Seasonal use case for the RTS,S/AS01 malaria vaccine: a mathematical modelling study

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Summary

Background A 2021 clinical trial of seasonal RTS,S/AS01$_E$ (RTS,S) vaccination showed that vaccination was non-inferior to seasonal malaria chemoprevention (SMC) in preventing clinical malaria. The combination of these two interventions provided significant additional protection against clinical and severe malaria outcomes. Projections of the effect of this novel approach to RTS,S vaccination in seasonal transmission settings for extended timeframes and across a range of epidemiological settings are needed to inform policy recommendations.

Methods We used a mathematical, individual-based model of malaria transmission that was fitted to data on the relationship between entomological inoculation rate and parasite prevalence, clinical disease, severe disease, and deaths from multiple sites across Africa. The model was validated with results from a phase 3b trial assessing the effect of SV-RTS,S in Mali and Burkina Faso. We developed three intervention efficacy models with varying degrees and durations of protection for our population-level modelling analysis to assess the potential effect of an RTS,S vaccination schedule based on age (doses were delivered to children aged 6 months, 7·5 months, and 9 months for the first three doses, and at 27 months of age for the fourth dose) or season (children aged 5–17 months at the time of first vaccination received the first three doses in the 3 months preceding the transmission season, with any subsequent doses up to five doses delivered annually) in seasonal transmission settings both in the absence and presence of SMC with sulfadoxine–pyrimethamine plus amodiaquine. This is modelled as a full therapeutic course delivered every month for four or five months of the peak in transmission season. Estimates of cases and deaths averted in a population of 100 000 children aged 0–5 years were calculated over a 15-year time period for a range of levels of malaria transmission intensity (*Plasmodium falciparum* parasite prevalence in children aged 2–10 years between 10% and 65%) and over two west Africa seasonality archetypes.

Findings Seasonally targeting RTS,S resulted in greater absolute reductions in malaria cases and deaths compared with an age-based strategy, averting an additional 14 000–47 000 cases per 100 000 children aged 5 years and younger over 15 years, dependent on seasonality and transmission intensity. We predicted that adding seasonally targeted RTS,S to SMC would reduce clinical incidence by up to an additional 42 000–67 000 cases per 100 000 children aged 5 years and younger over 15 years compared with SMC alone. Transmission season duration was a key determinant of intervention effect, with the advantage of adding RTS,S to SMC predicted to be smaller with shorter transmission seasons.

Interpretation RTS,S vaccination in seasonal settings could be a valuable additional tool to existing interventions, with seasonal delivery maximising the effect relative to an age-based approach. Decisions surrounding deployment strategies of RTS,S in such settings will need to consider the local and regional variations in seasonality, current rates of other interventions, and potential achievable RTS,S coverage.

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Introduction

Progress in the reduction of malaria morbidity and mortality has stalled, despite substantial gains made since the early 2000s. In 2020, there were an estimated 241 million malaria cases and 627 000 deaths, with the largest burden of mortality among children younger than 5 years in sub-Saharan Africa.[1]

The RTS,S/AS01$_E$ (RTS,S [GlaxoSmithKline, Biologicals SA; Rixensart, Belgium]) malaria vaccine is being

considered for introduction into routine childhood vaccination schedules in malaria-endemic regions.[2,3] Since 2019, RTS,S has been piloted in the Malaria Vaccine Implementation Programme as part of the Expanded Programme on Immunization routine services in Ghana, Kenya, and Malawi.[4] With more than 2·3 million vaccine doses delivered so far, the Malaria Vaccine Implementation Programme has provided evidence of the effectiveness of RTS,S when delivered in routine

Research in context

Evidence before this study

We searched PubMed using the search terms (RTS,S [Title/Abstract]) AND (model*[Title/Abstract]) AND (malaria [Title/Abstract]) AND (seasonal*[Title/Abstract]) from inception to Jan 5, 2022, with no language restrictions. This search returned seven entries; one of these papers did not report modelling the effect of RTS,S at the population level. Of the remaining six studies, all considered the effect of RTS,S/AS01$_E$ (RTS,S) at the population level and in settings of seasonal malaria transmission; however, only one study estimated the effect of RTS,S with a seasonally targeted approach. This study assessed the potential of seasonal RTS,S vaccination (SV-RTS,S) or seasonal malaria chemoprevention (SMC) in settings with a 3-month transmission season and low baseline parasite prevalence rates (1–20%) to reach malaria elimination and prevent resurgence. However, none of the identified studies compared age-based or seasonally targeted RTS,S vaccination strategies in settings of variable seasonality and high transmission intensity or their effects when combined with SMC.

Added value of this study

Following the evidence provided by the clinical trial of the effect of seasonally targeted vaccination with or without SMC, we use population-level mathematical modelling to generalise these findings by estimating the public health effect of these approaches over a longer timeframe and across a range of epidemiological settings. These estimates can help national governments and international agencies to systematically evaluate the potential effect of seasonally targeted RTS,S compared with age-based administration, as well as the value of combining this intervention with SMC.

Implications of all the available evidence

Our modelling results suggest that seasonally targeted RTS,S vaccination could have a greater public health effect than age-based delivery across seasonal malaria transmission settings commonly found in west Africa. We also identify epidemiological settings in which combining vaccination with SMC can have the greatest effect. Our results show that decisions surrounding deployment strategies of RTS,S in seasonal malaria transmission settings will need to consider the local and regional variations in seasonality, current rates of other anti-malarial interventions, and the potential achievable RTS,S coverage.

settings (30% reduction in severe malaria), has shown that delivery is feasible, and has helped increase equity in access to malaria interventions.[5] These findings support the recent positive recommendation from WHO's Strategic Advisory Group of Experts on Immunization (SAGE) and Malaria Policy Advisory Group committees for countries with a medium or high burden of malaria to consider incorporation of RTS,S into their national malaria control programmes, and to the board of Gavi, the Vaccine Alliance, to provide funding for initial implementation programmes.[5,6]

