

# 1 **Determinants of high residual post-PCV13** 2 **pneumococcal vaccine type carriage in Blantyre,** 3 **Malawi: a modelling study.**

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**Keywords:** pneumococcus, pcv13, modelling, malawi, intervention

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## **Abbreviations:**

32

VT - vaccine type

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NVT - non-vaccine type

PCV - pneumococcal conjugate vaccine

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CI - confidence interval

bMCMC - Bayesian Markov chain Monte Carlo

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ODE - ordinary-differential equations

FOI - force of infection

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dVP - duration of vaccine-induced protection

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## Abstract

44

**Background:** In November 2011, Malawi introduced the 13-valent pneumococcal conjugate vaccine (PCV13) into the routine infant schedule. Four to seven years after introduction (2015-2018), 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. A dynamic transmission model was fit to survey data using a Bayesian Markov-chain Monte Carlo approach, to obtain insights into the determinants of post-PCV13 age-specific VT carriage.

**Results:** Accumulation of naturally acquired immunity with age and age-specific transmission potential were both key to reproducing the observed data. VT carriage reduction peaked sequentially over time, earlier in younger and later in older age-groups. Estimated vaccine efficacy (protection against carriage) was 66.87% (95% CI 50.49-82.26%), similar to previous estimates. Ten-year projected vaccine impact (VT carriage reduction) among 0-9 years old was lower than observed in other settings, at 76.23% (CI 95% 68.02-81.96%), with sensitivity analyses demonstrating this to be mainly driven by a high local force of infection.

**Conclusions:** We have identified both vaccine-related and host-related determinants of post-PCV13 pneumococcal VT transmission in Blantyre with vaccine impact determined by age-related characteristics of the local force of infection. These findings are likely to be generalisable to other Sub-Saharan African countries in which PCV impact has been lower than desired, and have implications for the interpretation of post-PCV carriage studies and future vaccination programs.

## 64 Introduction

*Streptococcus pneumoniae* (pneumococcus) is a bacterial human pathogen commonly carried asymptotically in the nasopharynx, which in a minority of carriers can cause severe disease such as pneumonia, meningitis or bacteremia<sup>1</sup>, posing a serious mortality risk, especially for young children (<5 years of age), the elderly (>65 years of age) and the immunocompromised<sup>2</sup>. Pneumococcal carriage is a necessary precursor of severe disease<sup>3</sup> 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 common pneumococcal serotypes associated with carriage and disease (also termed vaccine serotypes, VT). A frequently observed 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<sup>4-9</sup>.

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<sup>10-16</sup>. PCV vaccines have only recently been introduced

82 in Sub-Saharan African countries, such as Kenya<sup>17,18</sup>, Malawi<sup>19</sup>, The Gambia<sup>20</sup> and South Africa<sup>21</sup>. In  
November 2011, Malawi introduced the 13-valent pneumococcal conjugate vaccine (PCV13) as  
84 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,  
86 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  
88 observational study in Blantyre (Southern Malawi), four to seven years after PCV13 introduction  
(2015-2018), has shown that vaccine impact (VT carriage reduction) has been slower than expected  
90 and heterogeneous across age-groups<sup>22</sup>. Epidemiological mathematical models have previously been  
employed successfully to improve our understanding of pneumococcal dynamics<sup>5,9,23-27</sup>, as well as  
92 having contributed to explain, estimate and project PCV impact<sup>8,11,28</sup>. The main advantage of models  
is their cost-free potential to test hypotheses and gain a mechanistic, ecological and immunological  
94 understanding of carriage and disease dynamics, estimating epidemiological parameters which are  
difficult to otherwise quantify from raw epidemiological data. For example, models have  
96 successfully yielded estimates of VT and non-VT pneumococci transmission potentials<sup>26,29-31</sup>,  
pneumococcal competition factors<sup>8,9,23,28,32,33</sup> and measures of vaccine-induced protection from  
98 carriage at the individual level<sup>11,17,28,34,35</sup>, none of which are readily observed or quantified in cross-  
sectional observational studies.

100 In this study we use a Bayesian Markov chain Monte Carlo fitting approach and a dynamic model  
to investigate the post-PCV13 pneumococcal VT carriage dynamics in Blantyre, Malawi. We find  
102 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  
104 vaccine efficacy (individual-level protection from carriage) was close to expected values, but  
impact (population-level reduction of VT carriage) was lower both in the short- and long-term. We  
106 show that vaccine impact was likely being offset by a high local force of infection compared to  
other regions of the world. Our study offers key insights into the lower than expected PCV13  
108 impact in Malawi and more generally on the heterogeneous nature of pre- and post-vaccination  
pneumococcal VT carriage across age-groups and regions. These results can be translated to other  
110 Sub-Saharan African countries in which PCV impact has been lower than desired.

## Methods

### 112 **Prospective cross-sectional observational study**

An observational study using stratified random sampling was conducted to measure pneumococcal  
114 nasopharyngeal carriage in Blantyre, Malawi<sup>22</sup>. Sampling was performed twice a year, between June  
and August 2015 (survey 1), October 2015 and April 2016 (survey 2), May and October 2016  
116 (survey 3), November 2016 and April 2017 (survey 4), May and October 2017 (survey 5);  
November 2017 and June 2018 (survey 6), and June and December 2018 (survey 7). In this study,  
118 we use the mid-point dates of the surveys for model fitting and presentation of results. A total of  
7148 individuals were screened with nasopharyngeal swabs processed following WHO  
120 recommendations<sup>36</sup>. Isolates were serotyped by latex agglutination (ImmuLex™ 7-10-13-valent  
Pneumotest; Statens Serum Institute, Denmark). In this study, we use all the data from three age-  
122 groups: 499 vaccinated children 2 years old, 2565 vaccinated children 3–7 years old and 1402

124 unvaccinated children 3–10 years old. For the first three surveys, data on vaccinated 2 years old  
126 individuals was not collected. Observed VT carriage levels are presented in Figure 1d (and Table  
S7). Further details on collection, processing and observations, have been previously described in  
detail <sup>22</sup>.

