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Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa

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ABSTRACT

Background: RTS,S/AS01 is a safe and moderately efficacious vaccine considered for implementation in endemic Africa. Model predictions of impact and cost-effectiveness of this new intervention could aid in country adoption decisions.

Methods: The impact of RTS,S was assessed in 43 countries using an ensemble of models of Plasmodium falciparum epidemiology. Informed by the 32 months follow-up data from the phase 3 trial, vaccine effectiveness was evaluated at country levels of malaria parasite prevalence, coverage of control interventions and immunization. Benefits and costs of the program incremental to routine malaria control were evaluated for a four dose schedule: first dose administered at six months, second and third - before 9 months, and fourth dose at 27 months of age. Sensitivity analyses around vaccine properties, transmission, and economic inputs were conducted.

Results: If implemented in all 43 countries the vaccine has the potential to avert 123 (117;129) million malaria episodes over the first 10 years. Burden averted averages 18,413 (range of country median estimates 156–40,054) DALYs per 100,000 fully vaccinated children with much variation across settings primarily driven by differences in transmission intensity. At a price of $5 per dose program costs average $39.8 per fully vaccinated child with a median cost-effectiveness ratio of $188 (range $78–$22,448) per DALY averted; the ratio is lower by one third - $136 (range $116–$220) - in settings where parasite prevalence in children aged 2–10 years is at or above 10%.

Conclusion: RTS,S/AS01 has the potential to substantially reduce malaria burden in children across Africa. Conditional on assumptions on price, coverage, and vaccine properties, adding RTS,S to routine malaria control interventions would be highly cost-effective. Implementation decisions will need to further consider feasibility of scaling up existing control programs, and operational constraints in reaching children at risk with the schedule.

1. Introduction

With its safety and efficacy upheld in the phase 3 trial [1,2] and a positive scientific opinion issued by the European Medicines Agency [3], the RTS,S/AS01 malaria vaccine is closer to domestic licensure and implementation in endemic Africa. A global recommendation with respect to vaccine use has been issued by the WHO [4]. It argues for pilot implementation in distinct epidemiological settings to demonstrate feasibility of delivering the schedule to the target age group and to assess vaccine's impact on mortality and potential adverse effects. The recommendation has been informed with modelled estimates of vaccine's impact and cost-effectiveness in generic prevalence settings [5]. Relevance of these predictions to endemic countries requires further evaluation of the vaccine given geographic specific distribution of malaria exposure, coverage of preventive and control interventions and their dynamics, as well as cost of care in these specific settings. Countries might be interested in these data and explorations of predictions of vaccine impact taking into account local contexts before engaging in a considered effort identifying and testing strategies to deploy this new intervention.

Stochastic models of malaria epidemiology have previously been used to predict the likely epidemiological impact [6–8] and

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cost-effectiveness [5,9] of pre-erythrocytic vaccines against *Plasmodium falciparum*. These studies indicate that both the disease burden averted and the cost-effectiveness will be highly dependent on transmission intensity and on vaccine properties including the decay rate of the vaccine effect, and the degree of homogeneity in host response. Recent data make it necessary to revise these predictions. *Plasmodium falciparum* transmission has decreased dramatically over the last decade owing to scale-up of control interventions and roll-out of artemisinin combination therapy; infection prevalence in endemic Africa halved and incidence of clinical disease fell by 40% between 2000 and 2015 [10]. Updated distributions of malaria exposure that capture these trends along with the methodology to translate them for inputs into models for geographic locations have only recently become available [10,11]. With the release of the final phase 3 data in 2015 the vaccine properties can now be determined with greater confidence. These data suggest that the initial efficacy against infection of RTS,S is higher but that the effect decays more rapidly, than was previously estimated from phase 2 and from the shorter follow-up from phase 3 [12,13].

Using the most recent phase 3 data, a series of new methodologies [6,11,14,15] are applied to obtain predictions of the likely public health impact and cost-effectiveness of RTS,S administered in a four dose schedule starting at six month. We predict at national level for each of the 43 endemic Sub-Saharan African (SSA) countries and avoid speculative choice on geographic areas for pilot studies or sub-national implementation. In contrast to a recent study [5], our geographic specific predictions allow for differences in epidemiological context and health systems across settings, thus the generated predictions are apt to inform policy decision-making for malaria control in those settings.

2. Methods

2.1. Intervention

The RTS,S vaccine prevents infection by inducing humoral and cellular immunity, with high antibody titers, that block the parasite from infecting the liver [16]. It is a monovalent lyophilized vaccine reconstituted with an adjuvant (AS01); both require cold chain storage [17]. Trial data showed the vaccine to be more efficacious and enabling protection against severe disease only when administered in a four dose schedule in children [2]. Mapping trial design into the routine immunization schedule representative of SSA suggests a program targeting children between six and nine months with three doses and an additional fourth dose administered 18 months after the third. This schedule aligns with routinely administered vitamin A supplementation at six months and measles containing vaccine at nine months, reducing the number of new visits to only two in countries where these interventions already exist.