In seasonal malaria transmission settings, it has been suggested that RTS,S could be used as a seasonally targeted vaccine, such that the period of peak protection from the vaccine coincides with the period of maximum malaria risk.[7–9] Previous modelling of such an approach in low-transmission-intensity or near-elimination settings showed that mass RTS,S vaccination, when combined with mass drug administration in a seasonally targeted manner, was likely to achieve substantial reductions in parasite prevalence and, in some settings, transmission interruption.[10] A seasonal malaria vaccination with RTS,S (SV-RTS,S) phase 3b clinical trial, which was published in 2021, assessed the impact of this vaccination approach on clinical and severe malaria outcomes in Mali and Burkina Faso.[9] Trial results showed that SV-RTS,S was non-inferior to seasonal malaria chemoprevention (SMC) in preventing clinical malaria over 3 years of administration in a cohort of children aged 5–17 months of age (hazard ratio 0·92 (95% CI 0·84–1·01). Additionally, compared with either intervention given alone, the combination of SMC and SV-RTS,S resulted in a substantially lower incidence of clinical malaria (62·8% efficacy vs SMC and 59·6% vs SV-RTS,S), severe malaria (71·5% efficacy vs SMC and 70·6% vs SV-RTS,S), and deaths from malaria (72·9% efficacy vs SMC and 75·3% vs SV-RTS,S).[9] These findings suggest that this combined vaccination and SMC approach could substantially reduce the malaria burden in areas of seasonal malaria transmission.

Given the sparse resources available for malaria control, understanding where and how to deploy interventions to ensure the greatest effect is vital. Mathematical models of malaria dynamics have been useful for estimating the public health effect of malaria vaccination beyond the estimates obtained from clinical trials.[11] In this study, we combine data from the phase 3b trial[9] and an individual-based transmission model of *Plasmodium falciparum* transmission to understand the case for seasonal use of the RTS,S vaccine. We aim to evaluate if RTS,S is more effective if delivered seasonally (ie, vaccination of all children in a specified age range in a seasonally targeted strategy at a fixed calendar time) or with an age-based approach (in which calendar time of vaccination of each child varies as doses are delivered when a child reaches the specified age for each dose) in seasonal settings, and if RTS,S delivers an additional benefit relative to SMC alone in these settings. Additionally, we explore how effectiveness varies by transmission intensity, seasonality patterns, and wider health system and operational factors.

Methods

Transmission model

In this modelling study, we used an established mathematical model of *P falciparum* malaria transmission.[12–15] The model is an individual-based transmission model that has been fitted to data on the relationship between entomological inoculation rate and parasite prevalence, clinical disease, severe disease, and deaths from multiple sites across Africa. The model additionally incorporates the current suite of core malaria interventions (long-lasting, insecticide-treated bednets, indoor residual spraying, first-line treatment, SMC, and RTS,S vaccination). Briefly, the model pairs human transmission processes with a stochastic compartmental model that captures mosquito behaviours. When a susceptible individual is exposed to the infectious bite of a mosquito, the rate at which an individual is bitten and becomes infected is driven by mosquito density and infectivity and is moderated by immunity. In the first 6 months of life, infants are partly protected from malaria transmission through maternally acquired immunity. With age, children acquire natural immunity through repeated exposure. If an individual develops clinical disease, they might be successfully treated and then have a period of post-treatment prophylaxis before returning to the susceptible state. A proportion of those with clinical disease progress to severe disease with an associated risk of death. Those who do not develop disease harbour asymptomatic infections that progress to subpatent (low-parasite density) malaria before clearing naturally and returning to the susceptible state. Superinfection (in which individuals who are already infected are reinfected) can occur from all infected states. Onward infectivity to mosquitoes occurs from each infected state, and those with clinical disease are the most infectious before treatment (appendix pp 3–9).

RTS,S as a pre-erythrocytic vaccine, is assumed to reduce the probability of infection. We assume that vaccine efficacy decays over time following a biphasic pattern, and we simulated the initial rapid decay and a subsequent slower decay based on an individual's changing vaccine-induced antibody titre over time and related these titres to efficacy against infection using a Hill function.[16] SMC is the administration of a full therapeutic course of two antimalarial drugs, sulphadoxine–pyrimethamine and amodiaquine, to children aged 3–59 months at monthly intervals during the peak of the malaria transmission season, regardless of whether the recipient is infected, in order to prevent malaria cases. SMC is assumed to treat existing infections and provides a period of drug-dependent prophylaxis, reducing the probability of infection to all individuals regardless of infection status. The initial efficacy of, and the waning protection from, SMC over time is captured in the model as a Weibull distribution (appendix pp 14–15).

Seasonal intervention model validation

The transmission model was used to replicate the three trial arms in the phase 3b trial[9] and results from the trial were compared with model predictions to determine whether or not the current intervention parameterisations reflect the observed trial data (appendix pp 18–25). As a result of the model validation, three intervention efficacy models with varying degrees and durations of protection were used in the population-level modelling analysis. These models result from deviations from the original parameter estimates of RTS,S and sulfadoxine–pyrimethamine plus amodiaquine efficacy that were required to ensure model results were consistent with the trial estimates (panel 1; figure 1).