## Vaccine type transmission model

128 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)<sup>22</sup>.  
130 Fitting was implemented using a Bayesian Markov chain Monte Carlo (bMCMC) approach  
developed and used by us in other modelling studies<sup>37–39</sup>, including informative priors for duration  
132 of carriage (Figure 1b, Table S1) and uninformative uniform priors for vaccine efficacy (individual-  
level protection against carriage) and transmission potential. The methodology is summarised in  
134 this section and further details such as equations, literature review on priors and expected parameter  
values (Tables S1, S2, S5, S6) and complementary results can be found in Supplementary Text S1.

136

## Pneumococcal infection dynamics and human demographics

138 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-  
140 groups with a rate ( $a_{\text{age-group}}$ ) equal to the inverse of the time spent at each age class. The seven age-  
groups were further divided into vaccinated ( $S_{\text{age-group}}^v$ ,  $C_{\text{age-group}}^v$ ) and unvaccinated ( $S_{\text{age-group}}$ ,  $C_{\text{age-group}}$ )  
142 susceptibles (S) and carriers (C). The population size was assumed to be constant, with total deaths  
equal to births (details in Supplementary Text S1). Death rates were age-specific ( $\mu_{\text{age-group}}$ ) and  
144 relative to a generalized total life-span of 70 years.

## 146 Natural immunity

Pneumococcal colonization increases both humoral (anti-capsular serotype-specific and anti-protein  
148 non-serotype-specific) and T-cell (anti-protein) immunity<sup>40</sup>. Acquisition of this immunity correlates  
with colonization in children and increases with age as colonization decreases. In our model (Figure  
150 1a), all individuals were assumed to be born susceptible but can acquire infection (colonization) at  
any age with a particular force of infection  $\lambda_{\text{age-group}}$ , becoming carriers ( $C_{\text{age-group}}$ ) for an age-  
152 specific period ( $1/\gamma_{\text{age-group}}$ ), and returning to the susceptible state ( $S_{\text{age-group}}$ ) after clearance. Hence,  
the development of complete (sterile) immunity to the pneumococcus was not considered. We  
154 nonetheless allowed for decreasing duration of carriage with age ( $1/\gamma_{\text{age-group}}$ ) as a proxy for the  
development of pneumococcal immunity with age. To quantify differences in age, we used carriage  
156 duration data as reported by Hogberg and colleagues<sup>41</sup> to define informative priors related to the  
aggregated age-groups: 0-2 years ( $1/\gamma_{0-2}$ ), 3-5 years ( $1/\gamma_{3-5}$ ), 6-8 years ( $1/\gamma_{6-8}$ ), and 8+ years ( $1/\gamma_{8+}$ ) as  
158 represented in Figure 1b (Table S1 for literature review).

## 160 Vaccination, efficacy and impact

162 For simplicity, routine vaccination was implemented at birth with coverage ( $\rho$ ) at 92.5%<sup>22</sup>, and  
164 catch-up ( $k$ ) implemented as a one-off transfer of a proportion of individuals from the unvaccinated  
166 susceptibles with 0 (<1) years of age ( $S_0$ ) to the vaccinated susceptible class with the same age ( $S^v_0$ )  
168 with coverage of 60%<sup>22</sup>. We assumed the vaccine to reduce the risk of infection (colonization) of  
vaccinated individuals by a proportion  $\zeta$  (between 0 and 1, with  $\zeta=1$  equating to no risk). This  
reduction in risk was herein defined and interpreted as the individual-level vaccine efficacy against  
carriage ( $VE= 100 \times \zeta$ ), and was modelled directly on the force of infection ( $\lambda$ ) (Figure 1a, and  
Table S2 for literature review). We measured vaccine impact across age-groups as the post-PCV13  
percent reduction in population-level VT carriage compared to pre-vaccination levels.

170

### Force of infection

172 We considered several transmission matrices (Supplementary Text S1), and compared the resulting  
174 model fits using leave-one-out cross-validation (LOO) and the widely applicable information  
176 criterion (WAIC) measures. The inhomogeneous transmission matrix presented in Figure 1c over-  
performed the others and was used for the results presented in the main text. Its structure is based  
178 on epidemiological studies conducted in American, European and African populations reporting  
typical, strong, intrinsic variation in frequency, efficiency and environmental risk of transmission  
between age-groups<sup>10,31,42-47</sup>. In summary, the transmission matrix is generally populated with a  
baseline coefficient  $\beta$ , and a different coefficient  $\theta$  assigned to transmission occurring within and  
180 between ages 0-5 years, and within 6-7 and 8-9 years of age independently. Further literature  
support and results from the second best performing transmission matrix can be found in  
182 Supplementary Text S1.

