# Determinants of high residual post-PCV13 pneumococcal vaccine type carriage in Blantyre, Malawi: a modelling study.

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**Abbreviations:**

VT - vaccine type
NVT - non-vaccine type
PCV - pneumococcal conjugate vaccine
CI - confidence interval
bMCMC - Bayesian Markov-chain Monte Carlo
ODE - ordinary-differential equations
FOI - force of infection
dVP - duration of vaccine-induced protection

# Abstract

**Background:** In November 2011, Malawi introduced 13-valent pneumococcal conjugate vaccine (PCV13) into the routine infant schedule. Four to six years after introduction, rolling prospective nasopharyngeal carriage surveys were performed in the city of Blantyre. Carriage of *Streptococcus pneumoniae* vaccine serotypes (VT) remained higher than reported in developed countries, and VT impact was surprisingly asymmetric across age-groups with older individuals experiencing higher carriage reduction (35% for unvaccinated 8-9 years old, versus 26% for vaccinated 3-5 years old).

**Methods:** Bayesian Markov-chain Monte Carlo was used to fit a transmission model to age-specific VT carriage data. Simulations were used to reconstruct past and project future carriage dynamics, as well as to explore determinants of PCV13 impact across ages.

**Results:** Accumulation of naturally acquired immunity in age and age-specific transmission potentials with dominance of individuals younger than 5 years of age were key to reproduce observed post-PCV13 VT carriage. Age-groups experienced periods of faster VT carriage reduction sequentially in time, from younger to older groups. Individual-level protection against carriage (vaccine efficacy) was estimated as 68.8% (95% CI 41.6-88.1%). Population-level reduction in VT carriage (vaccine impact) over the first 10 years and among children aged 0-9 years was estimated at 70% (CI 95% 41-82%), much lower than observed elsewhere.

**Conclusions:** In Blantyre, estimated vaccine efficacy has been similar to other regions, but vaccine impact is being offset by a high, age-heterogeneous local force of infection. Such age-dependent profiles strongly determine regional PCV impact and need to be better characterised if we are to maximize intervention impact in high transmission settings.


# Introduction

*Streptococcus pneumoniae* (pneumococcus) is a bacterial human pathogen commonly carried asymptomatically in the nasopharynx, which in a minority of carriers can cause serious disease such as pneumonia, meningitis or bacteremia[1], posing a serious mortality risk, especially for young children (<5 years of age), the elderly (>65 years of age) and the immunocompromised[2]. Pneumococcal carriage is a necessary precursor of severe disease[3] and transmission, such that reduction of carriage through active control is an important, universal public health goal.

Currently, pneumococcal conjugate vaccines (PCV) are the best available tool to reduce carriage and disease both within risk groups and the general population. These vaccines have consisted of either 7, 10 or 13 polysaccharides conjugated to a carrier protein (PCV7, PCV10, PCV13, respectively). All have been demonstrated to be highly protective against 7, 10 or 13 of the most common pneumococcal serotypes associated with carriage and disease (also termed vaccine serotypes, VT). A common consequence of PCV introduction is the increase in both carriage and disease of non-VT pneumococci (NVT), likely due to increased niche availability and reduction of competition between VT and NVT[4–9].

PCV routine vaccination has been a common control strategy for over a decade in developed countries, with past experience showing that both pre- and post-PCV pneumococcal carriage can be highly variable within and between countries [10–16]. PCV vaccines have only recently been introduced in Sub-Saharan African countries, of which Kenya[17,18], Malawi[19], The Gambia[20] and South Africa[21] are examples. In November 2011, Malawi introduced the 13-valent pneumococcal conjugate vaccine (PCV13) as part of the national extended program of immunization with a 3+0 schedule (at 6, 10 and 14 weeks of age). With high routine coverage (>90%) and a small catch-up campaign of young children, PCV13 was expected to quickly reduce carriage as previously reported in developed countries. However, recently published data on nasopharyngeal carriage as measured in a cross-sectional observational study in Blantyre (Southern Malawi), four to six years after PCV13 introduction, shows that impact has been slower than expected and heterogeneous across age-groups[22]. Epidemiological mathematical models been employed successfully to improve our understanding of pneumococcal dynamics[5,9,23–27], as well as having contributed to explain, estimate and project PCV impact[8,11,28]. The main advantage of models is their cost-free potential to test hypotheses and gain a mechanistic, ecological and immunological understanding of carriage and disease dynamics, estimating epidemiological parameters which are difficult to otherwise quantify from raw epidemiological data. For example, such models have yielded estimates of VT and non-VT pneumococci transmission potentials[26,29–31], pneumococcal competition factors[8,9,23,28,32,33] and measures of PCV-induced protection from carriage at the individual level[11,17,28,34,35], none of which are readily observed or quantified in cross-sectional observational studies.

In this study we use a Bayesian Markov-chain Monte Carlo fitting approach and a mathematical model to investigate the post-PCV13 introduction pneumococcal VT carriage dynamics in Blantyre. We find that natural immunity and age-specific transmission potentials are necessary to reproduce observed VT carriage. When compared to numerous literature reports from other regions, our estimated vaccine efficacy (individual-level protection from carriage) was close to expected, but impact (population-level reduction of VT carriage) was lower both in the short- and long-term. We show that hampered impact was likely due to a high local force of infection compared to other regions of the world. Our study offers key insights into the lower than expected PCV13 impact in Blantyre, and more generally on the heterogeneous nature of pre- and post-vaccination pneumoccocal VT carriage across age-groups and regions.

# Methods

## Prospective cross-sectional observational study

An observational study using stratified random sampling was conducted to measure pneumococcal nasopharyngeal carriage in Blantyre, Malawi[22]. Sampling was performed twice a year for a total of 22.1 months, between June and August 2015 (survey 1), October 2015 and April 2016 (survey 2), May and October 2016 (survey 3), and finally November 2016 and April 2017 (survey 4). In this study, we use the mid-point dates of the surveys for model fitting and presentation of results. Nasopharyngeal swabs were collected from healthy, vaccinated 3-5 year old and unvaccinated 6-9 year old children, and processed following WHO recommendations[36]. Isolates were serotyped by latex agglutination (ImmuLex™ 7-10-13-valent Pneumotest; Statens Serum Institute, Denmark).

Observed VT carriage levels are presented in Figure 1d. Further details on collection, processing and observations, have been previously reported[22].

## Vaccine type transmission model

A deterministic, ordinary-differential equations (ODE) model (Figure 1a) was developed to fit VT carriage levels as reported in the cross-sectional observational study in Blantyre (Figure 1d)[22]. Fitting was implemented using a Bayesian Markov chain Monte Carlo (bMCMC) approach developed and used by us in other modelling studies[37–39], including informative priors for duration of carriage (Figure 1b) and uninformative uniform priors for vaccine efficacy (individual-level protection against carriage) and transmission potential. The methodology is summarised in this section and further details such as equations and complementary results can be found in Supplementary Text.