Population-level modelling

Two representative seasonality archetypes were considered in this analysis: a highly seasonal setting representative of the Sahel region with a single strong peak in rainfall annually, and a seasonal setting representative of west African coastal regions with a lower peak in rainfall annually (figure 2). The starting *P falciparum* prevalence for children aged 2–10 years, ($PfPR_{2–10}$; a standard metric used to describe the intensity of malaria transmission), was in the range 10–65%. These starting baseline prevalence rates are indicative of the range of transmission intensities across sub-Saharan Africa.[17] Baseline prevalence rates are intended to reflect existing rates of malaria vector control interventions and access to treatment (first-line Artemisinin Combination Therapy [ACT] received by 45% of the population with clinical malaria), with no change in coverage during the

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> **Panel 1: Summary of SV-RTS,S and SMC efficacy profile used in this modelling exercise (see appendix pp 14–25 for further details and figure 1 for graphical depictions of these models)**
>
> **Model 1**
> Represents the original fitted parameterisations of the models of RTS,S and sulfadoxine–pyrimethamine plus amodiaquine over time.
>
> **Model 2**
> Incorporates a higher peak efficacy of the fourth or fifth doses of SV-RTS,S than in model 1.
>
> **Model 3**
> Only used when SV-RTS,S is combined with SMC delivery. The model incorporates the higher peak efficacy of SV-RTS,S doses four or five alone from model 2 plus a slight increase in the duration of protection provided by all RTS,S doses and a significant increase in the duration of protection provided by sulfadoxine–pyrimethamine plus amodiaquine from 35 days to 41 days.
>
> SV-RTS,S=seasonal malaria vaccination with RTS,S/AS01$_E$. SMC=seasonal malaria chemoprevention.
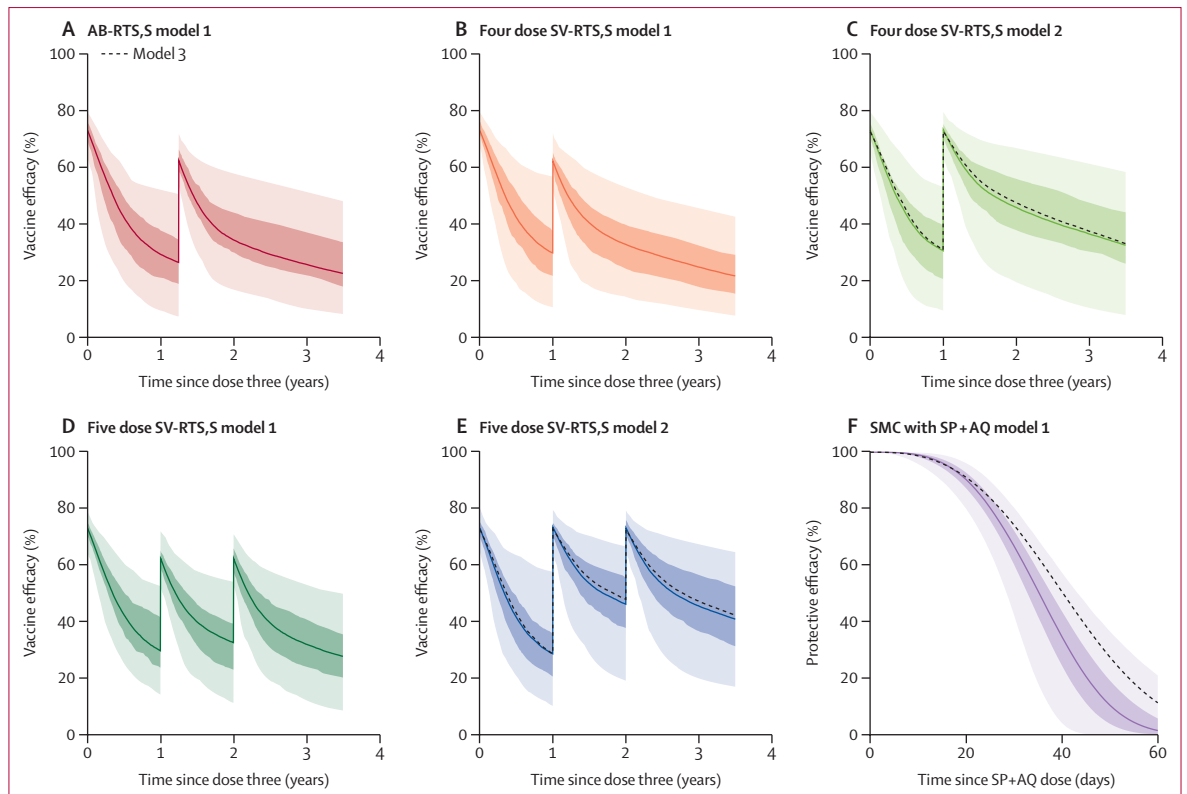
See **Online** for appendix

Figure 1: Intervention efficacy models used in the population modelling simulations, including RTS,S efficacy profile for age-based delivery that follows model 1 parameterisation, in which the fourth dose is delivered 18 months after the third dose (A); efficacy profile for the SV-RTS,S four-dose schedule following model 1 parameterisation in which the fourth dose is delivered 12 months after the third dose (B); efficacy profile for the SV-RTS,S four-dose schedule following model 2 parameterisation based on the results of the model validation exercise (C);* efficacy profile for the SV-RTS,S five-dose schedule following model 1 parameterisation in which the fourth dose is delivered 12 months, and the fifth dose 24 months, after the third dose (D); efficacy profile for the SV-RTS,S five-dose schedule following model 2 parameterisation based on the results of the model validation exercise (E);* SPAQ efficacy profile following model 1 parameterisation (F)†

Solid lines in all plots correspond to the model medians with the shaded areas the 50% and 95% credible intervals. Further details of model parameterisation and changes are in the appendix (pp 14–25). AB–RTS,S=age-based vaccination with RTS,S/AS01$_E$. RTS,S=RTS,S/AS01$_E$. SV-RTS,S=seasonal malaria vaccination with RTS,S/AS01$_E$. SMC=seasonal malaria chemoprevention. SPAQ=sulfadoxine–pyrimethamine plus amodiaquine. *The dashed line represents the model 3 parameterisation for SV-RTS,S when delivered in combination with SMC only. †The dashed line represents the efficacy following model 3 parameterisation based on the results of the model validation exercise for SMC when delivered in combination with SV-RTS,S.

timeframe in which we estimated the effect of RTS,S vaccination in isolation. A sensitivity analysis to the rate of access to treatment was also included: treatment coverage rates with first-line ACT were reduced to 35% and increased to 65% (appendix p 26).

