Cost-effectiveness and public health impact of RTS,S/AS01E malaria vaccine in Malawi, using a Markov static model

[version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: The RTS,S/AS01E malaria vaccine is being assessed in Malawi, Ghana and Kenya as part of a large-scale pilot implementation programme. Even if impactful, its incorporation into immunisation programmes will depend on demonstrating cost-effectiveness. We analysed the cost-effectiveness and public health impact of the RTS,S/AS01E malaria vaccine use in Malawi.

Methods: We calculated the Incremental Cost Effectiveness Ratio (ICER) per disability-adjusted life year (DALY) averted by vaccination and compared it to Malawi's mean per capita Gross Domestic Product. We used a previously validated Markov model, which simulated malaria progression in a 2017 Malawian birth cohort for 15 years. We used a 46% vaccine efficacy, 75% vaccine coverage, USD5 estimated cost per vaccine dose, published local treatment costs for clinical malaria and Malawi specific malaria indicators for interventions such as bed net and antimalarial use. We took a healthcare provider, household and societal perspective. Costs were discounted at 3% per year, no discounting was applied to DALYs. For public health impact, we calculated the DALYs, and malaria events averted.

Results: The ICER/DALY averted was USD115 and USD109 for the health system perspective and societal perspective respectively, lower than GDP per capita of USD398.6 for Malawi. Sensitivity analyses exploring the impact of variation in vaccine costs, vaccine coverage...
rate and coverage of four doses showed vaccine implementation would be cost-effective across a wide range of different outcomes. RTS,S/AS01 was predicted to avert a median of 93,940 (range 20,490–126,540) clinical cases and 394 (127–708) deaths for the three-dose schedule, or 116,480 (31,450–160,410) clinical cases and 484 (189–859) deaths for the four-dose schedule, per 100 000 fully vaccinated children.

**Conclusions:** We predict the introduction of the RTS,S/AS01 vaccine in the Malawian expanded programme of immunisation (EPI) likely to be highly cost effective.

**Keywords**
Malaria, Malawi, cost-effectiveness, RTS, S, vaccine, Markov Chain, Modelling

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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**Introduction**

Malawi is one of three countries participating in a large-scale pilot implementation programme of the RTS.S AS01E (GSK) malaria vaccine (henceforth RTS,S). Even if impactful, its cost-effectiveness will be a crucial determinant of subsequent introduction.

RTS,S has been predicted to be highly cost-effective in areas in sub-Saharan Africa with moderate-to-high malaria transmission across different model approaches. However, health care programmes, vaccination schedules and related cost assumptions vary considerably between LMIC countries. Cognisant of this, national policy makers increasingly seek in-country evidence to inform their decisions. There are no published RTS,S national level cost-effectiveness data for Malawi or for regional countries.

We sought to predict the RTS,S cost-effectiveness and public health impact in Malawi.

**Methods**

An intervention is considered cost-effective if the ICER per disability-adjusted life year (DALY) averted is less than three times the GDP per capita and is highly cost effective if the ICER per DALY averted is less than the per capita GDP.

**Model description**

We used a Markov static cohort model developed by GSK for the RTS,S vaccine that has been validated for sub-Saharan Africa; the model is described in depth by Sauboin et al. The model simulates a birth cohort followed over 15 years under fixed-exposure levels of malaria transmission, taking into account parameters reflecting healthcare provider and societal perspective to calculate the incremental cost effectiveness ratio per DALY averted (ICER) of the RTS,S vaccine.

Figure 1 is a diagrammatic representation of the model. The model has compartments susceptible (S), infected (I), clinical disease (C) and severe disease (F) divided into six successive immunity levels following each infection levels.

The model assumes initial protection against malaria from maternal antibodies (M). Neonates are considered either protected from (M) or are susceptible to (S1) malaria infection. Initial immunity is presumed to wane exponentially over three months, leaving the child susceptible to infection. An infected (I1) child will have asymptomatic parasitaemia which clears and susceptibility returns (Si), or the child will develop clinical disease (C1). From clinical disease a child may recover (r1) or develop severe disease (F1) where they could either survive returning to a susceptible state or they could die. Immunity is enhanced every level from an asymptomatic state to clinical malaria and to severe disease. The model permits up to six repeated infections to cumulatively increase immunity. Beyond six infections, a fixed proportion of children is assumed to develop a state of resistance (R).