Our assumptions on coverage adjust for the challenges of scaling-up new interventions and those of reaching children outside of routine schedule: 75% of the country Diphtheria-Tetanus-Pertussis (DTP) rate was taken for the primary schedule, a 20 percentage point drop-off was assumed between third and fourth doses consistent with observed drop-off for measles vaccination [18]. The vaccine is assumed to be rolled-out through routine outlets and to achieve projected coverage within the first year of implementation.

2.2. Vaccine protection against infection

Vaccine profiles were parameterized with data from the 32 month or longer follow-up of the phase 3 clinical trial of RTS, S/AS01 [1]. Vaccine efficacy profiles were estimated by Bayesian MCMC fitting of model predictions to the site-and time-specific incidence of clinical malaria in both trial arms over the follow-up [12]. For the primary schedule, the initial efficacy against infection at third dose was estimated at 91·1% with a half-life of 7·32 months (with non-exponential decay); the initial efficacy at fourth dose reached only 49% [12].

2.3. Estimating the public health impact of RTS,S immunization

Using a micro-simulation model of malaria epidemiology and control [19,20], disease burden was predicted for a range of immunization schedules, vaccine properties, entomological inoculation rates (EIR), and levels of treatment both in the absence and with the addition of the vaccine. Impact estimates were then computed as weighted averages over all simulations with weights dependent on country levels of treatment, coverage, and exposure [6]. $Pf\mathrm{PR}_{2-10}$ distributions in 2014 for each country were taken from [10] and treatment rates - from a previous analysis [14]. Assumptions on coverage of control interventions including LLINs reflect those underlying MAP 2014 prevalence surface estimates. Produced by the Oxford group [10] coverage of control interventions (ITNs, ACTs, IRS) for the region is estimated with a spatiotemporal Bayesian geostatistical model that draws on national malaria control program and household survey data. The level of malaria prevalence (measured by patent parasitemia in children between ages 2 and 10 ($Pf\mathrm{PR}_{2-10}$)), control interventions, immunization rate, population growth, and demography were held constant throughout the evaluation period. Further details on methodology and data are given in SI p 3.

By relating clinical disease to severe outcomes and death using historical data, the model enables predictions of vaccine's impact for clinical outputs not explicitly measured in the trial, such as mortality, and under levels of coverage of preventive and control interventions representative of the endemic Africa [21]. In this analysis public health impact of the vaccine was expressed in terms of uncomplicated and severe malaria episodes, deaths, and disability-adjusted life years (DALYs) [22], enabling comparison to other malaria interventions and vaccines. DALYs were estimated based on a comprehensive measure of deaths that included both direct malaria deaths and deaths due to malaria co-morbidities [21]. For comparison, estimates based on direct malaria deaths only were also reported.

2.4. Estimating program costs

Vaccine price was assumed to be $5 per dose; thresholds of $2 and $10 per dose were evaluated in the sensitivity analysis consistent with assumptions in [5]. Program costs included service delivery and direct household expenditures related to vaccination visit. These were extrapolated from a recent micro-costing study that estimated prospectively cost of RTS,S introduction in 6 SSA countries [15]. Costs capture the economic value of the program and cover activities carried out both in the introductory stage and routine delivery. Given the broad scope of the analysis country specific values were not estimated for this study, instead a median of service delivery costs from [15] was applied to all countries. Heterogeneity in operational aspects of the program, unit costs, and use of resources within the EPI across the region, however, were addressed in the sensitivity analysis by re-estimating cost-effectiveness ratios over a broad and representative range of service delivery costs informed by [15].

Total program costs were based on the number of doses in the schedule, assumed coverage, and the cohort of surviving infants in each country. Further details in SI p 5.

2.5. Estimating treatment cost savings

Treatment costs savings were estimated by multiplying the number of cases averted by the vaccine over routine malaria control with respective cost per case. It included cost of diagnostics, antimalarial drugs, consumables (syringes, etc.), as well as facility charges such as labour and overheads, and direct household expenditures related to treatment-seeking. Costs reflect country levels and patterns in health seeking for malaria, compliance with the recommended first-line treatment, adherence with the drug regimens [14], and cost of care [23]. Costing methodology is detailed in SI p 6.

2.6. Estimating cost-effectiveness

The impact of the program was evaluated from the societal perspective; only direct benefits and costs were considered in this analysis. Cost of the RTS,S immunization program net of treatment cost savings was related to burden averted by the vaccine; the two outputs were summarized in terms of an incremental cost-effectiveness ratio (ICER). Unless otherwise noted, cost-effectiveness ratios are presented without discounting of health effects and with discounting of costs (3%) [24]; ratios based on discounted DALYs averted are reported for comparison with previous analyses.

Program impact and cost-effectiveness were evaluated over a 10 year horizon with an assumed introduction date in 2017.

2.7. Sensitivity analysis

We assessed robustness of the impact predictions by varying key model inputs along their plausible ranges singly and in combination (SI Table S3). Choice of parameters was informed by an earlier extensive analysis of uncertainties around RTS,S predictions [25] that identified malaria transmission, price, and vaccine properties as key drivers. Further, multivariate scenarios were defined to capture the higher ranges of ICERs under conservative assumptions about vaccine properties, coverage, and transmission. Broad ranges over which parameters were varied were chosen to inform our understanding of the direction and magnitude of the potential bias in impact estimates induced by uncertainty around these key inputs at the country level.

