Comparing modelled impact and cost-effectiveness estimates for the RTS,S/AS01 malaria vaccine with evaluation results observed in phased pilot introductions

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EXECUTIVE SUMMARY

Overall assessment

This report references results and information collected as part of the Malaria Vaccine Implementation Program (MVIP), a project made possible by an unprecedented collaboration between in-country and international partners: the Ministries of Health of Ghana, Kenya, and Malawi; in-country evaluation partners; WHO, PATH, GSK, UNICEF, and others; and Gavi, the Global Fund and Unitaid, the funders of the program. The MVIP was designed to assess the feasibility of administering the recommended 4 doses of the RTS,S/AS01$_E$ malaria vaccine (RTS,S) in children; the vaccine's potential role in reducing childhood deaths; and its safety in the context of routine use. The pilot introduction of RTS,S as part of the MVIP study started in 2019 in areas in Ghana, Kenya, and Malawi . The pilots utilized a cluster randomized design, whereby some districts/sub-counties within the selected areas introduced the vaccine into their immunization schedules at the start of the programme, while other districts/sub-counties served as comparator areas during the initial vaccine implementation.

The MVIP successfully demonstrated a significant reduction in all-cause mortality in age-eligible children (13% (95% CI: 2—22)) based on a four-dose schedule for RTS,S, with the first dose starting at five or six months of age. In the initial 24 months of implementation (19 months in Kenya), hospital admissions for severe malaria dropped by 32% (95% CI: 5%, 51%). Over the entire 46-month implementation period, the reduction in hospitalized severe malaria was 22% (4%, 37%). Despite the overlapping confidence intervals, these impacts align with expectations from the 2009-2014 Phase 3 clinical trial, considering waning vaccine efficacy and changing age demographics in the eligible population. In the context of analyzing the 46-month (final) results from the MVIP pilot introductions

of RTS,S, the Swiss Tropical and Public Health Institute (Swiss TPH) and Imperial College London, in collaboration with PATH, were involved in two modelling analyses. Applying modelling approaches enables the estimation of the RTS,S public health impact and cost-effectiveness beyond the evidence in the Phase 3 trials and the MVIP evaluations.

For the initial analysis, predictions of vaccine impact on hospitalised severe malaria were generated by both the Swiss TPH and Imperial College London models and were compared with 46-month MVIP evaluation analytic results from the three pilot countries: Ghana, Kenya, and Malawi. The second analysis focused on providing estimates of vaccine public health impact and cost-effectiveness from the two models. Similar analyses were previously conducted by this collaborative group, as part of the 24-month MVIP analysis, which informed the WHO in October 2021 to recommend deployment of RTS,S, as the first malaria vaccine for children at risk.

In this report, we present findings from these modelling analyses and explore their implications for informing WHO guidance on implementation of the vaccine.

Comparison of model outputs with MVIP results

In the first analysis, RTS,S malaria vaccine coverage estimates from MVIP household surveys for the three pilot countries reflecting the first 30-36 months of vaccine introduction were used to parameterise vaccine coverage in both models. Model impact estimates expressed as incidence rate ratios (IRRs) for severe disease were compared with IRRs for eligible children hospitalized with severe malaria from the MVIP during 46 months of pilot evaluations. Model-based IRRs were found to fall within the confidence intervals of MVIP IRR estimates from 46-months of pilot evaluations and were thus considered to be **consistent** with the MVIP data. Median IRRs from the two models, pooled across the pilot countries were 0.77 (Imperial) and 0.80 (Swiss TPH) compared to the MVIP IRR, pooled across all three countries at 0.78 (95% CI of 0.63 to 0.96).

These findings, together with a similar comparison conducted in 2021 as part of the analysis of the 24-month MVIP results, demonstrates **consistency** across results. Taken together, these findings demonstrate RTS,S malaria vaccine effectiveness at preventing severe malaria in children across the three pilot countries in sub-Saharan Africa.

Public health impact and cost-effectiveness analyses

In 2021, vaccine impact and cost-effectiveness estimates were produced from both models for a wide range of perennial transmission settings representing *Plasmodium falciparum* parasite rates among 2- to 10-year-olds ($Pf\text{PR}_{2-10}$) from 3 to 65%. This analysis was conducted across the range of prevalence settings with assumed 80% vaccine coverage of dose three. In addition, MVIP-generated cost of delivery estimates, including recurrent vaccine delivery expenses, were taken into account alongside vaccine and supply costs. Findings were presented to the WHO Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG) and published by the WHO in a *Full Evidence Report on the RTS,S/AS01 Malaria Vaccine* (2021) [1].

The models estimated that in low transmission settings ($Pf\text{PR}_{2-10}$ <10%), RTS,S could prevent between 20,000 and 28,000 clinical cases and 100 to 200 malaria deaths per 100,000 children vaccinated with three vaccine doses over 15 years. At a vaccine cost of $10 per dose, the estimated median incremental cost-effectiveness ratio (ICER) per clinical case averted ranges from $204 to $279, with a median cost per disability-adjusted life year (DALY) averted between $480 and $682. In

moderate to high transmission settings (*Pf*PR_{2-10} 10–50%), the vaccine could avert 100,000 clinical cases and 400 malaria deaths per 100,000 children vaccinated with three vaccine doses over 15 years. The median ICER per clinical case averted is estimated as $52 to $105, with a median cost per DALY averted ranging from $175 to $187. Further cost-effectiveness estimates were provided across a range of vaccine costs ($2, $5, and $10 per dose). At a vaccine cost of $5 per dose, the estimated median incremental cost-effectiveness ratio (ICER) per clinical case averted ranges from $113 to $156, with a median cost per disability-adjusted life year (DALY) averted between $267 and $381.

In 2023, alongside the model comparison to 46-month MVIP results, model parameters and RTS,S costing values used for the 2021 modelling round were examined if they were still applicable and appropriate for estimating vaccine impact. Using available evidence including values related to the RTS,S product profile and other mosquito-host model parameters, it was concluded that existing model parameters and costing values are still applicable and appropriate for estimating vaccine impact and cost-effectiveness. Therefore, the public health impact and cost-effectiveness model estimates generated from both models in 2021 did not need to be updated in 2023.

Analyses conducted in 2013, 2015, 2018, and 2021, together with the assessment presented here, showed that the estimates were within statistical bounds and were therefore considered to be **consistent** between models. The analyses also consistently underscored RTS,S's effectiveness at preventing clinical cases and malaria-related deaths in children. Assuming a price of $10 per dose, the vaccine was found to be cost-effective in moderate to high transmission perennial settings (median cost per DALY averted: $175 to $187) by standard norms and thresholds. ICERs were considerably higher and more uncertain in the lowest transmission settings when considering a cost per dose of $10 ($PfPR_{2-10} < 10\%$, median cost per DALY averted: $480 and $682). Further country-specific cost-effectiveness evaluations reflecting the healthcare system and local priorities will be important.