**Model assumptions and inputs**

The model uses an estimated 2017 annual birth cohort for Malawi and projected for 15 years. This birth cohort was the mean of four prior birth cohorts using the United Nations...
population data. The model accounts for heterogeneity of individual level exposure and a fixed probability of infection within each transmission category. Malaria transmission intensity in the model was defined categorically as low, medium or high based on *Plasmodium falciparum* parasite prevalence (PIP) in children aged 2–10 years old of <5%, 5–40% and >40% was respectively, using the Malaria Atlas Project.

Table 1 shows the input parameters used in the model. The inputs were point estimates extracted from published literature or reasonable assumptions. The vaccine price was based on previously published assumptions since the product has not yet been priced by GSK. The cost of RTS,S vaccine delivery per dose was assumed equal to DTP3 (given as part of pentavalent) in Malawi. Service delivery make up the bulk (63%) of vaccine delivery costs whilst supply chain and logistics constitute the remainder of vaccine delivery costs. Vaccine delivery costs mainly comprise of cold chain management, transportation of vaccines to health facilities, waste disposal and additional training for health workers. We sought to calculate cost savings from a healthcare and household perspective. Societal costs are a combination of healthcare and household costs.

The Phase III RTS,S/AS01 trial vaccine schedule of 6, 7, 8 and 26 months of age and 18-month follow-up results, following the third dose, were fitted in the model. Vaccine efficacy against clinical and severe malaria in children was 46% (95% CI 42–50%) and 34% (95% CI 15–48%) respectively. Third and fourth dose RTS,S coverage were assumed to be 75% and 60% of the DTP3 dose 1 coverage respectively. The fourth dose was assumed to restore waning efficacy. Access to artemisinin combination therapy (ACT) or private dispensaries was extracted from the 2014 Malawi Malaria Indicator Survey.

We used published treatment costs for mild-moderate and severe gastroenteritis, respectively, since published treatment costs for malaria were outdated or unavailable. These health costs including drugs, laboratory investigations, staff salaries and

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**Table 1. Model inputs.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description and value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission</td>
<td>More than half of the population (54.5%) fell in the moderate intensity category, 42.2% in the high intensity category and only 3.4% were in the low intensity category. Assumed fixed seasonal.</td>
</tr>
<tr>
<td>Access to case</td>
<td>38%</td>
</tr>
<tr>
<td>Bed net coverage</td>
<td>82% own at least one bed net</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>Clinical malaria 46% (95% CI 42% to 50%) Severe malaria 34% (95% CI 15% to 48%)</td>
</tr>
<tr>
<td>Vaccine schedule</td>
<td>In Malawi, the first dose of the RTS,S/AS01 vaccine is expected to be administered to children at 5 months with the second and third at one month intervals; the fourth dose is to be given 15–18 months after the third dose.</td>
</tr>
<tr>
<td>Vaccine coverage</td>
<td>The coverage of dose 3 of RTS,S was estimated at 75% of DTP3 coverage to account for the challenge in reaching older children and also for the difference in schedule of the RTS,S with traditional vaccines such as the pentavalent vaccine. Dose 4 coverage of RTS,S was 80% of dose 3.</td>
</tr>
<tr>
<td>Cost of vaccination</td>
<td>Vaccine delivery costs USD 2.50 were estimated from the cost of delivering a single dose of the injectable DTP vaccine.</td>
</tr>
</tbody>
</table>

**Clinical malaria estimated costs USD**

| Healthcare system | USD 8.02 These include drugs, laboratory investigations, staff salaries and facility costs such as laundry, kitchen, sanitation and security. |
| Household-direct  | USD 1.21 These include transportation costs, costs of consultations, drugs and diagnostics.                                                              |
| Household-indirect| USD 0.50 These are lost income by the carer attributable to the episode of disease.                                                                     |

**Severe malaria costs USD**

| Healthcare system | USD 12.8 These include drugs, laboratory investigations, staff salaries and facility costs such as laundry, kitchen, sanitation and security. |
| Household-direct  | USD 14.1 These include transportation costs, costs of consultations, drugs and diagnostics.                                                              |
| Household-indirect| USD 4.13 These are lost income by the carer attributable to the episode of disease.                                                                     |