3. Results

3.1. Overview of transmission, health system, economic, and demographic inputs

*Pf*PR$_{2-10}$ averages about 15% across the continent with an equal number of countries with parasite prevalence below and above 10%; weighted average *Pf*PR$_{2-10}$ is above 40% only in Guinea and Mali (Tables 1 and S4). Coverage and effectiveness of malaria case management is highest in settings with higher transmission intensity; however, the immunization rate appears to be substantially lower in medium compared to low *Pf*PR$_{2-10}$ countries. Treatment health savings only marginally offset the cost of the RTS,S program; with about half of fevers treated and cost of care significantly below cost per FVC even at conservative price assumptions. There is much variation across these key inputs within the narrow transmission ranges; differences that help explain variation in predicted effectiveness and cost-effectiveness of the vaccine across countries.

3.2. Public health impact and cost-effectiveness of RTS,S immunization

Across the 43 countries the program is estimated to avert over 123 million malaria episodes and over half a million malaria

Table 1
Summary of key inputs used for country specific predictions of RTS,S impact and cost-effectiveness grouped by levels of *Pf*PR$_{2-10}$ and Gavi eligibility status.

Input	*Pf*PR$_{2-10}$				GAVI eligible (GNI<$1580)	All countries
	<5%	5–10%	10–40%	>40%		
*Pf*PR$_{2-10}$ (%)[a]	2.6 [2.0–4.8]	7 [5.1–9.2]	23.3 [10.7–39.9]	43.8 [42.2–45.5]	15.7 [2.0–45.5]	14.8 [2.0–45.5]
EIR[b]	0.29 [0.00–1·04]	1.64 [0.43–3.53]	5.27 [0.18–17.38]	6.68 [6.56–6.81]	3.27 [0.01–17.38]	3.12 [0.00–17.38]
Health seeking (%)[c]	48.3 [13.0–75.6]	53.5 [16.0–77.3]	61.9 [32.0–84.0]	44.1 [40.2–48.1]	51.8 [13.0–84.0]	55.3 [13.0–84.0]
Effective coverage (%)[d]	31.7 [7.8–71.3]	34.4 [8.3–54.3]	36.4 [16.7–65.9]	20.6 [19.9–21.3]	30.6 [7.8–65.9]	33.8 [7.8–71.3]
Coverage 3rd dose (%)[e]	63.1 [31.5–74.0]	58.6 [34.7–72.0]	55.9 [11.8–70.0]	49.1 [44.3–54.0]	58.4 [29.2–74.0]	58.4 [11.8–74.0]
Coverage 4th dose (%)[f]	50.5 [25.2–59.2]	46.9 [27.8–57.6]	44.7 [9.4–56.0]	39.3 [35.4–43.2]	46.8 [23.4–59.2]	46.7 [9.4–59.2]
Cost per uncomplicated case (USD)	3.82 [1.62–13.19]	3.49 [0.56–10.01]	4.04 [1.08–22.70]	1.45 [1.31–1.59]	2.18 [0.56–4.02]	3.76 [0.56–22.70]
Cost per severe case (USD)	102.93 [40.91–422.59]	86.98 [36.20–238.78]	179.84 [37.07–1884.67]	45.95 [45.36–46.54]	54.24 [36.20–86.90]	133.46 [36.20–1884.67]
GDP per capita (USD)[g]	1648 [133–7411]	1697 [267–5783]	2528 [237–20,581]	629 [531–726]	744 [133–1610]	2018 [133–20,581]
Government health care expenditures per capita (USD) [h]	113 [17–423]	78 [18–267]	113 [13–714]	39 [25–53]	44 [13–110]	103 [13–714]
Total infants (millions) [i]	7.5	5.3	18.9	1.1	22.1	32.8
Total population (millions) [j]	230.3	145.6	500.3	27.8	610.8	904.0
Number of countries	14	7	20	2	32	43

Estimates represent medians across countries within the group, range (min-max) reported in parenthesis below; Nominal values are expressed in 2013 USD.
[a] Population weighted median *Pf*PR$_{2-10}$ based on 2014 *estimates* from MAP [12].
[b] Population weighted median EIR based on 2014 estimates from MAP [12].
[c] Author tabulations based on country DHS data, 14 day recall.
[d] Defined as an expected probability of clinical and parasitological cure for an episode of malaria fever. Updated country estimates based on [15].
[e] Projected from country DTP coverage [19] assumed 75% of country DTP3 coverage.
[f] Projected from country DTP coverage [19] assumed 60% of country DTP3 coverage.
[g,h,i,j] [38]; Country estimates are reported in SI Table S4.

related deaths within the first ten years (Tables 2, S5 and S6). Countries with higher levels of $Pf\text{PR}_{2-10}$will benefit most from the vaccine introduction. At these higher $Pf\text{PR}_{2-10}$ ranges, vaccine's impact averages over 26,000 DALYs and about 500 deaths averted per 100,000 FVC; the impact is half as large when estimated across countries with $Pf\text{PR}_{2-10}$ between 5 and 10%, and about a quarter - in countries with prevalence below 5%. Half of the total predicted impact of RTS,S vaccination will be incurred in four countries: Nigeria, Democratic Republic of the Congo, Uganda, and Tanzania; Nigeria alone accounts for over 20% of total DALYs averted (SI Fig. S1).

