Public health impact and cost-effectiveness of malaria vaccine RTS,S/AS01

This summary highlights key outcomes from a systematic comparison of estimates of the potential public health impact and cost-effectiveness from four independent modelling groups.

This report is based on the results provided to the WHO Joint Technical Expert Group in June 2015. The details here are provided as part of the evidence for the WHO SAGE/MPAC joint committee meeting on 21st October 2015.

These results are not for citation or further distribution.

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(1) Mathematical models

Four mathematical models were fitted to the final Phase III trial results of RTS,S. These models are GlaxoSmithKline Vaccines (GSK), Institute for Disease Modelling (IDM, model name EMOD DTK), Imperial College London (Imperial) and Swiss Tropical and Public Health Institute (Swiss TPH, model name OpenMalaria). Full details of each model have previously been published.

The runs were performed under a set of harmonised assumptions. Projections were made for two immunisation schedules: 3 doses given between 6 and 9 months of age (referred to as 6-9 month implementation) and the three doses with an addition of a booster at 27 months of age (referred to as 6-9 month with booster). Predictions were made under a set of harmonised assumptions regarding vaccine implementation and other key drivers of impact, including demography, transmission intensity and access to care. Outputs are summarized as events averted per 100,000 fully vaccinated children over a 15-year time horizon. In both schedules a fully vaccinated child is defined as having received at least three doses. Cost-effectiveness ratios (ICERs as cost per DALY averted) were estimated using a single set of agreed costs and a harmonised methodology at vaccine price of $2, $5 and $10 a dose.

(2) Vaccine efficacy against infection & waning

All four groups estimate a high initial post 3rd dose efficacy against infection (>75% on average, Figure 1) and a similar pattern of waning over the first 18 months. For the non-booster schedule, from 18 months onwards, the estimated profiles diverge.

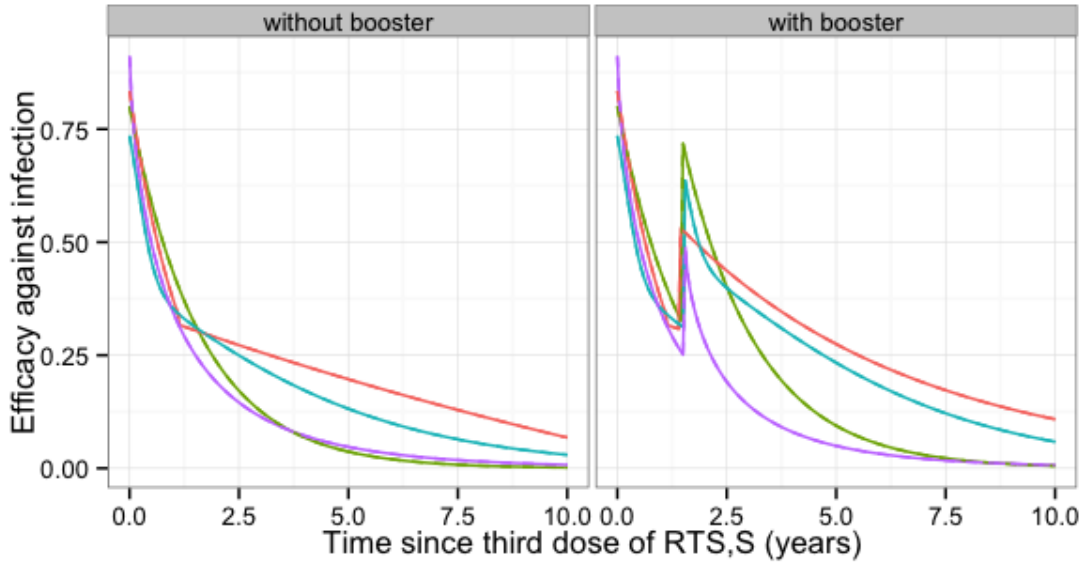

Figure 1 | Estimated efficacy against infection profiles after the third dose of the primary course in children receiving their first dose between 5 and 17 months (age of cohort at first vaccination in Phase 3). Colours indicate groups (green EMOD DTK, red GSK, blue Imperial and purple OpenMalaria). The left panel shows the fit to the cohort without the booster and the right panel with booster. Note that efficacy against infection translates differently into clinical efficacy for the four models.

There are three potential reasons for divergence in the waning profile. Firstly, these models translate efficacy against infection into efficacy against clinical disease differently. Secondly, due to the trial design, there is a 50% decrease in statistical power because the 5-17m cohort is split into the booster and no booster arms. This, combined with a shorter follow-up

time for the boosting dose compared to non-boosting, results in limited power to estimate waning profile after 18 months and the boosting dose waning profile. Thirdly, the groups made different parametric assumptions for the waning profiles and for the relationship between initial waning and waning following the booster. Fits to clinical efficacy for both the 5-17 month cohort boosting and no-boosting arms are shown in Supplementary Figures D.1-D.8.

(3) Public health impact by prevalence

Key outcomes for generic parasite prevalence settings (*Pf*PR_{2-10}) are summarized in Table 1. A significant positive impact was predicted within the range of *Pf*PR_{2-10} >3% by all four models for both schedules (with and without the booster dose), although there was more divergence between model predictions for *Pf*PR_{2-10} <10%. At *Pf*PR_{2-10} of 3% the uncertainty intervals include zero. The incremental impact of the booster dose was estimated to be significant for *Pf*PR_{2-10}≥10% and consistent with the incremental impact on severe disease observed in the trial. A wider range of outcomes is shown in supplementary Table A.

Table 1| Estimated deaths per 100,000 fully vaccinated children (FVC) and Incremental Cost Effectiveness Ratios (ICERs) at $5 (USD) per dose. Estimates are presented as median and ranges across the models in parentheses.