Key findings

In summary, model estimates of hospitalised severe disease reductions, represented by the IRR metric were found to be consistent with the MVIP 46-month implementation results, aligning with a comparison of outputs after 24-months MVIP implementation between the two models. Taken together with the model impact and cost-effectiveness analysis, these findings show that RTS,S is cost-effective at preventing *P. falciparum* malaria and disease in children in perennial settings.

BACKGROUND

Objective

The objective of this analysis was to assess the impact and cost-effectiveness of the RTS,S malaria vaccine in the context of final results from the MVIP at 46-months of vaccine implementation. This report summarises findings from two separate RTS,S modelling analyses. The first analysis and primary focus of this report is a comparison of model impact outputs against MVIP results. The second analysis involved generating public health impact and cost-effectiveness estimates from the two models and comparing outputs between models. These analyses were performed using extensively validated models from the Swiss Tropical and Public Health Institute (Swiss TPH) and Imperial College London.

Introduction

Development of RTS,S, which targets the pre-erythrocytic stage of the *Plasmodium falciparum* parasite and stimulates production of anti-circumsporozoite protein antibodies, has been ongoing over the last 30 years. As part of this development process, several clinical trials have been carried out among children in countries in sub-Saharan Africa. PATH has collaborated with Imperial College and the Swiss TPH to use evidence on RTS,S, including from these trials, to inform individual-based models of malaria and vaccine impact and assess their model-based predictions in 2013, 2015, 2018, 2021, and again in 2023. Over these modelling rounds, models, model calibrations, and resulting estimates have been extensively reviewed.

From the start of MVIP vaccine implementation in Ghana, Kenya and Malawi in 2019, and through October 2023, over 6 million doses had been administered and over 2 million children reached [2]. It was reported that demand and uptake continued to be relatively high in all three pilot countries, despite the challenges brought about by external factors, including the coronavirus disease (COVID-19) global pandemic. The findings from the MVIP after 46-months of surveillance in each pilot country showed high impact, specifically a 22% reduction in hospitalised severe malaria and a 13% reduction in all-cause mortality excluding injuries among children age-eligible for vaccination [3]. The many lessons learned through pilot implementation and findings from evaluation of the pilot are being documented and disseminated to inform guidance for vaccine rollout in other endemic countries. The WHO malaria vaccine recommendations in 2021 were informed by evidence from the RTS,S clinical trials and the MVIP. In October 2023, WHO updated its recommendation for use of malaria vaccines for the prevention of P. falciparum malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission. This applies to both RTS,S/AS01 and R21/Matrix-M vaccines.

Here we provide a brief overview of RTS,S modelling analyses conducted over more than a decade by this collaborative working group, with primary focus on assessing the vaccine effectiveness in the context of final results from the MVIP at 46-months.

Methods

Model descriptions

Swiss Tropical and Public Health (Swiss TPH) model: OpenMalaria

Swiss TPH's individual-based model of malaria dynamics, OpenMalaria, features comprehensive individual-based model components that capture the complete life cycle of mosquitoes, parasitaemia levels throughout an infection, and the transmission dynamics between humans and mosquitoes alongside a range of medical and vector interventions. Model structure and calibration to extensive diverse data sources on exposure and age-patterns of malaria prevalence, clinical, severe disease and mortality have been documented in [4] and [5]. Model code is open source and available at https://github.com/SwissTPH/openmalaria.

Imperial College London model

Imperial College's individual-based model pairs human transmission processes with a stochastic compartmental model that captures mosquito behavior and the combined effect of multiple

interventions. The model has been extensively fitted to data on the relationship between entomological inoculation rate and parasite prevalence, clinical disease, severe disease, and deaths [6-8]. Model code is open source and available at https://github.com/mrc-ide/malariasimulation.

Description of modelling exercises

PATH, in partnership with WHO, has collaborated with the Swiss TPH and Imperial College to employ their separate malaria transmission and vaccine impact models to perform model-based analyses and assessments of RTS,S. For both models, fundamental model structure and vaccine parameterisation have remained consistent over the modelling assessment rounds conducted in 2013, 2015, 2018, 2021, and 2023, unless otherwise specified. In addition to the model calibrations to epidemiological data, extensive calibration of modelled vaccine properties were undertaken against Phase 3 clinical trial results for 11 sites reflecting various parasite prevalence and transmission settings [9-11]. Model vaccine calibrations and vaccine impact and cost-effectiveness studies were reviewed, including a 2012-2015 review by the WHO immunization and vaccines related implementation research advisory committee (IVIR-AC) sub-group. For all scenarios of vaccine impact considered, fully vaccinated children were defined by WHO as those who had received the initial three doses of the vaccine.

Comparison of model outputs with MVIP results

In-silico simulations of the MVIP were undertaken by Swiss TPH and PATH (using the Imperial College model). This involved replicating the vaccine roll out in the three MVIP pilot countries in both vaccine implementing and comparison areas by using the previous vaccine models, fitted to the Phase 3 trial data and inputting transmission model parameters to capture the geographic specific variation in exposure (prevalence), intervention coverages, access to treatment of uncomplicated and severe malaria, and entomology (Figure 1).

In 2023, RTS,S coverage data from the final MVIP household survey for the three pilot countries (Ghana, Kenya, and Malawi) was used to parameterise vaccine coverage in both models. Coverage for doses one to three was assessed approximately 30-36 months of vaccine introduction via home-based record or recall among children 12-23 months of age. Coverage values were only provided by MVIP by pilot country (sub-national data within the implementing areas were not accessible) as shown in Appendix Table A1.

Other simulation input parameters used to inform the model are provided in Appendix Table A2. These include demographic data provided by the WHO and estimates from UN World Population Prospects. Vaccine timing was based on the malaria vaccine schedule implemented in each pilot country through the childhood immunization program. Parasite prevalence estimates were informed by publicly available data, such as the Malaria Atlas Project (MAP) and by DHS/MIS household survey data (independent to MVIP survey data). The impact from other existing baseline malaria prevention (insecticide treated nets and indoor residual spraying) and treatment (artemisinin-based combination therapy (ACT)) interventions were simulated. Levels of case-management and other intervention coverage levels were informed using publicly available data for each pilot country. Vaccine efficacy and duration was informed by previous fittings [13] against the Phase 3 clinical trial data [10].