### Infection dynamics and population size

As depicted in Figure 1a, the population was divided into seven non-overlapping age-groups: 0 (<1), 1, 2, 3-5, 6-7, 8-9, 10+ years old. Ageing was approximated by moving individuals along age-groups with a rate ($a_{age\text{-}group}$) equal to the inverse of the time spent at each age class. The seven age-groups were further divided into vaccinated ($S^{v}_{age\text{-}group}$, $C^{v}_{age\text{-}group}$) and unvaccinated ($S_{age\text{-}group}$, $C_{age\text{-}group}$) susceptibles (S) and carriers (C). The population size was assumed to be constant, with total deaths equal to births (details in Supplementary Text). Death rates were age-specific ($\mu_{age\text{-}group}$) and relative to a generalized total life-span of 70 years.

### Natural immunity

Pneumococcal colonization increases both humoral (anti-capsular serotype-specific and anti-protein non-serotype-specific) and T-cell (anti-protein) immunity[40]. Acquisition of this immunity correlates with colonization in children and increases with age as colonization decreases. In our model, all individuals were assumed to be born susceptible but could acquire infection (colonization) at any age with a particular force of infection $\lambda_{age\text{-}group}$, becoming carriers ($C_{age\text{-}group}$) for an age-specific period ($1/\gamma_{age\text{-}group}$), and returning to the susceptible state ($S_{age\text{-}group}$) after clearance. Hence, the development and accumulation of complete (sterile) immunity to the pneumococcus was not considered. We nonetheless allowed for decreasing duration of carriage with age ($1/\gamma_{age\text{-}group}$) as a proxy for the development of immunity with age. To quantify such differences in age, we used carriage duration data as reported by Hogberg and colleagues[41] to define informative priors related to the aggregated age-groups: 0-2 years ($1/\gamma_{0\text{-}2}$), 3-5 years ($1/\gamma_{3\text{-}5}$), 6-8 years ($1/\gamma_{6\text{-}8}$), and 8+ years ($1/\gamma_{8+}$) as represented in Figure 1b.

### Vaccination and vaccine efficacy

For simplicity, routine vaccination was implemented at birth with coverage ($\rho$) at 93%[22], and catch-up ($k$) implemented as a one-off transfer of a proportion of individuals from the unvaccinated susceptibles with 0 (<1) years of age ($S_0$) to the vaccinated susceptible class with the same age ($S^{v}_{0}$)

with coverage of 60%[22]. We assumed the vaccine to reduce the risk of infection (colonization) of vaccinated individuals by a proportion ζ (between 0 and 1, with ζ=1 equating to no risk). This reduction in risk was herein defined and interpreted as the individual-level vaccine efficacy against carriage (VE= 100 x ζ), and was modelled directly on the force of infection (λ)(Figure 1a).

### Vaccine impact

We measured vaccine impact across ages as the post-PCV13 percent reduction in population-level pneumococcal VT carriage compared to pre-vaccination levels.

### Force of Infection

We used an inhomogeneous transmission matrix (Figure 1c) based on epidemiological studies conducted in American, European and African populations reporting strong, intrinsic variation in frequency, efficiency and environmental risk of transmission between age-groups[10,31,42–47]. In summary, we defined an age-specific transmission matrix, generally populated with a baseline coefficient $\beta$, and a different coefficient $\theta$ assigned to transmission occurring within and between ages 0-5 years, and within 6-7 and 8-9 years of age. This formulation followed reports of strong age-assortative patterns and higher contribution of younger individuals to transmission[31,43,47].

### Fitting to survey data

The model's carriage outputs for vaccinated 3-5 (V3-5y), unvaccinated 6-7 (NV 6-7y) and 8-9 (NV8-9y) years of age, were fitted to observed levels in Blantyre between 2015 and 2017, approximately four to six years post-vaccination (Figure 1d). A total of seven parameters were fitted: vaccine efficacy against carriage (ζ, uninformative prior), coefficients of transmission (β, θ, uninformative priors) and durations of carriage in ages 0-2, 3-5, 6-7, 8+ years ($1/\gamma_{0\text{-}2}$, $1/\gamma_{3\text{-}5}$, $1/\gamma_{6\text{-}8}$, $1/\gamma_{8+}$, informative priors, Figure 1b). The transmission model was initialized at time t=0 with a proportion of susceptibles of 0.99 and infected 0.01, with numerical simulations run until an equilibrium was reached. At equilibrium, vaccination was introduced and the first 15 years recorded. Levels of carriage in the model were calculated as the proportion of individuals within an age-group that are carriers (i.e. *C/(S+C)*, see Supplementary Text for expressions). The model was run with parameters scaled per year. MCMC chains were run for 5 million steps, with burn-in of 20%.

# Results

### Observational study and modelling objectives

VT carriage levels as reported in the observational study (Figure 1d), approximately four to six years after the introduction of PCV13 in Blantyre, showed a surprisingly slow mean reduction of 26% for the vaccinated 3-5 age-group (from 23%, CI 95% 17.9-27.1%, to 17%, CI 95% 13.4-

21.2%)[22]. In contrast, the mean observed reduction in VT carriage for the unvaccinated 6-7 age-group was higher, at 31% (from 26%, CI 95% 20-31.9%, to 18%, CI 95% 12.2-22.1%) and for the unvaccinated 8-9 age-group it was even higher at 35% (from 20%, CI 95% 15.8-23.6%, to 13% CI 95% 9.3-17.4%). We hypothesised that the faster reduction in the older age groups was likely to be due in part to indirect protection through a reduction in transmission, as reported in other countries such as the USA and UK[48,49]. We performed a literature review on observed reduction of VT carriage in time after the introduction of PCV13 vaccines (Table S4), and concluded that residual 17% of VT carriage in the vaccinated 3-5 age-group, 6 years after PCV13 introduction, was high when compared to other countries. For instance, residual carriage of PCV13 types was 0.4% after 4 years of vaccination in England[50], 9.1% after 2 years of vaccination in Italy[51], and 7% after 3 years of vaccination in Alaska, USA[16] (more examples in Table S4).

We resorted to our deterministic transmission model and bMCMC approach to fit the observed post-vaccination VT carriage data from Blantyre (2015 – 2017). Based on this fit, we could reconstruct carriage dynamics for the unobserved first four years (2011 – 2015), and project VT carriage reduction into the future, to identify the mechanistic nature of the slow PCV13 impact on the vaccinated age-group and strong herd-effects in the older unvaccinated age-groups.

**Model fit and posteriors**

VT carriage levels across age-groups reported from the surveys were closely reproduced by the mean and 95% CI of the model using the bMCMC approach (Figure 2a). Our initial assumption of natural immunity accumulating with age was generally respected in the bMCMC solution (Figure 2b); i.e. the estimated posterior distributions of the durations of carriage ($1/\gamma_{age\text{-}group}$) were similar to the informed priors for the groups 0-2 and 3-5 years of age, and were adjusted by the bMCMC by approximately +0.6 and -1.8 days for the groups 6-7 and 8+ years of age, respectively. The posterior distribution of vaccine efficacy (individual-level protection against carriage) across ages was estimated to be 68.8% (95% CI 41.6 – 88.1). While we used an uninformative prior (uniform, 0 to 1) in the bMCMC, this posterior was similar to others recently estimated with different models and in multiple epidemiological settings (Figure 2c); and we therefore argue that it serves as partial validation for the robustness of the modelling framework. Finally, the solutions for the transmission coefficients $\beta$ and $\theta$ suggested that in order to reproduce the Blantyre survey data, the risk of infection associated with contacts within and between younger age-groups (0-5 years old) would have to be higher than that of the general population (i.e. $\theta >> \beta$). Literature support for all estimated posteriors is detailed in Supplementary Text.