**Sequelae costs USD**

| Healthcare system | USD 40.1 The neurological sequelae was adapted by the cost of treatment of malaria sequelae for the Tanzanian health system |
facility costs. Where these specific costs were unavailable for clinical and severe malaria, we used malaria sequelae costing data from Tanzania\(^2\), as cost data from Malawi were not available. Direct and indirect household costs incurred in care seeking were also based on those locally empirically observed in gastroenteritis\(^1\). Direct household costs included travel, consultation fees, treatment sought before and after health facility visit and the costs of food and shelter for the carer. Indirect costs comprised income lost while caring for the child\(^1\). Bed net use and access to and usage of ACTs and the proportion of those who seek treatment at a private dispensary were derived from the Malawi Malaria Indicator Survey\(^1\). Vaccine price per dose has not yet been set by GSK, so we assessed a range of costs of USD1, USD5 and USD10. RTS,S delivery in the Malawi EPI was taken from the administration cost pentavalent vaccine\(^2\). The cost of delivery includes all the necessary materials and health worker time required to administer a vaccine in the EPI. The mean Malawi GDP per capita from 2010 to 2015, as reported by the World Bank, was used to compare with the ICER per DALY averted\(^1\).

Sensitivity analysis
Univariate analysis was conducted by running the model through different values of vaccine price and vaccine coverage rate whilst the other input parameters were held constant.

Results
Based on a 15-year cohort of 711,743 children, the model calculated an ICER of USD 115 and 109 per DALY averted in the health system and the societal perspective respectively compared to no vaccination. Based on a vaccine schedule of four doses, this is less than the Malawi mean GDP per capita of USD 398.6, suggesting that the introduction of RTS,S vaccine to the Malawian EPI programme would be highly cost-effective. The model predicted 721,768 (95% CI: 529,296–894,991) averted clinical malaria cases per year, 14% of current burden. The model demonstrated that 117,260 clinical cases and 700 malaria attributable deaths would be prevented per 100,000 fully vaccinated children per year. The vaccine introduction was also very cost effective at an assumed vaccine price of USD 1 and USD 10 with four doses of the RTS,S vaccine. We predicted cost savings for the society, healthcare system and household as USD 3,025,521, USD 2,433,777 and USD 591,744, respectively. Healthcare costs contributed to over two-thirds of societal costs.

Modelling findings
Table 2 shows the cumulative cost-effectiveness results for a birth cohort followed up over 15 years, using assumed vaccine prices of USD 1, USD 5, and USD 10. At USD 5, the ICER was 115 USD per DALY averted. At USD 1 vaccine price the ICER was USD 40 per DALY averted and at USD 10 the ICER was USD 209 per DALY averted. We showed that the vaccine would remain very cost-effective even at an inflated vaccine price of USD 10 per dose. However, the societal cost savings remain unchanged with a change in vaccine price.

Table 3 shows the cumulative public health impact results over 15 years with comparison of different vaccine coverage versus the number of malaria clinical cases averted. The number of DALYs and malaria cases and deaths avoided are largely dependent on the vaccine coverage in the population. At an assumed coverage of 75% of DTP3 coverage, the model predicted 10,826,521 clinical cases averted (Table 4). This is equal to 721,768 malaria clinical cases per year. The highest number of malaria clinical cases avoided was with a 93% vaccine coverage which is similar to current DTP3 coverage for Malawi.

### Table 2. Discounted cost-effectiveness results over a 15-year period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No vaccination</th>
<th>6–9m schedule plus 4th dose</th>
<th>Cost savings*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>USD 1 per dose</td>
<td>USD 5 per dose</td>
</tr>
<tr>
<td>Healthcare system ICER (USD per DALY averted)</td>
<td>---</td>
<td>40</td>
<td>115</td>
</tr>
<tr>
<td>Societal ICER (USD per DALY averted)</td>
<td>---</td>
<td>34</td>
<td>109</td>
</tr>
<tr>
<td>DALYs</td>
<td>1,237,356</td>
<td>1,176,557</td>
<td>1,176,557</td>
</tr>
<tr>
<td>Vaccination costs</td>
<td>---</td>
<td>6,334,532</td>
<td>13,573,997</td>
</tr>
<tr>
<td>Healthcare system costs</td>
<td>26,396,028</td>
<td>23,962,251</td>
<td>23,962,251</td>
</tr>
<tr>
<td>Incremental costs for healthcare system</td>
<td>3,900,755</td>
<td>11,140,220</td>
<td>20,189,552</td>
</tr>
<tr>
<td>Household costs</td>
<td>6,576,176</td>
<td>5,984,432</td>
<td>5,984,432</td>
</tr>
<tr>
<td>Societal costs*</td>
<td>32,972,204</td>
<td>29,946,683</td>
<td>29,946,683</td>
</tr>
<tr>
<td>Incremental costs for the society</td>
<td>3,309,011</td>
<td>10,548,476</td>
<td>19,597,808</td>
</tr>
</tbody>
</table>

DALY = disability-adjusted life year; ICER = Incremental Cost Effectiveness Ratio. Note 1. Societal costs = health care system + household level costs.

