Appendix file 2: Description of the calibration method and parameters for the vaccine effect

Parameters included in the calibration

The vaccine effect is modelled as a percentage reduction of the force of infection resulting from an infected mosquito bite. This mechanism is plausible from the biological mode of action for pre-erythrocytic vaccines. Other transitions between health statuses from infected (I) to clinical malaria (C) and from clinical malaria (C) to severe malaria (F) are not modified by the vaccine.

The percentage initial reduction of the force of infection, shortly after having received the 3 doses, and the waning over time are calibrated jointly based on the incidence of clinical malaria in each arm of the Phase III trial using follow-up periods of 3 months until study end in the intent-to-treat analysis. For the primary series of 3 doses of vaccine, the waning is modelled using a bi-phasic exponential decay which is reproducing the dynamics of short and longer term immune response. A single exponential decay model was tested as well but didn’t provide an accurate fit (data not shown). The waning of the fourth dose is assumed to follow a single exponential decay. The shorter follow-up period after the fourth dose prevented the calibration of a bi-phasic exponential decay function.

Four parameters are used to characterise the vaccine effect after the 3 doses: initial reduction of the force of infection shortly after having received the 3 doses, half-life for the first phase of exponential decay, half-life for the second phase of exponential decay and the time between onset of both 2 phases (transition time).

Two additional parameters are used to characterise the effect of the fourth dose: additional risk reduction at the time of the fourth dose and the half-life of the exponential decay.

Calibration process

The parameters are estimated independently for infants and children vaccination schedules.

First, estimates of the parameters for the primary series (3 doses) were generated. The distribution of parameters was based on a Monte Carlo Markov Chain generated with a Metropolis-Hastings algorithm. New candidate estimates were generated with a random process using the previous accepted estimates in the chain. The new candidate estimates were retained if their likelihood is higher than from the previous estimates in the chain; if the new likelihood is lower than for previous estimates, the new candidate estimates will be retained with a probability corresponding to the ratio of likelihoods of the new candidate estimates and previously retained estimates.
The likelihood function is based on the distance between trial data and model estimates of the vaccine efficacy against clinical malaria for 3-month follow-up periods; the smaller the distance, the higher the likelihood. The trial data was pooled into 3 transmission intensity levels (low, moderate and high) as described in a previously published manuscript\(^1\). The likelihood is computed for moderate and high transmission intensity simultaneously, therefore the same set of parameters is used across transmission intensities. The small number of cases in low transmission intensity sites (Kilifi and Korogwe) resulted in large efficacy variations for the 3-monthly periods. These sites were therefore excluded from the likelihood computation.

Second, estimates corresponding to the fourth dose are generated following the same process using 3-monthly incidence from the time the fourth dose was administered. The median values obtained for the primary series parameters in the first step are used.

**Comparison of the model estimates and trial data on vaccine efficacy**

Figure A-1a. Comparison of model estimates and trial data for vaccine efficacies over 3-monthly periods in children 5-17 months
Each box represents a clinical site ordered according to increasing transmission intensity. The blue dots and vertical bars indicate the point estimates of vaccine efficacy against clinical malaria and corresponding confidence interval per 3-month period over the follow-up period (up to 4 years) from the clinical trial data. The red shading indicates the model prediction and confidence interval per 3-month period, showing the uncertainty in the model.

**Figure A-1b. Comparison of model estimates and trial data for vaccine efficacies over 3-monthly periods in infants 6-12 weeks**

Each box represents a clinical site ordered according to increasing transmission intensity. The blue dots and vertical bars indicate the point estimates of vaccine efficacy against clinical malaria and corresponding confidence interval per 3-month period over the follow-up period (up to 4 years) from the clinical trial data. The red shading indicates the model prediction and confidence interval per 3-month period, showing the uncertainty in the model.

**Distribution for fitted vaccine parameters**

Distributions of vaccine parameters fitted with the procedure described above are provided in the figures below for both vaccination schedules.

**Figure A-2a. Distribution of vaccine parameters for the children vaccination schedule (first dose at 5 to 17 months)**
The top row shows the distribution for 4 parameters associated to the primary series of 3 doses. The bottom row shows the distribution for 2 parameters associated with the 4th dose.

Figure A-2b. Distribution of vaccine parameters for the infant vaccination schedule (first dose at 6 to 12 weeks)

The top row shows the distribution for 4 parameters associated to the primary series of 3 doses. The bottom row shows the distribution for 2 parameters associated with the 4th dose.