**Title** Impact of Vaccine Introduction on Malaria Cases and Deaths in Sub-Saharan Africa: A Modelling Study

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**Abstract**

***Introduction*** Malaria is a highly fatal vector-borne disease that primarily affects children under 5 years old. While progress has been made in reducing malaria burden with clinical and environmental interventions, improvements have stalled, indicating a need for new tools for disease control. New pre-erythrocytic vaccines such as R21/Matrix-M (R21) hold the potential to greatly reduce malaria burden in Sub-Saharan Africa, and mathematical modelling can be used to estimate vaccine impact across endemic settings. For this work, we estimate the potential long-term impact of vaccine rollout across moderate to high malaria transmission settings in Sub-Saharan Africa.

***Methods*** To estimate vaccine impact on malaria cases and deaths we utilised *malariasimulation*, an individual-based malaria transmission model developed at Imperial College London. Vaccine efficacy parameters were previously estimated from fitting a model of the relationship between antibody titre and vaccine efficacy to 3 years of follow up of phase 2b trial data from Nanoro, Burkina Faso. We estimated the impact on malaria cases and deaths in moderate-to-high transmission admin-1 units in Sub-Saharan Africa based on GAVI forecasts of vaccine coverage in children under 3 years old. Models were run with and without vaccination from 2000 to 2100 to capture lifetime vaccine impact. We calibrated the model to Malaria Atlas Project (MAP) prevalence of infection data, incorporating information on seasonality, vectors, demography, and coverage of other non-vaccine malaria intervention. We assumed continuous coverage of non-malaria vaccine interventions from 2023 through 2100.

***Results*** Under a routine vaccination scenario where vaccines are introduced in 2023, we estimate 818 million (95% uncertainty interval: 590 million-1.06 billion) malaria cases and 2.54 1.91 million (1.33-3.55) deaths averted in Africa through 2050. Through 2100, the vaccine averted 4.26% 3.8% (3.76-5.05) of malaria cases and 7.90% 5.8% (3.68-12.66) of all malaria deaths in this region, but there were still 1.1 1.2 million (565,000-1.73 million) deaths per year on average. The impact was greatest in children under 5 years. Due to predicted delayed malaria effects in older children and young adults, we estimate that vaccine impact would be greatest in the initial years following vaccine introduction and begins to decline after 10 years as efficacy and immunity wanes into older adulthood and populations age.

**Discussion** Malaria vaccination could avert a substantial number of cases and deaths across Sub-Saharan Africa. However, layered administration of malaria vaccines with non-vaccine malaria interventions will be needed to bolster impact, as they will be insufficient in disrupting residual transmission and eradicating malaria over a long-time horizon. These estimates are dependent on uncertain assumptions about the dynamics of both naturally acquired and vaccine-acquired immunity. As longer-term follow up data on vaccine efficacy becomes available, more context-specific modelling will be needed to assess the long-term impact of vaccination in endemic settings and what factors, such as older target populations and additional booster doses, contribute to greater impact.

**Introduction**

Malaria, a potentially fatal disease caused by the *Plasmodium* parasite and transmitted by female *Anopheles* mosquitoes, kills approximately 600,000 people each year, with 76% of these people residing in Sub-Saharan Africa1. While progress was made between 2000 and 2015 through interventions such as insecticide-treated bed nets (ITNs) and clinical treatment1, control efforts have stalled in recent years. Malaria eradication has grown more challenging due to the emergence of partial resistance to artemisinin-combination therapies (ACTs)2 and common insecticides3, which may reduce the effectiveness of ITNs and ACTs throughout much of Africa. Moreover, major events such as the COVID-19 pandemic4 and political conflicts5 have disrupted clinical care and public health supply chains in several African countries, impacting intervention coverage. Climate change also has increased the frequency of extreme weather events, potentially extending seasons of peak malaria transmission6. Despite this, international financing for malaria control has remained stagnant, limiting the resources available for disease control7. This is expected to worsen as American funding for malaria programs shrink8.

