Modelling The Relative Cost-Effectiveness Of The Rts,S Vaccine Compared To Other Recommended Malaria Interventions

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SUMMARY

- Using a previously developed modelling framework, we undertook an evaluation of the relative cost effectiveness (CE) of the RTS,S malaria vaccine compared to the introduction or scale up of other recommended malaria interventions

- We considered 4 options for investment – increasing coverage of insecticide-treated nets (ITNs) by 10%, switching to pyrethroid and piperonyl-butoxide (PBO) ITNs for areas with insecticide resistance, introducing seasonal malaria chemoprevention (SMC) at 85% coverage, and introducing the RTS,S vaccine through either standard or seasonal implementation.

- We compared the cost-effectiveness of these options across a range of generic settings capturing different levels of transmission intensity (parasite prevalence), seasonality profiles, ITN usage and levels of pyrethroid insecticide resistance.

- The generic scenarios do not represent the distribution of settings in endemic countries and therefore outputs quantifying the percentage of scenarios in which interventions are more or less cost-effective should not be interpreted as a percentage of endemic countries or as a percentage of the population at risk.

- We assumed a cost per dose of the RTS,S vaccine (not including delivery, consumables etc.) of $9.30 USD (using an average EUR to USD exchange rate = 1 as of September 2022)[1]. Costs for other interventions were based on current data and already capture economies of scale that may not be captured in the vaccine introduction price.

- Results are presented as the relative cost effectiveness. Absolute total costs and comparisons with defined (setting-specific) cost-effectiveness thresholds cannot therefore be made.

- Results are specifically for the RTS,S vaccine for the two implementation schedules recommended by WHO. They are not applicable to second generation vaccines with different efficacy profiles or to different implementation schedules.

- At a cost per dose of $9.30 USD, the cost per DALY averted across scenarios modelled was $169 USD (IQR: 130 to 224) for seasonal RTS,S vaccination and $193 USD (IQR: 150 to 257) for age-based RTS,S vaccination.

- The median cost per dose for RTS,S to be the most cost effective choice was $0.47 USD (IQR: $0.06 - $3.7) across all settings, $0.98 USD (IQR: -0.26 to 4.23) in perennial settings, $0.27 USD

(IQR: -0.10 to 0.43) in seasonal settings, and $3.51 USD (IQR: 0.65 to 11.83) in highly seasonal settings. It is important to note that these threshold values do not indicate the proportion of places or population at risk but rather the proportion of scenarios modelled. Caution is therefore advised in their interpretation.

- Settings in which RTS,S introduction would be the most cost-effective next intervention at a price of $9.30 were high transmission settings (40% PfPR) in which ITNs (75%) and SMC (85%, where applicable) were already implemented at high coverage. Our analysis was not designed to calculate this coverage level precisely. In these settings, the cost per DALY averted was $115 (IQR: 96 to 167) for seasonal RTS,S vaccination and $149 USD (IQR: 118 to 202) for age-based RTS,S vaccination.

- Whilst CE rankings under these generic scenarios were consistent relative to a few key drivers, there were significant uncertainties in the estimated impact of all interventions. Country-level and context specific factors not included in this analysis, such as dose-constraints, implementation costs, operational feasibility, and systems limitations, will be influential. This exercise therefore needs to be performed with local data by endemic countries.

INTRODUCTION

In 2021, the World Health Organization (WHO) recommended the use of a four-dose schedule RTS,S/AS01$_E$ (RTS,S) malaria vaccine for children in moderate to high malaria transmission settings beginning from 5 months of age[2,3]. Gavi, the Vaccine Alliance, has approved malaria vaccine funding for eligible countries with $155.7 million USD to be allocated from 2022- 2025[4]. Despite the recommendation of RTS,S and pledged financial support, wide-scale implementation of RTS,S is likely to be limited by dose supply[5]. To inform decision making, both for country programmes and international donors, it is important to consider the relative cost- effectiveness (CE) of RTS,S in comparison to the introduction or scale up of other recommended malaria interventions, and how this CE varies across epidemiological and ecological contexts.

Previous studies have shown that RTS,S (at an assumed cost per dose of $5 USD) is cost- effective across a range of generic[6] and specific[7–12] contexts. Fewer studies have compared the CE of RTS,S relative to other intervention options. We previously showed that the scale up of existing recommended interventions: treatment, insecticide-treated nets (ITNs) and seasonal malaria chemoprevention (SMC) come earlier in the cost-effectiveness pathway than RTS,S across most malaria transmission settings[13,14]. A separate modelling study found contrasting results for the Ghanaian context, with RTS,S being more cost effective than, and introduced prior to, SMC in the cost-effectiveness pathway[15]. Differences between modelled results can be ascribed to the choice of outcome measure, choice of population evaluated (with the latter study focusing on the impact among children, and the former across the whole population), and the set of intervention options considered. Importantly, both of these studies comparing the relative CE of RTS,S were conducted before the recent malaria vaccine implementation programme (MVIP), which has provided further information about the operational and technical feasibility of delivering RTS,S at scale and the costs associated with doing so[16]. Furthermore, a recent report by UNICEF has provided the first point estimate of the cost per dose for the RTS,S vaccine at €9.30 EUR[1]. This estimate is significantly higher than the mid-range estimate used of $5 USD per dose used in many previous studies.

Any new recommendation for an intervention presents an opportunity to assess and evaluate the equity of current interventions and the potential for a new tool to address observed imbalances. Whilst the current distribution of malaria interventions is broadly equitable across certain equity-relevant variables (e.g. male-female differences in ITN usage), across others they are not (e.g. urban-rural populations and wealth quintiles)[17]. Comparing ITN and diphtheria tetanus toxoid and pertussis (DTP3) vaccination coverage from survey data, there are clear gaps in malaria intervention coverage that could be filled using RTS,S given the existing reach of the Expanded Immunization Programme (EPI)[18]. Given the likely dose-constraints for RTS,S, targeting of delivery may be necessary and may provide an opportunity to address outstanding equity issues in intervention coverage.

Here, we use an individual-based mathematical model of *P. falciparum* to assess the CE and equity impact of RTS,S across a range of generalized settings in sub-Saharan Africa, including seasonal profiles, parasite prevalence bands, current ITN usage levels, treatment coverages, and levels of resistance to the pyrethroid insecticide. We compare age-based and seasonally-targeted RTS,S administration to a set of alternative intervention options, including increasing ITN usage by 10% (chosen to give an increase in cost of a similar magnitude to implementing RTS,S), switching to pyrethroid and piperonyl-butoxide (PBO) ITNs in settings with insecticide-resistance, and introduction of SMC.

RESULTS

Figure 1 summaries the combinations of scenarios considered. We generated scenarios for 3 seasonality profiles (perennial, seasonal and highly seasonal), 3 baseline levels of transmission (summarised by the parasite prevalence in 2–10-year-olds, $PfPR_{2-10}$), four levels of current ITN usage, 3 levels of access to first-line treatment with artemisinin-combination therapy (ACT), and 3 levels of resistance to pyrethroids. In the highly seasonal setting only, we additionally considered the addition of SMC at 85% coverage in children aged 3 months to 5 years. For each of these settings, we modelled 4 intervention options – increasing usage of ITNs by 10%, switching to PBO nets in areas with pyrethroid resistance (medium or high), introduction of SMC (in seasonal settings only) and introduction of the RTS,S vaccine, either as an age-based programme or implemented seasonally. This resulted in 2,574 unique intervention combination scenarios including the 270 baseline settings in which no intervention was added. For each scenario we captured uncertainty by performing 50 random parameter draws.

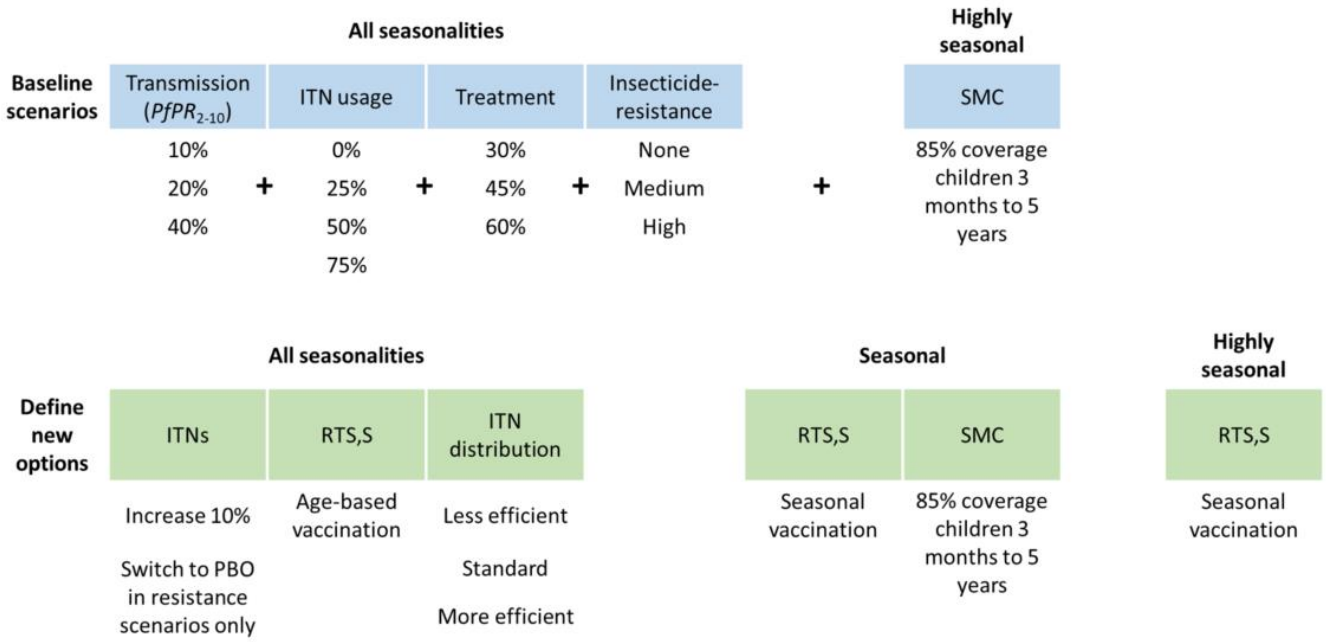

Figure 1. Baseline and added interventions. *P. falciparum* mosquito model baseline and intervention settings. ITNs, SMC, and RTS,S were modelled both as single interventions and in combination. Full details on model parameterization can be found in the original publications,[19,20] including references for parameters.