As in previous work, aged-based RTS,S (AB-RTS,S) doses were delivered to children aged 6 months, 7·5 months, and 9 months for the first three doses, and the fourth dose at 27 months of age (figure 1).[11] For seasonally targeted vaccination, all children aged 5–17 months at the time of first vaccination received the first three doses in the 3 months preceding the transmission season, with any subsequent doses delivered annually as per the recent seasonal trial.[8,9] We considered two SV-RTS,S schedules: a four-dose schedule to make a direct comparison to the four-dose age-based schedule and a five-dose schedule, as was delivered in the seasonal trial.[9] Three models of RTS,S efficacy under a SV-RTS,S schedule were used to reflect our uncertainty

in the dynamics of RTS,S efficacy as a result of the model validation reported in the appendix (pp 18–25) and summarised in panel 1 and figure 1. We assumed full vaccine coverage of 64%, resulting from 80% coverage of the first three doses with a 20% drop-off between the third and fourth dose in four-dose schedules and a 10% drop-off for both dose four and dose five in a five-dose schedule.

SMC with a full treatment course of sulfadoxine–pyrimethamine plus amodiaquine was delivered in the model to children aged 3 months to 5 years at monthly intervals over the peak in the transmission season. Two delivery schedules were considered in this analysis: four month and five month durations of delivery, with doses timed to occur at the seasonal peak in transmission.[18] We modelled efficacy of SMC according to the Weibull survival function in figure 1, with a median duration of protection of 35 days (95% credible interval 28–44; appendix pp 14–15). A secondary efficacy profile was

considered when SMC was combined with SV-RTS,S as a result of the model validation described in the appendix (pp 18–25) and figure 1, and summarised in panel 1. Coverage of 75% was assumed on the basis of coverage rates observed in routine SMC use and coverage was defined as the proportion of eligible children who received all four or five cycles.[19] We did not model the effect of incomplete adherence to the 3-day course. When interventions were delivered in combination, interventions were distributed randomly to individuals in the model. Panel 2 summarises key modelling parameterisations and intervention delivery schedules are summarised in figure 2.

Health systems considerations sensitivity analysis

Within the model framework, we can align delivery of interventions to the peak in malaria transmission in order to maximise effect. To understand each intervention's robustness to delivery challenges, we did a sensitivity analysis by including adjustments in delivery from those identified as optimal (2 months before, 1 month before, 1 month after, and 2 months after; appendix p 27).

Outcome measures

We summarised outputs as cumulative events averted over a 15-year time period. 15 years was chosen to align with previous large-scale modelling exercises of RTS,S and because it is long enough to capture any shifts in cases to older ages as a result of interventions reducing exposure to malaria parasites and hence delaying the development of naturally acquired immunity.[11] We assessed the effect of intervention strategies on clinical cases and deaths from malaria. We reported these health outcomes per 100 000 children aged 0–5 years, and for one-year age groupings from 0 to 20 years of age per 100 000 population. Unless otherwise stated, events averted were calculated relative to a no-vaccine or SMC baseline scenario. Outputs are presented as median estimates from 50 parameter draws.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The introduction of RTS,S, either through age-based delivery or seasonal vaccination campaigns, was predicted to result in a substantial reduction of clinical malaria cases and deaths in settings with seasonal transmission, with the absolute effect of vaccination increasing with higher transmission intensity (figure 3; appendix p 28). SV-RTS,S resulted in a greater reductions of cases and deaths than AB-RTS,S across all endemicity settings in both seasonal and highly seasonal settings over 15 years (figure 3; appendix p 28). Delivering a fifth dose of RTS,S consistently resulted in greater malaria case reductions
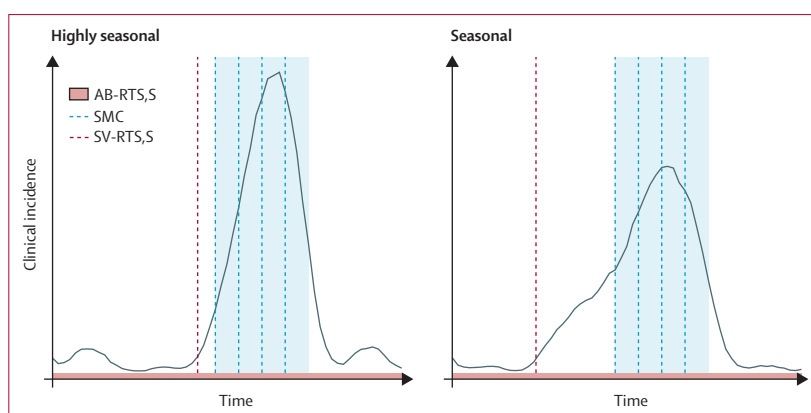

Figure 2: Modelled intervention delivery timings relative to the modelled seasonality in malaria transmission

At any time throughout the year when a child is aged 6 months, 7·5 months, 9 months, and 27 months they will be vaccinated with RTS,S under an age-based regimen represented here by the shaded red bar across the bottom of each plot. SV-RTS,S and SMC dose timings are timed relative to the peak in the malaria transmission season. All children in the population aged 5–17 months before the transmission season will be vaccinated with RTS,S under a seasonally targeted schedule (dashed red line) and then fourth or fifth doses at the same time of year in the following 1–2 years (when children will be aged 17–29 months and 29–41 months depending on their age at the delivery of the primary series). SMC is represented by the dashed blue lines, as four monthly cycles delivered within the period of prophylactic cover represented by the shaded blue area. SMC is delivered to children aged 3–59 months every year. Delivery timings of seasonal interventions were selected to maximise effect relative to the transmission season with ages of interventions informed by previous clinical trials for RTS,S and WHO policy on SMC delivery. AB–RTS,S=age-based vaccination with RTS,S/AS01$_E$. RTS,S=RTS,S/AS01$_E$. SMC=seasonal malaria chemoprevention. SV–RTS,S=seasonal malaria vaccination with RTS,S/AS01$_E$.

than any four dose schedule. Additionally, the efficacy improvements of model 2 substantially increased potential reductions in malaria cases and deaths relative to model 1 (figure 3; appendix p 28). AB-RTS,S was predicted to avert 11 000–80 000 clinical cases (from a total of 74 000–1 020 000 cases without intervention) in children aged 0–5 years, dependent on seasonality and transmission intensity (an 8–15% reduction) whereas SV-RTS,S was predicted to avert 15 000–152 000 cases (a 15–20% reduction) with a four-dose schedule and 17 000–172 000 cases (a 17–23% reduction) with a five-dose schedule, dependent on seasonality, transmission intensity, and the underlying efficacy model (appendix p 28).