**Vaccine impact across age-groups**

Using parameter samples from the bMCMC estimated posteriors, we simulated vaccine impact in terms of VT carriage reduction across age-groups in the first 10 years post-vaccination (Figure 3).

After the first year, reduction in VT carriage was estimated to be 38% (23 - 44, CI 95%) for the 0 (<1) years old, followed by 23% (15 - 26, CI 95%) for the 1 years old, 12% (8 - 13, CI 95%) for the 2 years old and 7% (5 - 8, CI 95%) for 3-5 years old (Figure 3a). With time, as carriage generally

dropped and vaccinated individuals aged, the older groups were estimated to benefit from increasingly similar reductions in carriage compared to the initially vaccinated group. Since during the first year only the 0 (<1) years of age were vaccinated, the short-term reductions in carriage of the other groups were due to indirect herd-effects alone.

At the target point of 10 years into the post-vaccination era, impact was estimated to be similar across all age-groups, with VT carriage reduced by 71% (CI 95% 42-81%) for the 0 (<1) years old, 69% (CI 95% 41-80%) for the 1 years old, 68% (CI 95% 42-80%) for the 2 years old and 69% (CI 95% 42-79%) for 3-5 years old. We further projected vaccine impact on aggregated age-groups 0-5 and 6-9 years of age, which showed equivalent reductions in VT carriage (Figure 3b), with the larger aggregated age-group 0-9 years old having a reduction of 70% (CI 95% 41-82) after 10 years.

**Post-vaccination changes in force of infection**

The model had so far been able to reproduce survey data on VT carriage of vaccinated and unvaccinated individuals, with projections further suggesting that impact on older age-groups would be slower to gain momentum but would eventually converge to the observed impact on younger age-groups. To try to understand these non-linear and asynchronous responses to vaccination across age-groups, we explored the post-vaccination dynamics of the force of infection (FOI). The FOI is a useful epidemiological measure as it is the overall rate by which a certain age-group of susceptible individuals is infected, comprising the transmission rate ($\beta$ or $\theta$) weighted by the number of infectious individuals within the same and other age-groups.

Although we modelled six independent age-groups under 10 years of age, only three unique FOIs are defined in the transmission matrix for individuals under 9 years of age (0-5, 6-7 and 8-9 years of age, Figure 1c). As expected by the posteriors of $\beta$ and $\theta$, the absolute FOI of these age-groups was originally different and decreased in time after the introduction of PCV13 (Figure S4). We looked at the FOI derivative in respect to time as a measure of speed of reduction (Figure 4), and found that the time period of fastest FOI reduction for the 0-5 years old was between the years 2012 and 2014 (when no carriage data was collected), while for the older age-groups the period of fastest reduction was predicted to be just before or during the observational study (for 6-7 and 8-9 age-groups, respectively).

This temporal response suggested that although there is now a rather slow reduction of VT carriage in Blantyre for the younger age-groups, this seems to have been preceded by period of high, short-term impact on VT carriage for that age-group (also seen in dynamics of Figure 3b). Similarly, the surprisingly faster reduction in VT carriage observed during the surveys for the older age-groups is predicted by the model to take place specifically during the years of the surveys. Overall, projected FOI dynamics suggest that impact of the vaccine is non-linear in time within age-groups, with predicted periods of faster reductions in VT carriage being witnessed by different ages in a sequential manner, from younger to older individuals.

**Sensitivity of vaccine impact based on transmission setting**

The projected impacts of Figures 3 and 4 were based on the estimated transmission coefficients for Blantyre (Figures 1c and 2d). To contextualize this particular transmission setting, we searched the literature for pre-vaccination VT carriage levels in other countries (Table S5). The reported age-groups were highly variable, and we therefore focused on the 0-5 years old group for which more data points were available from a range of countries in North America, Africa, Europe and South-east Asia (Figure 5a). Reported VT carriage in this age-group was highly variable both between and within countries, with our estimation for Blantyre being on the higher end (62%, 95% CI 37 - 76%).

We further searched the literature for post-vaccination VT carriage levels in other countries and again focused on the age-group 0-5 years old for which more data points were available (Table S4, points with whiskers in Figure 5b). The projected impact for Blantyre according to our model (dashed line), was notably lower than observed for other countries. A Malawi data point reported in the context of the Karonga District (Northern Malawi) had the closest impact to our projections in Blantyre (Southern Malawi), 4 to 5 years after PCV13 introduction[19].

Given that our posterior of vaccine efficacy (individual-level protection against carriage, Figure 2c) was close to estimations from other regions of the world, we hypothesised that both the higher pre- and post-PCV13 VT carriage levels in Blantyre were likely due to a higher local force of infection compared to other regions. To demonstrate this, we simulated a range of alternative transmission settings in Blantyre, by varying both the transmission coefficients ($\beta$ and $\theta$) between -70% and +120% of the estimated posteriors. This sensitivity exercise showed that lowering local transmission by -30% was sufficient for the model to appoximate short- and long-term vaccine impact observed in several other countries (Figure 5b). Other age-groups, for which far less data points were available, presented similar patterns (Figures S2 and S3).

# Discussion

Using a dynamic model, we have reproduced observed changes in pneumococcal VT carriage following the introduction of PCV13 in Blantyre (Malawi). Similarly to other modelling frameworks we have considered the accumulation of natural immunity with age and have also allowed for heterogeneous transmission potentials within and between age-groups. Including these factors allowed us to characterise both vaccine-related and host age-dependent determinants of post-PCV13 pneumococcal VT transmission.

A main motivation for this study was the observation of high residual VT carriage levels six years post-PCV13 introduction[22]. Studies from Kenya, The Gambia and South Africa have reported similar trends, with VT carriage remaining higher than in industrialised countries at similar post-vaccination time points. Compared to studies from other geographical regions (Figures 2c, 5a, 5b, Supplementary Material), pre- and post-vaccination VT carriage in Blantyre was at the upper end of reported values across many countries. Given that our estimate of vaccine efficacy (individual-level protection against carriage) was similar to reports from elsewhere, we tested the hypothesis that the observed and projected lower vaccine impact was likely a result of a higher force of infection in Blantyre compared to other regions. This force of infection was found to be characterised by different transmission potentials within and between age-groups, and particularly dominated by individuals younger than 5 years. Reflecting a variety of approaches and assumptions that can be found in other models[8,11,28], our framework is not able to discern if this assortative relationship with

age is due to age-specific contact type patterns or susceptibility to colonization. Nonetheless, our results strongly argue for the need of more research characterising local contact, risk and transmission-route profiles (e.g [42]), if we are to understand the myriad of reported PCV impacts across different demographic, social and epidemiological settings.