Outcome	*Pf*PR_{2-10} 10% to 65%	*Pf*PR_{2-10} 30% to 50%	*Pf*PR_{2-10} 10%	*Pf*PR_{2-10} 7.5%	*Pf*PR_{2-10} 5%
Non-booster schedule					
Deaths averted per 100,000 FVC	394 (127-708)	451 (287-708)	205 (127-251)	146 (106-225)	100 (74-178)
ICER at $5 dose	$80 ($44-279)	$65 ($49-82)	$139 ($117-279)	$189 ($130-334)	$283 ($159-500)
Booster schedule					
Deaths averted per 100,000 FVC	484 (189-859)	534 (406-859)	229.5 (189-344)	162.5 (147-297)	106.5 (102-249)
ICER at $5 dose	$87 ($48-244)	$73.5 ($49-96)	$158 ($105-244)	$214 ($120-312)	$316 ($143-462)
Incremental impact: proportion of additional deaths averted per 100,000 FVC[a]	22% (3%-49%)	22% (6%-41%)	20% (3%-49%)	28% (-2%-42%)	33% (-8%-40%)

[a] by boosting schedule compared to non-boost

(4) Cost-effectiveness impact by prevalence

Table 1 and Figure 2 show the incremental cost effectiveness ratios (ICERs) by *Pf*PR_{2-10}. Overall there is good agreement between the models. ICERs are lowest at intermediate levels of parasite prevalence. All four models predict higher ICERs at low parasite prevalence (*Pf*PR_{2-10} <10%), and similar or slightly higher ICERs at high parasite prevalence (*Pf*PR_{2-10} >50%), compared to intermediate levels of parasite prevalence. For *Pf*PR_{2-10} below 10% there is less agreement between the models, reflecting the variability between models and wider uncertainty in predictions of impact (Figure 2, Figure A). Similar ICER estimates were predicted for the non-boosted and boosted schedules because the additional public health benefit of the boosted schedule is offset by the incremental cost of implementing the additional dose. This is in part due to our assumption that 80% of children receiving the first 3 doses would return for the booster dose under the booster schedule. Table A contains estimated ICERSs for $2 and $10 (USD).

A one-way sensitivity analysis by Swiss TPH using OpenMalaria at moderate prevalence indicates the cost per DALY averted with a 15 year time horizon at most doubles from the baseline estimate across the ranges considered, with cost per DALY averted most sensitive to changes in vaccine price.

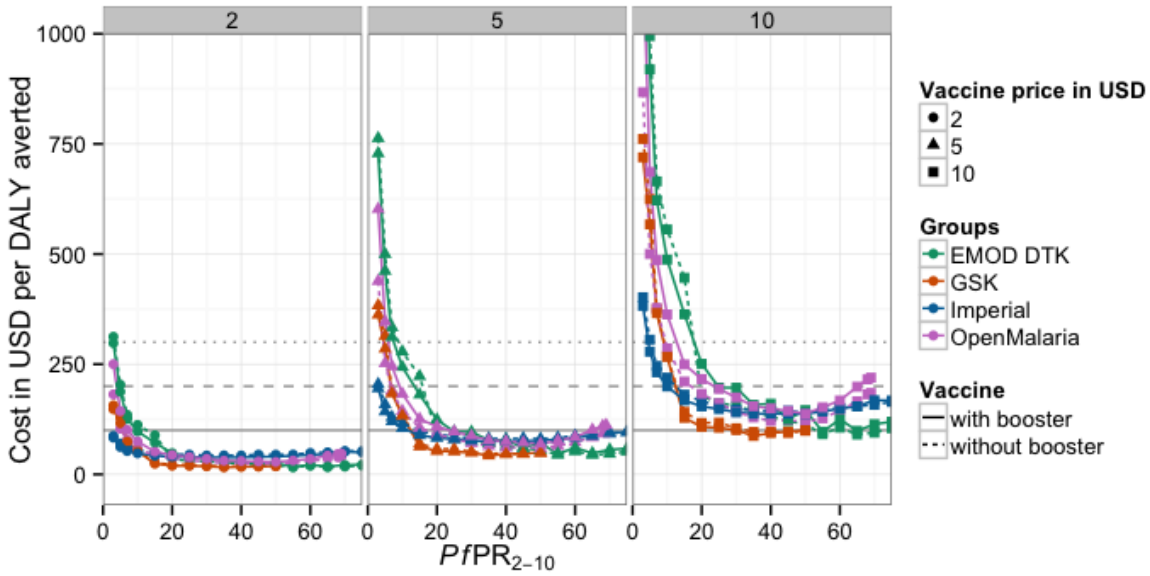

Figure 2 | Cost (USD) per DALY (median) over 15 years of use of RTS,S via 6-9 month immunisation schedule with and without booster (**Figure A** illustrates the same but different axis limits to illustrate lower prevalence levels). Columns indicate an assumed vaccine price of either $2, $5, or $10 and colour indicates models (green EMOD DTK, orange GSK, blue Imperial, purple OpenMalaria). An immunisation schedule of three doses between 6 and 9 months of age is indicated by dashed lines, and a schedule including the booster dose by solid lines. Similar ICER estimates were obtained for the non-boosted and boosted schedules because the additional public health benefit of the boosted schedule is offset by the incremental cost of implementing the additional dose. The grey reference lines correspond to $100, $200 and $300 per DALY averted by solid, dashed and dotted lines respectively. The cost per DALY averted for the 6-9 month immunisation schedule with booster dose is the average cost-effectiveness ratio, and not incremental to primary schedule of three doses. Uncertainty estimates that surround the model predictions are omitted for readability, but overlap one another.

(5) Country specific projections of impact and cost-effectiveness

Predictions were also made for 6 anonymised countries that broadly represent the range of transmission patterns and implementation capacity in Africa: 3 countries at low endemicity (mean *Pf*PR_{2-10} under 10%), 2 countries at moderate endemicity (mean *Pf*PR_{2-10} 20-40%) and one at high endemicity (mean *Pf*PR_{2-10} >50%). In the country-specific simulations we assumed the vaccine would be introduced in 2017.

The predicted country-specific impact is similar in magnitude to that predicted from the mean generic prevalence level and hence this factor alone may be sufficient to provide an indication of the likely impact in different geographical settings (Figure B). The estimated ICERs varied from the predictions based on mean prevalence level due to differences in costs of implementation and health services between the countries (Figure A). The estimated ICERs (Table B) are below the national GDPs, which range from $500-1800 per capita for these countries. In settings with *Pf*PR_{2-10}>10%, RTS,S would be considered a highly cost-effective intervention: at vaccine price of 5 USD a dose ICERs are estimated to

be below or close to $100, with a range across the 6 countries of 41-150 USD. This is comparable with the range for other malaria interventions. For example a 2011 review summarized average incremental costs per DALY averted (2009 prices) for LLINs of $27 ($8.15-$110), for IRS of $143 ($135-$150), and for IPT of $24 ($1.08-$44.24). However, there was a wide variation in the costing methodologies employed and economies of scale captured by these studies and hence these give indicative ranges rather than figures that can be directly compared.