* Cost savings are the difference in costs between no vaccination scenario and vaccination scenario.
Table 5 shows the comparison in vaccine cost-effectiveness between a three-dose schedule and a four-dose schedule with an assumed vaccine price of USD 5 per dose. It shows that more DALYs are averted with a four-dose schedule than a three-dose schedule, but a four-dose schedule has higher societal costs because of ancillary costs associated with an additional visit.

Discussion
This analysis has shown that the introduction of the RTS,S vaccine in the Malawi EPI would be a highly cost-effective malaria intervention. Cost-effectiveness of interventions affects decisions to introduce and invest in their sustainable use. Additional economic analyses will further inform budget impact, domestic funding required and long-term financial sustainability of such interventions. With the Markov model, we predicted the incremental cost-effectiveness ratio and public health impact of vaccinating children with four doses of RTS,S as recommended by WHO in the pilot implementation programme.

As the vaccine price is currently unknown, we tested the model at different vaccine prices with other input parameters held constant to determine if the vaccine programme would remain

Table 3. Public health impact results cumulative over a period of 15 years.

<table>
<thead>
<tr>
<th>Events averted</th>
<th>Absolute vaccine coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>93%</td>
</tr>
<tr>
<td>DALYs</td>
<td>120,101</td>
</tr>
<tr>
<td>malaria cases</td>
<td>13,424,866</td>
</tr>
<tr>
<td>severe malaria cases</td>
<td>313,359</td>
</tr>
<tr>
<td>malaria hospitalisations</td>
<td>260,329</td>
</tr>
<tr>
<td>malaria deaths</td>
<td>81,824</td>
</tr>
</tbody>
</table>

β = coverage of DTP3 in Malawi.

Table 4. Events averted across different outcome.

<table>
<thead>
<tr>
<th>Events averted</th>
<th>Assessed scenario</th>
<th>Average per year</th>
<th>per 100,000 vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Over a 15 year follow up (% reduction compared with no vaccination)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>malaria cases</td>
<td>10,826,521 (14%)</td>
<td>721,768</td>
<td>117,260</td>
</tr>
<tr>
<td>severe malaria cases</td>
<td>252,709 (11%)</td>
<td>16,847</td>
<td>2,737</td>
</tr>
<tr>
<td>malaria hospitalisations</td>
<td>209,943 (11%)</td>
<td>13,996</td>
<td>2,274</td>
</tr>
<tr>
<td>malaria deaths</td>
<td>65,987 (11%)</td>
<td>4,993</td>
<td>714.7</td>
</tr>
</tbody>
</table>

Table 5. Comparison of public health impact results over 15 years follow-up between the three- and four-dose schedules.

<table>
<thead>
<tr>
<th>Events averted</th>
<th>6-9m schedule without a 4th dose</th>
<th>6-9m schedule plus a 4th dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DALYs</td>
<td>73,361</td>
<td>96,799</td>
</tr>
<tr>
<td>malaria cases</td>
<td>8,504,970</td>
<td>10,826,521</td>
</tr>
<tr>
<td>severe malaria cases</td>
<td>200,322</td>
<td>252,709</td>
</tr>
<tr>
<td>malaria hospitalisations</td>
<td>166,421</td>
<td>209,943</td>
</tr>
<tr>
<td>malaria deaths</td>
<td>52,308</td>
<td>65,987</td>
</tr>
</tbody>
</table>

DALY = disability-adjusted life year.
cost-effective. Our results showed that even at an inflated vaccine price of USD 10 per dose, the ICER per DALY calculated was USD 209 suggesting the RTS,S vaccination programme would remain highly cost-effective. We analysed the cost-effectiveness ratio of a three-dose versus a four-dose schedule of the RTS,S vaccine programme. Despite higher vaccine and delivery costs of the four-dose than three-dose schedule, cost-effectiveness is maintained due to greater DALYs averted with the four-dose schedule.