There was also the unexpected observation that vaccine impact (reduction in carriage), four to six years post-PCV13, was higher in the older unvaccinated age-group. The dynamic model helped explain this, by showing that age-groups can experience periods of faster vaccine impact at different time points, from younger to older groups, as a likely consequence of routine vaccination at very early age, vaccinated cohort ageing and age-specific transmission potentials. Similarly to the conclusions of another modelling study[28], our results thus advocate for the essential role of dynamic models to understand and project VT carriage, by critically accounting for local non-linear effects of pneumococcal transmission and vaccination.

Critical for developing countries, as well as global initiatives such as Gavi, is that the impact of PCVs on pneumococcal VT carriage and transmission needs to be further improved if we are to maximize disease reduction. For countries like Malawi, in which post-vaccine VT carriage data suggests that local epidemiological factors may dictate lower vaccine impact than elsewhere, region-specific improved vaccination schedules[19,22] and catch-up campaigns[28] could help speed-up VT carriage reduction and maximise cost-effectiveness. For this to be possible, we need to better understand local transmission profiles across ages, which are likely dictated by demographic and socio-economic factors, and strongly determine short- and long-term PCV impact as demonstrated in the case of Blantyre.

# Limitations

Data suggests that immune responses to PCV vaccines wane with time from vaccination[22,34]. In a meta-analysis study, PCV7 efficacy was estimated at 62% (CI 95% 52-72%) at four months post-vaccination, decreasing to 57% (CI 95% 50-65%) at six months, but remaining 42% (CI 95% 19-54%) at five years post-vaccination[34]. Models implicitly parametrising for duration of vaccine-induced protection (dVP) have typically followed a prior with minimum mean duration of six years[8,11,28,34], but in one study dVP was estimated as 8.3 years (95% CI 5 – 20)[8]. Our framework does not explicitly include dVP. In the context of these reported time ranges, and since we fit data up to 6 years post vaccine introduction, further restricting our analyses to the first 10 years, we argue that our projections should be robust. In light of the possibility that dVP is shorter than previously reported[22], our projections of vaccine impact should be seen as a best-case scenario; i.e. real long-term vaccine impact in Blantyre would likely be lower than projected by our model.

Our framework also does not include niche competition between VT and non-VT pneumococci[11,28,34]. It is difficult to assert the impact of such competition in our main results, but its unlikely that our main conclusions would be affected, since they are mostly based on factors (e.g. age-specific transmission) which have not been reported to be associated with type competition directly.

# Conclusion

In Blantyre, vaccine efficacy (individual-level protection against carriage) across ages and time is estimated at 68.8% (95% CI 41.6 – 88.1), similar to reports from other countries. However, local transmission potential is likely to be higher than in such countries, and also heterogeneous among age-groups, with a particular contribution from younger children. While PCV13 is achieving positive outcomes in Blantyre[19,52], such local higher force of infection is dictating a much lower long-term vaccine impact (population-level carriage reduction) than reported elsewhere. Finally, the combination of age-related transmission heterogeneities and routinely vaccinating infants has led to non-linear responses in terms of vaccine impact across ages and time, with general implications on post-vaccination VT carriage data interpretation.

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# Contributions

JL, UO, TDS designed the modelling study. JL and UO designed the model. JL implemented the model and the fitting approach. JL, UO analysed and interpreted model output. JL and UO searched and curated the literature data. TDS supervised, while AG, NBZ, DE, AWK, TSM, AAM, CM and MB collected and curated the Malawi observational data. SG, NF and RSH supervised both the modelling and observational sides of the study. JL wrote the first draft of the manuscript which all authors revised. JL, UO and TDS revised other iterations of the manuscript. All authors revised the last version of the manuscript.

# Declaration of interests

No other competing interests were reported by authors.

# Figure legends

**Figure 1: Transmission model framework and survey data. (a)** Seven age-groups were modelled: 0, 1, 2, 3-5, 6-7, 8-9, 10+ years of age (circles), each divided into unvaccinated (top) and vaccinated (bottom). Labels $a_{age\text{-}group}$ mark ageing rates per age class; $\mu_{age\text{-}group}$ mark age-specific death rates; b marks births, at which point a proportion (ρ) are vaccinated (purple); ζ marks vaccine-induced protection, expressed as reduction in susceptibility to infection of vaccinated individuals (magenta); $\lambda_{age\text{-}group}$ mark age-specific forces of infection; $\gamma_{age\text{-}group}$ mark age-specific rates of clearance from infection; k marks catch-up vaccination (green). **(b)** The informative priors used in the fitting exercise for mean (standard deviation) infectious periods (days) of 47 (1.8) for 0-2 years old; 34 (1.3) for 3-5 years old; 26 (1.4) for 6-8 years old; 26 (2.0) for 8+ years old (taken from [1]). The posterior values of these periods ($1/\gamma_{0\text{-}2}$, $1/\gamma_{3\text{-}5}$, $1/\gamma_{6\text{-}8}$, $1/\gamma_{8+}$) are estimated when fitting the survey data. **(c) A** transmission matrix is used in the model, with two transmission coefficients β and θ, where the latter is the specific coefficient for transmission within and between particular age-groups. β and θ are estimated when fitting the survey data and can be any positive numbers. **(d)** Observational study data (surveys) per age-group, with means 0.23, 0.21, 0.20, 0.17 for vaccinated 3-5 years old (V3-5y, purple), 0.26, 0.21, 0.19, 0.18 for unvaccinated 6-7 years old (NV3-5y, green), 0.20, 0.16, 0.19, 0.13 for unvaccinated 8-9 years old (NV8-9y, orange); bars are the 95% CI.

**Figure 2: Model fit and estimated posteriors. (a)** Model fit to carriage data from the observational study for different age-groups: vaccinated 3-5 years old (V3-5y, purple), unvaccinated 6-7 years old (NV6-7y, green) and unvaccinated 8-9 years old (NV8-9y, orange). The survey data is represented with means as empty squares, the model output with means as full circles; the whiskers are the 95% CI. Grey and white areas mark the different surveys of the observational study. **(b)** Priors (lines) and estimated posterior distributions (shaded) of duration of carriage per age-group. **(c)** Estimated mean and 95% CI of posterior of vaccine efficacy against vaccine-type carriage (red) in the context of estimates from other studies (in legend, Table S2). **(d)** The estimated posterior distributions of the transmission coefficients β and θ are shown in two dimensions (coloured area). The estimated actual distribution for β is in the x-axis and θ in the y-axis (visualised in grey). Note that, for visualisation purposes, the axes are $\log_{10}$-transformed and the grey distributions' height has no scale (height is not quantified). **(a,b,c,d)** Solutions presented are obtained from sampling 100,000 parameter values from posteriors and simulating the dynamic model.

**Figure 3: Impact projections of vaccine-type carriage reduction. (a)** Projected reduction in carriage relative to the pre-vaccination era for age-groups 0 years (magenta), 1 year (blue), 2 years (yellow) and 3-5 years (purple) old. **(b)** Projected reduction in carriage relative to the pre-vaccination era for aggregated age-groups 0-5 years (green) and 6-9 years (red) old (with corresponding 95% CIs). **(a,b)** Solutions presented are obtained from sampling 100,000 parameter values from posteriors and simulating the dynamic model. The shaded areas are red for the pre-vaccination period, yellow for the post-vaccination period with no carriage data, white for the post-vaccination period with survey carriage data, and grey for the post-vaccination projected period up to 10 years. The grey arrows mark the year of PCV13 introduction and years of the four surveys.