Effectiveness outputs were summarised over a 15-year time horizon. Unit cost assumptions are detailed below (**Table 1**). A non-linear relationship between cost per net delivered and ITN usage was introduced based on net distribution and use data from sub-Saharan Africa[21].

Table 1. Unit costs for malaria interventions. AL = Artemether-lumefantrine, PBO = pyrethroid + piperonyl-butoxide, SSA = sub-Saharan Africa, USD = United States Dollar.

INTERVENTION	UNIT COST (USD)	REFERENCE / NOTES
Insecticide-treated nets	2.52 per net (pyrethroid) 3.51 per net (pyrethroid-PBO) 1.50 delivery cost per net	Average net costs: The Global Fund 2022[22] Delivery cost: Sherrard-Smith *et al.* 2022[23] Non-linear relationship between usage and distribution: Bertozzi-Villa *et al.* 2021[21]
Seasonal malaria chemoprevention	0.9075 per dose (including delivery)	Gilmartin et al. 2021[24]
RTS,S	9.30 2.71 consumables per dose 1.62 delivery per dose	Delivery costs from the MVIP[16] Costs assumed to be the same for both age-based and seasonally-targeted. $9.30 based on quoted price of EUR9.30 (assuming an average EUR to USD exchange rate = 1 as of September 2022)[1]
Treatment (clinical cases)	0.53 rapid diagnostic test per person (0.46 unit cost + 15% delivery mark-up) 0.3 per dose of AL (24 doses adult, 12 doses children) 1.87 outpatient cost (9.60 total for adults, 6.00 for children < 5years)	RDT unit cost: The Global Fund 2022[25] RDT delivery mark-up: Patouillard et al. 2017[26] AL dosage: WHO Guidelines for Malaria 2022[3] AL pricing: The Global Fund 2022[27] Outpatient: Median WHO-Choice cost for SSA[28] 77% of costs are from the public sector, 23% are covered privately[29]
Treatment (severe cases)	0.53 rapid diagnostic test per person 0.3 per dose of AL (24 doses adult, 12 doses children) 8.71 inpatient cost (16.44 total for adults, 12.84 for children < 5years)	RDT unit cost: The Global Fund 2022[25] RDT delivery mark-up: Patouillard et al. 2017[26] AL dosage: WHO Guidelines for Malaria 2022[3] AL pricing: The Global Fund 2022[27] Inpatient: Median WHO-Choice cost for SSA[28] , 3 day duration of stay[26] 77% of costs are from the public sector, 23% are covered privately[29]

Cost per Dose

We first calculated the maximum cost per dose (the cost not including consumables and delivery costs which are considered fixed) at which RTS,S would be the most cost-effective choice of all eligible interventions. The median value was $0.98 USD (IQR: -0.26 to 4.23) in perennial settings, $0.21 USD (IQR: -0.15 to 0.34) in seasonal settings with age-based delivery, $0.36 (IQR: -0.04 to 0.50) with seasonal delivery, $3.35 (IQR: 0.58 to 11.22) in highly seasonal-settings with age-based delivery, and $3.71 USD (IQR: 0.71 to 12.48) in highly seasonal settings with seasonal delivery (**Figure 2**). Negative values occur when other intervention options are cost-saving and indicate that RTS,S would not be the most cost-effective option at any cost. Negative values primarily occurred in settings experiencing insecticide resistance or with low ITN usage. The higher maximum cost per dose in the highly seasonal settings reflects the higher efficacy associated with seasonal implementation of the vaccine.

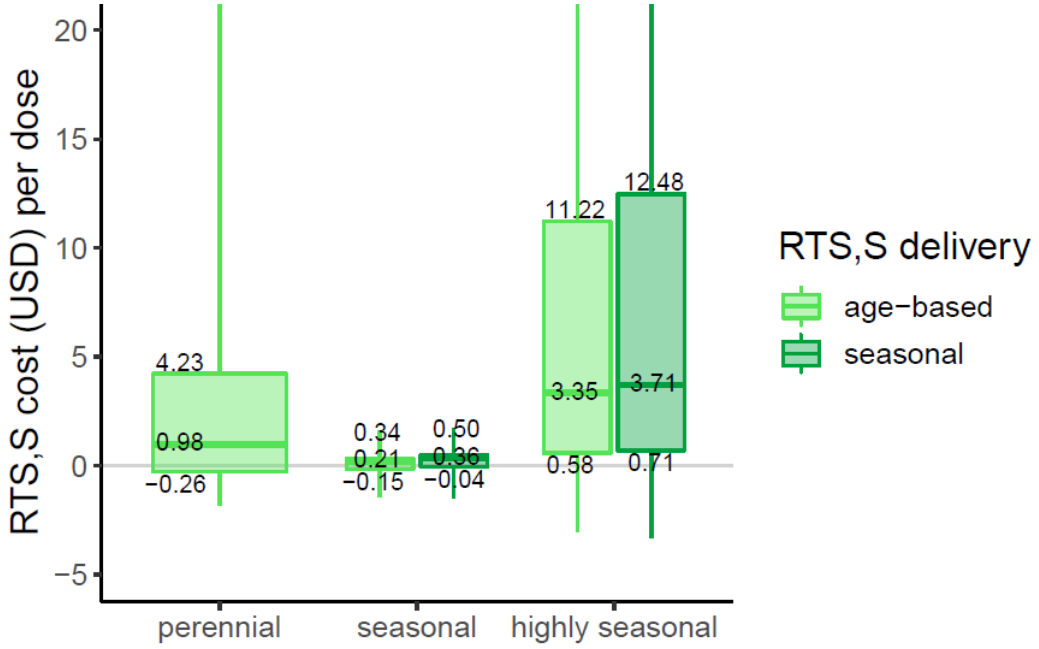

Figure 2. **The maximum cost per dose of RTS,S that would result in its introduction as the most cost-effective intervention option.** The median, interquartile range and 95% whisker bars across the scenarios are shown stratified by seasonality and RTS,S delivery type.

Figure 3 summarises the percentage of scenarios in which RTS,S would be the most cost-effective intervention to introduce for a range of different costs per dose. For RTS,S to be the most cost effective choice in greater than 50% of scenarios, the cost per dose would need to be $0.47 USD or less. At the current published cost per dose of $9.30 USD, introducing RTS,S would be less cost effective than other options in 85.9% of scenarios.

It is important to bear in mind that these percentages do not translate to populations at risk or the percentage of countries or sub-national units. It is therefore also instructive to identify those settings in which RTS,S would be the most cost-effective next intervention. At the published cost of $9.30 USD per dose, we found that >95% of these scenarios were settings with high ITN usage (modelled here as 75%) and/or with SMC already implemented. These results are consistent with

our earlier work that showed that in most settings RTS,S would only be the most cost-effective intervention to introduce in settings where ITNs and SMC usage had reached high levels.

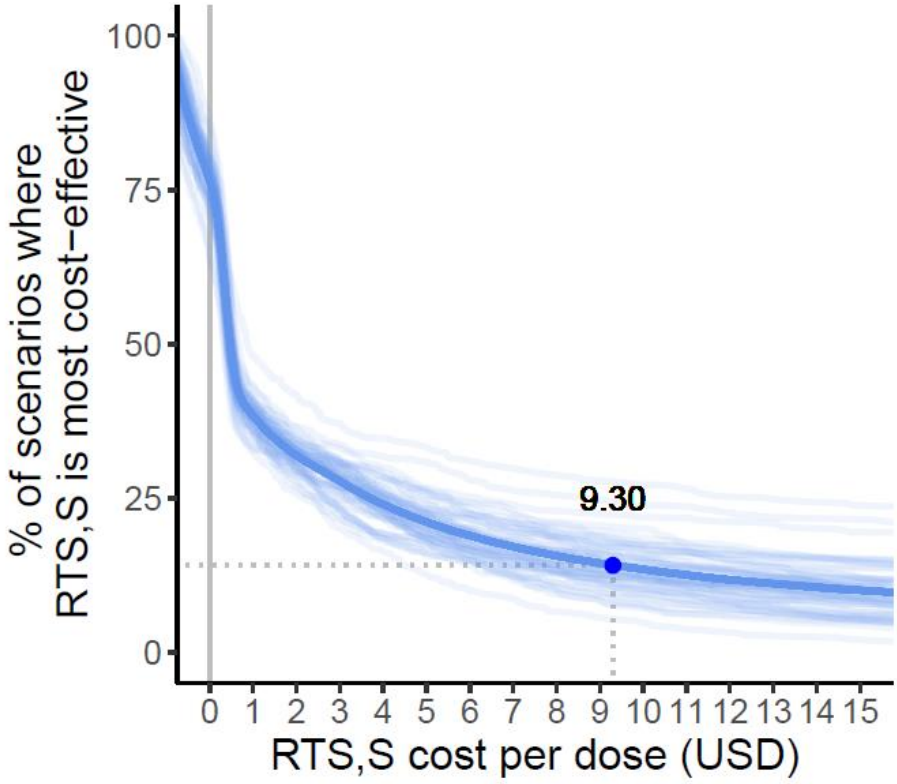

Figure 3. **The proportion of scenarios where RTS,S is the most cost-effective intervention to introduce as a function of the cost per dose.** Faint blue lines represent each of 50 parameter draws to capture model uncertainty. The solid blue line represents median values across all parameter draws. Age-based and seasonal RTS,S are combined. A similar plot, stratified by comparison intervention is shown in **Figure S4**.