### 184 Fitting to survey data

The model's carriage outputs for vaccinated 2, vaccinated 3-5, unvaccinated 6-7 and unvaccinated  
186 8-9 years of age, were fitted to observed levels in Blantyre's 1-7 surveys (Figure 1d, values in Table  
S7), approximately four to seven years PCV13 introduction (2015-2018). A total of seven  
188 parameters were fitted: vaccine efficacy against carriage ( $\zeta$ , uninformative prior), coefficients of  
transmission ( $\beta$ ,  $\theta$ , uninformative priors) and durations of carriage in ages 0-2, 3-5, 6-7, 8+ years ( $1/\gamma_{0-2}$ ,  
190  $1/\gamma_{3-5}$ ,  $1/\gamma_{6-8}$ ,  $1/\gamma_{8+}$ , informative priors). The transmission model was initialized at time  $t=0$  with a  
proportion of 0.99 susceptibles and 0.01 infected, with numerical simulations run until an  
192 equilibrium was reached. At equilibrium, vaccination was introduced and the first post-vaccine 15  
years recorded. Levels of carriage in the model were calculated as the proportion of individuals  
194 within an age-group that are carriers (i.e.  $C/(S+C)$ , expressions in Supplementary Text S1). The  
model was run with parameters scaled per year. bMCMC chains were run for 5 million steps, with  
196 burn-in of 20% (bMCMC details in see Supplementary Text S1).

## Results

198 We used our deterministic transmission model and bMCMC approach to fit the observed post-  
vaccination VT carriage data from Blantyre, Malawi (2015 - 2018). Based on this fit, we could

200 reconstruct age-specific 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  
202 impact on the vaccinated age-groups and strong herd-effects in the older unvaccinated age-groups.

## 204 **Model fit and posteriors**

VT carriage levels across age-groups reported from the surveys were closely reproduced by the  
206 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  
208 2b); i.e. the estimated posterior distributions of the durations of carriage ( $1/\gamma_{\text{age-group}}$ ) were adjusted  
by the bMCMC by approximately -0.7, +0.64, +0.58 and -1.73 days for the age-groups 0-2, 3-5, 6-7  
210 and 8+ years of age, respectively. The posterior distribution of vaccine efficacy (individual-level  
protection against carriage) across ages was estimated to be 66.87% (95% CI 50.49-82.26). While  
212 we used an uninformative prior (uniform, 0 to 1) in the bMCMC, this efficacy posterior was similar  
to others recently estimated with different models and in multiple epidemiological settings (Figure  
214 2c). We therefore argue that it serves as partial validation for our modelling framework. Finally, the  
solutions for the transmission coefficients  $\beta$  and  $\theta$  suggested that in order to reproduce the Blantyre  
216 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.  $\theta \gg \beta$ ).

218

## **Vaccine impact across age-groups**

220 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).

222 After the first year, VT carriage reduction was estimated to be 42.38% (95% CI 37.23-46.01%) for  
the 0 (<1) years old, followed by 29.25% (95% CI 26.4-31.4%) for the 1 years old, 17.45% (95%  
224 CI 16.47-18.36%) for the 2 years old and 4.95% (95% CI 8.78-10.89%) for 3-5 years old (Figure  
3a). With time, as carriage generally dropped and vaccinated individuals aged, the older groups  
226 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-  
228 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  
230 across all age-groups, with VT carriage reduced by 76.9% (CI 95% 68.93-82.32%) for the 0 (<1)  
years old, 75.72% (CI 95% 67.78-81.24%) for the 1 years old, 75.51% (CI 95% 67.55-81.05%) for  
232 the 2 years old and 75.86% (CI 95% 68.29-80.97%) 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  
234 VT carriage (Figure 3b), with the larger aggregated age-group 0-9 years old having a total reduction  
of 76.23% (CI 95% 68.02-81.96%) after 10 years.

236 We performed a literature review on observed reduction of VT carriage in time after the  
introduction of PCV vaccines (Table S5) in numerous countries, and concluded that both the  
238 observed carriage levels during the surveys and during the model's projection for the first 10 years  
were high when compared to other countries. For instance, residual carriage of PCV13 types was

240 0.4% after 4 years of vaccination in England<sup>48</sup>, 9.1% after 2 years of vaccination in Italy<sup>49</sup>, and 7%  
242 after 3 years of vaccination in Alaska, USA<sup>16</sup>. Similarly, for 0-5 year old individuals, PCV10 in  
244 Kenya<sup>18</sup> has reduced VT carriage by 73.92% in the first 5 years, while in Portugal<sup>50</sup>, PCV7 has  
reduced VT carriage by 78.91% in the same age-group and amount of time (more examples can be  
found on Table S5).

### Post-vaccination changes in force of infection

246 To try to understand responses to vaccination across age-groups, we further explored the post-  
PCV13 force of infection (FOI) dynamics. The FOI is the overall rate by which a certain age-group  
248 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  
250 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).