**Figure 4: Time periods of fastest reduction in force of infection across ages.** The post-vaccination force of infection (FOI) of different age groups was calculated for each of 100,000 simulations using parameter samples from posteriors. For each FOI time series of each age-group, the time point of minimum derivative was calculated as a proxy for the time period of fastest FOI reduction, resulting in one distribution per age-group (coloured curves, 0-5 years of age in green, 6-7 in blue, 8-9 in red). The shaded areas are red for the pre-vaccination period, yellow for the post-vaccination period with no carriage data, white for the post-vaccination period with survey carriage data, and grey for the post-vaccination projected period up to 10 years. The grey arrows mark the year of PCV13 introduction and years of the four surveys.

**Figure 5: Estimated vaccine-type carriage and sensitivity of impact projections to baseline transmission in the context of other studies. (a)** Estimated pre-vaccination vaccine-type carriage (and 95% CI) for the age-group 0-5 years of age (red) in the context of carriage levels reported in other studies (in legend, Table S5). **(b)** The baseline transmission coefficient (β) is varied by considering the 70%, 60%, 50%, 40%, 30%, 20%, and 10% lower, and 10%, 20% higher transmission than the estimated for Blantyre (Malawi, $\beta_{Malawi}$) when fitting the observational study (e.g. 10% lower is $0.9*\beta_{Malawi}$). The impact projections for the age-group 0-5 years old using the β estimated for Blantyre (Malawi) are presented by the dashed line (as in Figure 3b). For visual purposes only the means are shown, obtained from simulations sampling 100,000 parameter values from posteriors. The symbols and whiskers are measures of reported impact (carriage reduction) and 95% CIs for several published studies (in legend, Table S4). The grey arrows mark the year of PCV13 introduction and the years of the four surveys.

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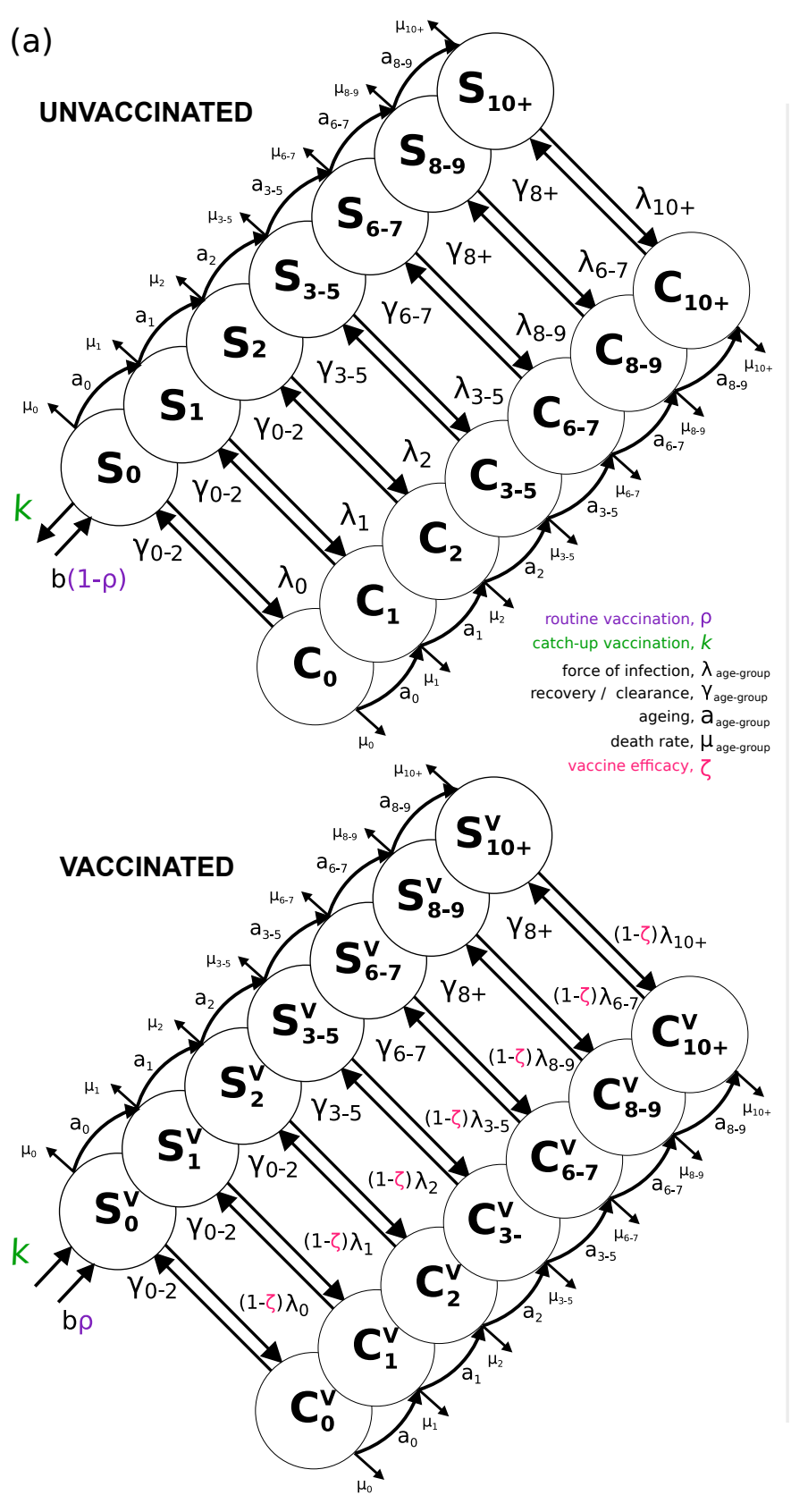
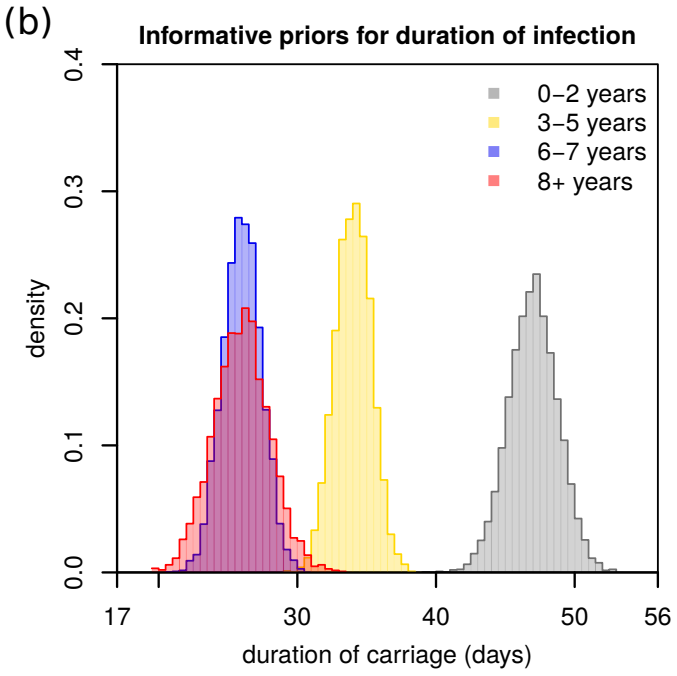
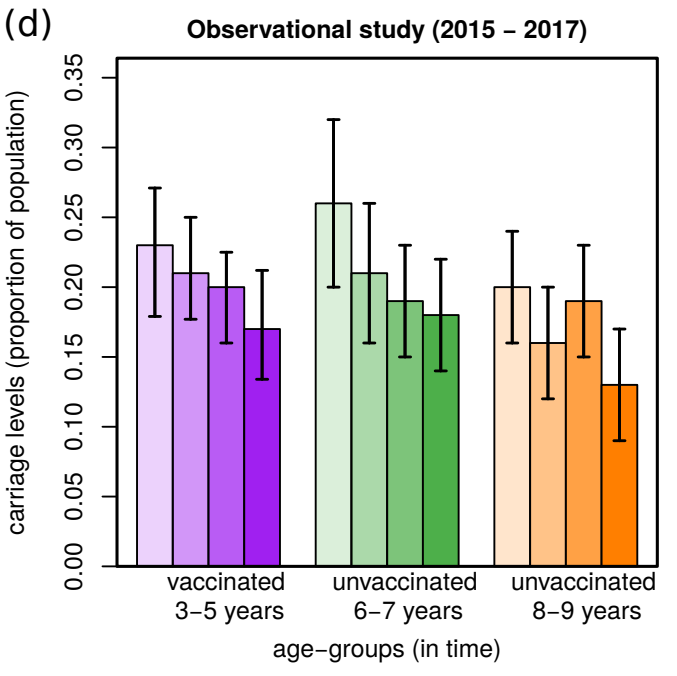