Considering the effect of seasonality, the incremental benefit of SV-RTS,S over AB-RTS,S (defined as the proportion of additional events averted with SV-RTS,S *vs* AB-RTS,S) was slightly larger in highly seasonal settings than in seasonal settings. On average, across all baseline $PfPR_{2-10}$ levels (transmission intensity), relative to an age-based strategy in which there was an average of 46 000 cases averted, SV-RTS,S averted an additional 19 000–47 000 (41–102%) cases in children aged 5 years and younger in highly seasonal transmission settings, depending on dose number and efficacy model (data not shown). When considering deaths, compared with the 190 deaths averted on average for AB-RTS,S, SV-RTS,S averted an additional 80–180 (42–94%) deaths in children aged 5 years and younger in highly seasonal transmission settings. In seasonal transmission settings, relative to an age-based strategy in which there was an average of 44 000 cases averted, SV-RTS,S averted an additional

Transmission intensity

Baseline $PfPR_{2-10}$s are 10%, 15%, 20%, 25%, 35%, 45%, 55%, and 65%. We assume that $PfPR_{2-10}$ reflects current rates of insecticide-treated beds, indoor residual spraying, and access to treatment, which remain static following vaccine introduction in all scenarios.

Seasonality

The highly seasonal archetype is based on seasonality patterns in Fatik, Senegal. The seasonal archetype is based on seasonality patterns in Upper East, Ghana.

Demographics

The constant population size and demographic age structure is based on the life table for Tanzania, 2010, with an average life expectancy of 21 years.[13]

Case management

Effective coverage with artemisinin-based combination therapy for clinical malaria at 45%.

Vaccine scenarios

Two main vaccination scenarios are considered:

- AB-RTS,S, in which primary doses given at 6 months, 7·5 months, and 9 months of age with a fourth dose at 27 months of age, to match the schedule delivered in the phase 3b clinical trial.
- SV-RTS,S, in which primary doses are delivered to all children aged 5–17 months in the 3 months preceding the transmission season, with a fourth dose delivered 12 months after the third dose and a fifth dose 24 months after the third dose. A four-dose SV-RTS,S and five-dose SV-RTS,S are considered.

Vaccine efficacy and waning

Model estimates of RTS,S efficacy are based on fitting to the phase 3b trial data, termed model 1.[16] Both vaccination schedules are run assuming this fitted profile. Additionally, given the results of the model validation, several additional changes to the RTS,S efficacy profile are considered for seasonal campaigns to represent uncertainty in the potential vaccine efficacy under this schedule:

- Model 2: improved fourth and fifth dose efficacy, matching that of the third dose.
- Model 3: slight reduction in the rate of decay of RTS,S efficacy when combined with SMC.

Vaccine coverage

80% coverage of the first three doses is assumed with a 20% drop off in coverage of the fourth dose in the four-dose schedule and a 10% drop off for each of the fourth and fifth doses in a five-dose schedule, giving a full vaccine coverage of 64%.

Seasonal malaria chemoprevention

Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine is explicitly modelled when assessing the effect of vaccination and SMC combined. This scenario was modelled as four or five monthly cycles of SMC delivered to children aged from 3 months to 5 years during the peak in transmission season, with a coverage of 75%.[19]

Time period

15 years.

$PfPR_{2-10}$=*Plasmodium falciparum* parasite prevalence rate in children aged 2–10 years old. AB–RTS,S=age-based vaccination with RTS,S/AS01E. SV–RTS,S=seasonal malaria vaccination with RTS,S/AS01E.

14 000–39 000 (32–88%) cases (data not shown). Compared with the 180 deaths averted on average with AB-RTS,S in seasonal transmission settings, SV-RTS,S averted an additional 60–150 (33–83%) deaths.

Stratifying effects by age, we observed a decreasing number of averted cases and deaths with increasing age (between 0 and 20 years; figure 4). This finding was expected as this partly protective malaria intervention could reduce malaria exposure, leading to delays in the development of natural immunity.[20] Therefore, we predict higher relative incidence at older ages resulting in slightly higher numbers of cases in the intervention groups than baseline, shown in figure 4 as negative case reductions for older ages. Despite this prediction, overall cumulative effect of RTS,S on the absolute number of clinical cases and mortality over 15 years remains positive. The higher relative incidence at older ages was delayed with the introduction of a fifth SV-RTS,S dose and was of similar magnitude across all efficacy models and seasonality profiles (figure 4). Despite this finding, the overall cumulative effect of all schedules and efficacy models averted a positive number of cases and deaths over this

15-year time period in all settings. Further, we also found that AB-RTS,S resulted in a greater number of cases and deaths averted in children aged 0–1 years than SV-RTS,S over the 15 years of model simulations (figure 4).

The introduction of RTS,S and SMC was found to have a substantially greater effect than either intervention given alone in seasonal settings. SV-RTS,S plus SMC resulted in a greater number of cases and deaths averted than AB-RTS,S plus SMC across all transmission intensities (figure 3; appendix p 30). Again, we predicted a decreasing number of averted cases and deaths with increasing age that was of a slightly higher magnitude than when only vaccination was modelled (appendix p 33).