Given these issues, novel tools are needed to accelerate the fight against malaria and progress towards eradication. Among these tools are RTS,S/AS01 (RTS,S) and R21/Matrix-M (R21), malaria vaccines which have recently been approved by the WHO for use among children in sub-Saharan Africa9,10. Both RTS,S and R21 are pre-erythrocytic vaccines which act upon the circumsporozoite protein (CSP) of *P. falciparum*. Both vaccines are recommended to children from age 5 months, with the first three doses administered in the first year of life and a booster dose administered 12-18 months after the third dose11. Both vaccines are only partially effective, and their efficacy wanes over time. In a phase 3 clinical trial where RTS,S was administered seasonally to children in Mali and Burkina Faso, RTS,S and SMC demonstrated 72% (95% CI 64–78) 12-month vaccine efficacy compared to SMC alone. Across 7 countries, RTS,S demonstrated 12-month vaccine efficacy of 51% (95% CI 47–55) in children aged 5-17 months who received an age-based regimen12. Impact waned to 39% (95% CI 34–43) after 4 years. R21 demonstrated a 12-month vaccine efficacy of 75% (95% CI 71–79) in a phase 3 trial of children aged 5-36 months across both seasonal and perennial malaria transmission sites13. Further results on vaccine efficacy are anticipated with a longer period of follow-up in the phase 3 trial.

RTS,S was piloted through programmatic administration in Ghana, Kenya, and Malawi, where 900,000 children were reached through the Malaria Vaccine Implementation Programme (MVIP), resulting in high uptake and reduced all-cause mortality14. As of June 2025, distribution of RTS,S and R21 has begun in 20 countries including Burkina Faso, Nigeria, and Cameroon, with over 13 million doses delivered15. R21 has a cheaper cost and greater manufacturing capacity than RTS,S although the situation is constantly developing16. High demand and limited supply due to funding constraints is expected to be an issue for both malaria vaccines, with vaccine allocation prioritized to areas of highest malaria burden and expected highest health impact17.

Long-term public health impact of malaria vaccines is complex to estimate as impact varies according to transmission intensity of malaria, long-term duration of protection, as well as coverage of other interventions and long-term immunity dynamics in vaccinated vs unvaccinated people. Mathematical models have been used to synthesise these many variables and to estimate the health impact of vaccine rollout in different scenarios, informing prioritisation and allocation decisions. A modelling exercise indicated that routine R21 delivery could avert an average of 181,825- 202,017 clinical cases per 100,000 fully vaccinated people over 15 years, depending on seasonality in the implemented settings18. Modelling exercises have predicted large net reductions in clinical malaria after malaria vaccine introduction, particularly in young children, contrasted by smaller increases in clinical disease in older children and adults. These increases in clinical disease in older individuals are attributable to reduced acquisition of natural immunity and a rapid waning of vaccine efficacy after administration19. The extent of this “rebound” in malaria, alternatively termed delayed malaria in older age groups, remains unclear but could affect the long-term impact of exposure-reducing malaria interventions20. As delayed malaria complicates the long-term dynamics of malaria transmission after the introduction of exposure-reducing interventions, long-term analyses may help elucidate how vaccine impact varies over time.

While previous analyses of vaccine impact have been conducted for both RTS,S21,22 and R2123, work has largely focused on generic scenarios in which transmission intensity, intervention coverage, population demography, and seasonality were fixed, and a limited 15-year timeline. Here, we estimate the long-term impact of the rollout of R21 across moderate-to-high-transmission settings in specific countries in Africa, allowing for sub-national parameterization of population growth, non-vaccine interventions and current estimates of longer-term vaccine impact based on recent trials. This work was completed as part of the Vaccine Impact Modelling Consortium (VIMC). Funded by Gavi and the Gates Foundation, the VIMC produces vaccine impact estimates for 11 different pathogens across 98 countries24.

