**Reference sheet: Malaria modelling for Vaccine Impact Modelling Consortium, Imperial College London**

*Model*

To estimate vaccine impact, we utilised the Imperial College malaria model open-source R package [*malariasimulation*](https://mrc-ide.github.io/malariasimulation/index.html)version 2.0.1(1), a previously developed individual-based and age-stratified malaria transmission model. The model tracks several kinds of immunity, including:

* Pre-erythrocytic immunity, which reduces the chance of infection upon receiving an infectious bite and is dependent upon exposure;
* Immunity to clinical disease, which depends on past exposure and, in infants, maternal antibodies;
* Immunity to severe malaria, which is dependent on both past exposure and age, as well as maternal antibodies.
* Immunity to blood stage parasitaemia, which reduces the chance an infection will be detected and increases with past exposure.

Mortality is a fixed proportion of severe disease (~.2). *malariasimulation* incorporates input data to characterize malaria transmission in sub-Saharan Africa at the resolution of transmission intensity, demography, seasonality profiles, and coverage of non-vaccine interventions. Data on intervention coverages were sourced from the Malaria Atlas Project (MAP) and the World Malaria Report(2,3).

*Vaccine Efficacy*

We used a previously published R21 vaccine efficacy model from Schmit & Topazian (4), briefly summarized here. R21 induces an immune response to the central repeat amino acid region of the *P. falciparum* circumsporozoite protein (CSP), thereby reducing the probability of infection. First, the dynamic of CSP antibody titre over time was modelled assuming a boost upon the 3rd vaccine dose and booster dose up to peak levels, followed by a biphasic exponential decay. The R21 model was fit to Phase 2b trial data(5) from Burkina Faso over 3 years of follow up within a Bayesian framework. RTS,S vaccine efficacy was modelled in a similar fashion from phase 3 trial data across 11 clinical trial sites. Vaccine efficacy beyond the 3 years of follow up in the trial is projected forwards assuming antibodies continue to decay at the same rate longer term and have the same relationship with efficacy against clinical infection.

*Modelling scenarios*

We modelled vaccine impact by running models with and without vaccination for each of the first administrative subnational units (admin-1s) in the malaria endemic countries of interest from 2000-2100. In the baseline scenario, vaccines were not introduced. In the vaccine scenario, vaccines were administered to children in all admin-1 units with moderate-to-high malaria transmission, defined as PFPR > 10% in 2019 according to MAP estimates(2). For countries where all admin-1 units report parasite prevalence under this threshold, such as Ethiopia and Sudan, vaccination is modelled in the highest prevalence admin-1 units which approximate the population at risk provided by the VIMC.

We define clinical malaria as fever and parasitemia.

Vaccine coverage projections were sourced from Gavi scenario forecasts, which included estimated routine vaccine coverage for R21 and RTS,S for 31 malaria endemic countries from 2023 through 2100. We assumed that doses were delivered in an age-based strategy at 6, 7, 8, and 20 months of age.

For all modelled scenarios, we assumed constant coverage of non-malaria vaccine interventions from 2022 onwards, based on various data sources. These interventions include seasonal malaria chemoprevention (SMC), indoor residual spraying (IRS), insecticide-treated bed nets (ITNs), perennial malaria chemoprevention (PMC), and access to clinical treatment. Insecticide-treated net (ITN) usage follows a 3-year cyclical pattern based on administrated and time-based waning of net efficacy, and the pattern of the last 3-year cycle observed is carried out for the remainder of the simulation period, to capture this temporal trend.

Models were run with outputs recorded for single-year age groups up to age 20, followed by 10-year age groups from 20 to 100 years. Models were run on the admin 1 level, then aggregated up to the country level to estimate country-level cases and deaths. We applied bias correction to estimates based on World Malaria Report cases for each country, such that the average modelled number of cases from 2018-2020 approximated estimated malaria cases from the World Malaria Report in the same years. We also provided bias correction such that modelled population at risk approximated the population and risk values provided by the VIMC for each country. Central estimates were calculated as the average value across stochastic model runs using 50 random parameter draws each. 95% uncertainty intervals were constructed by pulling the 2.5% and 97.5% quantile values from 50 stochastic model runs. Cases and deaths averted were calculated by taking the difference between model outputs in the vaccine scenario and the no vaccination counterfactual.

*Key questions related to modelled results*

**Key assumptions used in Gavi forecast modelling**

Gavi vaccine coverage forecasts vary largely by country, with some countries achieving scaleup in the first 15 years following vaccine administration and other countries achieving scaleup after 2050. It would be useful to know what informs the varying scaleup periods by country, as this impacts country-level results.

**Stochasticity and negative values in estimates for Ethiopia and Madagascar:**

Ethiopia and Madagascar are modelled countries where all admin-1 units fall under the PFPR threshold for vaccine targeting (< 10% according to MAP estimates from 2019). To model vaccine administration in this location, we administered the vaccine to the highest prevalence admin-1 unit approximating the population at risk in these countries (Gambela for Ethiopia and Toliary for Madagascar, respectively).

In lower-transmission settings, malaria burden is more concentrated in older children and adults, whereas in high-transmission settings malaria burden is largely concentrated in children under 5. Given that the vaccine targets young children, with waning efficacy over time, these factors contribute towards reduced vaccine impact in lower-transmission settings. Additionally, impact results have greater stochasticity in these locations because a small portion of the total population receives the vaccine, meaning fewer model runs relative to other countries and therefore greater variation.

**Differences between modelled estimates for R21 and RTS,S**

Our submitted model runs indicate much larger impact for R21 than RTS,S in all VIMC countries, which we assume is related to the greater contribution of long-term immunity in immune response and greater duration of protection.  However, we recognize that uncertainties related to differences in trial design and follow-up duration complicate the interpretation of observed differences in vaccine impact.

**Differences between modelled estimates for different VIMC malaria modelling groups**

Estimates of vaccine impact in terms of deaths averted were quite similar in magnitude for all modelling groups, whereas estimates of cases averted varied more dramatically between groups. In general, the Imperial College (IC) and UAC models were more aligned in terms of cases averted than the Swiss TPH/ TKI model. Both the Imperial College and UAC models demonstrated a fluctuating incidence pattern over time, reflecting the impact of insecticide-treated nets (ITNs) which were assumed to be distributed routinely every few years. The Swiss TPH/TKI model demonstrated lower and sometimes negative vaccine impact in lower-transmission countries, like Ethiopia. This could potentially be attributed to delayed malaria and a shift in malaria cases to older ages.

Given that both the IC and Swiss TPH/TKI models produce outputs at the subnational level, with inputs pertaining to transmission intensity and coverage of non-vaccine malaria interventions varying by admin unit, it is relatively difficult to pinpoint the source of differences in vaccine impact estimates at the national level. This point has been echoed by malaria modelling groups at several VIMC and GAVI meetings, underscoring the importance of alignment in inputs at the subnational level and more granular inputs for vaccine coverage and demography from GAVI/VIMC. This information would potentially aid modellers in identifying methods differences between the groups and downstream impacts on model outputs.

**References**

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