



MALARIA PREVENTION

**SHAPING NEXT-GEN MEDICAL
INTERVENTIONS**

iTPP3 OUTCOMES REPORT

**NEXT-GENERATION SEASONAL
MALARIA CHEMOPREVENTION**

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EXTENDED EXECUTIVE SUMMARY

This report presents quantitative evidence for the Bill and Melinda Gates Foundation's interventional Target Product Profile (iTTP) criteria for next-generation Seasonal Malaria Chemoprevention (SMC). The iTTP guides development of new SMC oral drugs for a malaria intervention, deployed to children at monthly intervals in highly seasonal settings with intense malaria transmission. Next-generation SMC is intended to prevent resistance experienced to existing SMC, and aims to provide children with protection against infection throughout the malaria season through multiple rounds of deployment. Novel SMC interventions are in early stages of development and it is not yet known which intervention properties will prove most critical for greatest public health benefit.

Through a combination of stakeholder engagement and analytic approaches using detailed malaria transmission models of intervention dynamics (Figure 1), we present initial evidence-informed recommendations for updating the Bill and Melinda Gates Foundation's iTTP3's development criteria. These recommendations are based on a breadth of analyses from a range of modelled scenarios, examining and linking key 'performance characteristics' to the related public health impact expected from next-generation SMC. The scenarios and questions addressed are informed by stakeholders and extensive literature reviews of both antimalarial drug characteristics and SMC modelling studies, and include: a range of seasonality profiles and malaria prevalence levels, multiple levels of access to treatment and SMC coverage, various deployment strategies in terms of the target population and number of rounds of SMC, and a broad range of intervention properties, including efficacy and duration of protection.

The full report provides suggested edits to the iTTP criteria based on the key recommendations and key results below.