Cost-Effectiveness of Malaria Interventions

Across all simulations, implementing SMC in seasonal settings resulted in the lowest median cost per DALY averted at $23 USD (IQR: 17 to 32) (**Figure 4**), relative to maintaining baseline levels of interventions. Switching from pyrethroid to pyrethroid + PBO ITNs in areas with insecticide resistance resulted in a median cost per DALY averted of $50 USD (IQR: 22 to 116), followed by boosting ITN coverage by 10% ($68 USD, IQR: 26 to 157), seasonal RTS,S vaccination ($169 USD, IQR: 130 to 224), and age-based RTS,S vaccination ($193 USD, IQR: 150 to 257). Estimates for RTS,S were similar to previous results at the assumed $10 USD per dose price[6]. In settings in which RTS,S was generally identified as the most cost-effective intervention (40% PfPR, 75% ITN usage, and 85% SMC where applicable), the cost per DALY averted was $115 (IQR: 96 to 167) for seasonal RTS,S vaccination and $149 USD (IQR: 118 to 202) for age-based RTS,S vaccination. As SMC and pyrethroid + PBO ITNs were only applied in limited settings, increasing ITN use by 10% had the lowest CE ratio of interventions that were applied across all settings (**Figure 4, Figure S2**). Some CE ratios fell below 0, indicating that interventions were cost-saving as a result of averting treatment costs. Mixed strategies involving two or more interventions resulted in varying levels of CE. Similar trends were observed when the outcome of interest was cost per case averted (**Figure S3**). The addition of RTS,S to high coverage of existing interventions still resulted in additional marginal impact. This was

estimated to result in a median 3,005 (IQR: 2,118 to 4,215) cases averted per 100,000 people annually.

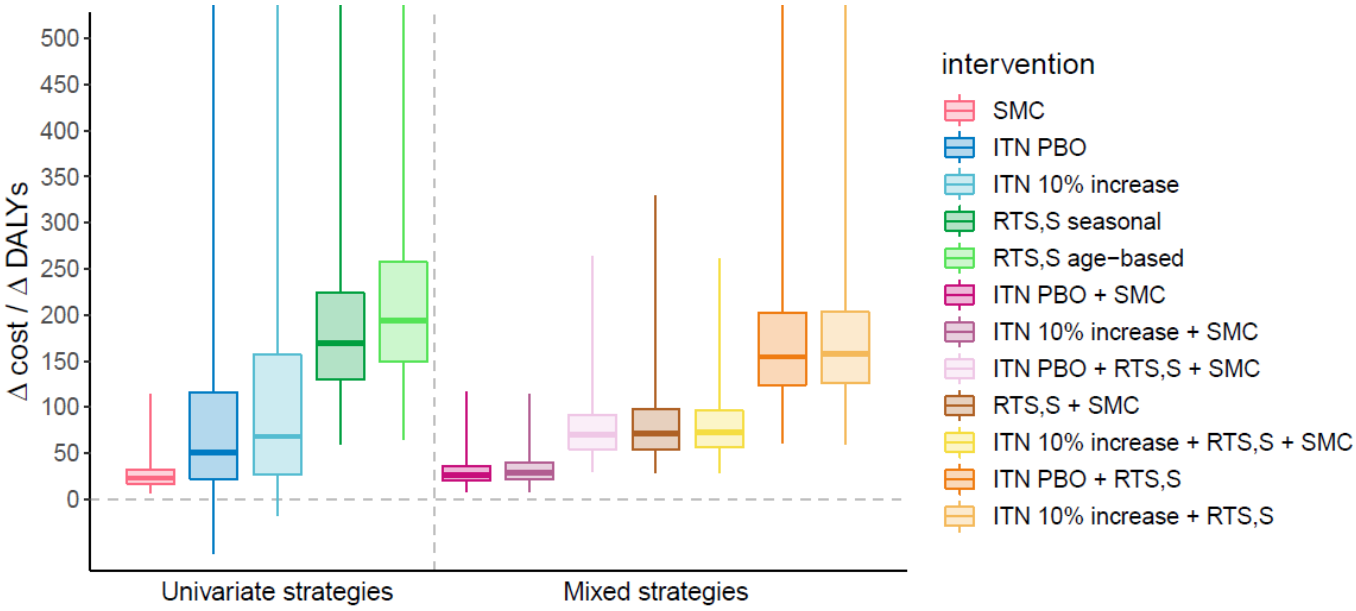

Figure 4. CE distributions for interventions and intervention combinations. Change in cost per change in DALYs averted. Each scenario is compared relative to a baseline setting matched on seasonality, parasite prevalence, ITN use, treatment coverage, and insecticide-resistance, with no intervention. RTS,S age-based and seasonal vaccination intervention results are combined under mixed strategies involving RTS,S. Note: DALY = disability-adjusted life year, ITN = insecticide-treated net; SMC = seasonal malaria chemoprevention. Number of scenarios: SMC = 4,500, ITN PBO = 7,146, ITN 10% increase: 12,652, RTS,S seasonal = 9,000, RTS,S age-based = 13,500.

Perennial Settings

Focusing just on perennial setting runs, age-based RTS,S was the most cost-effective strategy in 12.4% of all scenarios (**Figure 5**), with *Pf*PR_{2-10} and ITN use being the main determinants of intervention ranking. RTS,S became more cost-effective in higher transmission settings, ranging from the most cost-effective scenario in 0.53% of 10% *Pf*PR_{2-10} settings to 31.7% of settings with a *Pf*PR_{2-10} of 40%. Similarly, RTS,S was the most cost-effective intervention in 1.1% of scenarios with 0% established ITN use, 2.7% of scenarios with 25% ITN use, 8.9% of scenarios with 50% ITN use, and 29.3% of scenarios with 75% ITN use. Under scenarios of no resistance where pyrethroid + PBO was not an option, RTS,S was the most cost-effective intervention in 11.1% of scenarios. RTS,S was the most cost-effective intervention in 5.5% of moderate resistance areas, and 21.0% of high resistance areas. This pattern occurs as a result of the non-linear impact of pyrethroid resistance on ITN efficacy. Age-based RTS,S CE varied with ITN distribution efficiency, ranging from 10.2% under more efficient distribution

to 20.8% with less efficient distribution. RTS,S CE was relatively constant across treatment levels, ranging from 11.4% to 13.9%.

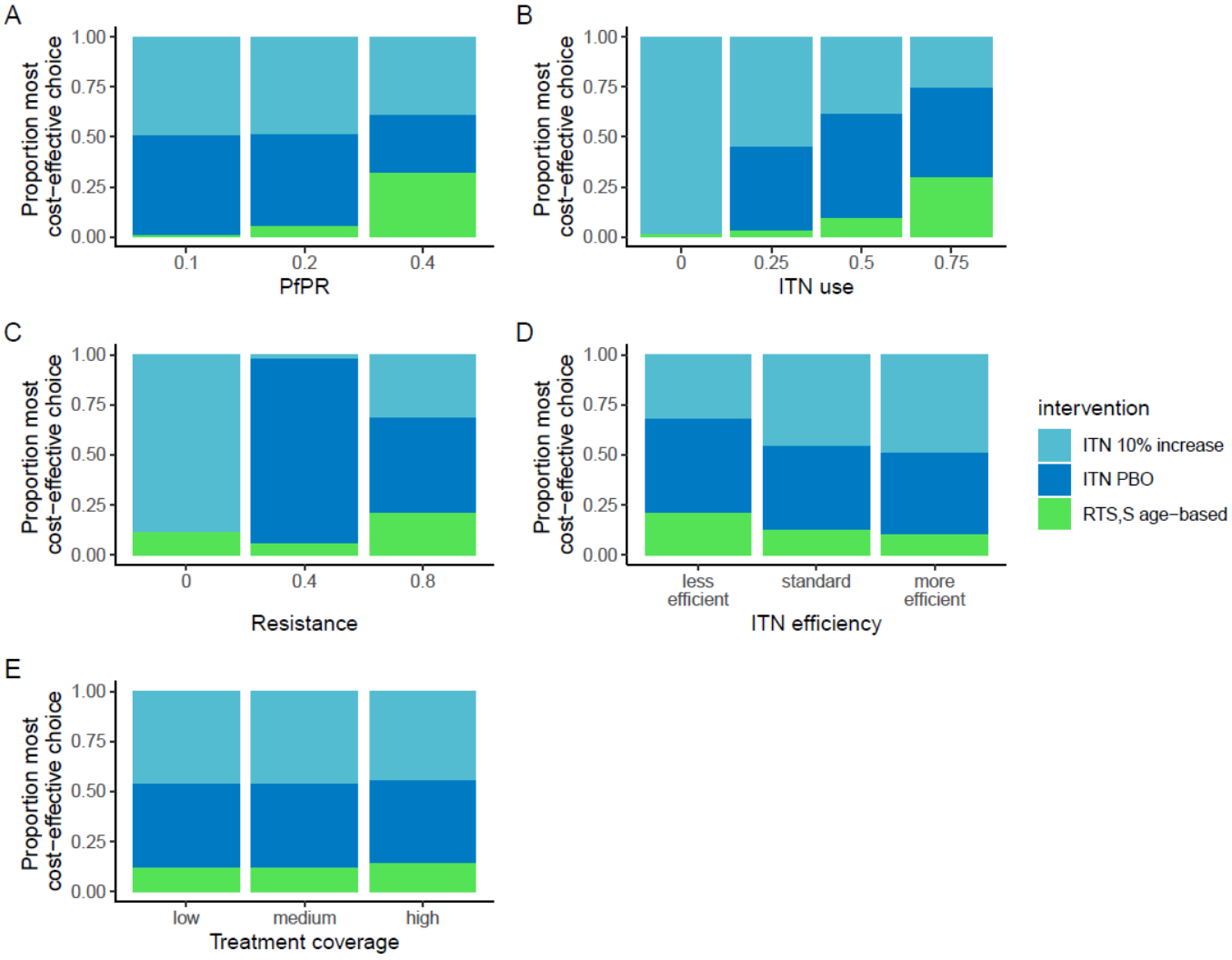

Figure 5. Determinants of CE ranking in perennial settings. Proportion of times an intervention was the most cost-effective out of all scenarios, stratified by seasonality and A) *Pf*PR$_{2-10}$, B) baseline ITN use, C) insecticide resistance level, D) ITN distribution efficiency, and E) treatment coverage. Note: DALY = disability-adjusted life year, ITN = insecticide-treated net; PBO = pyrethroid + piperonyl-butoxide.