Predicted cost-effectiveness ratios vary similarly with $Pf\text{PR}_{2-10}$: at a vaccine price per dose of $5 the ICER averages $188 (range of country median estimates 78–22,448) per DALY averted across the 43 countries. The range is widened substantially by a handful of countries with low $Pf\text{PR}_{2-10}$ including Botswana, Djibouti, Eritrea, and Ethiopia where predicted impact is highly imprecise. When averaged across countries with $Pf\text{PR}_{2-10}$ above 10% the estimated ICER is about $136 per DALY averted with a much more narrow range between $115 and $220.

The impact of the vaccine increases with $Pf\text{PR}_{2-10}$ and generally plateaus between $Pf\text{PR}_{2-10}$ 10 and 40% (Fig. 1). While impact estimates are always positive, the uncertainty around them is large. It reflects both structural and stochastic uncertainty in the modelled estimates. Variation in the vaccine's impact and cost-effectiveness between countries within the narrow transmission ranges is due to epidemiological and health systems factors; their role can be illustrated by examining predictions for Gabon and Niger-countries with the same estimated weighted $Pf\text{PR}_{2-10}$ of 15%. Compared to Gabon, the immunization rate in Niger is lower, and so is the risk and distribution of *P. falciparum*, all resulting in a projected impact of the vaccine of about 20% lower and an ICER twice as high (Tables S4 and S6). On average, however, the ratio is fairly similar with predicted median ICERs below $200 per DALY averted across countries with $Pf\text{PR}_{2-10}$ above 10%.

Predicted impact is highest in Central African Republic and a group of coastal West African countries, where over 500 deaths averted per 100,000 FVC are estimated compared to an average of about 350 for the region (Fig. 2). Lowest impact is predicted for countries at the Horn of Africa. It is in these low prevalence settings, including Ethiopia, Eritrea, and Djibouti that the ICERs are also highest (Table S6).

3.3. Sensitivity analysis

Over the ranges tested and when varied singly parameter uncertainty translates in predicted ICER and DALY ranges that are on average, at most, double or half the baseline values (Fig. 3). There is more heterogeneity across countries in response to varying parameters related to transmission (scenarios 1, 2) and immunization coverage (scenarios 3, 19). Small changes in these inputs result in disproportionally large changes in predictions in lower $Pf\text{PR}_{2-10}$ settings. The largest increase in the ICER is estimated for scenarios 5 and 20. In the prior the vaccine price per dose is set to $10-twice the baseline assumption- resulting in predicted ICERs that are also doubled. In the latter, the vaccine is evaluated under low assumptions on efficacy, half-life, and coverage; here again the predicted ICERs double.

4. Discussion

Following 10 years of implementation, RTS,S/AS01 is predicted to substantially reduce malaria burden in children across endemic countries in SSA. Consistent with the predictions of a recent multi-

Table 2
Cumulative predictive impact and cost-effectiveness of RTS,S immunization: disease averted, costs of the program, and cost-effectiveness grouped by country levels of $Pf\text{PR}_{2-10}$ and GAVI eligibility status.

	$Pf\text{PR}_{2-10}$				GAVI eligible	All countries
	<5%	5–10%	10–40%	>40%		
Total episodes averted (millions)	7 (6.5; 7.5)	21.8 (20.3; 23.3)	89.3 (85.3; 93.3)	5.1 (5.0; 5.3)	81.3 (77.4; 85.3)	123.2 (117.3; 129.1)
Total deaths [a] averted (thousands)	36 (32.3; 39.7)	106.2 (96.3; 116.1)	443.9 (415.1; 472.8)	28.1 (26.5; 29.6)	404.2 (375.7; 432.6)	614.2 (571.7; 656.8)
Total direct deaths [b] averted (thousands)	20.5 (18.4; 22.6)	56.3 (50.9; 61.7)	221 (205.7; 236.3)	13.5 (12.6; 14.3)	206.1 (190.7; 221.4)	311.2 (288.4; 334.0)
Total DALYs averted (millions)	1.9 (1.7; 2.1)	5.6 (5.1; 6.1)	23.4 (21.8; 24.9)	1.5 (1.4; 1.6)	21.2 (19.7; 22.7)	32.3 (30.0; 34.5)
DALYs averted/100,000 FVC	6006 [156–26,135]	15,289 [4822–36,946]	25,949 [8937–40,054]	28,402 [17,730–36,008]	18,050 [156–40,054]	18,413 [156–40,054]
Deaths averted/100,000 FVC	115 [3–500]	291 [92–703]	495 [170–761]	540 [337–682]	345 [3–761]	350 [3–761]
Total net program costs (millions)[c]	1396 (1395; 1396)	1198 (1197; 1199)	3329 (3327; 3331)	189 (189; 189)	4309 (4307; 4310)	6111 (6108; 6114)
$/DALY averted	581 [133–22,448]	226 [93–723]	132 [78–387]	122 [96–196]	192 [87–22,448]	188 [78–22,448]
$/Direct DALY averted	994 [271–67,529]	407 [174–1678]	267 [147–763]	261 [182–358]	369 [161–67,529]	360 [147–67,529]
$/Discounted DALY averted	1140 [262–43,601]	444 [182–1419]	260 [154–759]	241 [190–385]	378 [171–43,601]	370 [154–43,601]
$/Discounted direct DALY averted	1937 [532–133,830]	797 [342–3292]	525 [288–1492]	514 [358–704]	725 [316–133,830]	707 [288–133,830]