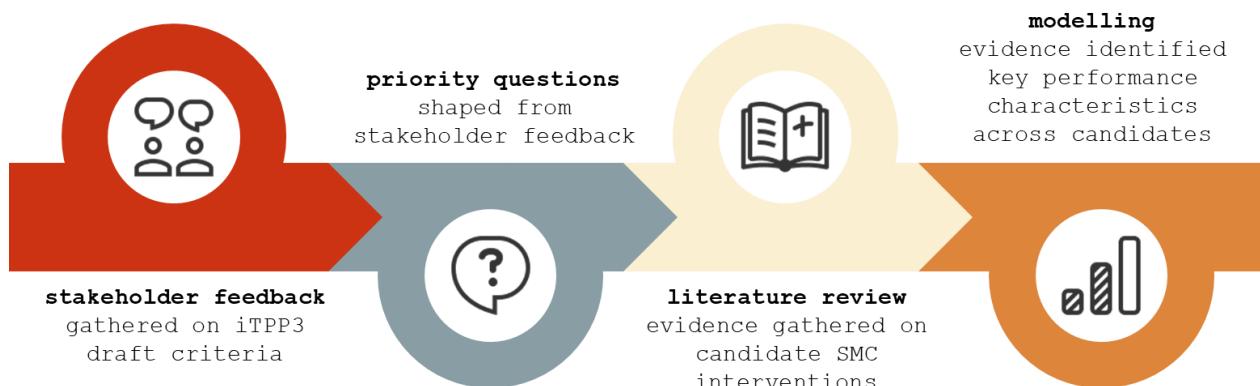


Figure 1. Summary of sources of evidence

KEY RECOMMENDATIONS FOR iTTP3: NEXT-GENERATION SMC

RECOMMENDATION ONE: Clearly specify SMC efficacy targets and mode of action criteria. Both the meaning of and criteria for clinical efficacy, as well as targets of preventative efficacy and prevention of infection, should be clearly defined in the iTTP's base and upside indication criteria. The iTTP should also specify the evaluation period, the efficacy metric and in which phase of product development efficacy evidence should be generated. Our modelling supports recommended target prevalence reductions for SMC (equivalent to sulfadoxine-pyrimethamine and amodiaquine, SP+AQ) of 80% and 85% for the base and upside case respectively. For clinical incidence, we recommend base case target reductions of approximately: 55% for very high transmission settings (baseline $PfPR_{2-10}$ greater than 50%); 60% for moderate to high transmission (baseline $PfPR_{2-10}$ between 30% and 50%), and; 65% for low to moderate transmission (baseline $PfPR_{2-10}$ between 10% and 30%) to demonstrate equivalence to SP+AQ. For upside case target reductions, we recommend equivalence to SP+AQ +5%.

RECOMMENDATION TWO: Generate evidence of key drug characteristics for both first- and next-generation SMC candidates, including efficacy and duration of chemoprotection at both the blood and liver stages. Our modelling shows that the prophylaxis period is one of the most important properties influencing burden reduction from SMC. To select useful next-generation SMC candidates and to assess non-inferiority or superiority, it is crucial to address knowledge gaps surrounding clinical efficacy profiles for first-generation candidates such as SP+AQ and dihydroartemisinin and piperaquine (DHA+PPQ). Partners should be supported to generate a solid evidence base for SP+AQ's mechanism of action and pharmacokinetics/pharmacodynamics profile, as the efficacy of new interventions will be compared with this standard of care for SMC.

For next-generation SMC candidates, evidence of an intervention's duration of activity against *Plasmodium falciparum* activity will be critical to assessing if adequate burden control in seasonal settings will be achieved. A complete understanding of the intervention's time-course at both the blood and liver stages should be pursued. Protection longer than 28 days should be prioritized for development to achieve a five-month clinical incidence and severe disease reduction greater than 70%, particularly in settings where the number of monthly SMC rounds does not cover the entire high-transmission season.

RECOMMENDATION THREE: Generate evidence for an SMC intervention's likely achievable coverage. Modelling results indicate that the proportion of children reached by an SMC program is the most important determinant of impact for a next-generation intervention. This highlights the need to look beyond an intervention's clinical performance to evaluate its likely effectiveness. Product characteristics likely to improve an intervention's coverage, such as a single dosing regimen, favorable safety profiles and a pediatric formulation, should be optimized in parallel to the intervention's efficacy and duration of protection. Community access and acceptance should also be addressed through community engagement as they will be key to improving coverage.

KEY FINDINGS FOR iTPP3

Epidemiological outcomes for SMC

In June 2021, stakeholders including funders, researchers, product developers, implementation specialists and global health representatives, identified that a reduction in uncomplicated malaria is the key public health outcome of interest for SMC. While specific reduction targets for this and other epidemiological outcomes have not yet been specified, modelling evidence provides guidance on the likely burden reduction for a range of SMC performance characteristics under various scenarios. For reference, we have modelled next-generation SMC as a short-acting blood stage drug with a five-day duration in combination with longer acting chemoprotection against liver stage parasites (based on a previous analysis [1]). We also confirmed these results by modelling next-generation SMC as an efficacious, long-acting blood stage drug.

Clinical efficacy profile

Duration of protection

We found that the duration of the intervention's prophylaxis period is one of the most important properties for achieving adequate burden reduction in seasonal settings. Generating clinical evidence of the intervention's duration of protection at the parasite blood and liver stages is critical to understanding its potential for impact. In particular, there is a need to address knowledge gaps surrounding the prophylaxis period for first-generation SMC; a strong clinical evidence base is lacking for both SP+AQ's and DHA+PPQ's duration of protection, limiting our ability to compare the efficacy of a new intervention to standard of care.

Modelling evidence confirms that, for adequate burden control across a range of seasonal settings, an intervention should aim to provide as much protection as possible over the four weeks between rounds of SMC, especially if initial efficacy is less than 80%. For example, to achieve a five-month clinical incidence and severe disease reduction greater than 70%, an intervention's duration of protection should be greater than 28 days (Figure 2).