252 As determined by the posteriors of  $\beta$  and  $\theta$  (Figure 2d), the pre-vaccination absolute FOI of the 0-5,  
6-7 and 8-9 age-groups was different at PCV13 introduction, and with vaccine roll out the FOI of  
254 each age-group decreased in time (Figure 4a). We also examined the FOI derivative with respect to  
time as a measure of speed of FOI reduction (Figure 4b), and found that the time period of fastest  
256 FOI reduction for the 0-5 years old was between vaccine introduction and 2015 (when no carriage  
data was collected). This contrasted with the older age-groups (6-7 and 8-9), for which the period of  
258 fastest FOI reduction was predicted to be just before or during the first three surveys. Thus,  
although surveys 1 to 7 suggest a rather slow reduction of VT carriage for the younger age-groups  
260 during the observational study, this seems to have been preceded by a period of high, short-term  
impact on VT carriage for those age-groups (seen in the initial dynamics of Figures 3a and 3b).  
262 Indeed, vaccine impact (reduction in VT carriage) at the time of the first survey was estimated to be  
46.9% (95% CI 43.2-49.42) for the aggregated age-group 0-5 years old. At the same time, the  
264 fastest reduction in FOI for the older age-groups was predicted by the model to take place just  
before and during the first surveys, the time period in which survey data presents the largest  
266 reductions in VT carriage for those age-groups (Figure 1d). Overall, projected FOI dynamics  
suggest that PCV13 impact has been non-linear in time within age-groups, with predicted periods of  
268 faster reductions in VT carriage being experienced by different ages in a sequential manner, from  
younger to older individuals.

270

### Sensitivity of vaccine impact based on transmission setting

272 The projected impacts of Figures 3 and 4 were based on the estimated transmission coefficients for  
Blantyre (Figures 1b and 2d). To contextualize this particular transmission setting, we searched the  
274 literature for pre-vaccination VT carriage levels in other countries (Table S6). The reported age-  
groups were highly variable, and we therefore focused on the 0-5 years old group for which more  
276 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  
278 within countries, with our estimation for Blantyre being on the higher end (61.58%, 95% CI 50.0-  
70.9%).

280 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 S5,  
282 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  
284 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<sup>19</sup>.

286 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-  
288 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  
290 settings in Blantyre, by varying both the transmission coefficients ( $\beta$  and  $\theta$ ) between -70% and  
+120% of their estimated posteriors (full exercise in Figure S3). This sensitivity exercise showed  
292 that lowering local transmission by approximately -30% was sufficient for the model to  
approximate short- and long-term vaccine impact observed in several other countries (Figure 5b).  
294 Other age-groups, for which far less data points were available, presented similar patterns (Figure  
S4).

## 296 Discussion

Using a dynamic model, we have reproduced observed changes in pneumococcal VT carriage  
298 following the introduction of PCV13 in Blantyre, Malawi. Similar to other modelling frameworks  
we have considered the accumulation of natural immunity with age and have also allowed for  
300 heterogeneous transmission potentials within and between age-groups. Including these factors  
allowed us to identify age-related characteristics of the local force of infection as the main  
302 determinants of the high residual pneumococcal vaccine type carriage in Blantyre, seven years post-  
PCV13 introduction.

304 A main motivation for developing our dynamic model was to explain the high residual VT carriage  
levels seven years post-PCV13 introduction<sup>22</sup>. Studies from Kenya, The Gambia and South Africa  
306 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, pre- and  
308 post-vaccination VT carriage in Blantyre was at the upper end of reported values across many  
countries (Figure 5 and Tables S5, S6). Given that our estimate of vaccine efficacy (individual-level  
310 protection against carriage) was similar to reports from elsewhere (Figure 2c, Table S2), we tested  
the hypothesis that the observed and projected lower vaccine impact was likely a result of a higher  
312 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  
314 dominated by individuals younger than 5 years. Reflecting a variety of approaches and assumptions  
that can be found in other models<sup>8,11,28</sup>, our framework is not able to discern if this assortative  
316 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,  
318 risk and transmission-route profiles (e.g. <sup>42</sup>), if we are to understand the myriad of reported PCV  
impacts across different demographic, social and epidemiological settings.



320 There were also the observations of vaccine impact (reduction in VT carriage) in unvaccinated age-  
321 groups, and a particularly slow impact in younger vaccinated age-groups during the surveys (Figure  
322 1d). The dynamic model helped explain these age-related responses, by showing that age-groups  
323 have experienced periods of higher vaccine impact at different time points, sequentially, from  
324 younger to older groups. A major implication is that reduction in VT carriage in vaccinated younger  
325 age-groups has been fastest between PCV13 introduction and 2015, when no carriage data was  
326 collected in Blantyre, but consistent with data collected in rural northern Malawi<sup>19</sup>. Thus, similarly  
327 to the conclusions of another modelling study<sup>28</sup>, our results advocate for the essential role of  
328 dynamic models to understand post-PCV13 VT carriage, by critically accounting for local non-  
329 linear effects of pneumococcal transmission and vaccination which may have significant  
330 implications for data interpretation.

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

## 338 Limitations

339 Data suggest that immune responses to PCV vaccines wane over time<sup>22,34</sup>. In a meta-analysis study,  
340 PCV7 efficacy was estimated at 62% (CI 95% 52-72%) at four months post-vaccination, decreasing  
341 to 57% (CI 95% 50-65%) at six months, but remaining 42% (CI 95% 19-54%) at five years post-  
342 vaccination<sup>34</sup>. Models implicitly parametrising for duration of vaccine-induced protection (dVP)  
343 have typically followed a prior with minimum mean duration of six years<sup>8,11,28,34</sup>, but in one study  
344 dVP was estimated as 8.3 years (95% CI 5 – 20)<sup>8</sup>. Our framework does not explicitly include dVP,  
345 and this should be a line of future modelling research. Due to the time ranges studied for Blantyre  
346 (data were collected up to seven years post-PCV13 introduction and projections made only up to the  
347 first ten years), we argue that our results should be robust and only weakly influenced by not  
348 considering dVP. In light of the possibility that dVP is shorter than previously reported<sup>22</sup>, our  
349 projections of vaccine impact should be seen as a best-case scenario; i.e. real long-term vaccine  
350 impact in Blantyre would likely be lower than projected by our model. Our framework also does not  
351 include niche competition between VT and non-VT pneumococci<sup>11,28,34</sup>. It is difficult to assert the  
352 impact of such competition in our main results, but it is unlikely that our conclusions would be  
353 significantly affected, since they are mostly based on factors which have not been reported to be  
354 associated with type competition directly (e.g. age-specific transmission).