Group totals for events averted and program costs are reported as averages and 95th percentile prediction intervals cumulated over 10 years and over all countries in the respective group. Narrow prediction intervals on totals do not imply high precision of these estimates but rather are an artifact of variation being "cancelled out" when summing country predictions by model and stochastic seed. See SI File 1 for further details. Cumulative program output metrics per 100,000 FVC and cost-effectiveness ratios are reported as medians and min and max range of country median estimates averaged over uncertainty predictions from the model. Unless otherwise noted DALYs are estimated without age-weighting and discounting.

[a] "Total deaths" inlcude malaria deaths attributable to malaria and deaths that occur with a co-morbidity and malaria.

[b] "Total direct deaths" inlcude only deaths directly attributable to malaria.

[c] "Total net program costs" represent cumulative program costs minus any health savings resulting from averted malaria mortality and morbidity incurred by the health systems and patients; costs are discounted at 3%. Total net program costs and ICER's estimated from health systems perspective are reported in SI Table S7. Nominal values expressed in 2013 USD.

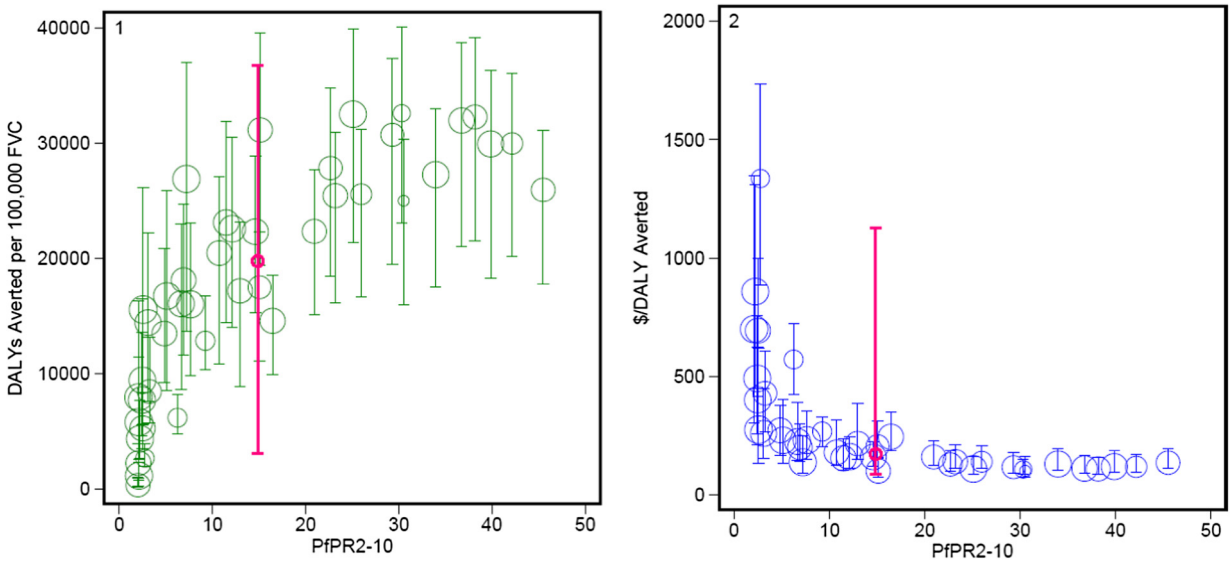

Fig. 1. Cumulative predicted impact and cost-effectiveness of RTS,S immunization by $Pf\text{PR}_{2-10}$. Predicted impact of the vaccine summarized in terms of DALYs averted per 100,000 FVC (A) and cost per DALY averted (B) are plotted against $Pf\text{PR}_{2-10}$ with data points proportional to immunization coverage. Estimates represent country cumulative statistics averaged across the uncertainty predictions from the model and are overlaid with 95th percentile prediction intervals. Four countries with extremely high cost per DALY averted were omitted from the plot for ease of viewing. These inlcude countries with very low weighted $Pf\text{PR}_{2-10}$ for which model estimates are highly uncertain, namely Botswana ($1389(208; 12,519)), Djibouti ($1858(877; 3696)), Eritrea ($3252(1522; 4532)), and Ethiopia ($12,764(3427; 22,448)). Median and 95th percentile prediction intervals across the 39 countries are plotted in pink.

model study [5], higher impact is expected in counties with higher $Pf\text{PR}_{2-10}$, and thus higher burden for RTS,S to avert. Country level estimates, however, differ in magnitude from the corresponding generic prevalence predictions in [5]. Local estimates reflect differences in assumptions on vaccination coverage (country range between 9 and 59% at fourth dose assumed in this study compared to 72% in [5]), exposure heterogeneity (not explored in ([5]), case management (country range between 8 and 71% compared to 45% in [5]), and country costs, including service delivery (only cost of commodities were included in [5]). We show that country specific epidemiological and health systems factors result in substantial variation around generic prevalence averages in both public health impact and cost-effectiveness estimates.