(6) Age-shifting of disease and predictions of severe disease

The predicted reduced force of infection that vaccinated children are exposed to, and the presumed delay that this has on their acquisition of natural immunity, is predicted to result in a shift of clinical disease to older ages (similar to other partially-protective malaria interventions) (Figure C). Even in the absence of any waning of vaccine efficacy, this leads to higher rates of disease in older children in the vaccinated compared to the control arm, especially in higher prevalence settings where natural immunity is acquired more rapidly. Combining this effect with the estimated biological waning of the vaccine means that some of the initial impact on the cases averted in very young children is predicted to be offset by higher comparative incidence at older ages, with this effect predicted to occur later under the booster schedule. Similar effects are also predicted for severe disease, with the age-shift occurring earlier than for clinical disease.

All four models predict a net positive impact on the downstream consequences of malaria infection - namely severe disease cases and deaths averted - despite predicting a shift in cases to older ages. Whilst this predicted impact against severe disease is consistent with the trial results for the boosting schedule (32.2% (13.7 to 46.9%)[1] at study end in the 5-17 month cohort), there was no statistically significant impact against severe disease measured in the trial for the non-boosting schedule (1.1% (95% CI -23 to 20.5%)[1] in the 5-17 month cohort). There are several possible reasons for this discrepancy. Firstly, severe disease incidence in the trial was low, reflected in the wide confidence intervals around the reported estimates (possibly as a consequence of high access to case-management), and thus the positive impact estimated by the models for the non-booster schedule may be consistent with the upper end of the trial confidence interval. Secondly, the inferences about severe disease made by the models are based on data from field studies from sites which have poorer quality of care and that use a broader case definition[2]. Thirdly, the results presented here are for follow-up over a 15-year time horizon whilst the trial data includes up to 4 years follow-up. All four models predict an age-shift in cases and deaths to older ages in the vaccinated arms, which will also be predicted to impact on the proportion of cases that are severe. Much of this effect is predicted by the models to occur after 4 years of follow-up and so is not directly comparable with the trial data. This highlights the need for longer-term follow-up of trial participants to fully understand any shifting of cases to older age-groups.

(7) Consensus across the modelling groups

Although broad consensus was reached across the groups, a systematic and harmonized comparison of the multiple epidemiological malaria models indicated that differences between both the overall impact of the vaccine on clinical disease and predictions of the age-shift in cases, related largely to model characteristics that were evident in baseline model relationships and baseline incidence in absence of the vaccine. These include differences in: relationships between parasite prevalence and clinical incidence, case

definitions, assumptions concerning rates of immune acquisition, immune decay and how immunity acts, as well as differences due to datasets used for parameterisation. Moreover, the models translate efficacy against infection into efficacy against clinical disease in different ways. Thus, by comparing the outputs from four independent models, our estimates capture structural model uncertainty.

(8) Summary conclusions from the modelling groups

- Implementation of the RTS,S vaccine in 6-9 month children schedule (with or without boosting) could have a substantial additional public health impact across a broad range of settings representative of malaria parasite prevalence in Africa in the presence of other ongoing interventions.
- For areas where *Pf*PR_{2-10} is currently 10% or higher, RTS,S is predicted to be cost effective depending on vaccine price compared to standard norms and thresholds (GDP per capita), though with median ICERs close to the upper estimate for LLINs and seasonal malaria chemoprevention (SMC) and close to the lower estimate for IRS at a price of $5 per dose.
- For areas with *Pf*PR_{2-10} below 10% but above 3%, we find that implementation of RTS,S is likely to have positive impact with potential for substantial public health benefits, but that careful consideration of the cost-effectiveness compared to other interventions should be made in the context of local priorities and health systems.
- However, to allow direct comparisons, the ICER of each malaria intervention should be estimated using the same key assumptions, and this was outside the scope of this exercise (see report on comparative cost-effectiveness). It should be noted that comparing small differences in absolute ICERs has limited economic relevance and budget impact differences would be more relevant. Introduction of the vaccine will therefore need to be made in relation to the potential for further scale-up of other interventions.

(9) References

1. RTS,S CTP. Efficacy and safety of RTS, S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *The Lancet* 2015.
2. Marsh K, Snow R. Malaria transmission and morbidity. *Parassitologia* 1999; **41**: 241--6.
3. World Health Organisation. World Malaria Report 2013. Geneva: World Health Organisation., 2014.

Supplementary Tables

Table A. Summary predictions of public health impact and cost-effectiveness of RTS,S for 6-9 month immunization schedule with or without 4th dose at 15 years follow-up.