## 355 Conclusion

356 In Blantyre, vaccine efficacy (individual-level protection against carriage) across ages and time was  
357 estimated at 66.87% (95% CI 50.49-82.26%), similar to reports from other countries. However,  
358 local transmission potential in Blantyre is likely to be higher than in other countries and also

360 heterogeneous among age-groups, with a particular contribution from younger children. While  
361 PCV13 is achieving positive outcomes in Blantyre<sup>19,51</sup>, a local higher and age-dependent force of  
362 infection is dictating a lower long-term vaccine impact (population-level carriage reduction) than  
363 reported elsewhere. Finally, the combination of age-related transmission heterogeneities and  
364 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. Together,  
366 these findings suggest that in regions with lower than desired PCV impact on VT carriage,  
alternative vaccine schedules and catch-up campaigns targetting children <5 years of age should be  
368 further evaluated.

## Acknowledgements

370 We would like to thank Ellen Heinsbroek for key literature references used in this manuscript, and  
Stefan Flasche for useful information regarding raw data of published studies. We thank the  
372 individuals who participated in this study and the local schools and authorities for their support. We  
are grateful to the study field teams (supported by Farouck Bonomali and Roseline Nyirenda) and  
374 the study laboratory team. We are grateful to the MLW laboratory management team (led by  
Brigitte Denis) and the MLW data management team (led by Clemens Masesa). RSH, NF and TS  
376 are supported by the National Institute for Health Research (NIHR) Global Health Research Unit on  
Mucosal Pathogens using UK aid from the UK Government. The views expressed in this  
378 publication are those of the author(s) and not necessarily those of the NIHR or the Department of  
Health and Social Care.

## Funding

380 Bill & Melinda Gates Foundation, Wellcome Trust UK, Medical Research Council, European  
382 Research Council, National Institute for Health Research.