RTS,S is predicted to be highly cost-effective in most countries; the estimated ICERs are significantly below the regional GDP per capita (median $842, IQR: $531–$1668) [26,27]. Affordability of this new intervention, however, is to be further assessed against program financing and budgets for other vaccines as well as broader resources for health. Direct comparisons of the vaccine with other malaria control interventions were not undertaken in this evaluation. Drawing on literature to provide indicative ranges for comparison is subject to a number of limitations including differences in methodological approaches, scope of costs and effects considered, scale of the program, relevance of operational aspects of the program to a particular setting, as well as transmission effects [28,29]. The importance of the latter is particularly well illustrated by the large differentials in the vaccine's predicted impact and cost-effectiveness across the transmission ranges, variation that has been documented for other malaria control interventions as well [29,30]. Ranges of cost-effectiveness from the literature suggest the vaccine might be more expensive than current means of malaria control [29] and some of the new vaccines being added to EPI schedules in the region [31–34]. However, incremental analyses that consider a control intervention package, including this new intervention, might be more favorable for the vaccine if effectiveness is evaluated in the same transmission intensity and scale-up beyond current levels of control programs is properly accounted for [28].

As with all modelling and simulation studies there are a number of limitations to our analysis. Firstly, predicted vaccine impact is dependent on the extent of follow-up of immunized children in the trial and if further follow-up data becomes available it will be important to reassess the underlying protection of the vaccine. Secondly, as indicated in a previous analysis [5], predictions of deaths and thus DALYs averted are dependent on the simulation model fits to historical data of clinical incidence and mortality. Results are also dependent on quality of data informing country levels of current burden, prevalence, immunization coverage, and demographics. We have attempted to partially address these uncertainties with sensitivity analysis.

Consistent with previous studies, the level of $Pf\text{PR}_{2-10}$ and heterogeneity in transmission are key drivers of the vaccine's impact and cost-effectiveness. Impact estimates presented here, however, are generated under an assumption of stable transmission, which implies that there is no additional benefit in terms of reduction in transmission that could be achieved with current levels of malaria control. Further, by assuming constant levels of control interventions the vaccine's impact may be overstated if one believes that the recent scale-up of control programs and economic development will be sustained into the future [35]. If these trends are to continue and as malaria intensity subsides, re-evaluation of vaccine's viability and cost-effectiveness might be needed. At low $Pf\text{PR}_{2-10}$ (<10%) the vaccine's impact is predicted to be modest; here the risk of the disease is shifting to older ages [36] and the new intervention competes with routine malaria control for cases to avert. Deployments considering sub-national implementation targeting pockets of malaria transmission rather than national campaigns might be more appropriate in these settings.

Coverage is another key parameter subject to uncertainty; tying it to routine immunization might have been optimistic given the vaccine's properties and short-lived protection it enables. Estimated ICERs increase to $256[$134-$12,528] per DALY averted when coverage is reduced by 25% (Table S8). Alternatively, if the program achieves coverage rates similar to country DTP levels, the ratio decreases to $139[$70-$7047] per DALY averted and in