Outcome	Vaccination Schedule	*Pf*PR$_{2-10}$ 3% to 65%	*Pf*PR$_{2-10}$ 10% to 65%	*Pf*PR$_{2-10}$ 10% to 50%	*Pf*PR$_{2-10}$ 30% to 50%	*Pf*PR$_{2-10}$ 10%	*Pf*PR$_{2-10}$ 7·5%	*Pf*PR$_{2-10}$ 5%
Public Health Impact								
Proportion of deaths under 5 averted	6-9 months with 4th dose	19.5% (6-33.3)	18% (6-29.1)	19.1% (9.7-29.1)	19.5% (9.7-26.3)	25.1% (10.3-29.1)	26.4% (9.1-28.5)	28.1% (8.9-32.5)
	6-9 months	15.5% (5.3-24.3)	13.8% (5.3-21.4)	14.7% (9-21.4)	15.5% (9-17.7)	19.5% (9.8-21.4)	19.9% (8.6-21.5)	21.2% (7.8-27.4)
Proportion of clinical cases under 5 averted	6-9 months with 4th dose	23.3% (7.9-33.5)	21.1% (7.9-30.6)	23.9% (12.6-30.6)	23.3% (12.6-27)	28.3% (16.4-30.6)	28.6% (16.5-31.6)	29.3% (16.7-33)
	6-9 months	16.4% (7.3-26.6)	16.2% (7.3-24.1)	17.5% (11.9-24.1)	16.4% (11.9-20)	20.7% (15.6-24.1)	21% (15.8-25.3)	21.45% (15.9-26.2)
Deaths averted per 100,000 fully vaccinated	6-9 months 4th dose	406 (61-859)	484 (189-859)	459 (189-859)	406 (406-859)	229.5 (189-344)	162.5 (147-297)	106.5 (102-249)
	6-9 months	350 (43-708)	394 (127-708)	392.5 (127-708)	350 (287-708)	205 (127-251)	145.5 (106-225)	100 (74-178)
Clinical cases averted per 100,000 fully vaccinated	6-9 months 4th dose	93609 (8579-160411)	116482 (31448-160411)	112653 (31448-160411)	93609 (93609-160411)	41060.5 (31448-55760)	29740.5 (21799-46784)	20299.5 (11072-34063)
	6-9 months	61553 (5771-126545)	93938 (20491-126545)	89264 (20491-126545)	61553 (61553-126545)	33661.5 (20491-47542)	24807 (14790-37273)	16788 (8854-25745)
Incremental benefit (% of additional events averted of boosting schedule compared to non-boosting)								
Incremental benefit	Deaths	22% (-8-49)	22% (3-49)	22% (3-49)	22% (6-41)	20% (3-49)	28% (-2-42)	33% (-8-40)
	Clinical cases	33% (-2-53)	33% (-1-53)	31% (-1-53)	31% (1-52%)	34% (-1-53)	35% (-1-53)	34% (-2-56)
Cost-effectiveness (ICER per DALY averted.)								
$2 a dose	6-9 months 4th dose	$42 ($18-298)	$38 ($18-97)	$37 ($18-97)	$31.5 ($18-40)	$64 ($48-97)	$87.5 ($53-126)	$130 ($62-188)
	6-9 months	$45 ($16-312)	$35 ($16-112)	$36 ($18-112)	$26 ($18-45)	$56.5 ($54-112)	$76.5 ($60-135)	$116 ($70-204)
$5 a dose	6-9 months 4th dose	$96 ($48-728)	$87 ($48-244)	$82 ($49-244)	$73.5 ($49-96)	$158 ($105-244)	$214 ($120-312)	$316 ($143-462)
	6-9 months	$84 ($44-763)	$80 ($44-279)	$78.5 ($49-279)	$65 ($49-82)	$139 ($117-279)	$189 ($130-334)	$283 ($159-500)
$10 a dose	6-9 months 4th dose	$197 ($99-1447)	$154 ($99-487)	$160 ($100-487)	$140 ($100-197)	$315 ($200-487)	$426 ($232-622)	$626.5 ($278-919)
	6-9 months	$155 ($90-1514)	$147 ($90-556)	$144.5 ($99-556)	$128.5 ($99-155)	$277.5 ($219-556)	$376.5 ($246-665)	$562.5 ($306-995)

Notes Estimates are presented as median and ranges across the model's medians

Table B Country-specific predictions of deaths averted per 100,000 fully vaccinated and cost per DALY averted by RTS,S for 6-9 month immunization schedule with or without booster at 15 years follow-up· Estimates are presented as median and ranges across the model's medians.

Outcome	Vaccination Schedule	All countries	Countries with $PfPR_{2-10}$ > 10%
Public health impact			
Deaths averted per 100,000 fully vaccinated	6-9 months with boost	324·5 (149-1074)	559 (271-1074)
	6-9 months	276·5 (109-922)	451 (251-922)
Cost-effectiveness			
ICER (at $2 a dose)	6-9 months with boost	$55 ($19-156)	$34·5 ($19-73)
	6-9 months	$52·5 ($16-151)	$32·5 ($16-62)
ICER (at $5 a dose)	6-9 months with boost	$130·5 ($49-312)	$80 ($49-152)
	6-9 months	$112 ($41-335)	$69·5 ($41-130)
ICER (at $10 a dose)	6-9 months with boost	$246·5 ($99-622)	$151·5 ($99-283)
	6-9 months	$210·5 ($84-667)	$136·5 ($84-243)

Supplementary Figures

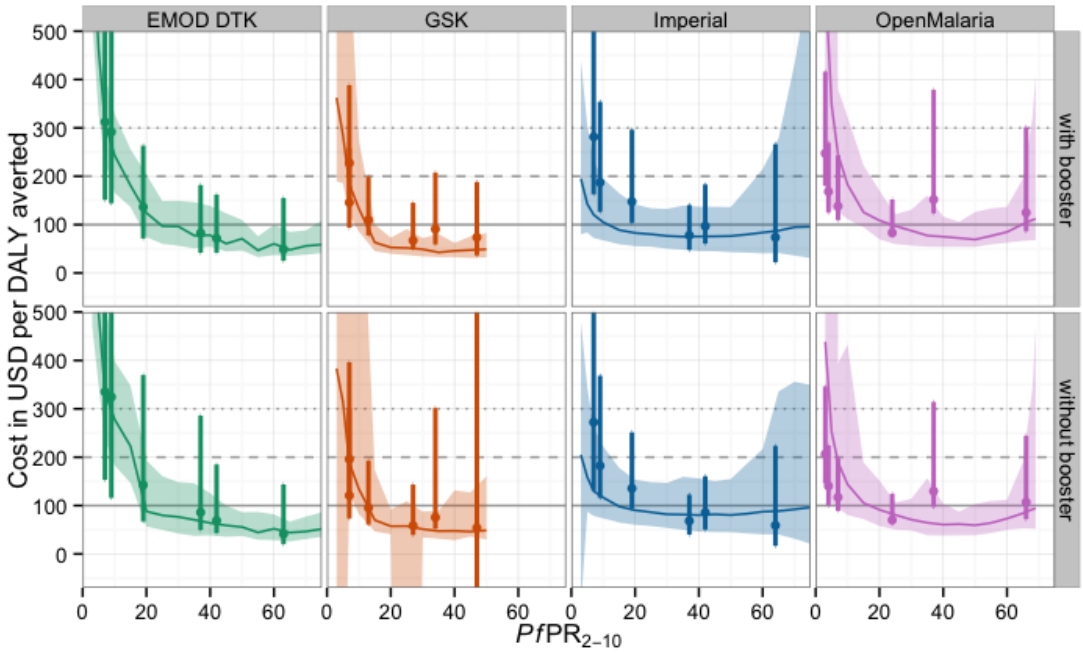

Figure A Cost (USD) per DALY averted with 15 years after the start of vaccination assuming a vaccine price of 5$ per dose for routine immunisation via 6-9 month schedule. Columns and colour indicate modeling groups (green EMOD DTK, orange GSK, blue Imperial, purple OpenMalaria), rows immunisation schedule. Shading represents 95% uncertainty bounds of predictions. Points with error bars represent the respective predicted costs per DALY averted for analysed countries, plotted at a country's average level of prevalence.