Model simulations using MVIP survey coverage captured vaccine implementing and comparison areas (to generate no-vaccine incidence rates). Incidence rate ratios for severe disease (encompassing both direct and indirect cases of severe malaria, includes hospitalised cases), hospitalisations, direct malaria mortality, and sums of direct and indirect malaria mortality were derived directly from vaccine implementing areas for Swiss TPH model simulations (no statistical model was applied to calculate model IRRs, as they are calculated directly from the simulations). For the Imperial College model only IRRs for severe malaria (hospitalised) were estimated. Model-based IRRs were compared with IRRs for hospitalized severe malaria from the MVIP at 46 months, marking the final data from the MVIP for the three pilot countries. Swiss TPH model outputs are reported below as median values with 95% credible intervals across simulations, for the Imperial College results outputs are reported as median values with no associated credible intervals due to computational limitations at the time of analysis. A similar comparison of both Imperial and Swiss TPH model outputs with MVIP results in 2021 after 24 months of vaccine implementation . The approach for this comparison process is depicted in Figure 1.

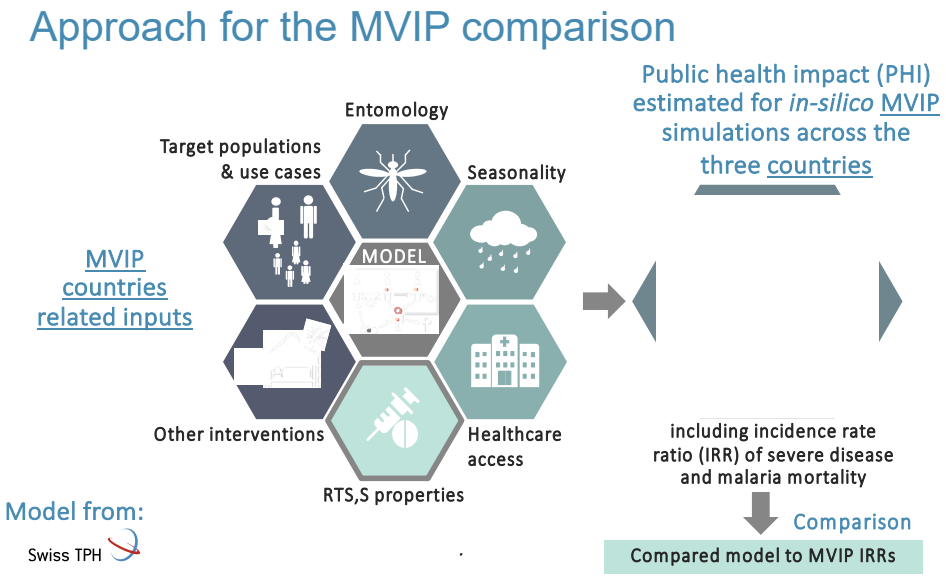

Figure 1. A schematic of the approach used for comparing MVIP results with model outputs. This approach involved informing models with vaccine coverage from Malaria Vaccine Implementation Programme (MVIP) household surveys for the three pilot countries (Ghana, Kenya, and Malawi) as well as other geographic specific information on baseline transmission, seasonality, interventions, access to treatment, etc. RTS,S properties reflect the initial vaccine efficacy and duration of protection fitted to data from the Phase 3 trial. The models were then used to simulate the MVIP generating vaccine impact estimates at desired time-points, and then using these outputs to derive the incidence rate ratio (IRRs) for severe malaria, and thus comparing these model-based IRRs with IRRs from MVIP results.

Vaccine calibration in the models and public health impact and cost-effectiveness analyses

Since 2012, Swiss TPH and Imperial College have used their individual-based models of malaria and vaccine impact to produce evidence of public health impact and cost-effectiveness beyond the evidence in the Phase 3 trials and the MVIP. The models allow estimates of impact in a range of transmission settings and for outcomes not observed in the trials.

In brief, in 2013, the Swiss TPH [14] and Imperial College [15] models were separately calibrated to a shorter follow-up Phase 3 clinical trial data [7, 9]), and assuming 90% vaccine coverage for dose three, a first estimate from multiple models of public health vaccine impact (PHI) and cost-effectiveness (CE) estimates were generated. Model calibrations were updated and reviewed in 2015, including first calibrations of fourth dose efficacy and duration [14, 15] informed by longer follow-up Phase 3 results [10]. Updated PHI and CE estimates were compared across four models including from the Institute for Disease Modeling (EMOD-DTK) [14], GSK Vaccines (GSK) [17], Imperial College London [7] and the Swiss Tropical and Public Health Institute (OpenMalaria) [4], with estimates across a range of perennial transmission settings from 3 to 65% *Pf*PR_{2-10}, with delivery of a primary series to 5-9 months of age and fourth dose 18 months later. Cost of delivery and health savings were informed by Galactionova et al. [18]. These PHI and CE were presented to the WHO advisory bodies, SAGE and MPAG, as published in Penny et al. 2016 [19]. The transmission models, vaccine model calibrations, and impact estimates were extensively reviewed between 2012 and 2015 by the WHO IVIR-AC sub-group. In 2018, models of Swiss TPH and Imperial were compared to seven-year follow-up Phase 3 data [12], and the models deemed to be consistent with the extended Phase 3 trial data and thus validated to this longer follow-up study of impact against clinical and severe malaria. Updated PHI and CE estimates were also produced.

In summary, the overall conclusions drawn progressively from 2013 to 2018 involved the separate calibration of Swiss TPH and Imperial College vaccine models to shorter and longer follow-up Phase 3 clinical trial data, incorporation of fourth dose efficacy and duration in 2015, extensive review by the WHO IVIR-AC sub-group from 2012 to 2015, comparison of public health vaccine impact (PHI) and cost-effectiveness (CE) estimates across four models in various transmission settings, presentation to the WHO SAGE and MPAG in 2015, and validation of the models against seven-year follow-up Phase 3 results in 2018, leading to updated PHI and CE estimates which showed consistency between estimates from the two models at each modelling round.

In 2021, PHI and CE estimates were provided from both models in conjuncture with availability of MVIP results following 24 months of vaccine implementation. These estimates were produced assuming 80% vaccine coverage (versus 90% previously assumed) for dose three delivered at 5 to 9 months of age, with a 20% drop in coverage for the fourth dose delivered at 27 months of age, and integrated cost of delivery estimates generated by PATH from the MVIP [20]. Costs include vaccines,

injection and reconstitution syringes, safety boxes, freight, insurance, and wastage as per Penny et al. [19] and Baral et al. [20]. The recurring cost of delivery excludes the initial set-up costs related to RTS,S introduction and delivery and are representative of the program costs in the long run and reflect the 24 month data from three MVIP countries (Ghana, Kenya, and Malawi) averaged across the three pilot countries. Additional model inputs for cost estimates are shown in Appendix Table A3 and Table A4, respectively.