We noticed that, when RTS,S was combined with SMC rather than when considered alone, the additional effect of vaccination over SMC was higher in seasonal settings than in highly seasonal settings. On average, in children aged 0–5 years across all baseline $PfPR_{2-10}$ intensities in seasonal settings, relative to the 111 000 cases and 420 deaths averted in children aged 5 years and younger with SMC, the addition of SV-RTS,S was predicted to
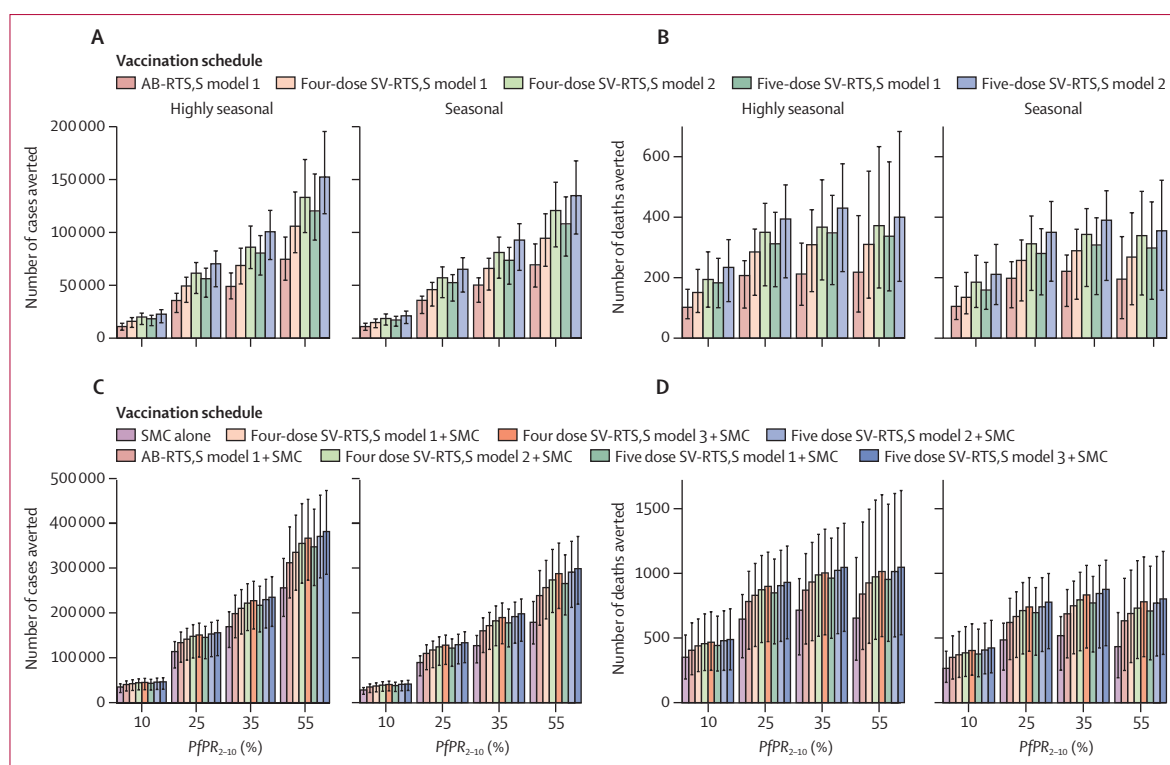
Figure 3: Population effects of different RTS,S vaccination strategies in seasonal settings, including cumulative clinical cases averted (A) and deaths averted (B) over 15 years as a function of baseline $PfPR_{2-10}$ and seasonality in children aged 0–5 years, and reduction in cases (C) and deaths (D) when vaccination schedules are combined with a single therapeutic course of SPAQ delivered every month for four months

Data are shown per 100 000 children. Four settings representative of medium to high transmission intensity (10–55%) are shown. Vaccination coverage is fixed at 80% for the first three doses with a 20% drop off (from the third dose) for the fourth and fifth doses. SMC is at 75% coverage. 95% CIs are shown with the error bars. RTS,S=RTS,S/AS01$_E$. SMC=seasonal malaria chemoprevention. AB–RTS,S=age-based vaccination with RTS,S/AS01$_E$. SV–RTS,S=seasonal malaria vaccination with RTS,S/AS01$_E$. SPAQ=sulfadoxine–pyrimethamine plus amodiaquine.

reduce a further 42 000–67 000 (38–60%) clinical cases and 190–300 (45–71%) deaths, depending on dose number and efficacy model evaluated. In highly seasonal settings, relative to the average 152 000 cases and 590 deaths averted with SMC alone, the addition of SV-RTS,S was predicted to reduce a further 43 000–68 000 (28–45%) cases and 200–290 (34–49%) deaths in children aged 5 years and younger, dependent on dose number and efficacy model evaluated. The incremental effect of AB-RTS,S over SMC was smaller, averting an additional 31 000 (28%) cases and 150 (36%) deaths in seasonal settings and 31 000 (20%) cases and 140 (23%) deaths in highly seasonal settings (data not shown).

As expected with a single therapeutic course of sulfadoxine–pyrimethamine plus amodiaquine once a month for five months in these seasonal settings, the number of cases averted was greater than with the same course once a month for four months (appendix p 33). However, the incremental effect of any RTS,S schedule on top of SMC was reduced as a larger proportion of the peak transmission season was covered by SMC (appendix p 31). Despite these reductions, RTS,S plus SMC still resulted in substantial additional cases of malaria averted compared to SMC alone in these settings. With the model estimating that RTS,S could result in an additional 28 000–64 000 cases averted dependent on schedule, dose number and efficacy model (data not shown).