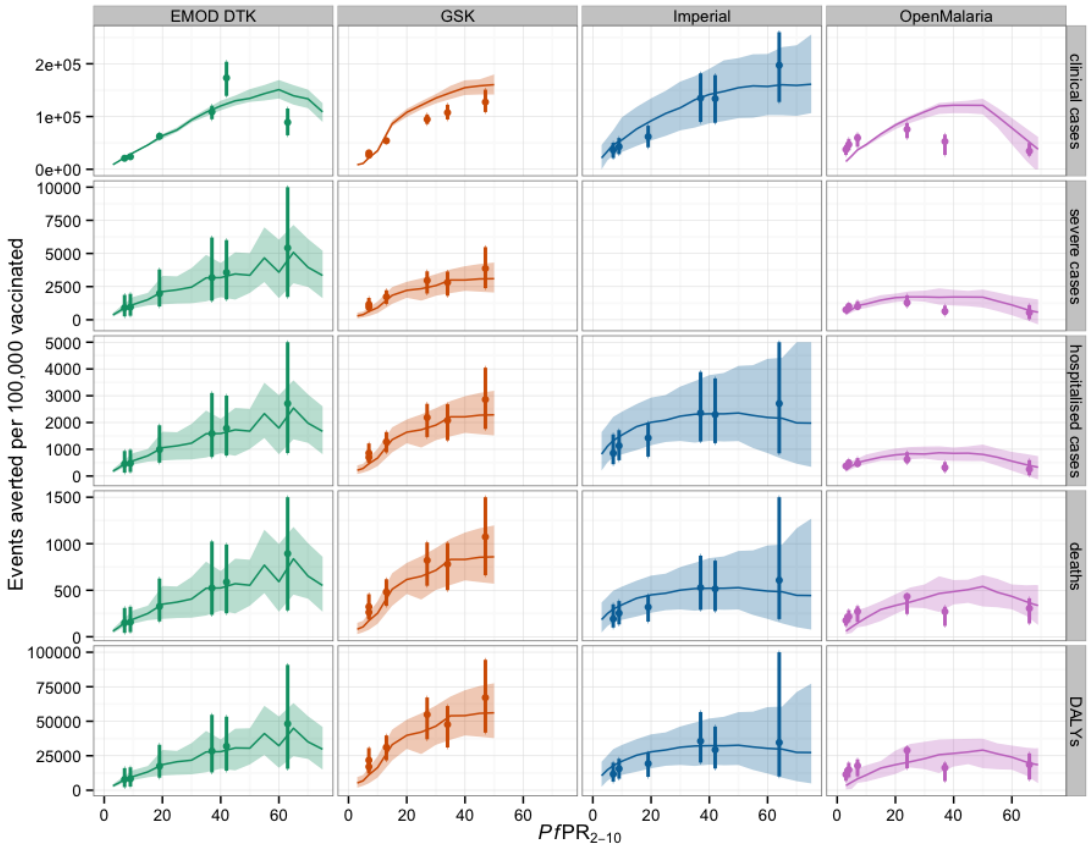

Figure B – Cumulative events averted per 100,000 fully vaccinated children after 15 years of routine use of RTS,S in a 6-9 month immunisation schedule with a booster dose at 27 months (vaccine efficacy profiles are best-fit by model). Rows indicate event (clinical, severe, hospitalized, deaths and DALYs), columns and colour indicate modelling group (green EMOD DTK, orange GSK, blue Imperial, purple OpenMalaria). Lines indicated median estimates from representative parasite prevalence levels with uncertainty indicated by shading. Point estimates with error bars are country specific predictions of events averted per 100,000 plotted at a country's average level of prevalence.