Finally, in 2023 as part of a model validation against the final MVIP results, available evidence was examined to determine whether model parameters and costing values were still applicable and appropriate for estimating vaccine impact and cost-effectiveness, or whether estimates need to be updated. For each modelling round from 2013 to 2021, calibrations were validated between models and estimates reflecting current vaccine properties and a wide range of perennial malaria transmission were examined and compared for consistency, with the approach for this process outlined in Figure 2.

Throughout this process, cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs) calculated for several outcomes including per clinical case averted and disability-adjusted life year (DALY) averted. In 2021, recurrent delivery costs were incorporated, in addition to vaccine and supply expenses, providing a more accurate reflection of program delivery expenditures. It is important to highlight that recurrent costs based on subnational and pilot introduction of RTS,S in MVIP areas were integrated in cost analyses, resulting in introduction costs being distributed over a smaller number of total doses de relative to a full-scale national rollout. All costs are expressed in US dollars. Finally, a sensitivity analysis to test the impact of varying coverage, and delivery and vaccine costs on cost-effectiveness was conducted.

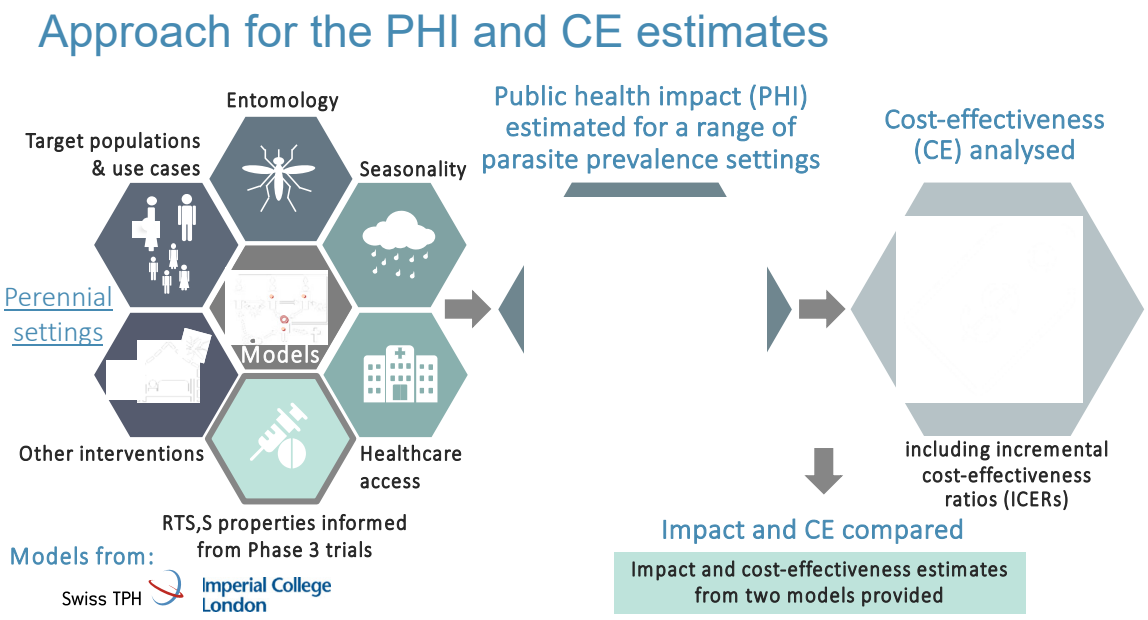

Figure 2. A schematic of the approach used by Swiss TPH and Imperial College for producing public health impact and cost-effectiveness estimates for RTS,S malaria vaccine. RTS,S properties reflect the vaccine efficacy and duration of protection fitted from the phase 3 trial. Steps for this approach include capturing model inputs, generating public health

impact estimates, calculating cost-effectiveness estimates, and comparing model estimates. Modelling rounds to produce these estimates were carried out in 2013, 2015, 2018, and 2021.

Results

Comparison of model outputs with MVIP results

In 2023, model impact estimates, informed with vaccine coverage from the final MVIP household surveys (Table A1), were used to derive IRRs for hospitalised severe malaria across pilot country-specific implementing areas for the three MVIP pilot countries (Ghana, Kenya, and Malawi). The MVIP was not designed to generate statistically significant estimates of impact at the country level. However, a comparison of these model-based IRRs (at country level and pooled) with IRRs for hospitalised severe malaria from the final MVIP data shows the modeled IRRs to be within the MVIP confidence interval bounds; the modeled estimates were therefore considered to be **consistent** with the results from the MVIP as shown in Table 1 and Figure 3. At 46-months, pooled median model-based IRRs were 0.80 from the Swiss TPH model and 0.78 from the Imperial College model which align with the pooled MVIP estimates of 0.78 (severe malaria broad, 95% CI 0.64, 0.96) (Table 1 and Figure 3).

This aligns with findings from the 2021 modelling round, whereby IRRs from both the Imperial and Swiss TPH models were consistent with MVIP results after 24-months of vaccine implementation (results not shown). Taken together these findings indicate a similar reduction in the incidence of severe malaria across the studies evaluated.

Using multiple mathematical models in this exercise allows different sources of uncertainty to be e captured. Although the Imperial model uses a different definition of severe malaria than Swiss TPH's model (hospitalized vs direct and indirect respectively), accounting for these slight differences the models still reach consensus with each other and with MVIP data in terms of RTS,S vaccine impact.

After 46 months of vaccine implementation, model-based median IRRs estimated from Swiss TPH for all malaria deaths ranged from 0.76 and 0.82 across the three MVIP pilot countries (Table 2). While the models estimated the impact on all malaria deaths, the estimates are not directly comparable to the to the MVIP results, which did not measure direct or indirect malaria deaths and demonstrate a reduction in all-cause mortality of 13%. MVIP-generated estimates on the impact for all-cause mortality provide a more comprehensive evaluation, taking into account broader factors influencing mortality rates beyond malaria-specific outcomes.