For countries to adopt and deploy seasonally targeted intervention packages, knowledge of the timing of the annual transmission season is vital. The effect of SMC was highly sensitive to modelled changes in delivery relative to the peak in transmission (appendix pp 34–35). This sensitivity can make operational deployment of SMC challenging due to annual fluctuations in the wet season and the consequent logistical or supply issues. SV-RTS,S, however, was more robust to modelled changes in delivery (appendix pp 34–35), and losses in health gains were not as large as they were with SMC. Therefore, when combined with SV-RTS,S the overall sensitivity of SMC was reduced (appendix pp 34–35). Given that RTS,S delivery through an age-based schedule is not reliant on calendar time, age-based delivery also mitigated some of the effects of misalignment of SMC delivery (appendix pp 34–35).

Discussion

Results from our modelling study show that RTS,S vaccination alone and, to a greater extent, when
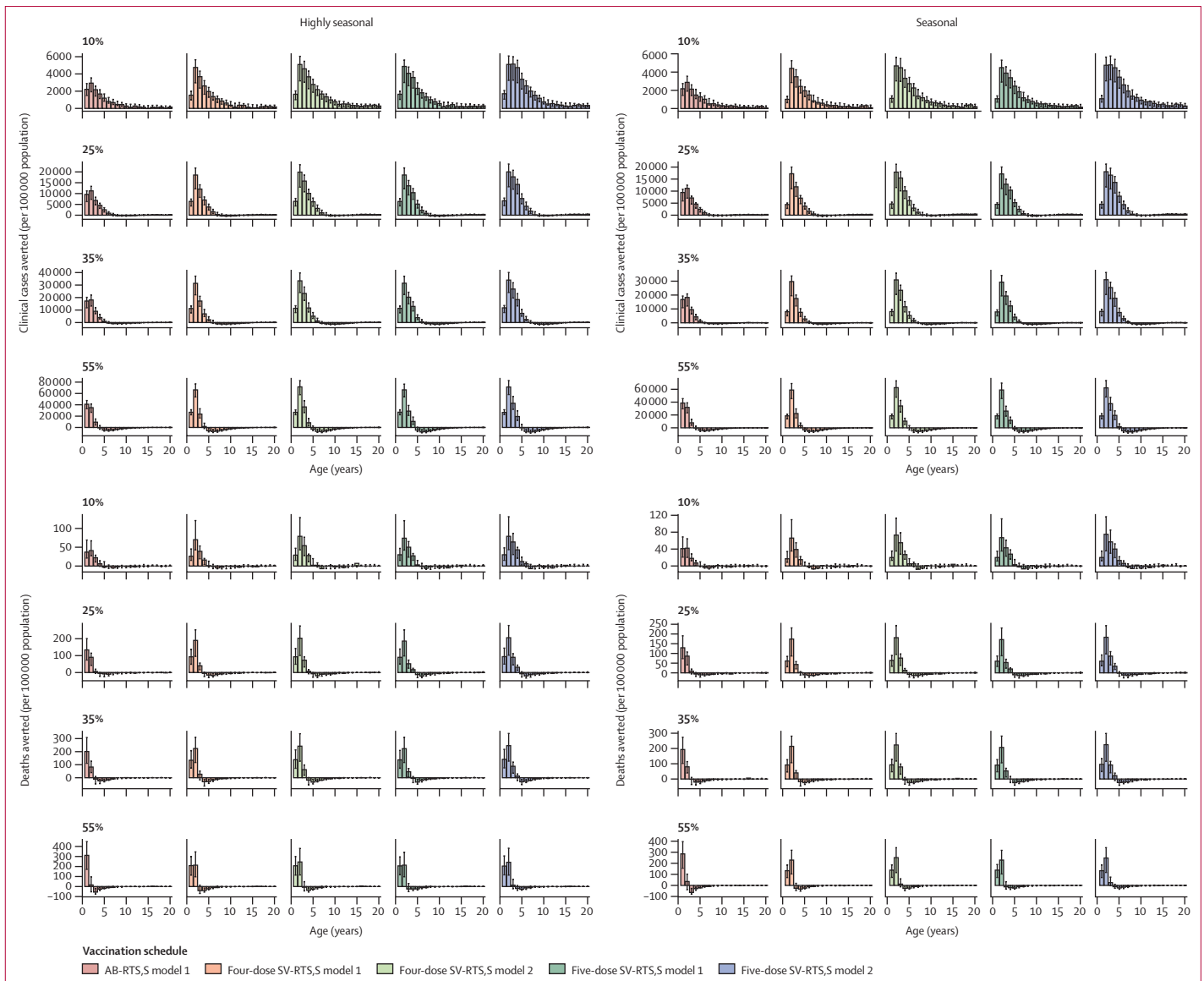
Figure 4: Cumulative number of clinical cases and deaths averted over 15 years as a result of different RTS,S vaccination strategies for individuals aged 0–20 years in 1-year age bands
The total cases averted are shown per 100 000 population for both seasonality settings. Results are presented for four baseline PfPR$_{2-10}$ settings representative of medium to high transmission intensity (10–55%). RTS,S=RTS,S/AS01$_E$. AB–RTS,S=age-based vaccination with RTS,S/AS01$_E$. SV–RTS,S=seasonal malaria vaccination with RTS,S/AS01$_E$. PfPR$_{2-10}$=Plasmodium falciparum parasite prevalence rate in children 2–10 years old.

combined with SMC could have a substantial positive effect in areas with seasonal malaria transmission when delivered at scale. Seasonally targeting RTS,S with a four-dose or five-dose schedule consistently resulted in greater predicted reductions in cases and deaths than age-based delivery at equivalent levels of coverage. However, the predicted superiority of SV-RTS,S over AB-RTS,S was reduced when vaccination was combined with SMC. SMC is widely used, having reached approximately 33·5 million children in 2020, and is a highly effective and key intervention in the Sahel region.[1] Our modelling results, along with those from the recent clinical trials, highlight the substantial

additional effect that RTS,S could have when given with SMC in these settings.[9,21]

Our results suggest that SV-RTS,S should not replace SMC as a control intervention despite the findings of non-inferiority from the clinical trial.[9] Interventions in the trial setting were delivered to children of a restricted age range, by which both SMC and RTS,S could be administered and compared. However, when considered outside of trial cohorts, SMC is delivered annually to children aged 3 months to 5 years and SV-RTS,S is delivered annually from age 5 months up to approximately 30–45 months. This sustained delivery and the higher per-month efficacy of SMC than SV-RTS,S resulted in

greater burden reductions at the population level than SV-RTS,S.