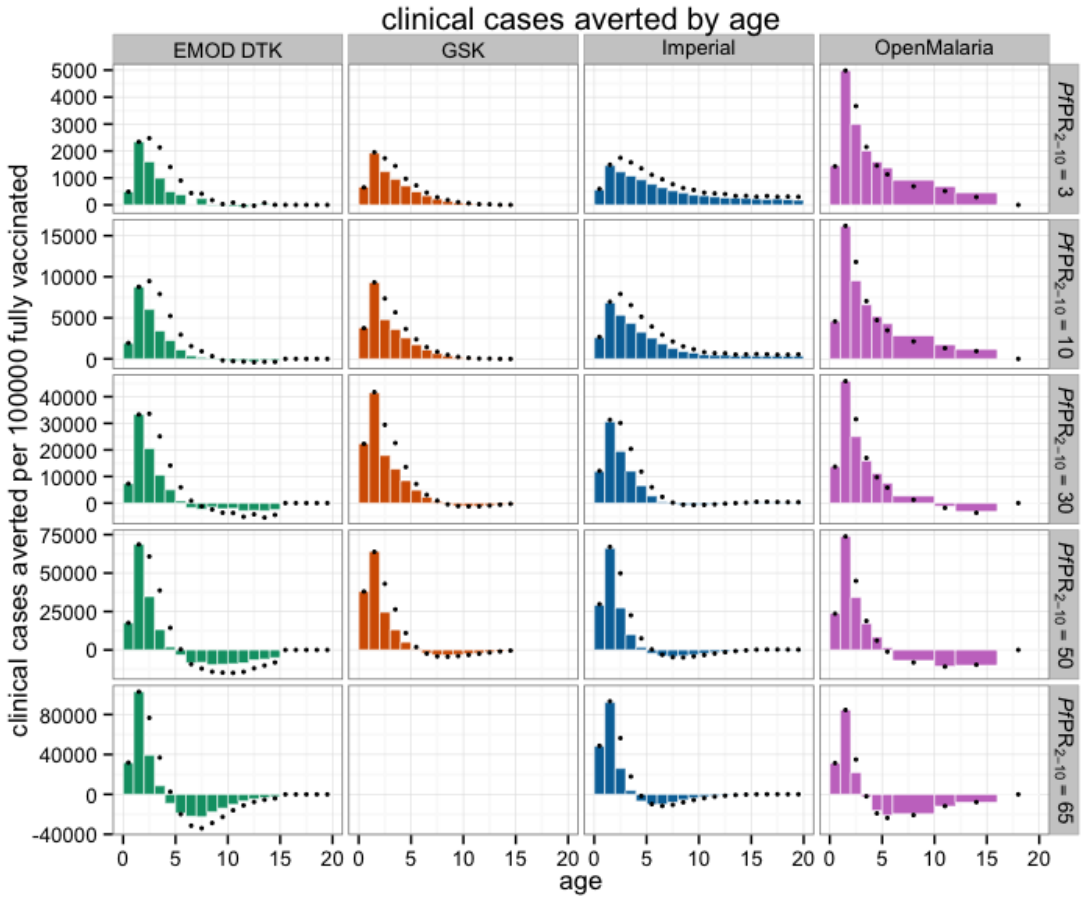

Figure C Clinical cases averted per 100,000 fully vaccinated children stratified by age group and parasite prevalence assuming model best-fit vaccine efficacy profiles. Rows indicate parasite prevalence, columns and colour modelling groups (green EMOD DTK, orange GSK, blue Imperial, purple OpenMalaria). Bars show events averted during 15 years of use of RTS,S within a 6-9 month immunisation schedule; black dots indicated events averted by the same schedule but administration of an additional booster dose at 27 months. Note the y-axis for each prevalence column are at different scales.

Figure D: Model fits to clinical efficacy for boosting and non-boosting 5-17 month cohort

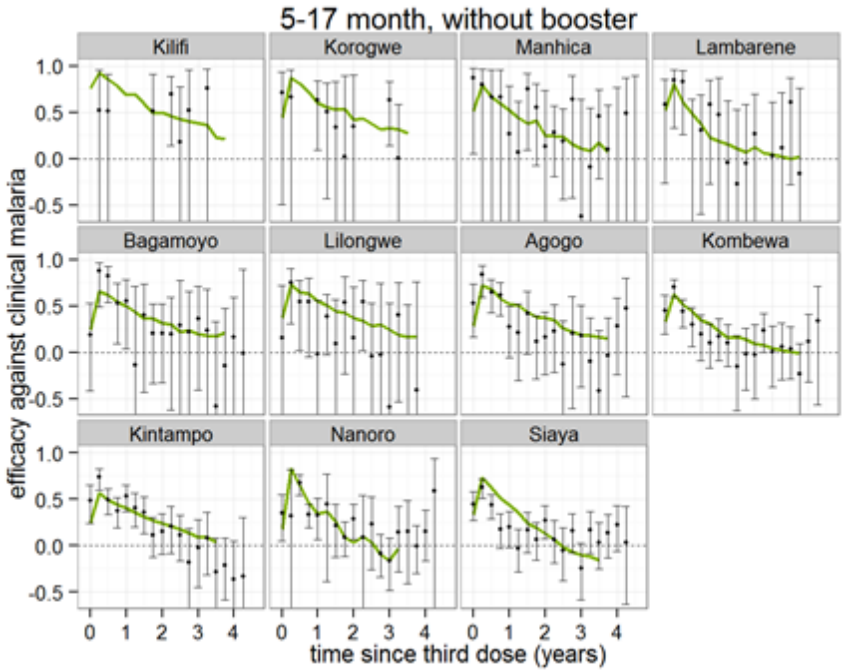

Figure D.1 Predicted efficacy against clinical disease by trial site compared to Phase III reported for the 5-17 month cohort using best-fitted vaccine profile from EMOD DTK

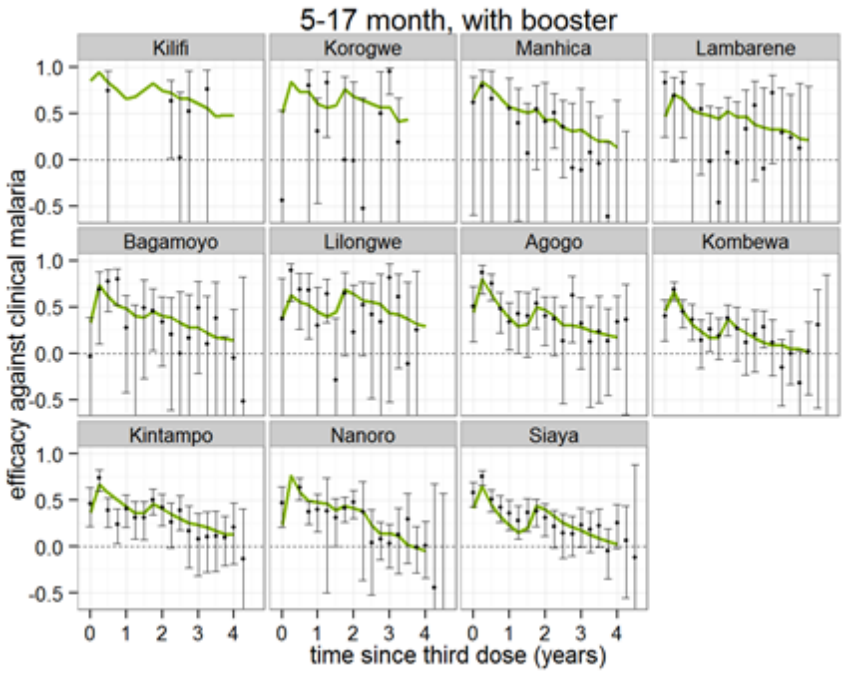

Figure D.2 Predicted efficacy against clinical disease by trial site compared to Phase III reported for the 5-17 month cohort with boost using best-fitted vaccine profile from EMOD DTK