Seasonal Settings

Focusing on seasonal setting runs, RTS,S was the most cost-effective strategy in 0% of all primary scenarios (**Figure 6**), as SMC was the dominant cost-effective strategy. The only settings where RTS,S was the most cost-effective intervention were under scenarios where ITN distribution was less efficient (16.9%). SMC was the most CE strategy overall (66.3%), and became more cost-effective with higher *Pf*PR$_{2-10}$, greater levels of established ITN use, and in areas with high insecticide resistance. The proportion of scenarios where SMC was the most cost-effective choice remained relatively stable across ITN efficiency and treatment coverage levels.

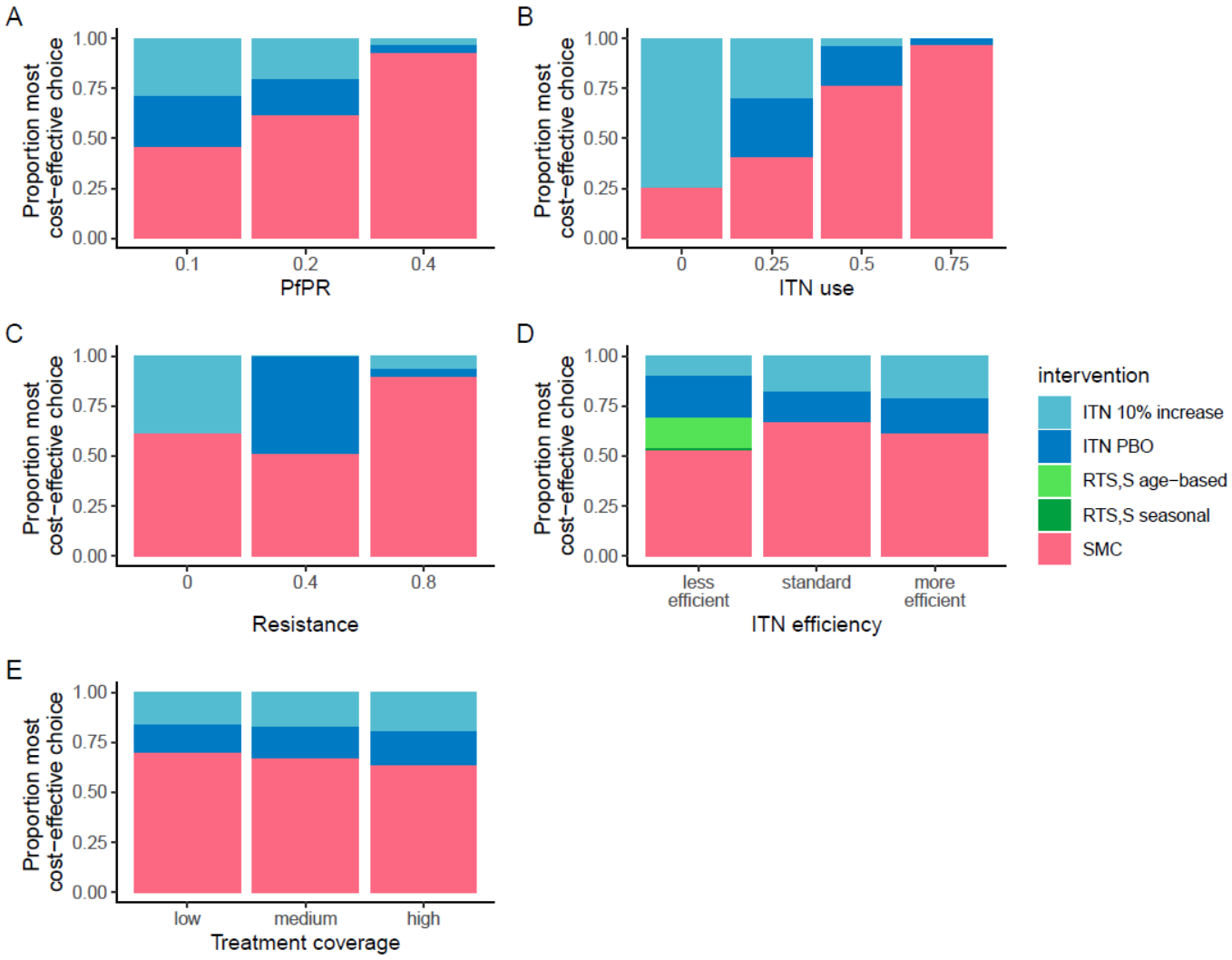

Figure 6. **Determinants of CE ranking in seasonal settings.** Proportion of times an intervention was the most cost-effective choice out of all scenarios, stratified by seasonality and A) *Pf*PR$_{2-10}$, B) baseline ITN use, C) insecticide resistance level, D) ITN distribution efficiency, and E) treatment coverage. Note: DALY = disability-adjusted life year, ITN = insecticide-treated net; PBO = pyrethroid + piperonyl-butoxide; SMC = seasonal malaria chemoprevention.

Highly Seasonal Settings

In highly seasonal settings (where SMC was assumed to already be implemented), RTS,S was the most cost-effective strategy in 30.47% of all scenarios (**Figure 7**). RTS,S became more cost-effective under higher transmission settings, ranging from the most cost-effective scenario in 5.4% of 10% *Pf*PR$_{2-10}$ settings to 63.1% of 40% *Pf*PR$_{2-10}$ settings. RTS,S was the most cost- effective intervention in 7.1% of scenarios with 0% established ITN use, 12.2% of scenarios with 25% ITN use, 29.3% of scenarios with 50% ITN use, and 57.6% with 75% ITN use. Under scenarios of no resistance, RTS,S was the most cost-effective intervention in 27.4% of scenarios. RTS,S was the most cost-effective intervention in 19.8% of moderate resistance areas, and 45.3% of high resistance areas. RTS,S CE varied with ITN distribution efficiency, ranging from 27.3% under more efficient distribution to 36.8% with less efficient distribution. RTS,S CE was relatively constant across treatment levels, ranging from 28.5% to 32.0%. Overall, seasonally-targeted RTS,S made up the majority of scenarios

where vaccination was the most cost-efficient; 27.2% of all scenarios, vs. 3.3% for age-based.