Table 1. Comparison of incidence rate ratios (IRRs) for severe malaria from Swiss TPH model predictions and MVIP results at 46-months

Source	IRRs for severe malaria at 46-months, median (95% credible interval[1])			
	Ghana	**Kenya**	**Malawi**	**Pooled**
Model predictions – Swiss TPH[1]	0.79 (0.76, 0.81)	0.81 (0.78, 0.83)	0.82 (0.79, 0.84)	**0.80 (0.77, 0.82)**
Model predictions – Imperial College[2]	0.76	0.83	0.78	**0.78**
MVIP results[3] (broad)[4]	0.58 (0.28, 1.22)	0.90 (0.62, 1.32)	0.76 (0.58, 1.00)	**0.78 (0.64, 0.96)**

[1]95% credible interval (CI) values are based on model stochasticity and model structural uncertainty.
[2] No CIs could be provided by the Imperial model due to computational limitations at the time of analysis, model median values are shown.
[3]Source: MVIP pilot, 2023.
[54] From the MVIP, severe malaria (broad) is defined as malaria cases diagnosed by rapid diagnostic test positive (RDT+) (or blood-stage positive (BS+) if RDT was not done) with at least one condition including anemia, respiratory distress, convulsions or low consciousness, but not positive for probable or confirmed meningitis.
IRR: incidence rate ratio.

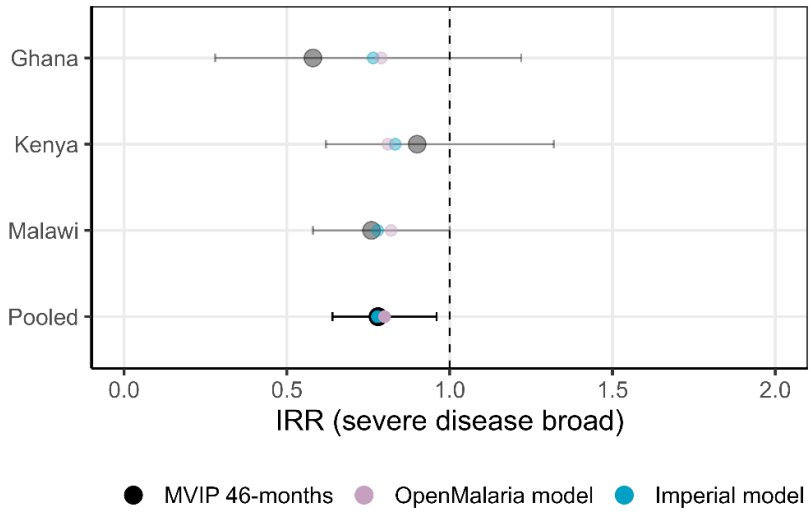

Figure 3. Comparison of Swiss TPH (OpenMalaria - purple) and Imperial College (blue) model-based incidence rate ratios (IRRs) for severe malaria disease with IRRs for severe malaria disease (broad definition) from final MVIP results (black) at 46-months. Model estimates are reported as median values.

Table 2. Incidence rate ratios (IRRs) for malaria mortality from Swiss TPH model at 46-months

Source	IRRs for malaria mortality at 46-months, median (95% credible interval[1])			
	Ghana	Kenya	Malawi	Pooled
Model predictions (direct malaria mortality)[2]	0.79 (0.75, 0.84)	0.81 (0.78, 0.86)	0.82 (0.79, 0.86)	0.80 (0.77, 0.85)
Model predictions (all malaria mortality)[3]	0.76 (0.73, 0.79)	0.78 (0.75, 0.82)	0.79 (0.76, 0.82)	0.77 (0.74, 0.81)

[1]95% credible interval (CI) values are based on model stochasticity, model structural uncertainty, and uncertainty based on coverage.
[2]Direct malaria mortality is directly attributable malaria death (with parasitemia and no coinfection).
[3]All malaria mortality is defined as both direct malaria deaths and those occurring with co-infection/comorbidity (with parasitemia).

Public health impact and cost-effectiveness analyses

PHI and CE estimates reflecting perennial settings with parasite prevalence ranging from 3 to 65% were generated in 2021 and found to be consistent between the Imperial and Swiss TPH models, and

were in alignment with PHI and CE analyses carried out by both group in 2013, 2015, and 2018. In 2023 the existing model parameters and costing values are still applicable and appropriate for estimating vaccine impact and cost-effectiveness; therefore, PHI and CE model estimates generated from both models in 2021 did not need to be updated in 2023.

For the latest analyses carried out in 2021 and still applicable in 2023, in low transmission settings with *Pf*$PR_{2–10}$ below 10%, it was estimated that over a 15-year time horizon RTS,S could avert approximately 24,000 clinical cases and 100 malaria deaths per 100,000 fully vaccinated children (Table 3 and Figure 4). Fully vaccinated children are defined as receiving the initial three doses, consistent with all previous analyses and as defined by the WHO over the 2013 to 2015 period. Incremental cost-effectiveness ratios (ICERs) were estimated across a range of initial RTS,S costs per dose ($2, $5, and $10). Assuming an initial cost of RTS,S per dose of $10, a median incremental cost-effectiveness ratio (ICER) per clinical case averted between $204 and $279 (full range $153 to $484) was estimated from both models over this time period, with a median cost per DALY averted estimated at between $480 and $682 (full range $409 to $1,181). Of note, ICERs were considerably higher and more uncertain in the lowest transmission settings. Prior analyses focused on median cost-effectiveness estimates at an initial cost of $5 per RTS,S vaccine dose.

In moderate to high transmission settings with *Pf*$PR_{2–10}$ between 10 and 50%, an estimated 100,000 clinical cases and 400 malaria deaths per 100,000 fully vaccinated children could be averted by RTS,S over the same time horizon (Table 4 and Figure 4). At a cost of $10 per dose, the models estimate a median ICER per clinical case averted of $52 to $105 (full range $35 to $160) over a 15-year period, with median cost per DALY averted of $175 to $187 (full range $146 to $412). For both models, estimates for cost per DALY averted are relatively insensitive to changes in prevalence in moderate transmission settings with *Pf*$PR_{2–10}$ below 20%. Some differences were observed for settings with prevalence rates between 10 and 20%.

Table 3. Public health impact estimates and incremental cost-effectiveness ratios (ICERs) for a four-dose schedule of RTS,S malaria vaccine at 15 years from the start of implementation in low transmission settings with *Pf*$PR_{2–10}$ <10% as reported for the 2021 analysis. These estimates remained applicable in 2023.