Malawi introduced the Rotavirus vaccine (Rotarix, GSK), in 2012. Similar to RTS,S, Rotarix is a moderately (64%) efficacious vaccine against rotavirus acute gastro-enteritis in Malawi. A cost-effectiveness analysis in Malawi found it to be highly cost-effective with USD 5.07 ICER per DALY averted with GAVI co-financing and USD 74.73 at vaccine market price. Rotarix is expectedly more cost-effective than RTS,S as it is delivered in the same schedule and existing vaccine deliver infrastructure as other existing EPI vaccines. The first RTS,S dose will be at 5 months and the last dose at 24 months. This means RTS,S will require a separate immunisation schedule driving the vaccine delivery costs higher. In addition, Rotarix is an oral vaccine with only two doses priced below USD 2.3 per dose whilst RTS,S is an injectable vaccine and has a four-dose schedule with a price assumed to be USD 5 per dose.

The WHO harmonisation exercise on RTS,S cost-effective analysis for sub-Saharan Africa involved four modelling groups: The Institute for Disease Modeling (EMOD-DTK), GSK Vaccines (GSK), Imperial College London (Imperial), and the Swiss Tropical and Public Health Institute (OpenMalaria). The EMOD DTK model is a discrete, stochastic, individual-based model for malaria in either local or spatially distributed settings. The model accounts for the combined effect of an extensive set of both vector- and human-directed interventions. The Imperial College model is a stochastic, individual-based simulation of a single population of humans linked to a stochastic compartmental model for mosquitoes. The model includes larval stages as well as adult female mosquitoes to capture the feedback of vector control that kills adult mosquitoes in the population dynamics. Swiss TPH – OpenMalaria is a stochastic, individual-based, single location simulation model of malaria in humans linked to a deterministic models of malaria in mosquitoes. The simulation model includes sub-models of infection of humans, blood-stage parasite densities, infectiousness to mosquitoes as a lagged function of asexual parasite density, incidence of morbidity including severe and hospitalisation and mortality.

The GSK Markov Model has the advantage of considering the three categories of transmission ($\text{PR}\leq 5\%$, $5\% < \text{PR}\leq 40\%$, $\text{PR}>40\%$) and capacity to factor in heterogeneity in exposure among individuals for each transmission level. This model does not report confidence bounds, which is expected from a cohort model nor can it account for possible herd protection. The GSK cohort-based model was the optimal option as the other models use individual level data which are unavailable in Malawi. Our findings were within the confidence bounds of 116,480 (31,450–160,410) clinical malaria cases averted per 100,000 vaccinated children as predicted by the other three models. The GSK model is unable to capture the effect of herd immunity as compared to the three other models which do. Should herd immunity occur, cost-effectiveness would be greater than our predictions. The modest efficacy of RTS,S and its short duration of protection may limit its potential for reducing the parasite circulation capacity. Our method provides point estimates but not 95% confidence bounds, the latter which require microsimulation on individual data which were unavailable to us. The fourth dose of RTS,S was assumed to restore waning immunity but recent data has shown the efficacy to be lower after dose four.

Models are input dependent. Cost data in Africa are sparse, may be out of date or insufficiently robust. Regional data or neighbouring country data may be used when available. A malaria cost of illness study in Tanzania, Kenya and Ghana estimated clinical malaria and severe malaria costs for household and the healthcare system. Malawian data were unavailable, we used Tanzanian data rather than data from Ghana or Kenya. This is because the Tanzanian and Malawian health financing systems are similar, both provide government funded free health care through primary and referral level systems, and both lack a national insurance system or any substantial private health sector. Additionally, direct household cost for clinical malaria was more similar for Malawi (USD 0.5) and Tanzania (USD 0.4) than it was for Kenya (USD 0.7) and Ghana (USD 4.4). Malawi and Tanzania are geographically contiguous and share similar malaria epidemiology.

In the absence of published malaria treatment cost data from the societal perspective, we used rotavirus empirical cost data. Our data on bed net usage, an important model parameter, was taken from the 2014 Malaria Indicator Survey which preceded the national wide bed net campaign that that distributed over 2.3 million bed nets from November 2014 to February 2015. The RTS,S vaccine is a complementary malaria intervention whose impact on the reduction malaria morbidity is also dependent on the coverage of other interventions such as bed net usage.