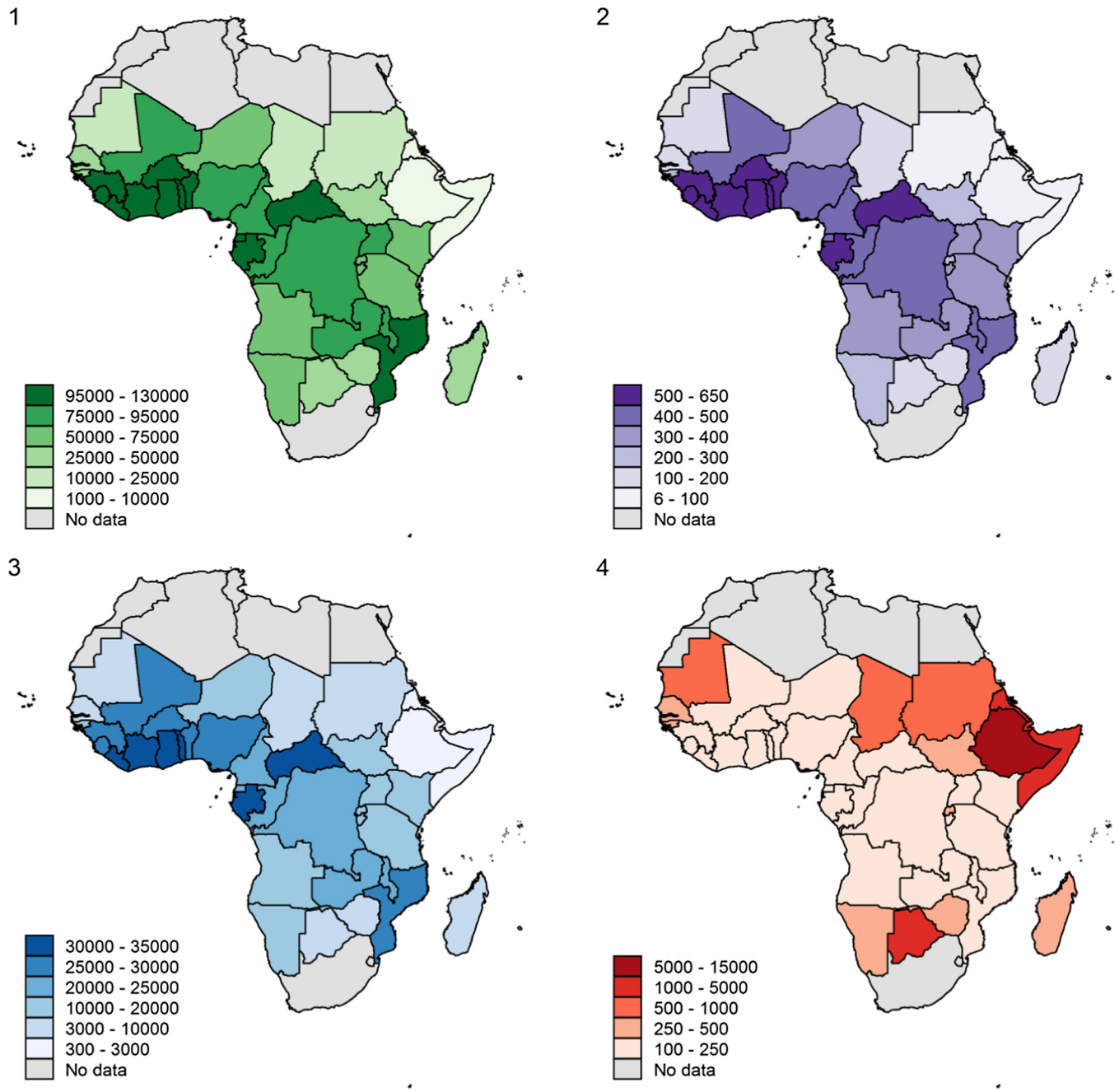

Fig. 2. Cumulative impact and cost-effectiveness of RTS,S immunization by country. Cumulative number of clinical cases (A), deaths (B), DALYs (C) averted per 100,000 FVC, and cost per DALY averted (2013 USD) (D) at year 10 following vaccine introduction. Country estimates represent mean values averaged over uncertainty predictions from the model.

settings with *Pf*PR_{2-10} above 10% it is reduced to \$95[\$70-\$173]. Several studies have been conducted to assess the vaccine's acceptability in endemic countries [37–40]; while community response has been positive, it is difficult to judge whether it will translate to as high uptake, particularly as protection begins to wane and vaccinated children continue to fall ill. Careful and sustained communication will be key to the program's success.

For an RTS,S program to reach its full potential, it is not only important to ensure vaccination at rates similar to those achieved with routine vaccines in the general population but reaching groups with the highest risk of malaria becomes pivotally important. Achieving high coverage for these vulnerable children will require addressing social and cultural perceptions about the vaccines, improving systems for providing health care, and devising innovative delivery strategies to reach these generally underserved populations.

Furthermore, the predictions were made at national levels of coverage of control interventions and immunization rates; these do not incorporate inequities in access to health services, particularly with respect to heterogeneity in malaria transmission. Not only is malaria risk higher among these marginalized groups, but given lower coverage of control interventions, the outcomes of malaria episodes are also more severe [41,42]. Policies should thus consider the operational advantages of targeting these populations with the vaccine, and the extent to which RTS,S immunization could be combined with strengthening delivery of other preventive and control measures, including interventions aimed at health risks other than malaria.