**Methods**

*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 2.0.125*. malariasimulation* isa previously developed individual-based and age-stratified malaria transmission model (**Supplemental Figure 1**). The modelhas previously been fit to extensive epidemiologic data from endemic African settings. The model has been described in detail elsewhere and tracks both humans and mosquitoes through stages of infection and disease 21,26. Full model details are available in the supplemental appendix (section X).

Briefly, in the model, an individual may become infected with malaria via a bite from an infected female *Anopheles* mosquito. From that point, the individual may either develop symptomatic uncomplicated malaria, severe disease or asymptomatic infection. If clinically diseased, a person may seek treatment and clear infection if treatment is successful or remain untreated. If they survive an untreated or unsuccessfully treated infection, a person may recover from clinical disease naturally and become asymptomatic. Severe disease is taken as a fixed proportion of clinical disease (SI section X). Asymptomatic infections eventually progress to low density sub-patent infections and recover naturally, in the absence of superinfection. Individuals in all stages of infection can infect a mosquito, which are infected at a rate depending on population-level transmission intensity. Mosquitoes become infectious after a 10-day incubation period post-exposure. The model tracks several kinds of immunity, including pre-erythrocytic immunity which reduces the chance of infection upon receiving an infectious bite. Immunity to clinical disease depends on past exposure and, in infants, maternal antibodies. Immunity to severe malaria is dependent on both past exposure and age, as well as maternal antibodies. Immunity to blood stage parasitaemia reduces the chance an infection will be detected and increases with past exposure.

*Vaccine Efficacy*

We used a previously published vaccine efficacy models from Schmit & Topazian18, briefly summarized here. Both vaccines induce 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 CSPpeak, followed by a biphasic exponential decay, representing short-lived (rs) and long-lived (rl) antibody components.

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Description automatically generated

Subsequently, a dose-response relationship between anti-CSP antibody titre and vaccine efficacy against infection was fit to data on clinical disease using the following function, where vaccine efficacy increases with antibody titre up to a maximum value (Vmax), with shape parameters alpha and beta:

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The R21 model was fit to individual-level Phase 2b trial data27 from Burkina Faso over 3 years of follow up within a Bayesian framework. 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 anald have the same relationship with efficacy against clinical infectiodn. This results in estimated efficacy against multiple clinical malaria episodes of about 35% at year 4, declining to about 25% at year 518. RTS,S vaccine efficacy models were fit to phase 3 trial data across multiple countries 12 from the 5-17 month and 6 to 12 week cohorts. Vaccine synergy with SMC or other malaria prophylactic drugs were not included. Median vaccine efficacy parameters and parameter descriptions are available in full in SI Section 3 (**Table S5**).

*Modelling scenarios*

*malariasimulation* incorporates input data28,29 to characterize malaria transmission in sub-Saharan Africa at the resolution of transmission intensity (meaning the equilibrium level of malaria transmission that would occur in the absence of interventions, determined by the carrying capacity of the environment), demography, seasonality profiles, and coverage of non-vaccine interventions such as indoor residual spraying, seasonal malaria chemoprevention, and insecticide-treated bed nets (see supplementary information Section 3). Data on intervention coverages were sourced from the Malaria Atlas Project and the World Malaria Report (**Table S6**)1.