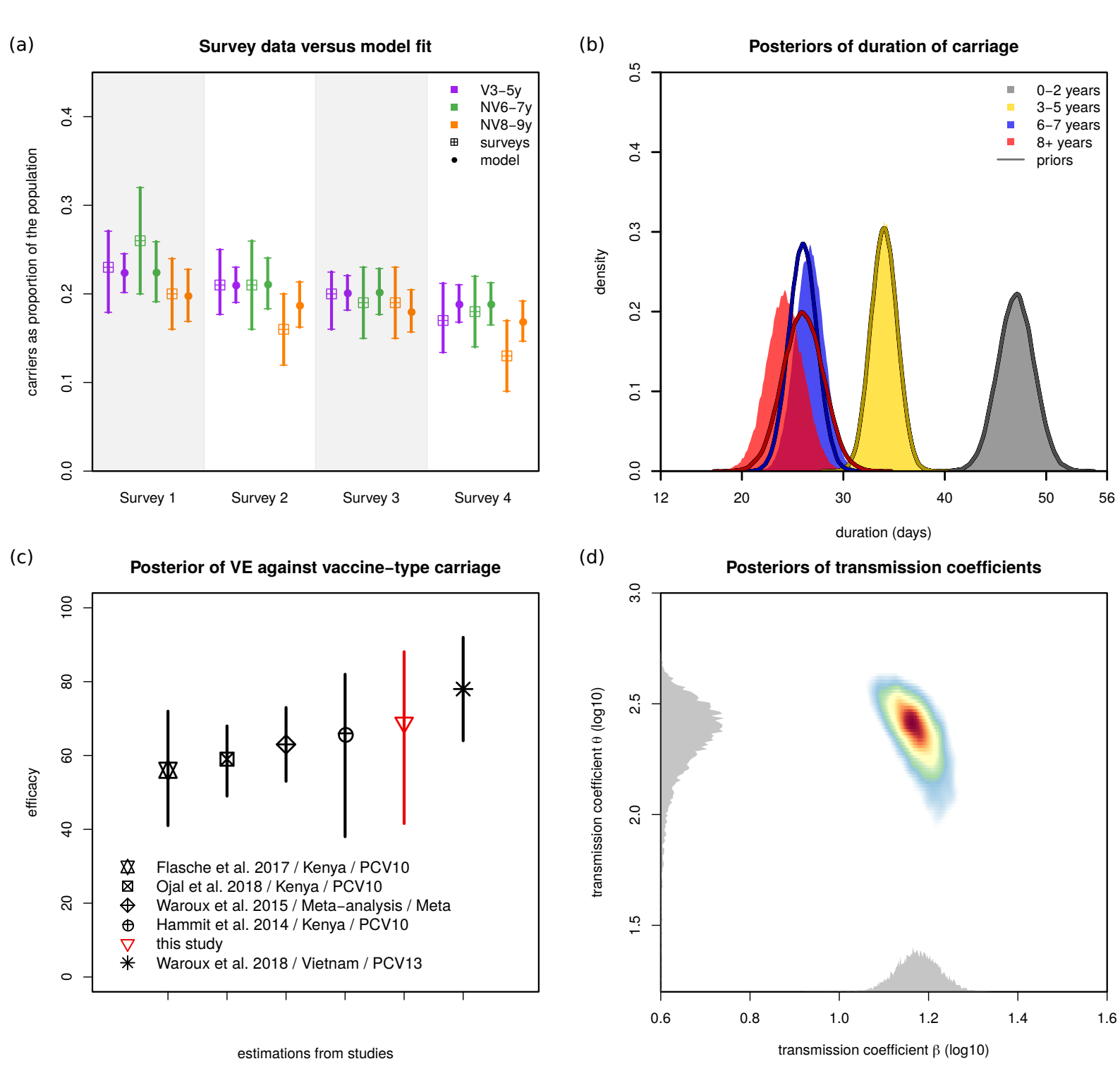



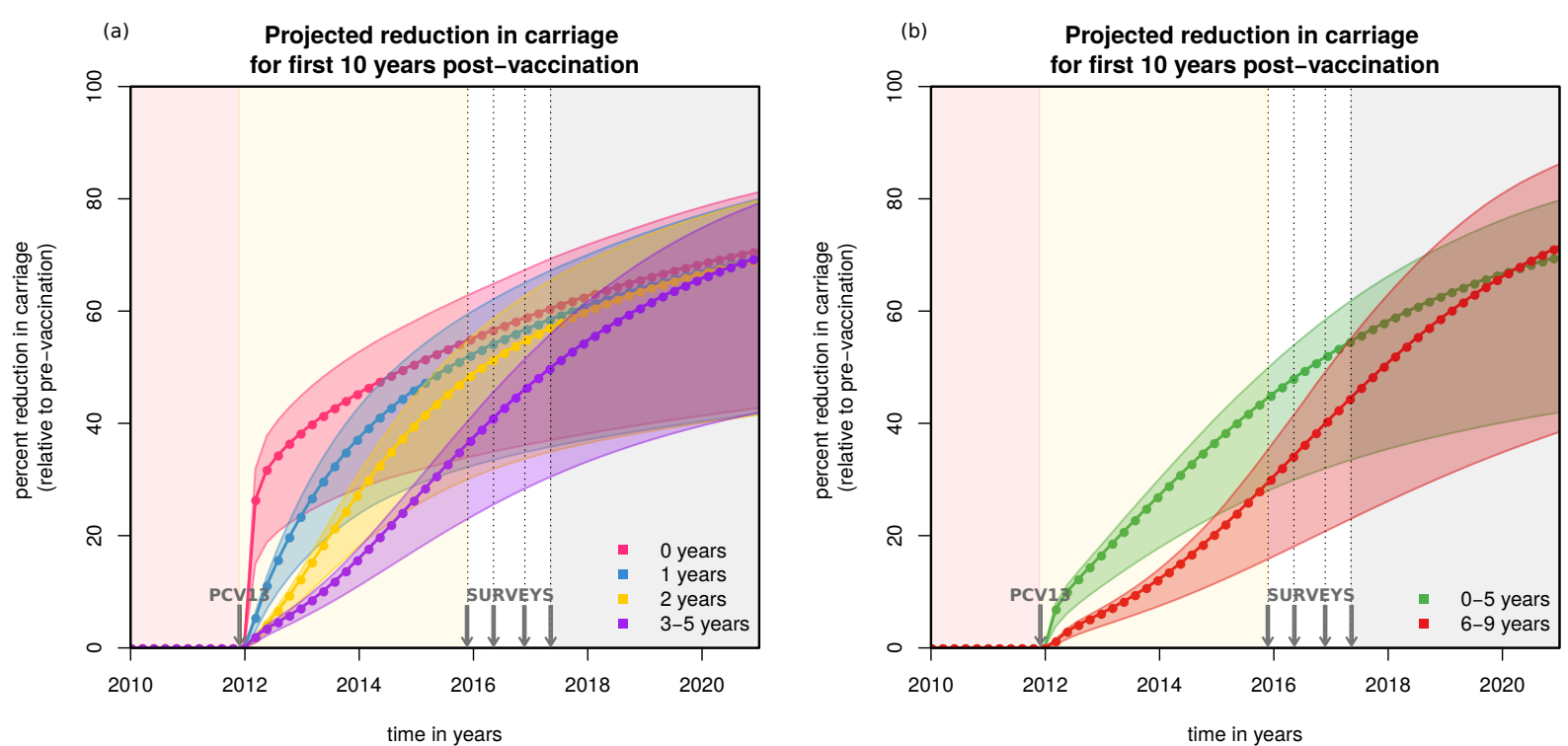

(c)