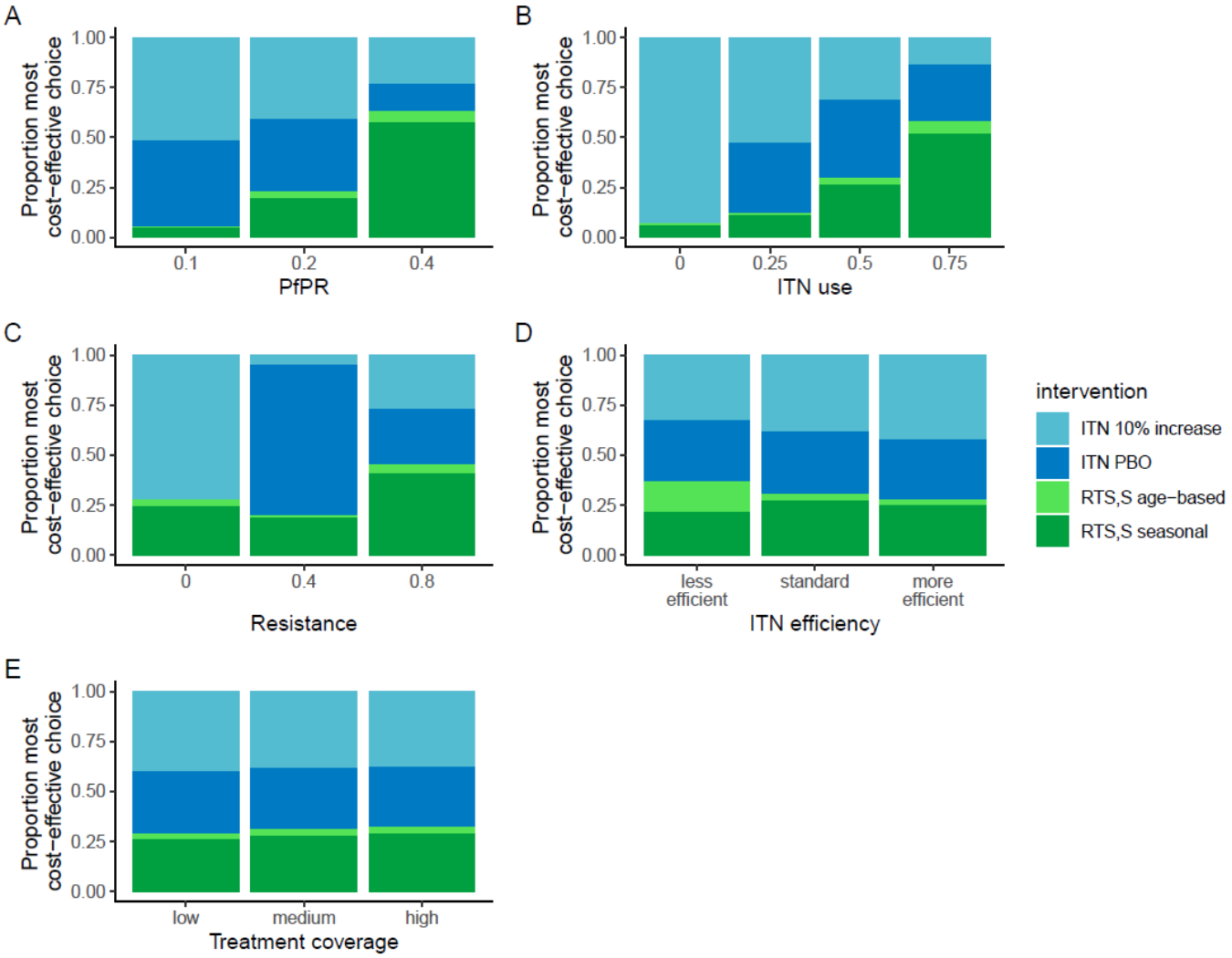

Figure 7. **Determinants of CE ranking in highly seasonal settings.** Proportion of times an intervention was the most cost-effective out of all scenarios, stratified by seasonality and A) *Pf*PR_{2-10}, B) baseline ITN use, C) insecticide resistance level, D) ITN distribution efficiency, and E) treatment coverage. Note: DALY = disability-adjusted life year, ITN = insecticide-treated net; PBO = pyrethroid + piperonyl-butoxide; SMC = seasonal malaria chemoprevention. We assume that SMC is already implemented at baseline in highly seasonal settings.

EQUITY

A secondary analysis examining urban and rural settings under various scenarios revealed differences in equity when spatially targeting interventions. Inequity was defined as the difference in total DALYs or total clinical cases between urban and rural settings, assuming equal population sizes. We assumed that interventions decreased inequity when the urban-rural disparity was lower with interventions than without, and increased inequity when the urban-rural disparity was higher with interventions than without. Targeted implementation of ITNs or age-based RTS,S to rural areas resulted in equal or lower disparities between rural and urban areas as compared to scenarios with no implementation of ITNs or age-based RTS,S (**Figure 8**). Mass ITN distribution led to small increases in disparities between urban and rural areas, increasing inequity in most settings.

Increasing ITN usage by 10% was more cost-effective in terms of cost per DALY averted than introduction of age-based RTS,S in most scenarios, except when a gap existed in *Pf*PR$_{2-10}$. However, this assumes that increasing intervention coverage is equally feasible for both interventions in the targeted populations which may not be consistent with observations of differences between the spatial distribution of children protected by an ITNs and coverage of the EPI programme[18].

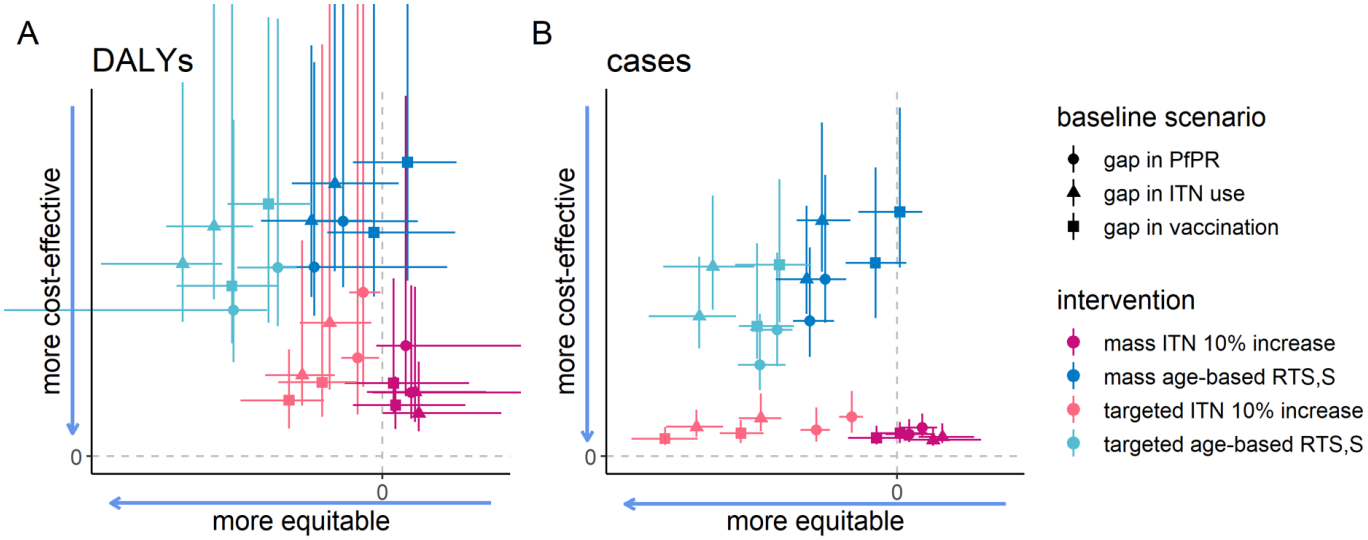

Figure 8. Intervention distribution modes, equity and CE. Equity scenarios assessing measures of cost-effectiveness and equity, for outcomes of A) DALYs, and B) clinical cases. Cost-effectiveness is measured as change in cost per change in outcome unit. Equity is measured as % change in the disparity between urban and rural settings with and without interventions. Results closest to the origin are the most cost-effective and most equitable. Point shapes indicate the baseline scenario: circles = a gap in PfPR2-10 (0.4 rural vs. 0.1 urban), triangles = a gap in ITN use (0.6 rural vs 0.3 urban), and squares = a gap in RTS,S coverage (0.5 rural vs 0.8 urban). Note: DALY = disability-adjusted life year, ITN = insecticide-treated net. Dashed lines indicate boundaries where baseline scenarios are equally cost-effective or have the same urban-rural disparity as intervention scenarios.

DISCUSSION

The results from the RTS,S implementation programme have demonstrated that introduction of the vaccine layered on top of existing malaria interventions can have a significant public health impact in malaria endemic settings. Wider introduction of the vaccine is therefore now being considered. However, given the constraints on the budgets available for malaria control and elimination, decisions about where to implement RTS,S should be assessed within the broad context of the complete set of currently available and implemented interventions. Relative cost-effectiveness models provide a method through which to make this comparison, and can be used alongside data on local contextual factors including supply chain management, current intervention utilization, and local costs to guide country programming. Here we provide such an overview that can help to inform country decision-making.

By assessing the maximum possible cost at which RTS,S ranks as the most cost-effective intervention to introduce across a broad range of contexts, we present a more detailed picture of its relative cost-effectiveness as compared to the commonly used range of estimated dose costs of $2, $5, and

$10. Our results show that within many transmission contexts, at the current price point of $9.30 USD, other malaria intervention options would be more cost-effective than introducing RTS,S. (**Figure 2**). Across the range of settings considered, the relative cost-effectiveness ranking of RTS,S is insensitive to price change around the $9.30 USD price, with the cost per dose required to be significantly lower before RTS,S is consistently ranked as the most cost-effective option (**Figure 3**). Thus, even when economies of scale are factored into the price, it is unlikely that introducing RTS,S would be the most cost-effective choice across all malaria-endemic settings.

Given this, we sought to identify the subset of transmission contexts in which RTS,S would be the most cost-effective next malaria intervention. We identified several key drivers of intervention cost-effectiveness ranking. Unsurprisingly, the current level of *P. falciparum* transmission remains a key driver; RTS,S was more likely to be ranked as the most cost-effective intervention at higher levels of *Pf*PR_{2-10}. At higher transmission levels, the distribution of malaria cases, severe cases, and deaths is focused in the younger age-groups[30] that are directly protected by RTS,S, and hence the direct benefit of the vaccine is stronger than in lower transmission settings . The existing level of ITN usage was also a key determinant; in most scenarios where ITN usage was low (<50%), increasing bed net usage is ranked as the most cost-effective option (**Figure 5, Figure 6, Figure 7**). This is due to the large indirect benefit that is estimated to result from ITN usage. As ITN usage increases, the marginal cost of increasing usage also rises, making it increasingly expensive to achieve high usage levels[21]. As a result, the relative CE of RTS,S when ITN usage is high (**Figure 5, Figure 6, Figure 7**). The efficiency of ITN distribution (characterized by the number of nets delivered to a setting to achieve an observed usage) additionally influences the relative cost-effectiveness of ITNs relative to RTS,S. In areas where distribution was more efficient, ITNs were relatively more cost-effective than in scenarios where distribution was less efficient. We currently do not have data to characterise the distribution or implementation efficiency ranges for SMC or RTS,S, and therefore our results here assume the average level of efficiency in the studies undertaken to date.