We modelled vaccine impact by running *malariasimulation* models with and without vaccination for each of 470 first administrative subnational unit (admin-1 level) in 31 malaria endemic African countries from 2000-2100 (**Supplemental Figure 2**). We devised a routine vaccine scenario for all VIMC countries, based on public data on the year of vaccine introduction, type, supply, and protected children (**Supplemental Methods Section X).** We assumed 50 million children would be protected between 2026-2030 and that vaccine supply would reach 80-100 million doses after this point, in line with Gavi public estimates30,31**.** In the baseline scenario, vaccines were not introduced, and in the vaccine scenario, routine vaccination was introduced in 2023 and continued through 2100. For all modelled scenarios, we assumed constant coverage of non-malaria vaccine interventions from 2022 onwards, based on various data sources (**Table S6**). 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 a simulated population of 50,000 individuals at the admin 1 level, then aggregated up to the country level and multiplied by national demography values to estimate country-level cases and deaths. The pre-intervention EIR in the model was calibrated so that the pre-vaccination prevalence of infection in 2–10-year-olds matches the Malaria Atlas estimates in the first administrative subnational area of each country. Where there were discordances between admin-1 level populations and national populations, we scaled modeled populations and outputs such that the sum of populations at the admin-1 level was equivalent to national UN populations. In the absence of subnational population data from 2050-2100, we assumed that the proportional breakdown of population by admin-1 was fixed from 2050-2100. We additionally applied bias correction to estimates based on World Malaria Report cases for each country, such that the modelled number of cases from 2018-2020 was equal to estimated malaria cases from the World Malaria Report in the same years. Central estimates were calculated as the average value across stochastic model runs using 50 random parameter draws each at the admin-1 level. 95% uncertainty intervals were constructed by pulling the 2.5% and 97.5% quantile values from 50 stochastic model runs.

In the vaccine scenario, vaccines were administered to children in all admin-1 units with moderate-to-high malaria transmission, defined as *plasmodium falciparum* parasite prevalence > 10% in 2019 according to Malaria Atlas Project estimates28. Vaccine coverage data were sourced from Gavi scenario forecasts, which included estimated vaccine coverage for R21 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. Cases and deaths averted were calculated by taking the difference between model outputs in the vaccine scenario and the no vaccination counterfactual.

**Results**

*Overall impact*

Under a baseline vaccine scenario beginning in 2023, we estimate that 16.5 16.3 billion (95% UI 11.2 billion-22.1 billion) cases of malaria and 38.5 40.2 million (19.4 -56.7 million) malaria deaths would occur through 2050. Under a routine vaccine scenario beginning in 2023, we estimate that 818 621 million (95% UI 590 million-1.06 billion) cases of malaria and 2.54 1.91 million (1.33-3.55) malaria deaths would be prevented through 2050. These figures represent a 5.05% (4.69-5.57) 3.8% decrease in malaria cases and a 6.67% 4.8% (4.55-8.89) decrease in deaths. Through 2100, we estimate a 4.26% 3.8% (3.76-5.05) decrease in malaria cases and a 7.90% 5.8% (3.68-12.66) decrease in malaria deaths, as compared to cases and deaths in the nonvaccinated scenario (**Figure 1**).

*Impact by country*

Vaccines averted an average of 156,000 101,000 cases (30,000-242,000) (11,000-190,000) per 100,000 fully vaccinated people (FVP) in countries in the first 15 years following vaccine introduction and 119,000 84,000 (18,000-144,000) (69,000- 139,000) cases per 100,000 FVP through 2100 (**Figure 2**). Under a routine 4-dose vaccination scenario, we estimate the greatest number of cases averted in Nigeria (493 677 million, 95% UI 330-655), followed by the Democratic Republic of the Congo (310 139 million cases [95% UI 210-410]) over the 100-year simulation period. We similarly estimate the greatest number of deaths averted from these countries (1.79 2.07 million deaths [95% UI 944,000- 2.74 million] and 1.28 642,000 million deaths (681,000- 2.18 million), respectively.

Impact by age and time

Vaccination is predicted to have the highest impact in children under 5 years, with some rebound malaria infections in older children, i.e. an increase in incidence compared to unvaccinated children of the same age, due to vaccine immunity waning and lack of developed naturally acquired immunity20. Previous model forecasts focussed on vaccine impact over 15 years after introduction18,32 – here we extend the time horizon for our forecasts and find that this modifies the predicted size of the impact.