Low transmission settings, *Pf*$PR_{2–10}$ <10%	**Median estimate (range)**	
	Swiss TPH model	**Imperial College model**
Malaria clinical cases averted per 100,000 fully vaccinated children (received 4 doses)	20,093 (18,578 to 21,289)	27,748 (12,439 to 49,674)
Malaria deaths averted per 100,000 fully vaccinated children (received at least 3 doses)[1]	82 (33 to 195)	194 (82 to 355)
Percentage of clinical cases averted in children younger than 5 years	14.8% (14.3 to 15.0%)	25.7% (25.1 to 26.2%)
Percentage of malaria deaths averted in children younger than 5 years	7.9% (4.7 to 12.7%)	25.2% (23.9 to 26.6%)
ICER per malaria clinical case averted (in US $)		
$2 per dose	$85 (57 to 143)	$59 (44 to 74)
$5 per dose	$156 (110 to 271)	$113 (85 to 142)
$10 per dose	$279 (197 to 484)	$204 (153 to 255)
ICER per malaria-related DALY averted (in US $)		
$2 per dose	$200 (142 to 348)	$139 (118 to 160)
$5 per dose	$381 (272 to 660)	$267 (227 to 307)

$10 per dose	$682 (488 to 1181)	$480 (409 to 550)

[1] Deaths from the Swiss TPH model include those directly attributable to the disease and those caused by co-morbidities. The absolute number of deaths, and how RTS,S impacts them, can differ between models, which can result in similar deaths averted per 100,000 children, despite there being a different percentage of deaths averted.
Outcomes are for a 4-dose schedule at 15-years from the start of implementation in regions with a parasite prevalence among 2 to 10-year-olds of less than 10%. DALY: disability-adjusted life year. ICER: incremental cost-effectiveness ratio. *Pf*$PR_{2–10}$: *Plasmodium falciparum* parasite prevalence rate among 2–10-year-olds.

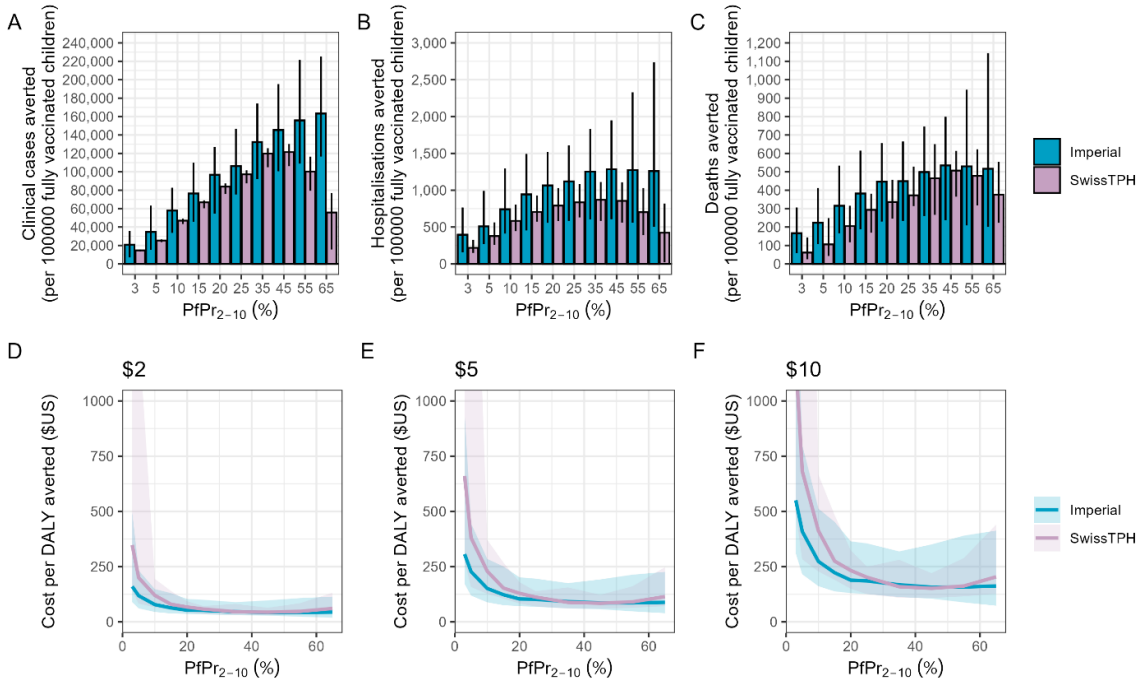

Figure 4. Summary of public health impact and cost-effectiveness predictions for RTS,S from the 2021 analysis. The figures presented above capture the full spectrum of possible *Plasmodium falciparum* parasite prevalence among 2–10-year-olds (*Pf*$PR_{2–10}$) transmission rates, ranging from 3 to 65%. The top row panels illustrate predictions of the impact in terms of clinical cases (panel A), hospitalisations (panel B), and malaria-related deaths (panel C) averted per 100,000 fully vaccinated children, as a function of baseline *Pf*$PR_{2–10}$. Results are shown for both Imperial (blue bars) and Swiss TPH (mauve bars) models, with bars representing the median estimates and the error bars denoting the 95% credible intervals. The bottom row panels depict the cost per DALY averted as a function of *Pf*$PR_{2–10}$, assuming a cost per dose of $2 (panel D), $5 (panel E), and $10 (panel F). These model estimates are provided for both Imperial (blue curves) and Swiss TPH (mauve curves) models. Curves represent the median estimate, while shaded areas indicate the 95% credible intervals. Source: WHO. Full Evidence Report on the RTS,S/AS01 Malaria Vaccine. 2021 (Available at https://www.who.int/initiatives/malaria-vaccine-implementation-programme).

Table 4. Public health impact estimates and incremental cost-effectiveness ratios (ICERs) for a four-dose schedule of RTS,S malaria vaccine at 15 years from the start of implementation in moderate to high transmission settings with *Pf*$PR_{2–10}$ from 10 to 50% as reported for the 2021 analysis, with estimates still applicable in 2023.

Moderate to high transmission settings, *Pf*$PR_{2–10}$ 10–50%	**Median estimate (range), 2021 analysis**	
	Swiss TPH model	**Imperial College model**
Malaria clinical cases averted per 100,000 fully vaccinated children (received 4 doses)	108,824 (46,978 to 121,182)	101,413 (57,839 to 145,301)

Malaria deaths averted per 100,000 fully vaccinated children (received at least 3 doses)[1]	417 (205 to 540)	448 (315 to 534)
Percentage of clinical cases averted in children younger than 5 years	13.2% (11.2 to 14.6%)	20.9% (20.1 to 23.6%)
Percentage of malaria deaths averted in children younger than 5 years	9.2% (8.7 to 10.1%)	18.6% (13.6 to 20.8%)
ICER per malaria clinical case averted (in US $)		
$2 per dose	$31 (25 to 46)	$14 (10 to 26)
$5 per dose	$59 (48 to 89)	$28 (19 to 50)
$10 per dose	$105 (87 to 160)	$52 (35 to 91)
ICER per malaria-related DALY averted (in US $)		
$2 per dose	$50 (42 to 120)	$52 (43 to 78)
$5 per dose	$97 (81 to 230)	$103 (86 to 151)
$10 per dose	$175 (146 to 412)	$187 (157 to 274)

[1] Deaths from the Swiss TPH model include those directly attributable to the disease and those caused by co-morbidities. The absolute number of deaths, and how RTS,S impacts them, can differ between models, which can result in similar deaths averted per 100,000 children, despite there being a different percentage of deaths averted.