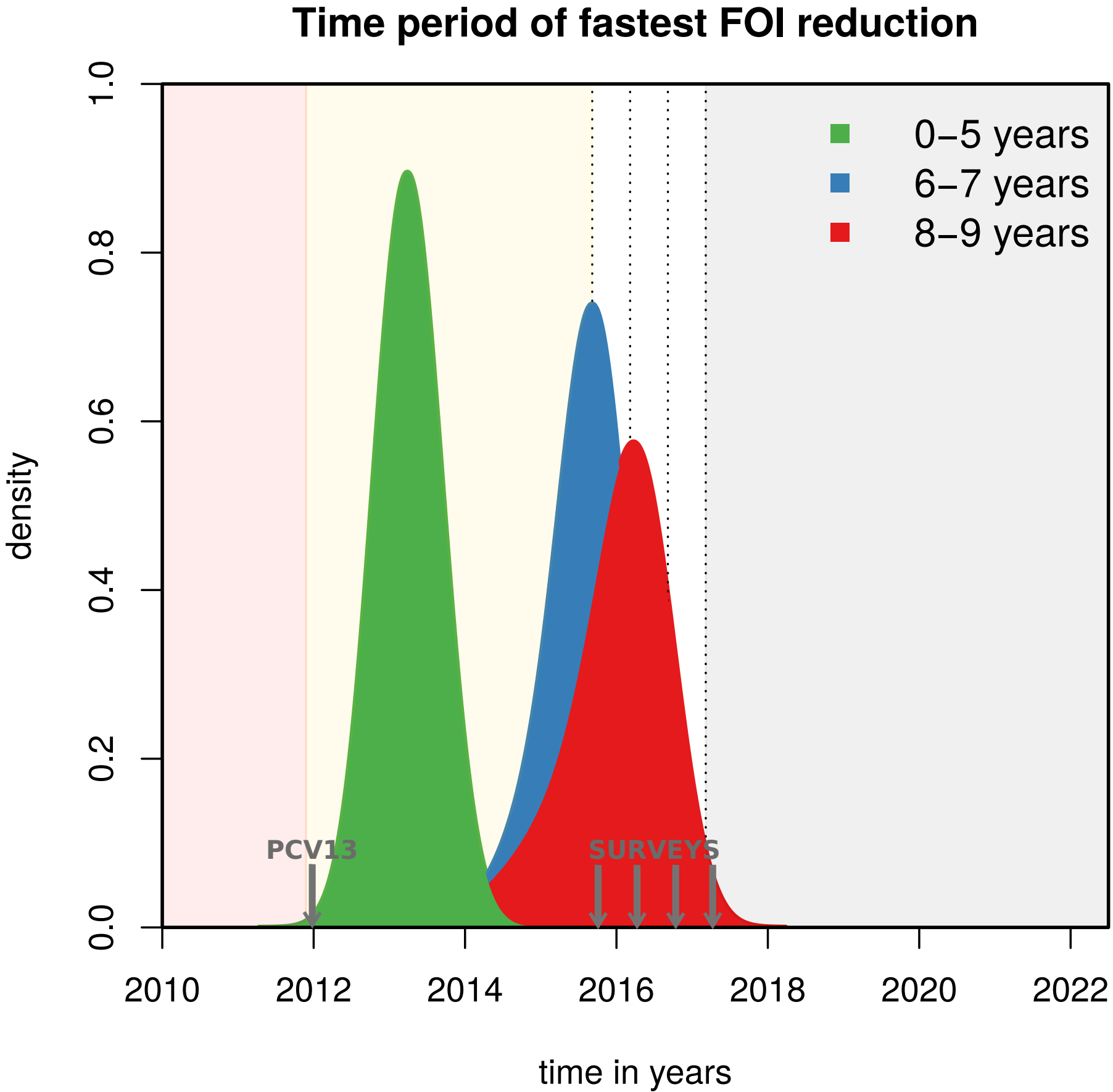
**Transmission matrix**

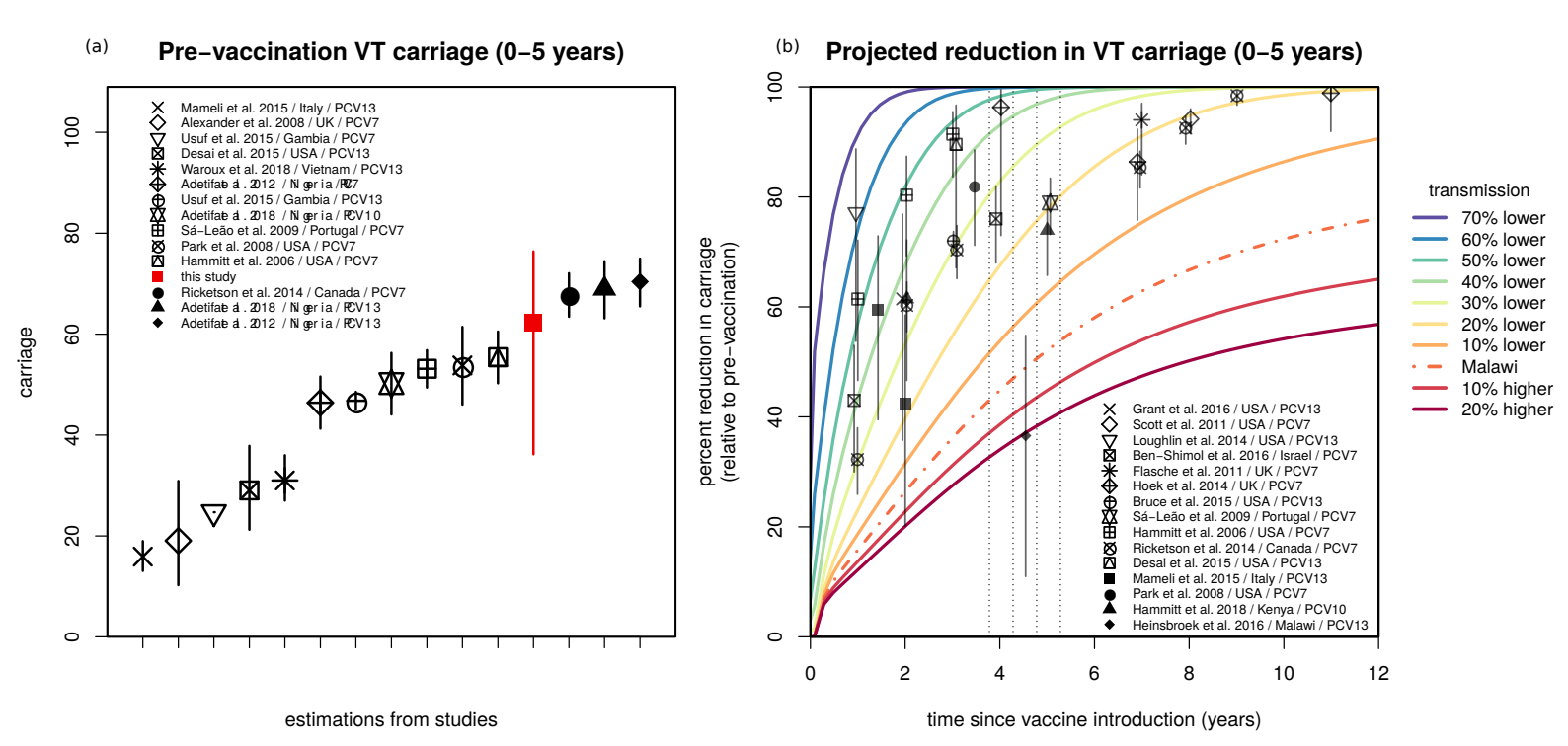
| transmission to \ transmission from | 0 | 1 | 2 | 3-5 | 6-7 | 8-9 | 10+ |
|---|---|---|---|---|---|---|---|
| 10+ | β | β | β | β | β | β | β |
| 8-9 | β | β | β | β | β | θ | β |
| 6-7 | β | β | β | β | θ | β | β |
| 3-5 | θ | θ | θ | θ | β | β | β |
| 2 | θ | θ | θ | θ | β | β | β |
| 1 | θ | θ | θ | θ | β | β | β |
| 0 | θ | θ | θ | θ | β | β | β |




(a)
Survey data versus model fit
carriers as proportion of the population
0.0
0.1
0.2
0.3
0.4
V3–5y
NV6–7y
NV8–9y
surveys
model
Survey 1
Survey 2
Survey 3
Survey 4
(b)
Posteriors of duration of carriage
density
0.0
0.1
0.2
0.3
0.4
0.5
0–2 years
3–5 years
6–7 years
8+ years
priors
12
20
30
40
50
56
duration (days)
(c)
Posterior of VE against vaccine–type carriage
efficacy
0
20
40
60
80
100
Flasche et al. 2017 / Kenya / PCV10
Ojal et al. 2018 / Kenya / PCV10
Waroux et al. 2015 / Meta–analysis / Meta
Hammit et al. 2014 / Kenya / PCV10
this study
Waroux et al. 2018 / Vietnam / PCV13
estimations from studies
(d)
Posteriors of transmission coefficients
transmission coefficient θ (log10)
1.5
2.0
2.5
3.0
0.6
0.8
1.0
1.2
1.4
1.6
transmission coefficient β (log10)


(a)
Projected reduction in carriage
for first 10 years post−vaccination
percent reduction in carriage
(relative to pre−vaccination)
0
20
40
60
80
100
2010
2012
2014
2016
2018
2020
time in years
PCV13
SURVEYS
0 years
1 years
2 years
3−5 years
(b)
Projected reduction in carriage