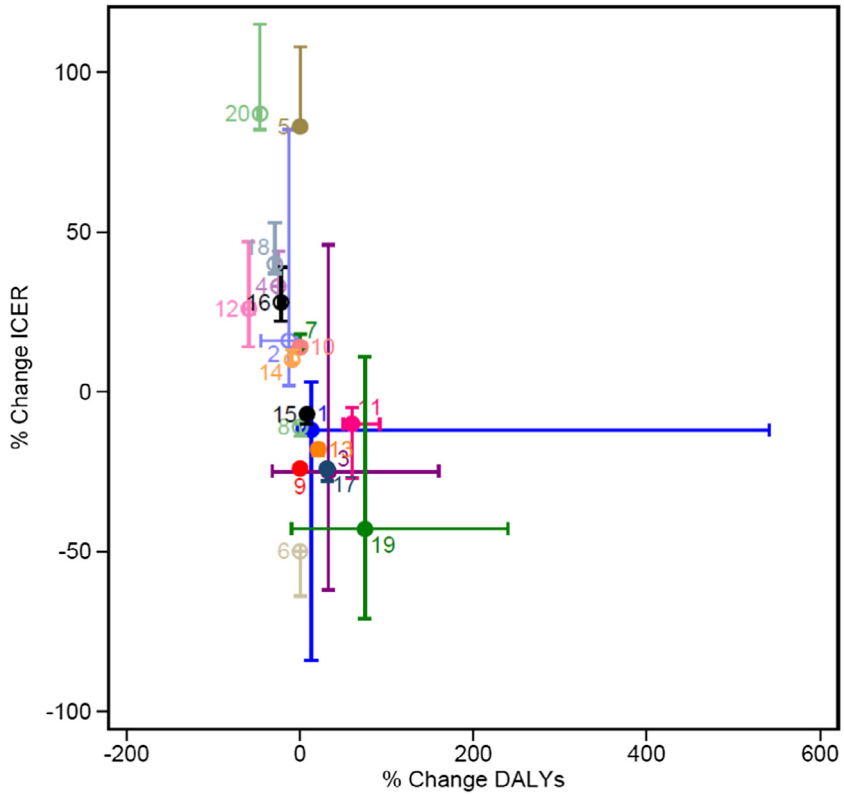

Fig. 3. Sensitivity analysis over range of vaccine properties and country specific inputs: percent change in predicted ICER and DALYs averted from baseline scenario. Estimates represent change in predicted DALYs averted and ICER in response to varying single or multiple parameters from baseline to its low and high values (see Appendix Table S3 for ranges simulated). The change in predicted DALYs averted is summarized as a median and a range (min-max) across 43 countries. Values of predicted ICERs and DALYs averted for each scenario are reported in Appendix Table S7. The following scenarios were simulated: 1 Transmission high; 2 Transmission low; 3 Immunization rate high; 4 Immunization rate low; 5 Price high; 6 Price low; 7 Delivery cost high; 8 Delivery cost low; 9 Discount rate high; 10 Discount rate low; 11 Time horizon high; 12 Time horizon low; 13 Half-life high; 14 Half-life low; 15 Efficacy high; 16 Efficacy low; 17 Initial efficacy and half-life high; 18 Initial efficacy and half-life low; 19 Initial efficacy, half-life, and immunization rate high; 20 Initial efficacy, half-life, and immunization rate low.

At country level, introducing the vaccine into the National Immunization Program (NIP) will have broad implications for the health systems [43]. It might undermine routine care provision if resources, including medical staff and cold chain, are diverted away to accommodate the new intervention. One the other hand, new vaccination visits provide another opportunity for health providers to reach children that may lead to improvements in health beyond malaria related outcomes. Most directly, malaria burden averted will reduce use of outpatient and, to a lesser extent, inpatient services by children. At assumed coverage rates for the new program and at current levels of malaria case management a reduction of 9.14% [1.29–18.86] in visits for uncomplicated malaria is predicted and 7.06% [0.79–14.84] for severe episodes across the 43 countries (Table S5) - a substantial decrease in service volume.

At the same time introduction of RTS,S will also require significant resources. Estimates of cost-effectiveness presented in this analysis rely on generic assumptions about cost of vaccine delivery and as such do not capture the heterogeneity cost of service delivery across countries. Yet, at vaccine price of $5 per dose these costs account for 10–26% of total program costs; the fraction is higher in settings where cost of labour is high [15]. This suggests that variation in cost of service delivery, assuming routine deployment, contributes only marginally to uncertainty in predicted ratios (Table S8, scenarios 7–8). As ICERs vary almost linearly with price, estimates can be updated with setting specific information on cost of service delivery or costs of alternate vaccine deployment modality if available.

WHO's recommendation for a large scale trial implementation of RTS,S targets primarily uncertainties around the operational aspects of the program, namely the feasibility of delivering a four dose schedule that includes new immunization visits in a weak health systems environment [4]. While the details of the program are best tested in a trial setting, our analysis provides further support to the recommendation's focus on "how best to" introduce the vaccine. We show that at higher transmission intensities RTS,S remains highly cost-effective even under most conservative assumptions on vaccine properties, coverage, and price. Pilot studies should prioritize deployment modalities that include delivery of the vaccine along other health services and seek broader synergies within the National Immunization Program. Our analysis suggests scope for sub-national implementation in settings with heterogeneous transmission and highlights the advantages of targeted and outreach strategies to populations at highest risk where most impact is likely to be achieved. Furthermore, the analysis offers some initial *setting-specific* predictions of potential vaccine impact against which trial results could be scaled to inform country adoption decisions.

Contributors

KG and MAP conceived the study and designed the analysis. PG provided prevalence data and advice. KG, MAP, FC did the analyses. TAS and FT supported the analyses. KG, MAP, TAS, and FT supported interpretation and policy contextualization. KG wrote the first draft of the manuscript. KG, MAP, TAS, and FT wrote the manuscript. All authors discussed the results and contributed to revision of the final manuscript.

Conflict of interest

All authors declare no competing interests.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.11.042.

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