We additionally found RTS,S to be the most cost-effective intervention more frequently in highly seasonal settings than in perennial or seasonal settings (**Figure 5, Figure 6, Figure 7**). There are two caveats to bear in mind here. Firstly, in highly-seasonal settings we assumed pre-existing SMC implementation, while in the seasonal setting we did not. As such, RTS,S was ranked against both SMC and ITN options in the seasonal setting, and only against ITN options in the highly-seasonal setting. Secondly, in highly seasonal settings seasonally-targeted RTS,S implementation was more cost-effective than implementation via the age-based approach in most scenarios. Seasonally targeted vaccination allows the period of peak vaccine protective efficacy to be most closely aligned with the period of peak risk during the malaria season, and has been demonstrated to result in significantly higher efficacy in clinical trials [31]. It should be noted that our modelling assumes that under this implementation schedule (and also for SMC delivery) the timing of the programme coincides perfectly with the period of peak risk. In other work, we have found RTS,S impact to be less sensitive to this timing than SMC [32]. It is important to note that the total population at risk in malaria endemic settings will not be equal across perennial, seasonal and highly season settings and hence these results cannot be generalised across malaria endemic areas.

Given these results, we found RTS,S introduction to be the most cost-effective intervention at its current price-point in settings with high transmission (*Pf*PR_{2-10} = 40%), high existing ITN usage (75%) and SMC coverage (85%) where applicable. In such settings, the cost per DALY averted was $115 (IQR: 96 to 167) for seasonal RTS,S vaccination (only considered in seasonal and highly seasonal settings) and $149 USD (IQR: 118 to 202) for age-based RTS,S vaccination (considered across

perennial, seasonal and highly seasonal settings). These levels are similar to the estimated cost-effectiveness of introduction of the PCV vaccine in Africa, for which the cost per DALY averted was estimated as $118 (95% confidence interval 45.7 - 320)[33]. Whilst precise costing methodologies differ between our study and the PCV modelling study, this provides a comparative indication to another recently introduced vaccine.

Mixed combinations of interventions were also assessed in addition to comparing implementation of interventions alone relative to no intervention (**Figure 4, Figure S2, Figure S3**). The cost-effectiveness of mixed strategies tended to fall somewhere between the cost-effectiveness of individual strategies alone, with ITN PBO + SMC being the most cost-effective, followed by ITN increase + SMC, RTS,S + SMC, ITN combinations with RTS,S + SMC, and finally, ITN combinations with RTS,S. Once sub-optimal strategies (higher cost for a lower change in DALYs averted) were removed from the cost-effectiveness pathway, implementing RTS,S alone was removed in many scenarios.

When considering equity as a factor in our analysis we saw that a targeted approach to ITN and RTS,S administration led to greater equity in health outcomes than mass distributions across urban and rural areas (**Figure 8**). As well as improving health equity, targeting interventions could also lead to a more optimal use of resources, resulting in a lower estimated cost per DALY averted . This is especially important when supply constraints are present, as with RTS,S.

LIMITATIONS

There are several extraneous factors that can influence the translation of these generic insights into decisions made at the local level. These include, but are not limited to, variable implementation costs, the operational feasibility of the different interventions, and systems limitations. Implementation and delivery costs can vary widely dependent on the setting. For example, in a recent analysis of the cost-effectiveness of SMC, non-commodity costs accounted for approximately two thirds of the total intervention cost and overall costs per child varied up to 4.5-fold across different countries and delivery modes[24]. ITN distribution and retention duration has also been shown to vary significantly within and between countries[21]. Similarly, the economic cost of RTS,S delivery in the MVIP varied 2-fold across the three pilot implementation countries[16]. Operational feasibility and systems limitations coupled with limits in systems capacity may also drive decisions around vaccine introduction and choices of where to focus additional malaria programming funding. Whilst vaccine uptake has been high (and in-line with other childhood vaccination uptake) in the pilot implementation countries[16], each country will need to consider the capacity within their immunisation programme to add a new vaccine. Similarly, investment in SMC or increasing ITN usage needs to take into consideration the operational needs to achieve this. It is also worth noting that the vaccine may still be sufficiently cost-effective to fall within a country's willingness to pay threshold, in combination with other existing interventions.

Further system-wide constraints such as the ring-fencing of financing for specific uses and the projected constrained dose-supply will also influence vaccine introduction. The interpretation of direct comparisons of cost-effectiveness with other interventions is more difficult to make when funds may be targeted for specific applications (e.g., GAVI funding of vaccines), or when assuming a fixed or variable total global resource envelope for malaria control. Similarly, dose supply constraints may mean that even in areas where RTS,S is the most cost-effective intervention, other interventions may be more feasible to fund and implement.

CONCLUSIONS

Our results highlight the importance of using local or regional data to inform subnational tailoring of interventions in order to maximise the efficiency of targeted delivery of interventions. The

introduction of RTS,S was found to be less cost-effective than increasing ITN usage and childhood implementation of SMC in settings in which the optimal use of these tools is not yet fully realised. However, in settings where the utilisation of existing tools is already optimised, RTS,S is estimated to have a similar cost-effectiveness to the PCV vaccine that has recently been introduced across Africa.

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APPENDIX 1: METHODS

MODEL

An individual-based mathematical model of *P. falciparum* was used for all model simulations, run using the *malariasimulation* (*v1.3.0*; Charles G, et al. 2022) package in R 4.1.0 (R Core Team, 2021). *malariasimulation* incorporates individual heterogeneity, simulating stochasticity and variation in exposure, age-structures, immunity, and intervention usage. Parameters in the original model were selected by fitting to severe disease, clinical disease, and parasite prevalence data by age across sub-Saharan Africa, as described previously[19,20]. Functions and documentation for *malariasimulation* are open source (https://github.com/mrc-ide/malariasimulation).

In short, individuals enter the model at birth, becoming susceptible to *P. falciparum* infection after a period of maternally acquired protective immunity. Throughout the life course following a bite from an infective mosquito, individuals become infected with an age-based probability and go on to develop asymptomatic infection or clinical disease. A proportion of those with clinical disease develop severe disease, which can lead to death, and a proportion of both groups receive treatment, which provides a period of drug-dependent partial protection from infection. Individual immunity is acquired at birth through maternal antibodies, and throughout the lifespan via antiparasitic immunity and antiinfection immunity as functions of age and exposure to infection. Mosquito vectors are modelled compartmentally, becoming infectious through the bite of an infected human.

Modelled interventions included use of treatment, ITNs, SMC, and RTS,S (**Figure S1**). Treatment is administered with a specified probability to individuals experiencing clinical disease. ITNs are modelled probabilistically using parameters specifying female mosquito attempts to feed and the resulting probabilities of being repelled, killed, or successfully biting. Probabilities for these parameters are affected by ITN efficacy which is specific to the type of insecticide used on the net and the level of insecticide-resistance in a particular setting[23]. Receiving SMC bestows a probability of clearing existing infection and offers a period of drug-dependent partial protection from infection following a Weibull survival curve. RTS,S efficacy begins following the third dose and follows a biphasic model with short and long lived anti-CSP antibody response decays, with parameters fit to data from the multi-site Phase III randomized controlled trial[34]. Antibody levels after the fourth dose follow a similar decay with a lower peak titre.

To capture model uncertainty all model runs were repeated 50 times using different parameter draws from the fitted model joint posterior distribution. Results were summarised by taking the median output measure across the 50 draws.

SCENARIOS

Three seasonal settings were defined using Fourier-transformed average rainfall data from three representative settings in sub-Saharan Africa: A) perennial (Central Africa), B) seasonal (West Africa coastal regions), and C) highly seasonal (Sahel region)[13]. Baseline *P. falciparum* prevalence bands in 2-10 year olds (*Pf*PR_{2-10}) were selected, with the model calibrated to equilibrium values of 10%, 20%, and 40%, after accounting for existing interventions already in place. These values are in line with the WHO definition of moderate (*Pf*PR_{2-10} = 10-35%) to high (*Pf*PR_{2-10} ≥ 35%) malaria transmission settings, in which RTS,S is recommended[3], and represent the range of transmission zones across sub-Saharan Africa[35]. Treatment was varied across all scenarios assuming 30%, 45%, or 60% of all clinical cases were successfully treated with artemether-lumefantrine (AL). Baseline settings included a range of pyrethroid ITN usages (0%, 25%, 50%, and 75%), representative of observed country-level usage distributions[21]. Three levels of pyrethroid resistance were also included in areas with established ITN use, with values of 0%, 40%, and 80% capturing increased levels of bioassay mortality. Combining varying levels of seasonality, *Pf*PR_{2-10}, treatment, ITN use, and pyrethroid resistance resulted in 270 baseline scenarios.

All settings contained a combination of the dominant vector species in sub-Saharan Africa, *Anopheles arabiensis* (25%), *A. funestus* (25%), and *A. gambiae* (50%)[36]. All scenarios were run with a population of 200,000 people, with the population age structure derived from a representative life table from Tanzania[6]. All simulations were run for 15 years, similar to the timescale of the Global Technical Strategy for Malaria[37], and long enough to capture shifts in disease trends after changes in intervention packages. Results are less applicable to settings outside of sub-Saharan Africa where key differences may change outcomes (e.g. vector bionomics, parasite species distribution etc.).

We assumed that ITN use was non-linearly associated with the number of ITNs distributed, with a greater number of nets distributed to reach high levels of usage than low levels of usage[21]. We ran each ITN usage rate through an algorithm to calculate the annual ITN distribution needed to maintain ITN usage at a particular value, assuming ITNs are replaced every 3 years as recommended[38], with data taken from country-level ITN distribution data[21]. ITN distribution efficiency was classified into three levels (low, standard, high), representing the minimum, global average, and maximum ITN distribution-to-use ratios in Africa[21].