Outcomes are for a 4-dose schedule at 15-years from the start of implementation in regions with a parasite prevalence among 2 to 10-year-olds of 10 to 50%. DALY: disability-adjusted life year. ICER: incremental cost-effectiveness ratio. *Pf*$PR_{2–10}$: *P. falciparum* parasite prevalence rate among 2–10-year-olds.

Measures are median values from both models and estimate ranges are driven by transmission prevalence and uncertainty from the models (including stochastic, model structural, and parameter uncertainty). Differences in median and ranges in cost per clinical case averted relate to differences between model baseline and prevalence assumptions, and case definitions used.

The cost-effectiveness estimates from the 2021 analysis from both modelling groups, reported in Tables 3 and 4, and still applicable in 2023, fell within the ranges generated in the 2015 modelling round (as published by Penny and colleagues (2016) [19]). Consistency of estimates between models and across valuation rounds suggest that RTS,S is cost-effective compared to global standards and thresholds and considering the initial price of the vaccine.

A sensitivity analysis was conducted in 2021 to examine the impact of varying coverage, and delivery and vaccine costs on cost-effectiveness. Results showed that for a given parasite prevalence, costs per clinical case averted and DALY averted are robust to changes in coverage. Cost per DALY averted were most sensitive to the cost per vaccine dose assumption, and somewhat sensitive to the estimated cost of delivery (Figure 5). Cost-effectiveness results are broadly consistent with previously published estimates [19].

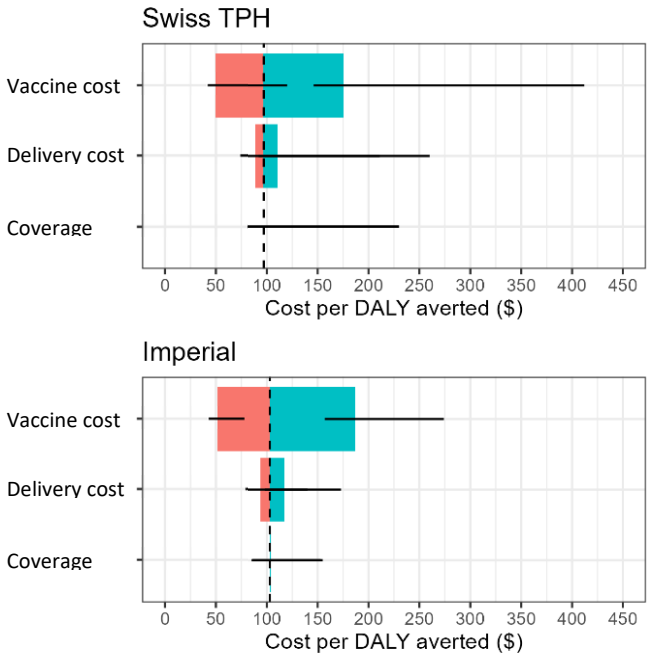

Figure 5. Colored bars indicate the minimum (coral) and maximum (teal) cost per event averted when varying the cost per dose, cost of delivery or coverage between their minimum and maximum value. Solid black lines show model uncertainty for the minimum and maximum estimate. All values are summarised over settings with parasite prevalence among 2–10-year-olds of 10 to 50% and presented in comparison with a baseline scenario of $5 per dose, mean cost of delivery estimate and 80% coverage (vertical black dashed line).

Both the Swiss TPH and Imperial College models predict a favourable public health impact following implementation of RTS,S in settings with *Pf*$PR_{2–10}$ ranging from 3 to 65% over a 15-year period (Figure 2), consistent with previously published estimates [19]. Across a *Pf*$PR_{2–10}$ of 10 to 50%, a reduction of 11% to 24% in clinical malaria and 9% to 21% in mortality is expected over this period. With a vaccine price of $10, a cost-effectiveness of $146 to $412 per DALY averted was estimated. This underscored the ongoing cost-effectiveness of the RTS,S, malaria vaccine, as it continued to meet established global thresholds and standards.

Conclusion

Across modelling exercises conducted in 2013, 2015, 2018, 2021, and most recently in 2023, both Swiss TPH and Imperial College models consistently yielded similar vaccine impact and cost-effectiveness estimates for RTS,S in settings with *Pf*PR_{2-10} from 10 to 50%. The models differ in estimates of cost-effectiveness in settings less than 10% *Pf*PR_{2-10}. The model *PHI* and *CE* estimates are a result of extensive model and vaccine parameter calibration (to Phase 3 data) and validation (to 7-year follow-up, and MVIP in 2021 and 2023). Modelling results for RTS,S are comparatively more robust than for other malaria interventions. In low transmission settings (*Pf*PR_{2-10} less than 10%) it is estimated that RTS,S could avert approximately 24,000 clinical cases and 100 malaria deaths per 100,000 fully vaccinated children over 15 years. Over the same 15-year time horizon from

implementation of RTS,S, in moderate to high transmission settings (*Pf*PR_{2-10} 10 to 50%) approximately 100,000 clinical cases and 400 malaria deaths could be averted per 100,000 fully vaccinated children. Overall RTS,S was shown to remain cost-effective in moderate to high transmission settings (*Pf*PR_{2-10} 10 to 50%) compared to thresholds even as low as $200 per DALY averted. The compilation of this collective evidence generated until 2021 was used to inform the World Health Organization recommendation in October 2021 for the use of the RTS,S malaria vaccine for prevention of *P. falciparum* malaria in children at risk.

The comparison of model impact outputs and MVIP-demonstrated impact on hospitalised severe malaria demonstrates consistency of model estimates with final MVIP results. These findings underscore the potential benefit of introducing the vaccine in young children, while maintaining cost-effectiveness and offer valuable insights to stakeholders in guiding decision-making around broader rollout of the RTS,S vaccine in preventing *P. falciparum* malaria.