Population coverage is crucial to the success of any vaccine programme. RTS,S will be given to older children, aged 5 months, not as part of the standard EPI schedule. Additional, the fourth dose of the RTS,S will be administered to children when they are about 2 years of age. This booster dose will be outside the normal immunisation schedule whilst the first 3 doses will be before the measles vaccine which is given at 9 months. In our study we assumed the RTS,S dose 3 coverage at 75% of DTP3 and the fourth dose to be even lower at 80% of RTS,S of the third dose. The coverage rate for the measles vaccine has been above 80% since 2010, even though the vaccine is given to older children. Almost all Malawians have been affected by malaria, which may translate to high vaccine acceptance despite the non-standard schedule.
Conclusion
Introduction of the RTS,S/AS01 vaccine would be a highly cost-effective malaria intervention in Malawi. This holds regardless of potential changes to key variables for the vaccine programme. Following full recommendation of vaccine use by WHO, individual level cost-effective analyses will provide more accurate data that can assist other sub-Saharan African countries.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

References
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Open Peer Review

Current Peer Review Status: ⬤ ✓

Version 1

Reviewer Report 26 April 2021

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The authors analysed the cost-effectiveness and public health impact of the RTS,S/AS01E malaria vaccine use in Malawi and predicted that introduction of the RTS,S/AS01 vaccine in the Malawian expanded programme of immunisation (EPI) to be highly cost-effective. The cost-effectiveness of vaccines affects decisions to introduce and invest in their sustainable use. Hence, the study findings are highly relevant in this regard.

I would like to give some suggestions for the authors to consider:

1. The introduction section is very short; they could have included the magnitude of malaria in Malawi in terms of morbidity and mortality data. It would have been better if they had provided information regarding vaccine efficacy, acceptance, and other relevant phase III trial data in the introduction.

2. The authors have used a range of vaccine price per dose, similarly they could have used a range of vaccine efficacy available from existing literature to calculate Incremental Cost-Effective Ratio (ICER), Disability-adjusted Life Year (DALYs) averted, and cost savings. Then it would have been easier for decision-makers to know the cost-effectiveness for a wide range of vaccine efficacy.

Is the work clearly and accurately presented and does it cite the current literature?  
Yes

Is the study design appropriate and is the work technically sound?  
Yes

Are sufficient details of methods and analysis provided to allow replication by others?  
Yes
If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Vaccinology; Epidemiology; Health system research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Reviewer Report 19 February 2021**

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Ndeketa et al., analyzed the cost-effectiveness and public health benefit of implementing the RTS,S/AS01 malaria vaccine in Malawian children. They authors found that the ICER/DALY averted was lower than the GDP per capita, supporting that RTS,S implementation is highly cost effective and beneficial in reducing malaria clinical cases and deaths. Given that RTS,S is currently being evaluated in a pilot implementation program, these findings are highly relevant and timely, and may contribute to further decision-making regarding the wider implementation of RTS,S.

I have concerns regarding the assumption that VE over 15 years is 46% against clinical malaria. i) In the phase 3 trial, 46% VE was calculated in children who received three vaccine doses over an 18-month follow-up. Why was the overall VE used and not the VE from the Malawi study site (Lilongwe), which was 42%? ii) The Methods state that the 4th dose was assumed to restore VE. However, in the phase 3 trial, VE in children who received the 4th dose was only 36% after a 4-year follow-up. Therefore, the booster dose did not restore VE (which continued to wane since the 18-month follow-up). Further, other trials have shown RTS,S vaccine efficacy to rapidly wane within years after immunization (Olotu et al., N Eng J Med 2016¹). iii) There is no evidence that RTS,S vaccine efficacy remains moderate at 46% for 15 years. These are incredibly important limitations to the model presented. I would suggest the assumed VE needs to be revised, or this limitation must be further emphasised in the discussion section (along with relevant published data on the...
true longevity of vaccine efficacy over time).

I have several minor comments for the authors to consider:
1. The introduction section is very brief and would benefit from additional background discussion on the RTS,S malaria vaccine. In particular, important information from the phase 3 trial as the model is based on a 4-dose vaccine regimen (which was tested in the phase 3 trial) and vaccine efficacy against clinical/severe malaria were also based on data from the phase 3 trial (in children).

2. Figure 1 appears quite blurred, could a higher-resolution image be uploaded?

3. The Methods “Sensitivity analysis” subsection says that univariate analysis was performed – are these data shown? If not, this should be specified.

Please note that I do not have expertise in modelling or cost-effective analysis and cannot confirm the analysis and interpretation are appropriate. However, the model has been previously validated in a peer-reviewed manuscript.

References

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Malaria; Immunology; Vaccines

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.