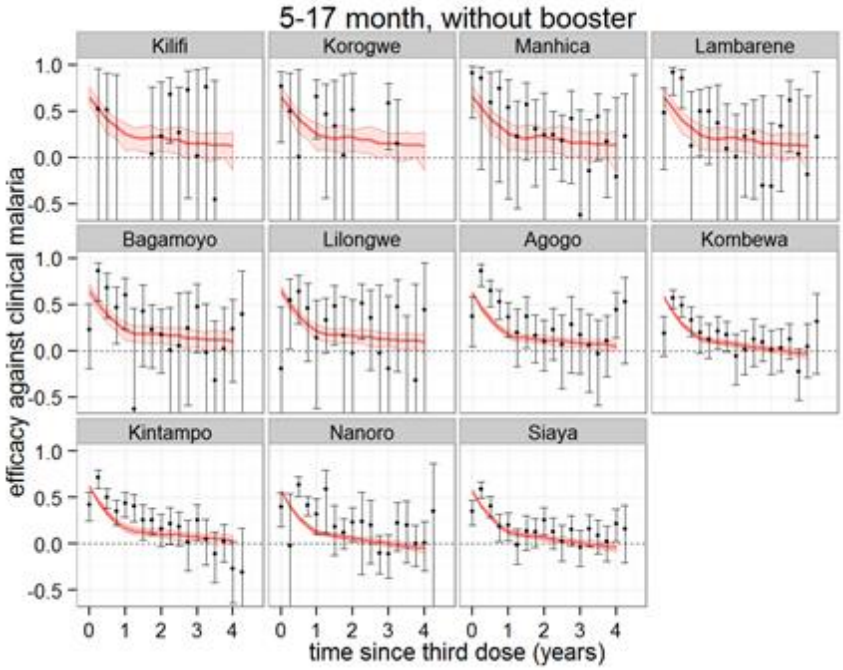

Figure D.3 Predicted efficacy against clinical disease by trial site compared to Phase III reported for the 5-17 month cohort using best-fitted vaccine profile from GSK

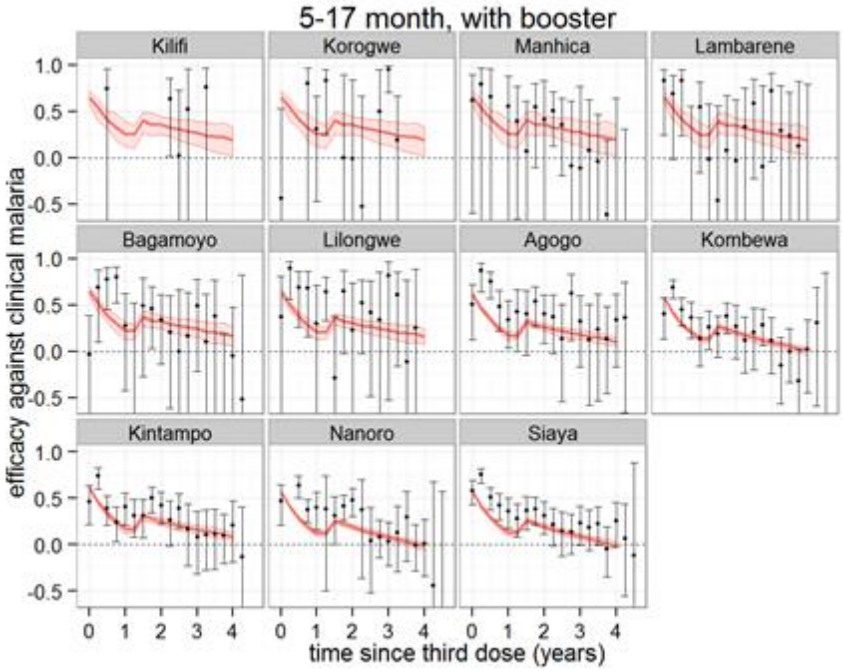

Figure D.4 Predicted efficacy against clinical disease by trial site compared to Phase III reported for the 5-17 month cohort with boost using best-fitted vaccine profile from GSK

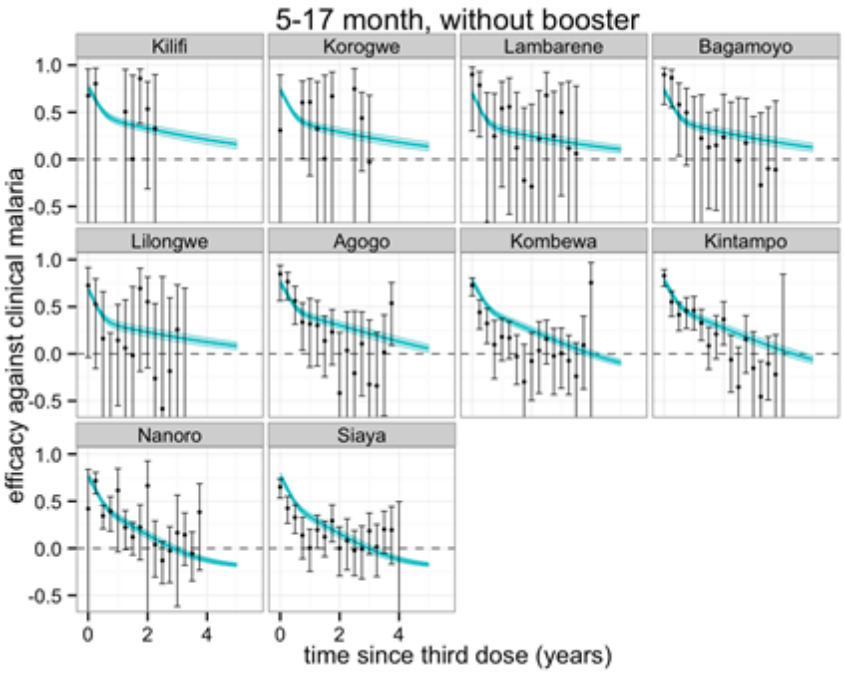

Figure D.5 Predicted efficacy against clinical disease by trial site compared to Phase III reported for the 5-17 month cohort using best-fitted vaccine profile from Imperial