SMC using amodiaquine plus sulphadoxine-pyrimethamine (AQ+SP) was administered with 85% coverage to children ages 3-59 months for use in highly seasonal and seasonal settings[39]. Four doses were administered in highly seasonal settings with a shorter, but more intense transmission season, while five doses were administered in seasonal settings with a longer transmission season. Doses were centred around peak seasonality and administered monthly, as SMC provides good individual protection against clinical malaria in the 28 days following treatment in programmatic settings[40]. In our models, SMC was assumed to already be implemented at baseline in all highly seasonal models, in line with recommendations for use of SMC in highly seasonal settings where more than 60% of clinical cases occur within 4 months[39].

Age-based RTS,S was administered in line with MVIP trial guidelines, with three doses at 6, 7.5, and 9 months, with a booster-dose at 24 months[41]. Seasonal vaccination was introduced for children ages 5-17 months, who received their first three doses 5.5, 4.5, and 3.5 months prior to peak seasonality. A booster dose was administered a year after receipt of the third dose. Coverage for the initial three doses was set at 85%, on the upper end of MVIP coverage estimates (Malawi reported an 82% uptake of dose three[41]), and 80% of children receiving the first three doses were assumed to subsequently receive a booster dose. Synergy between SMC and RTS,S was also incorporated based

on trial data, with both interventions in combination performing better than either intervention alone[31].

Eligible interventions and associated seasonal timings for each setting are shown in **Figure S1** and include boosting ITN usage by 10%, switching from pyrethroid to PBO ITNs in areas experiencing insecticide-resistance, and introducing SMC in seasonal settings. All interventions were compared in isolation and in combination with others where appropriate.

Individual variation was accounted for by drawing parameters from a normal distribution on the log-scale. Fifty unique parameter draws were run for each scenario to account for inherent model uncertainty.

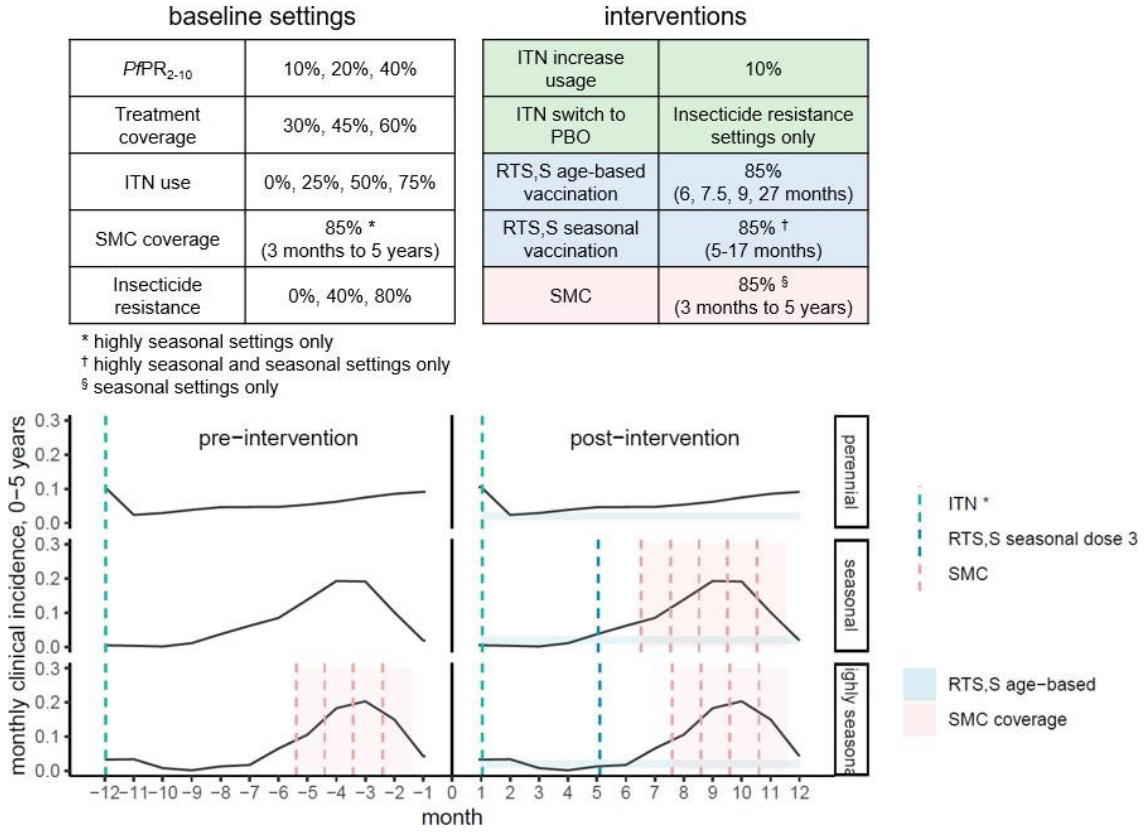

Figure S1. **Scenarios, interventions, and timings.** A) Description of baseline scenarios and intervention options. ITNs, SMC, and RTS,S were modelled both as single interventions and in combination. B) Timing of interventions throughout the year. RTS,S seasonal vaccination and SMC dose timings are based on peak seasonality with the intention to provide maximum protection during high transmission seasons. Note: ITN = insecticide-treated net; PBO = pyrethroid + piperonyl-butoxide; SMC = seasonal malaria chemoprevention. * ITNs are distributed on a 3-year cycle.

Equity Scenarios

Nine scenarios were run in addition to the main analysis to examine the impact of intervention implementation on equity. Urban and rural residences were examined as the primary exposure, as rurality is associated with a higher parasite prevalence and has been found to result in differences in malaria intervention coverage such as access to treatment and ITN use in certain locales[42]. Baseline parameterization used estimates of the gaps in ITN use and diphtheria, tetanus toxoid and pertussis vaccine dose 3 (DTP3) coverage in Demographic and Health (DHS) surveys in sub-Saharan Africa between populations reporting urban vs. rural residences. Models were run in perennial and highly seasonal settings, under the same vector species composition, population size, and population age structure as the main models. *Pf*PR_{2-10} was set at 20% in rural areas and 10% in urban, RTS,S coverage was 80% in both settings, and ITN use was 50% in both settings. No insecticide-resistance or seasonal RTS,S vaccination were included. Treatment was held constant at 45% coverage with AL. Four doses of SMC using AQ + SP was administered with 85% coverage to children ages 3-59 months in highly seasonal settings.

Three scenarios were examined where, for each, the baseline was modified to include: 1) a gap in *Pf*PR_{2-10} (0.4 rural vs. 0.1 urban), 2) a gap in ITN use (0.6 rural vs 0.3 urban), and 3) a gap in RTS,S coverage (0.5 rural vs 0.8 urban).

In each setting we tested four intervention packages: 1) increase ITN usage by 10% in both areas, 2) introduction of age-based RTS,S vaccination in both areas, 3) targeted increase of ITN usage in rural areas, 4) targeted age-based RTS,S in rural areas.

Analysis

Model outputs included age-disaggregated clinical incidence, severe incidence and deaths over the simulation period. Disability-adjusted life years (DALYs) were calculated as the sum of years of life lost (YLL) and years of life with disease (YLD). Years of life lost (YLL) was calculated based on a fixed age of 64.49 years, taken as the average lifespan at birth in Africa in 2019[43]. YLD were estimated using age- and severity-stratified disability weights[44], with deaths calculated as a proportion of those experiencing severe disease (0.215). DALYs and cases averted were calculated by taking the difference between scenarios with single interventions or combination intervention packages relative to the same baseline setting with no interventions.

Estimated costs for each intervention incorporated fixed and variable components (**Table 1**). The primary outcome of interest was cost per DALY averted. Secondary outcomes included cost per case averted and cost per death averted. For each seasonality setting, we examined the optimal sequencing of malaria interventions and measured the consistency of this ranking across regions with different epidemiological profiles. We also computed the maximum cost per dose for RTS,S to be the most cost-effective option in each setting and tested the limits of assumptions on cost and intervention effectiveness by varying ITN distribution effectiveness. Incremental cost-effectiveness ratios (ICERs) were calculated by taking the change in cost per DALY between each baseline setting with no intervention and the corresponding setting with each intervention combination. ICERS were ranked and dominated strategies, with higher cost and fewer benefits than at least one other intervention, were removed.