From 2000 through 2100, we estimate 3.79 2.13 billion cases (2.61-5.18) would be averted by vaccines in children under 5, in contrast to an estimated decrease of 767 5.8 million cases (124-228) in children between 5 and 15 and an increase of 1.01 439 million billion (615 million-1.46 billion) cases in people over 15 years old (**Figure 3**). An estimated 13.1 9.4 million (762,000-18.3 million) deaths were averted in children under 5, in contrast to an estimated increase of 4.54 2.8 million (2.01- 7.39) deaths in children between 5 and 15 and 965,000 927,000 (422,000-1.67 million) deaths in people over 15. Over the first 10 years following vaccine introduction, vaccine impact is uniformly positive across all age groups in terms of cases and deaths averted. Impact becomes negative for older children and adults when vaccinated children begin to become susceptible to infection as vaccine efficacy wanes. Despite different patterns of vaccine impact by age group, net vaccine impact is positive across the entire simulation period (**Figure 1**). Impact is also influenced by changing population structure over the simulation period (**Supplemental Figure S2).** While delayed malaria is observed overall in model results, impacts are uniformly positive across age in lower-transmission settings such as Sudan (**Supplemental Figure S3).**

We predict less rebound in malaria deaths than in uncomplicated cases of malaria (as a percentage of disease averted in children <5 yrs). This difference is a result of model assumptions that immunity against severe malaria is partially age-specific33, while immunity against uncomplicated malaria is purely exposure-dependent 33. These immunity patterns previously gave the best fit to age patterns of uncomplicated and severe disease across different levels of malaria transmission (see discussion). The rebound in malaria cases was largest in the 15+ age group, while the rebound in malaria deaths was largest in the 5-15 yr age group.

Factors influencing vaccine impact

When estimates of vaccine impact are disaggregated by admin-1 unit, impact is concentrated in locations with higher transmission intensity at the time of vaccination introduction, assuming constant coverage of non-vaccine interventions going forwards (**Figure 4**).

**Discussion**

Our results demonstrate a large impact of malaria vaccination across Africa, averting an estimated 818 million (95% UI 590 million-1.06 billion) malaria cases and 2.54 million (1.33-3.55) deaths through 2050 in a routine coverage scenario. Our projections additionally indicate the greatest impact in locations with highest transmission intensity. These results indicate the large expected impact of vaccines in reducing the burden of malaria across the African continent in coming years, saving millions of lives and reducing health system stress due to severe cases. Moreover, vaccine impact on clinical incidence was concentrated in the first 15 years post- vaccine introduction, with cases averted decreasing slightly as vaccinated populations age and outgrow more vulnerable age groups, though we predicted delayed malaria in older ages. In comparison, vaccine impact on mortality remained steady throughout the century.

Our vaccine impact results are generally similar in magnitude per vaccinated child in comparison to previous work over the first 15 years following vaccine introduction23. After this point, impact wanes due to delayed malaria and ageing populations. Delayed malaria is characterized by a resurgence of malaria in people who did not develop natural immunity as children due to exposure-reducing interventions with waning efficacy*.* Concurrently, the average age of Sub-Saharan African populations is increasing, meaning that a greater proportion of the population is less susceptible to severe disease and death. Despite this negative impact in older age groups, it is important to note that net vaccine impact remains positive over the entire modelling period.

Moreover, there remains great uncertainty in modelling the long-term impact of malaria vaccines, particularly given the lack of long-duration follow-up data on vaccinated individuals, and the limited number of sites which have introduced the vaccine. While initial unpublished results suggest our model is in line with longer-term data18, the duration of vaccine protection may be significantly shorter or longer than modelled here, or may vary depending on underlying population and transmission intensities. Our results indicate that long-term immunity dynamics hold the potential to significantly influence vaccine impact, even in a situation where vaccine coverage remains quite high over a long period of time. Our predictions of rebound malaria are, however, highly uncertain. *malariasimulation* was previously fitted to data on age patterns of uncomplicated and severe malaria from numerous transmission settings, which informs the age patterns of disease that are predicted during rebound. However, in all these settings we assumed relatively constant malaria transmission over time. The model has not been fitted to data where individuals are protected during early life and then exposed to a higher incidence of infection at older ages (as in vaccination after waning of vaccine-induced protection).