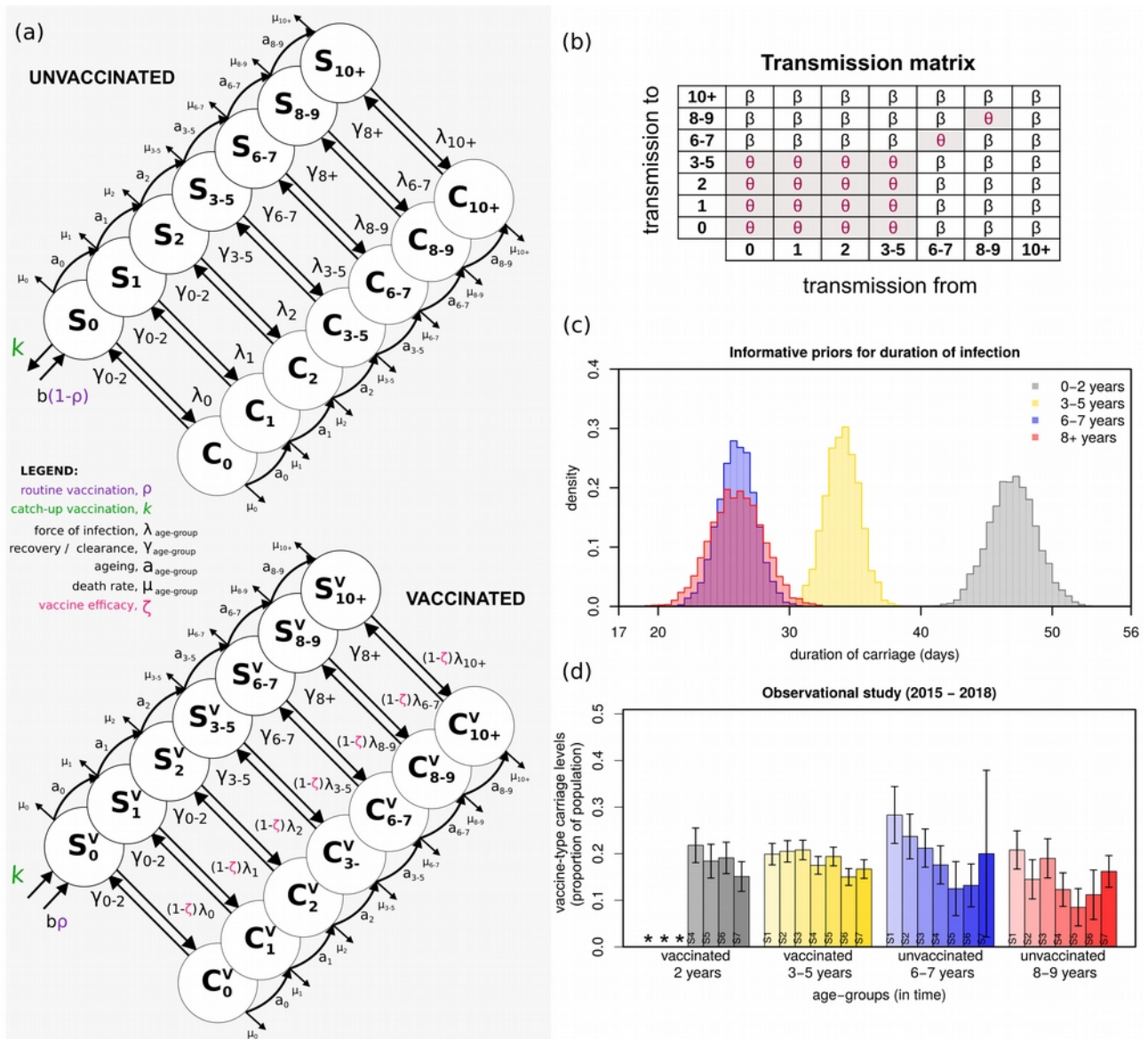
## Contributions

384 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  
386 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  
388 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  
390 last version of the manuscript.

## Declaration of interests

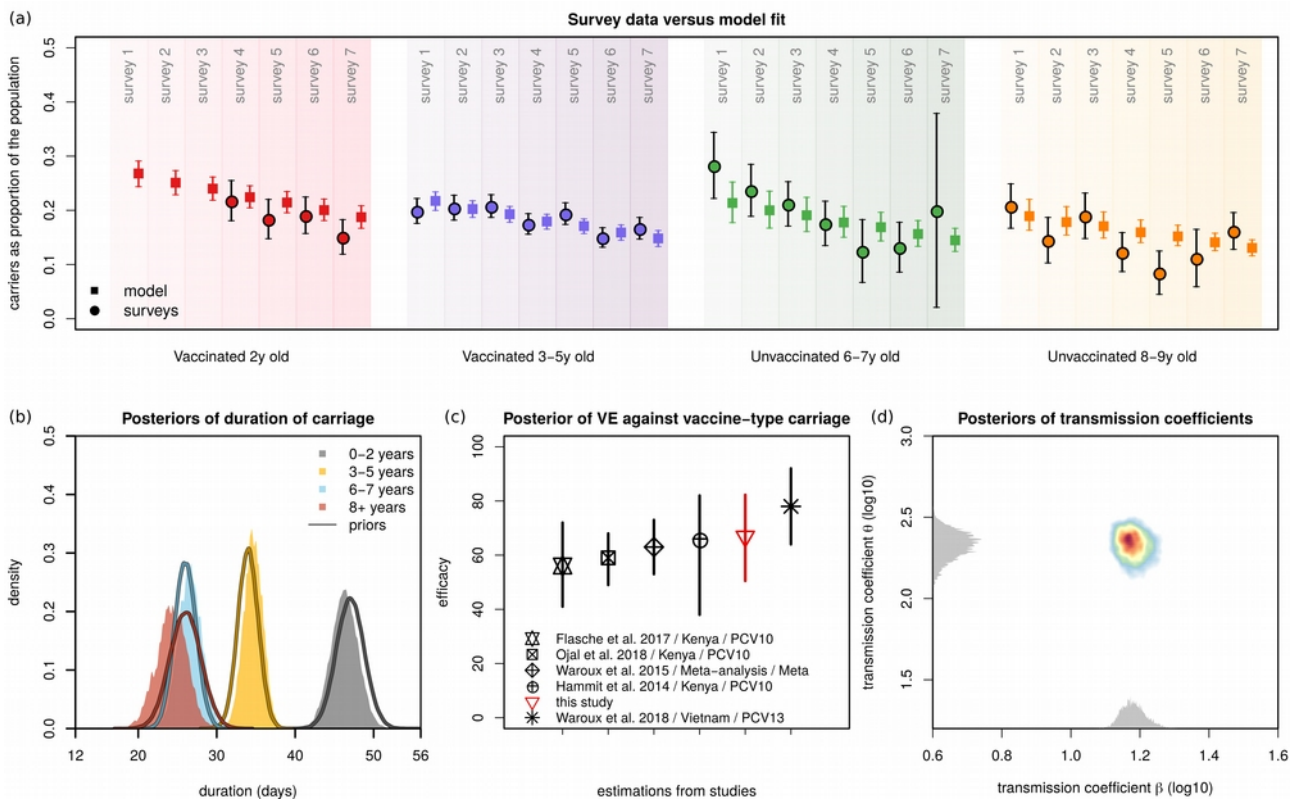
392 No other competing interests were reported by authors.

