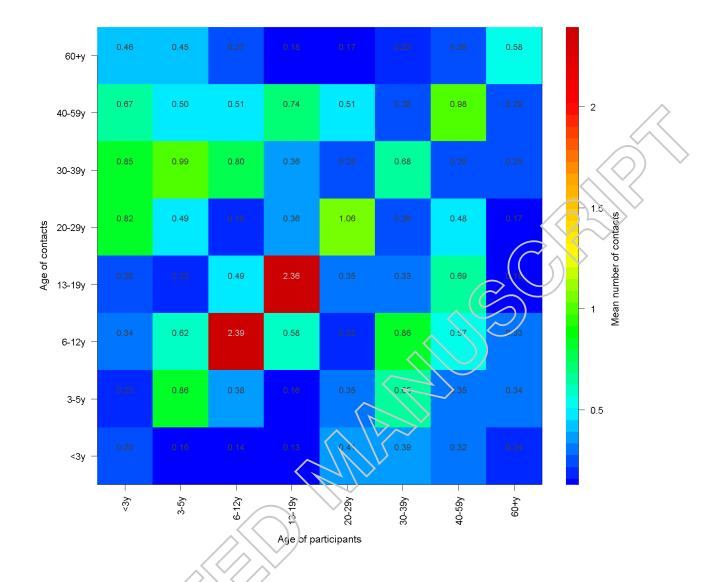
Figure 5: Mean number for physical contacts between age groups of study participants

Table 1: Parameters used in the model

Parameter	Value	Source*
Competition for carriage acquisition (C_N and C_V)$^\$$	0.1 (SD 0.01)	[18, 19]
Duration of carriage (δ_i)		
0 – 11 months	47.1 days	[49]
12 – 23 months	39.4 days	[49]
24 – 35 months	31.6 days	[49]
36 – 47 months	21.5 days	[49]
48 – 59 months	21.3 days	[49]
5 – 17 years	17.0 days	[48, 50]
18 years and over	18.0 days	[48, 50]
Vaccine efficacy against carriage		
Full protection (VE_{Cf})	63% (95%CrI 53 –73 %)	[17]
Partial protection (VE_{Cp})	0.78 (95%CI 0.64 – 0.92) * VE_{Cf}	Meta-analysis of [44-47] (Supporting Information Part Two)
Mean duration of protection against carriage		
In fully protected (D_F)	6.0 years	[17](Supporting Information Part Two)
In partially protected (D_P)	0.78 (95%CI 0.64 – 0.92) * D_F	Based on same assumptions as for Vaccine efficacy
Vaccine efficacy against IPD (VE_{IPD})	0.80 (0.61 – 0.90)	[51]
Vaccine efficacy against invasiveness (VE_{INV})	0.48 (0.34 – 0.65)	Derived from estimates of [51] and [17] (Supporting Information Part Two)
Mixing matrix	Social contact study (Nha trang)	Calculated as in Melegaro et al [42]

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