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Appendix

Table A1: RTS,S coverage values from MVIP household surveys for three MVIP pilot countries at 18- and 30-months

	MVIP survey RTS,S coverage at ≈18-months			MVIP survey RTS,S coverage at ≈30-months			
Country	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**
Ghana	75%	73%	67%	85%	81%	74%	48%
Kenya	79%	71%	62%	83%	78%	69%	33%
Malawi	73%	68%	62%	77%	71%	64%	33%

MVIP coverage for doses one to three was assessed approximately 30-36 months of vaccine introduction via home-based record or recall among children 12-23 months of age.

Table A2: Data sources and assumptions used to inform RTS,S model predictions for comparison with MVIP results

Parameter	Data source and assumption
Pilot country vaccine implementing areas	List provided by the WHO
Country shapefiles	WHO-supplied shapefiles based on analysis of implementing areas for MVIP pilot countries
Population size and demography	UN World Population Prospects, 2019
Life tables	Country-specific tables derived from WHO data
Vaccine coverage	See Table A1
Vaccine schedule (timing of doses, eligible age groups, and time of introduction)	Provided by MVIP by pilot country
***Pf*PR$_{2–10}$ estimates**	Household survey data[1] (Imperial model) Publicly available data (Swiss TPH model)
ITN coverage	Household survey data[1] (Imperial model) Publicly available data (Swiss TPH model)
IRS coverage	Household survey data[1] (Imperial model) Publicly available data (Swiss TPH model)
ACT coverage	Household survey data[1] (Imperial model) Publicly available data (Swiss TPH model)
Health care access	Household survey data[1] (Imperial model) Publicly available data (Swiss TPH model)
Vaccine efficacy and waning	Phase 3 clinical trial data [8]
Seasonality	Satellite-derived patterns of average rainfall (Imperial model) Publicly available data (Swiss TPH model)
Time frame	18- and 24-month pilot implementation periods
Uncertainty	Median and 95% credible interval across simulations

[1]For MVIP pilot countries (Ghana, Kenya, and Malawi) only, independent of MVIP household survey data.
ACT: artemisinin-based combination therapy. IRS: indoor residual spraying. ITN: insecticide treated nets. *Pf*PR$_{2–10}$: *Plasmodium falciparum* parasite prevalence rate among 2–10-years-olds.

Table A3. Parameters assumptions and data sources for the 2021 RTS,S public health impact and cost-effectiveness analyses, still applicable in 2023

Parameter	Assumption	Data source
Demographics	Constant population size and demography with an average life expectancy at birth of 46.6 years.	[12]
Transmission intensity	Parasite prevalence among 2–10-year-olds (*Pf*PR_{2-10}) between 3 and 65% representing transmission levels in Africa at the time of the analysis.	Malaria Atlas Project (MAP)
Case management	Effective coverage (i.e., treatment with parasitological cure) for clinical malaria is 45%. Access to care for severe malaria varied by model.	[12]
Other interventions (ITN, IRS, ACT, SMC, health care access)	Predictions assume that current interventions in place at the start of vaccination remain at static levels.	[12]
Vaccine efficacy and waning	Model predictions of RTS,S efficacy against infection profiles based on fitting to phase 3 trial efficacy.[1]	[12]
Vaccine schedule	Three doses of vaccine given at 6, 7.5, and 9 months old (6–9-month implementation) with a scheduled fourth dose at month 27[2] (6–9 months olds with fourth dose). The first two doses of the primary series are assumed to have 0% efficacy.	[12]
Vaccine coverage	80% (range 50 to 90%) coverage assumed for the first three doses. A 20% drop-off in coverage was assumed for the fourth dose (64% coverage (range 40 to 72%)).	Three dose coverage based on DTP3 coverage for MVIP pilot countries as proxy [19]. Drop-off based on [17].
Seasonality	Perennial transmission (no seasonality). Seasonal trends in rainfall, and therefore mosquito density, were assumed to be constant throughout the year.[3]	[12]
Vaccine price	$5 (range $2–$10) per dose. $6.52 (range $2.69–$12.91) when including injection and reconstitution syringes, safety boxes, freight, insurance, and wastage.	[12]
Cost of delivery estimate	An economic, recurring cost of delivery per dose of $1.62 (range $0.96–$2.67) was assumed.	Interim cost of delivery estimates from MVIP
Cost of malaria case management	Costs are estimated by severity of illness and cover first-line antimalarial drugs, diagnostics, and related supplies including freight and wastage. We assumed full compliance and adherence with the age dosage. The same costs were applied to all settings, ranging from $1.07 to $2.27 per uncomplicated case, and from $21.78 to $55.58 per severe case.	[12]

[1] The Phase 3 trial included data from 11 sites with varying transmission intensities, tracking efficacy against both clinical and severe disease at three-month intervals at each trial site for a median follow-up period of 48-months [12]. In 2015 and unchanged for analyses in 2021 and 2023, both modelling groups calibrated the efficacy characteristics, including RTS,S rate of decay, by replicating trial conditions in-silico and aligning them with the impact of uncomplicated malaria observed in the trial sites.

[2] It is worth noting that this schedule does not reflect vaccinations at 6, 7, 9, or 24 months. Instead, the previous modelling incorporated a 27-month implementation schedule, a practice maintained in the updated 2021 analysis.

[3] Outcomes of the seasonal use case scenario for RTS,S are detailed in [1].

Where applicable, ranges presented in parentheses were generated through a sensitivity analysis.

Source: Adapted from the WHO Full Evidence Report on the RTS,S/AS01 Malaria Vaccine, 2021.

MVIP: Malaria Vaccine Implementation Programme.

Table A4. Costs for the cost-effectiveness analyses (in US $)

Cost per vaccine dose	Cost per vaccination including vaccine cost[1]	Cost of delivery per dose (economic, recurring)[2]			Total cost per dose delivered		
		Mean	Minimum	Maximum	Mean	Minimum	Maximum
$2	$2.69	$1.62	$0.96	$2.67	$4.31	$3.65	$5.36
$5	$6.52	$1.62	$0.96	$2.67	$8.14	$7.48	$9.19
$10	$12.91	$1.62	$0.96	$2.67	$14.53	$13.87	$15.58

[1]Includes vaccines, injection and reconstitution syringes, safety boxes, freight, insurance, and wastage as per [17] and [18].

[2]The recurring cost of delivery excludes initial set-up costs related to RTS,S introduction and delivery and may be more representative of program costs in the long run. These reflect an average of interim data from three MVIP countries (Ghana, Kenya, and Malawi).

Costs were provided by the WHO are in US dollars.