for first 10 years post−vaccination
percent reduction in carriage
(relative to pre−vaccination)
time in years
PCV13
SURVEYS
0−5 years
6−9 years


Time period of fastest FOI reduction
0–5 years
6–7 years
8–9 years
PCV13
SURVEYS
density
0.0
0.2
0.4
0.6
0.8
1.0
2010
2012
2014
2016
2018
2020
2022
time in years


(a)
Pre−vaccination VT carriage (0−5 years)
carriage
estimations from studies
Mameli et al. 2015 / Italy / PCV13
Alexander et al. 2008 / UK / PCV7
Usuf et al. 2015 / Gambia / PCV7
Desai et al. 2015 / USA / PCV13
Waroux et al. 2018 / Vietnam / PCV13
Usuf et al. 2015 / Gambia / PCV13
Sá−Leão et al. 2009 / Portugal / PCV7
Park et al. 2008 / USA / PCV7
Hammitt et al. 2006 / USA / PCV7
this study
Ricketson et al. 2014 / Canada / PCV7
(b)
Projected reduction in VT carriage (0−5 years)
percent reduction in carriage
(relative to pre−vaccination)
time since vaccine introduction (years)
Grant et al. 2016 / USA / PCV13
Scott et al. 2011 / USA / PCV7
Loughlin et al. 2014 / USA / PCV13
Ben−Shimol et al. 2016 / Israel / PCV7
Flasche et al. 2011 / UK / PCV7
Hoek et al. 2014 / UK / PCV7
Bruce et al. 2015 / USA / PCV13
Sá−Leão et al. 2009 / Portugal / PCV7
Hammitt et al. 2006 / USA / PCV7
Ricketson et al. 2014 / Canada / PCV7
Desai et al. 2015 / USA / PCV13
Mameli et al. 2015 / Italy / PCV13
Park et al. 2008 / USA / PCV7
Hammitt et al. 2018 / Kenya / PCV10
Heinsbroek et al. 2016 / Malawi / PCV13
transmission
70% lower
60% lower
50% lower
40% lower
30% lower
20% lower
10% lower
Malawi
10% higher
20% higher