Our predictions of delayed malaria at older ages are informed largely by age patterns of disease in lower transmission settings where individuals are more likely to first be exposed to malaria at an older age26,34. To some extent this has been observed in vaccine trials, but data are limited. Longer follow up has only so far taken place for the RTS,S vaccine, not for the R21 vaccine. During 7 years of follow up of RTS,S vaccinated children in phase 2 trials in Kenya and Tanzania, vaccine efficacy was close to zero in the vaccinated cohort in the 4th year after vaccine introduction and negative in the 5th year, indicating the effects of delayed malaria35. In a phase 3 trial of RTS,S in children in Burkina Faso, vaccine efficacy against clinical malaria was also slightly negative over years 6 to 7, although data suggested long-term efficacy against severe malaria in all sites over a 7-year follow-up period36 in line with our model estimates of more consistent positive effects on severe malaria and mortality. Given the potential for delayed malaria over a long time horizon following vaccination, additional vaccine boosters at older ages or other targeted interventions could potentially mitigate excess incidence.

The size of the mortality impact of vaccination remains uncertain due to low numbers of trial participants, particularly in the long term given the limited RTS,S trial sites with follow up past 4 years. Our model may also underestimate impact of the vaccine on deaths: while we estimated a 7% decrease in malaria mortality from R21 over 50 years, the recent Malaria Vaccine Implementation Programme estimated a 9% reduction in all-cause mortality from RTS,S over 4 years14 - i.e. higher than would be expected given the recorded contribution of malaria to all-cause mortality. Malaria may contribute indirectly to deaths from other illnesses (cite), but we do not capture those effects here. Our modelled malaria mortality rates are based on verbal autopsy data which may not capture the indirect contribution to other deaths exacerbated by malaria, e.g. bacteraemia37.

It is important to note estimates of up to a 6.67% (4.55-8.89) total population decrease in malaria cases through 2050 are achieved within a scenario where coverage of non-vaccine malaria interventions remains constant, vaccines are introduced to all 31 VIMC countries within the next 5 years, and high coverage is achieved and sustained throughout the century. This scenario will not be achieved everywhere, although vaccine supply is due to become less constrained. While the manufacturing capacity of R21 is expected to be quite high38, large financial and operational commitments will be required from donors, multilateral organizations like WHO and GAVI, and local governments to achieve sustained high coverage on the African continent in coming years. Several factors may reduce vaccine impact upon widespread rollout, including issues of acceptability and vaccine uptake39. Community engagement and health promotion activities will be needed to increase the uptake of malaria vaccines on the continent and improve vaccine impact.

Models indicate that, despite the large estimated magnitude of cases and deaths averted due to vaccination, this amounts to a minority of total malaria burden if the vaccine is given only to young children11 and will not be sufficient to meet WHO Global Technical Strategy targets40. Sustained coverage of non-vaccine malaria interventions will be required to complement vaccination and contribute to reductions in malaria burden in coming years. Moreover, new tools in the development pipeline will be needed to contribute towards malaria eradication.

There are several new malaria vaccine candidates which, if successful, may complement R21 and RTS,S. Among these includes RH5, a vaccine targeting a P*. falciparum* blood-stage protein which has shown promise in early clinical trials41,42. RH5 has potential to be administered alongside R21, enhancing vaccine efficacy43. Additional research will be required to estimate the impact of such combined vaccine regimens, as well as to determine what factors contribute to greater impact.

We estimate large projected impact of a 4-dose R21 vaccination regimen on malaria burden across 31 African countries through 2100. Impact was greater in younger children, in higher transmission settings, and in the first 15 years after vaccination. Despite this impact, R21 will be insufficient to eradicate malaria deaths across Africa in the next century, and new tools will be required to complement R21 vaccination in reducing malaria burden.

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