The additional effect of RTS,S when combined with SMC was driven by the protection provided by RTS,S outside the SMC target window alongside increased protection during the transmission season. The former aspect leads to a more prominent effect of vaccination in settings with a longer seasonal transmission season where malaria burden is more uniformly spread over 7–8 months. In these settings, even when a single therapeutic course of sulfadoxine–pyrimethamine plus amodiaquine once a month for five months was being considered, the additional effect of SV-RTS,S in addition to SMC was substantial, averting up to 64 000 more clinical cases per 100 000 population than SMC alone. Conversely, when comparing vaccination schedules in the absence of SMC, the incremental benefit of SV-RTS,S over AB-RTS,S was greater in highly seasonal settings than seasonal settings due to the burden of malaria being concentrated in a shorter period. Given these results, seasonality is an important determinant of vaccination schedule effect in these settings alongside whether SMC is deployed or not.

Crucially for countries considering RTS,S adoption, the potential achievable coverage of each schedule will probably be an important determinant. For example, if other routine Expanded Programme on Immunization vaccine coverage levels are low, but SMC or historical campaign vaccination coverage is high, seasonal vaccination campaigns will probably have the greatest effect in that setting compared with low coverage up-take through age-based immunisation (and vice versa). Further to this, vaccine demand could outstrip initial supply and it will be vital to understand where and how to prioritise RTS,S, dependent on endemicity, seasonality, use of current interventions and their potential scale-up, and population growth in different settings. Previous modelling work has highlighted that subnational allocation of AB-RTS,S would maximise overall public health benefit if targeted to countries with the highest incidence—particularly countries in the Sahel region.[22] Given the potential for SV-RTS,S to have a greater public health effect than AB-RTS,S, further modelling work is needed to understand how the scarcely available doses can best be geographically allocated given this new mode of delivery and how the specific rates of SMC coverage in the Sahel region will influence this prioritisation in particular. Furthermore, with the R21 malaria vaccine (R21 Matrix/M, University of Oxford, Oxford, UK and Serum Institute of India, Pune, India) reaching late-stage clinical trials and showing promising efficacy results, the licensure of a second malaria vaccine will be a further important consideration for future allocation strategies.[23]

A further operational consideration highlighted by this work is the relative robustness of SV-RTS,S above that of SMC to fluctuations in the start of the transmission season. The relatively short duration of protection provided by each monthly SMC course means that potential case reductions are highly sensitive to optimised delivery. Along with the associated public health gains of combining RTS,S with SMC, this combined delivery also enhances the robustness of SMC. Given the threat of climate change affecting weather patterns across sub-Saharan Africa, flexible intervention packages that can adapt to fluctuations or changes in seasonality patterns are, and will be, vital.[24–26]

Importantly, coverage and uptake of different RTS,S vaccination schedules and SMC will also be determined by caregiver attitudes and acceptance of different interventions. Ongoing research into the acceptability of SV-RTS,S in the phase 3b trial communities is ongoing. Additionally, a further operational consideration for countries is that vaccination, once delivered, does not depend on caregiver or child behaviours, unlike SMC, which relies on adherence to the 3-day course of anti-malarials. Poor adherence could lead to subtherapeutic drug concentrations, increasing the risk of malaria and development of drug resistance and reducing the protective effectiveness of SMC.

There are several limitations to this work. First, modelling results are presented for a variety of SV-RTS,S and SMC efficacy profiles, due to the discrepancies between the trial and model results. Our results are therefore indicative of the potential levels of impact in these settings given current limitations in our understanding of SV-RTS,S efficacy over time. Further work is needed to characterise any immunological alterations that could potentially drive the improvements in efficacy of SV-RTS,S relative to the original dosing schedule. Secondly, it will be important to consider the cost-effectiveness of these different RTS,S vaccination strategies alone and in combination with SMC in future work given the scarce resources available for malaria control programmes. However, this consideration is outside the remit of this work because the associated costs of SV-RTS,S delivery are not yet available. Further, results are presented for a variety of generic malaria transmission settings, assuming constant coverage of vector control, access to treatment, and RTS,S and SMC coverage that are not scaled up over time. Although this is a large assumption, we wanted to understand the effect of seasonal interventions in isolation. Further modelling work that incorporates subnational variations in malaria epidemiology, coverage of interventions, and resistance to vector control will be important in helping countries to understand the best RTS,S vaccination strategy moving forwards. Although these changes will affect the potential absolute burden reductions, we expect the relative ranking of different vaccination strategies to remain consistent as was shown in the supplementary sensitivity analysis to baseline rates of treatment coverage. Finally, as was shown with the initial evaluation of the long-term effects of RTS,S and in the evaluation of mass drug administration programmes, it is beneficial to combine the predictions of different mathematical models to assess whether the same recommendations are made.[11,27] Combining

predictions in this way allows for differences in model assumptions and parameterisations of interventions to be brought within a single framework. Although the uncertainty in the underlying transmission model was accounted for in this work, future policy-relevant modelling of malaria vaccines should aim for consensus modelling approaches to improve our understanding of effects in light of different model assumptions.

Overall, this work along with the clinical trial results show that RTS,S vaccination in seasonal transmission settings could be a valuable tool to add to existing seasonal interventions. Results of the trial and modelling suggest that RTS,S should not replace SMC where it is already implemented, but that it can have substantial health benefits when combined with SMC or could be introduced in seasonal settings where SMC is currently not implemented because resistance to sulfadoxine–pyrimethamine plus amodiaquine is high. Decisions surrounding deployment strategies of RTS,S in seasonal settings will need to consider the local and regional variations in seasonality, current rates of interventions, and potential achievable RTS,S coverage.

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