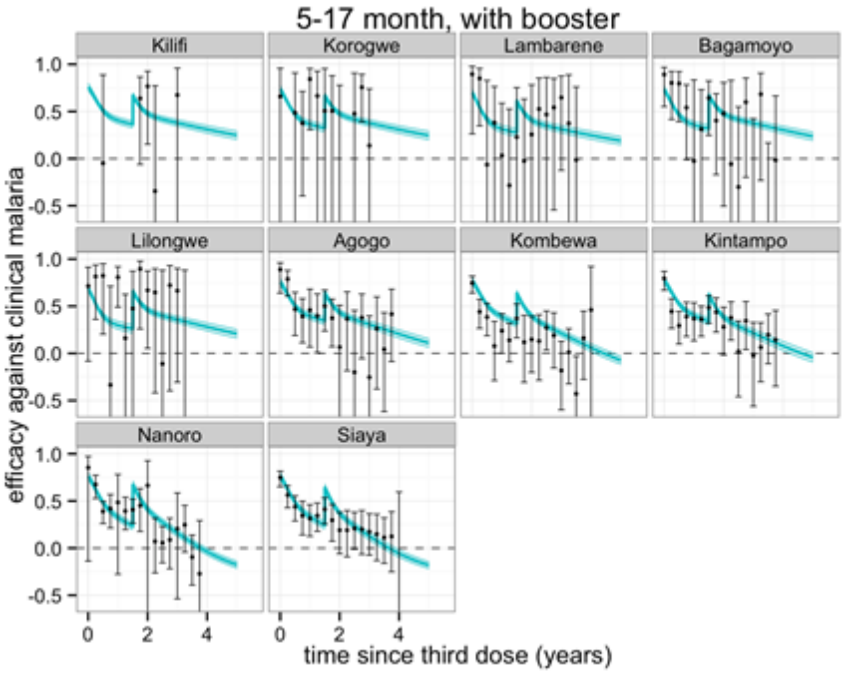

Figure D.6 Predicted efficacy against clinical disease by trial site compared to Phase III reported for the 5-17 month cohort with boost using best-fitted vaccine profile from Imperial

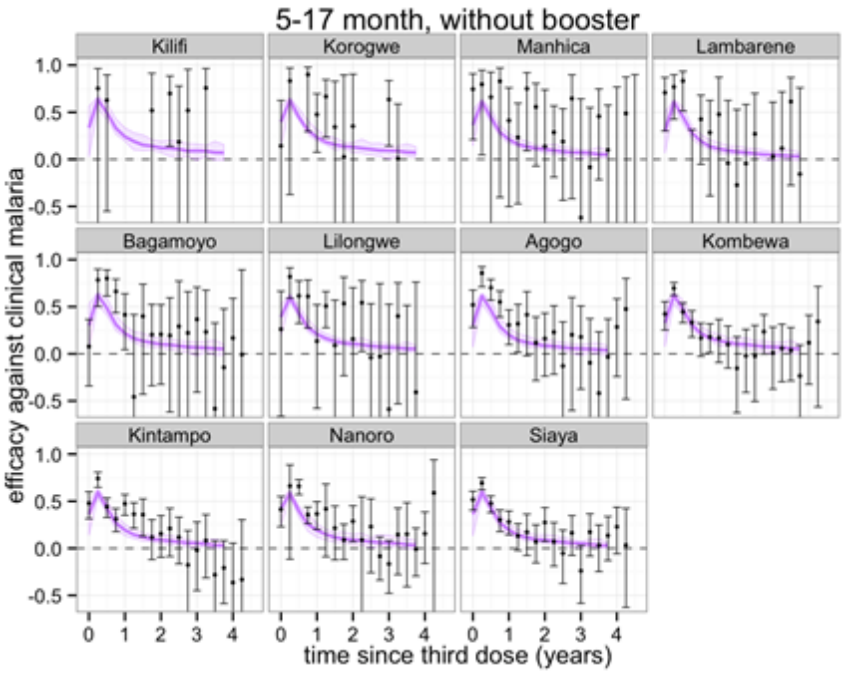

Figure D.7 Predicted efficacy against clinical disease by trial site compared to Phase III reported for the 5-17 month cohort using best-fitted vaccine profile from OpenMalaria

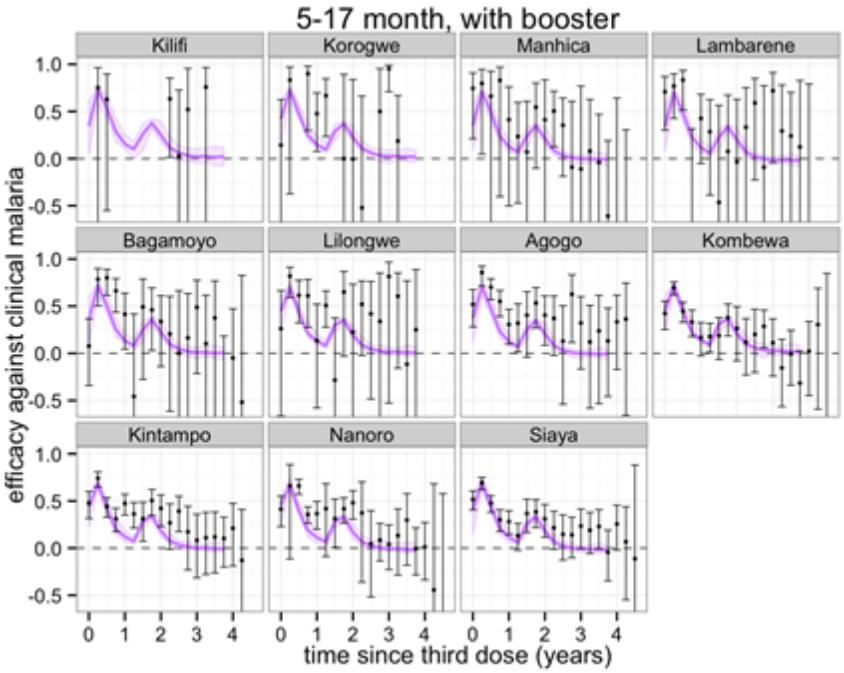

Figure D.8 Predicted efficacy against clinical disease by trial site compared to Phase III reported for the 5-17 month cohort with boost using best-fitted vaccine profile from OpenMalaria.