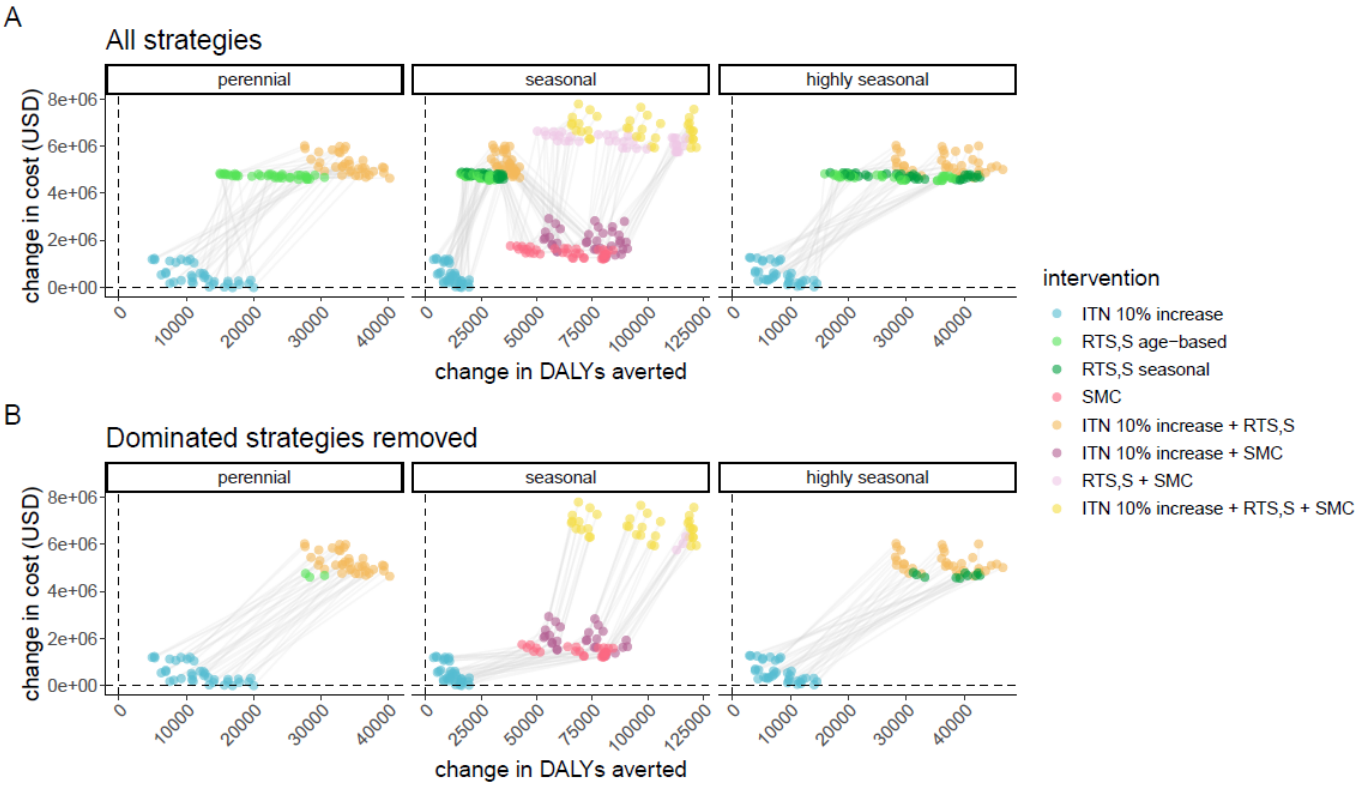

Figure S2. **Cost-effective planes.** Change in cost per change in DALYs averted among A) all scenarios, and B) scenarios where dominated strategies (higher cost, lower change in DALYS averted) are removed. All scenarios in settings experiencing insecticide-resistance are removed. Note: DALY = disability-adjusted life year, ITN = insecticide-treated net; SMC = seasonal malaria chemoprevention.

APPENDIX 2: SENSITIVITY ANALYSIS

OUTCOME MEASURE – CASES

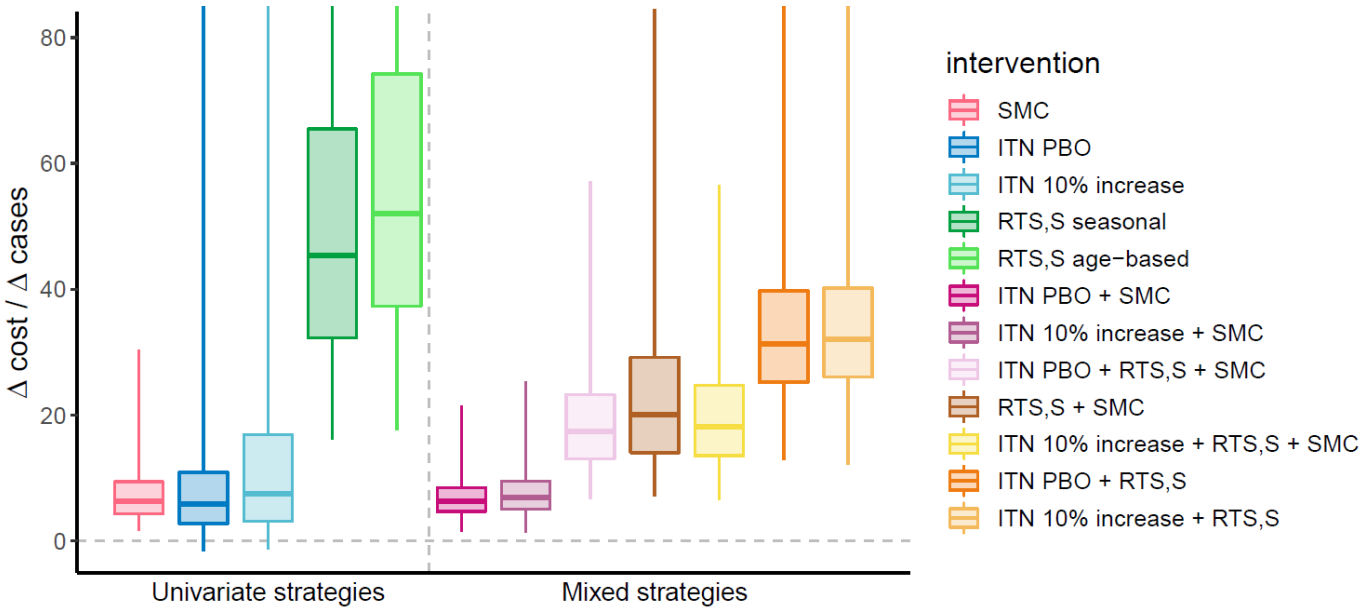

Figure S3. **CE distributions for interventions and intervention combinations**. Cost-effectiveness ratios (cost per case averted) of univariate and mixed strategies. Each scenario is compared relative to a baseline setting matched on seasonality, parasite prevalence, ITN use, treatment coverage, and insecticide-resistance, with no intervention. RTS,S age-based and seasonal vaccination intervention results are combined under mixed strategies involving RTS,S. Note: ITN = insecticide-treated net; PBO = pyrethroid + piperonyl-butoxide; SMC = seasonal malaria chemoprevention. N runs = 113,397.

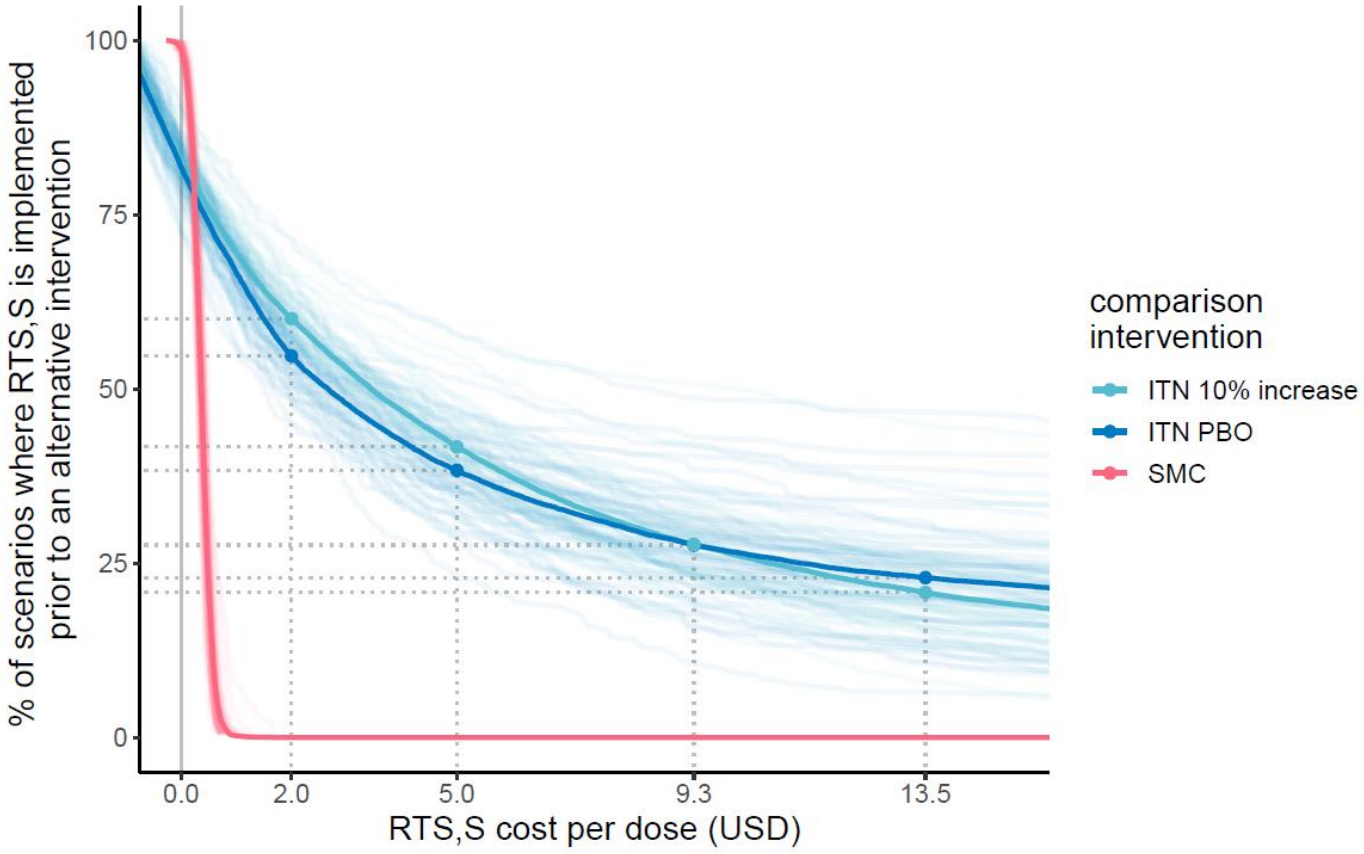

Figure S4. RTS,S cost-effectiveness ranking with respect to cost per dose. Percent of scenarios where RTS,S was the most cost-effective option over a range of costs per dose compared to each other comparison intervention separately. Faint lines represent each of 50 parameter draws to capture model uncertainty. Solid lines represent median values across all parameter draws. Age-based and seasonal RTS,S are combined. Dashed grey lines highlight the relationship between indicative cost per dose values.