## 394 Figures

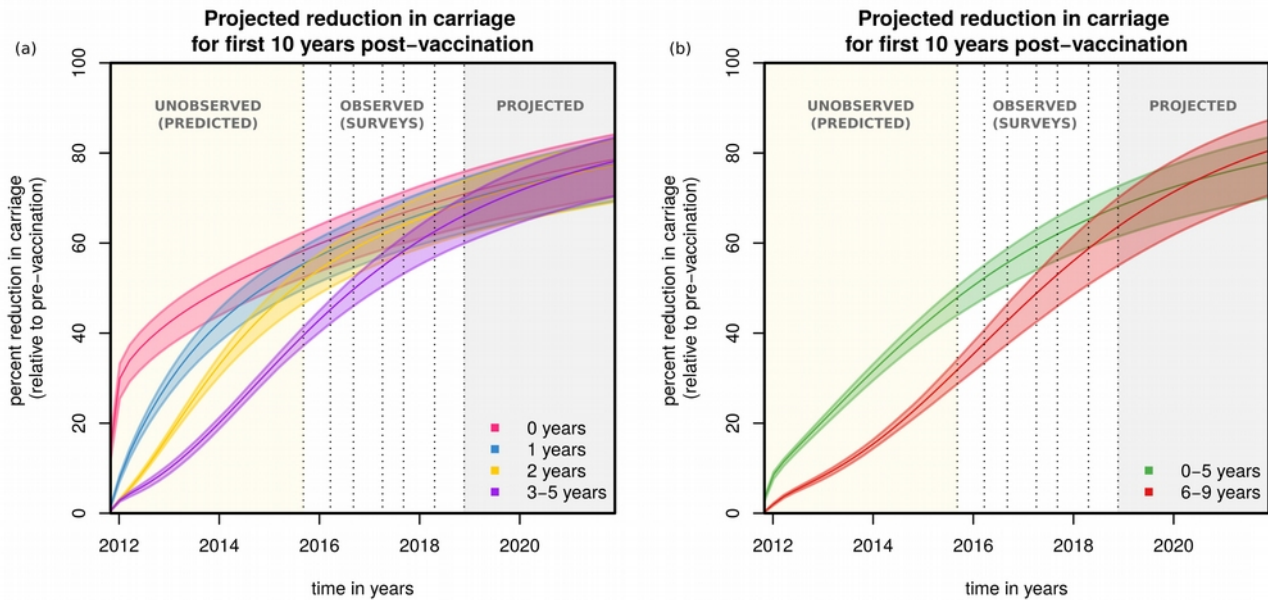


**Figure 1: Survey data and model framework, priors and transmission matrix.** (a) Seven age-groups were modelled: 0, 1, 2, 3-5, 6-7, 8-9, 10+ years of age (circles), each divided into unvaccinated (top) and vaccinated (bottom). Labels  $a_{age\text{-}group}$  mark ageing rates per age class;  $\mu_{age\text{-}group}$  mark age-specific death rates;  $b$  marks births, at which point a proportion ( $\rho$ ) are vaccinated (purple);  $\zeta$  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 transmission matrix used, with coefficients  $\beta$  and  $\theta$ , where  $\theta$  is the specific coefficient for transmission within and between particular age-groups.  $\beta$  and  $\theta$  are estimated when fitting the survey data. (c) 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 ( $1/\gamma_{0-2}$ ,  $1/\gamma_{3-5}$ ,  $1/\gamma_{6-8}$ ,  $1/\gamma_{8+}$ ) are estimated when fitting the survey data. (d) Mean and standard error for carriage as reported in the observational study data (surveys) per age-group (Table S7). S1 to S7 highlight the surveys 1 to 7. The \* mark data that was not collected.

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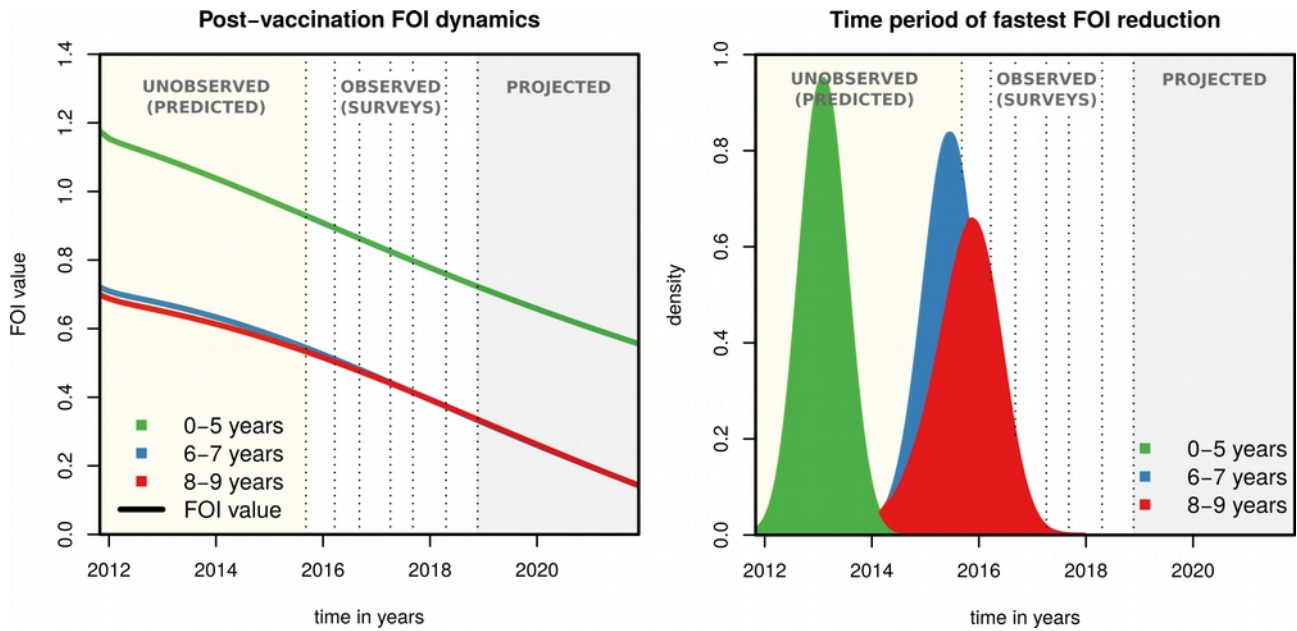


412 **Figure 2: Model fit and estimated posteriors.** (a) Model fit to carriage data from the  
 414 observational study for different age-groups: vaccinated 2 years old (red), vaccinated 3-5 years old  
 416 (purple), unvaccinated 6-7 years old (green) and unvaccinated 8-9 years old (orange). The survey  
 418 data is represented by full circles, the model output by full squares (data in Figure 1d, Table S7). (b)  
 420 Priors (lines) and estimated posterior distributions (shaded) of duration of carriage per age-group.  
 422 (c) Estimated mean and 95% CI of posterior of vaccine efficacy against vaccine-type carriage (red)  
 424 in the context of estimates from other studies (in legend, Table S2). (d) The estimated posterior  
 distributions of the transmission coefficients  $\beta$  and  $\theta$  are shown in two dimensions (coloured area).  
 The estimated actual distribution for  $\beta$  is in the x-axis and  $\theta$  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.

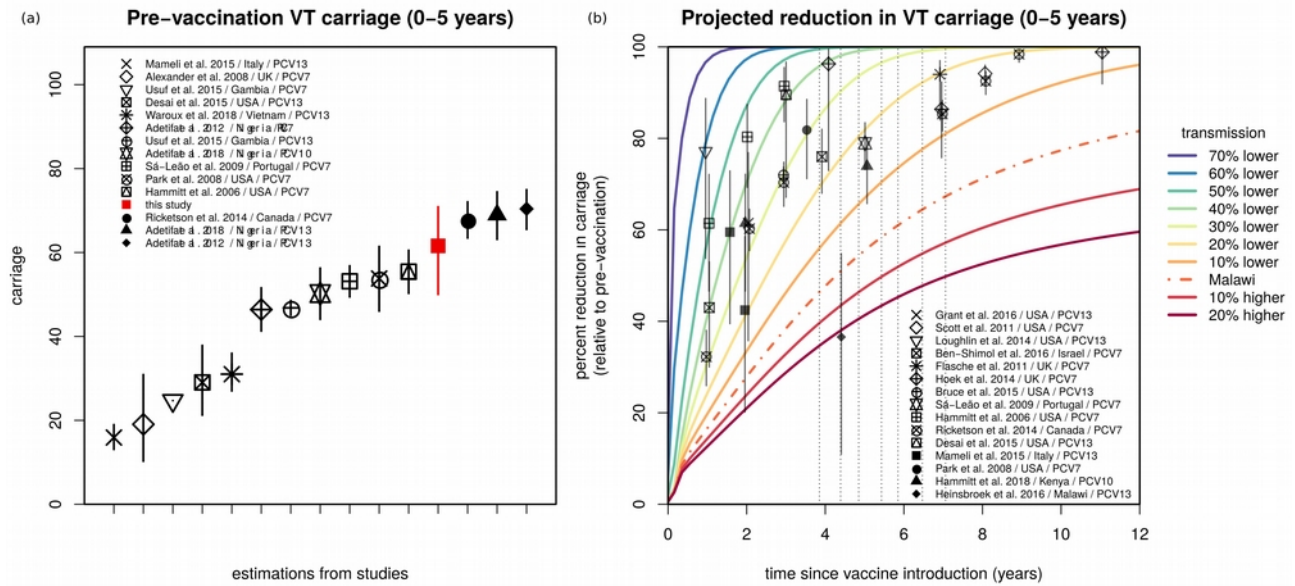


426 **Figure 3: Projections of post-vaccination vaccine-type carriage reduction.** (a) Projected  
428 reduction in carriage relative to the pre-vaccination era for age-groups 0 years (magenta), 1 year  
430 (blue), 2 years (yellow) and 3-5 years (purple) old. (b) Projected reduction in carriage relative to the  
432 pre-vaccination era for aggregated age-groups 0-5 years (green) and 6-9 years (red) old (with  
434 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 yellow for the post-  
vaccination period with no carriage data, white for the post-vaccination period with data, and grey  
for the post-vaccination projected period up to 10 years. Dotted vertical lines mark survey dates.  
The x-axis origin marks PCV13 introduction.

436



438 **Figure 4: Projections of post-vaccination changes in the force of infection.** (a) The post-  
440 vaccination force of infection (FOI) of different age groups (0-5 years in green, 6-7 in blue and 8-9 in  
442 red) as calculated for each of 100,000 simulations using parameter samples from posteriors. (b) For  
444 each FOI of each age-group and each 100,000 simulations using parameter samples from posteriors,  
446 the time point of minimum derivative was calculated, resulting in one distribution per age-group  
448 (coloured curves, 0-5 years in green, 6-7 in blue, 8-9 in red). This time point is as a proxy for the  
period of fastest FOI reduction. The shaded areas are yellow for the post-vaccination period with no  
carriage data, white for the post-vaccination period with data, and grey for the post-vaccination  
projected period up to 10 years. Dotted vertical lines mark survey dates. The x-axis origin marks  
PCV13 introduction.



**Figure 5: Estimated vaccine-type carriage and sensitivity of 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 S6). (b) The baseline transmission coefficient ( $\beta$ ) 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,  $\beta_{\text{Malawi}}$ ) when fitting the observational study (e.g. 10% lower is  $0.9 \cdot \beta_{\text{Malawi}}$ ). The impact projections for the age-group 0-5 years old using the  $\beta$  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 S5). The grey arrows mark the year of PCV13 introduction and the years of the four surveys.

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