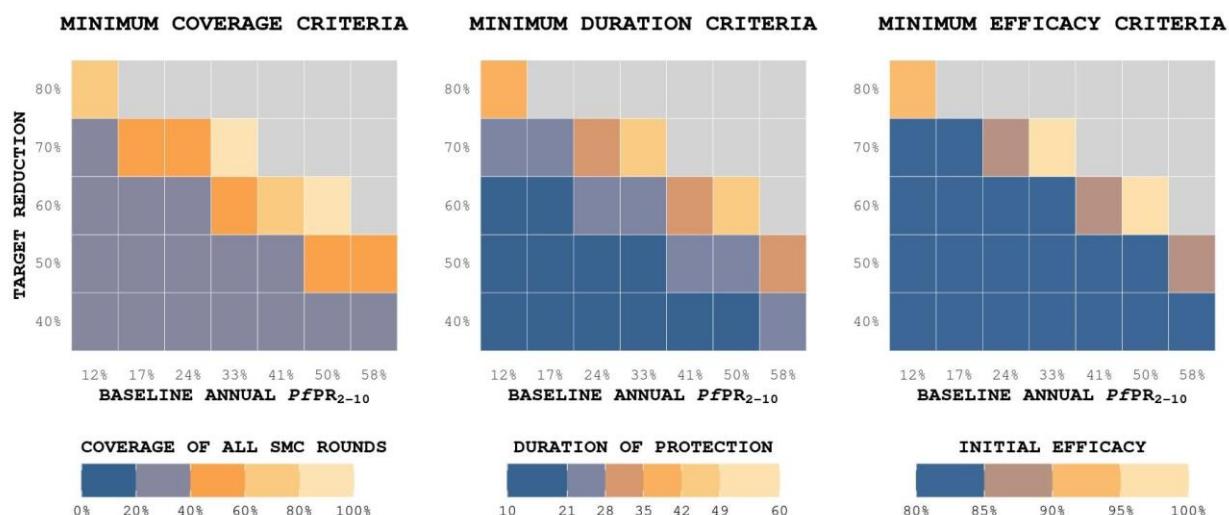


Figure 2. Summary of the predicted minimum performance criteria for next-generation SMC towards achieving a target clinical incidence and severe disease reduction across SMC deployments and target populations compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum values for each key performance characteristic required to achieve a given target reduction in clinical incidence and severe disease (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. This minimum is then aggregated by calculating the most conservative (maximum) criteria across outcomes (clinical incidence and severe disease reduction), SMC deployments (three, four and five rounds of SMC), and target populations (children aged three to 59 months, and three to 119 months). Results are shown for a five-month seasonal profile in a setting with high access to treatment, where the intervention is modelled as a drug with liver stage chemoprotection. See Section A.1 for the full range of modelled scenarios.

Results show that **a longer duration of protection leads to greater impact**, particularly in settings where the number of rounds of SMC does not cover the malaria season's length or when coverage decreases between rounds. For example, for the annual baseline $PfPR_{2-10}$ of 26% (moderate transmission) and for SMC deployment with a moderate level of coverage shown in Figure 3, an intervention with a duration of protection of 28 days and initial efficacy of more than 80% is likely to achieve a less than 55% reduction (calculated over five months) in clinical incidence in children between three and 59 months of age. An intervention with a 35-day duration of protection with initial efficacy of more than 80%, however, is predicted to achieve up to a 60% reduction in clinical incidence over a five-month period.

Duration requirements decrease in lower transmission settings. For example, an up to 55% clinical incidence reduction can be achieved with a duration of less than 28 days when baseline $PfPR_{2-10}$ is less than 25% (low to moderate transmission, Figure 3). An intervention's duration of protection is equally as critical for achieving burden reduction when targeting different populations (children aged three to 59 months and three to 119 months) and for different numbers of rounds of SMC.

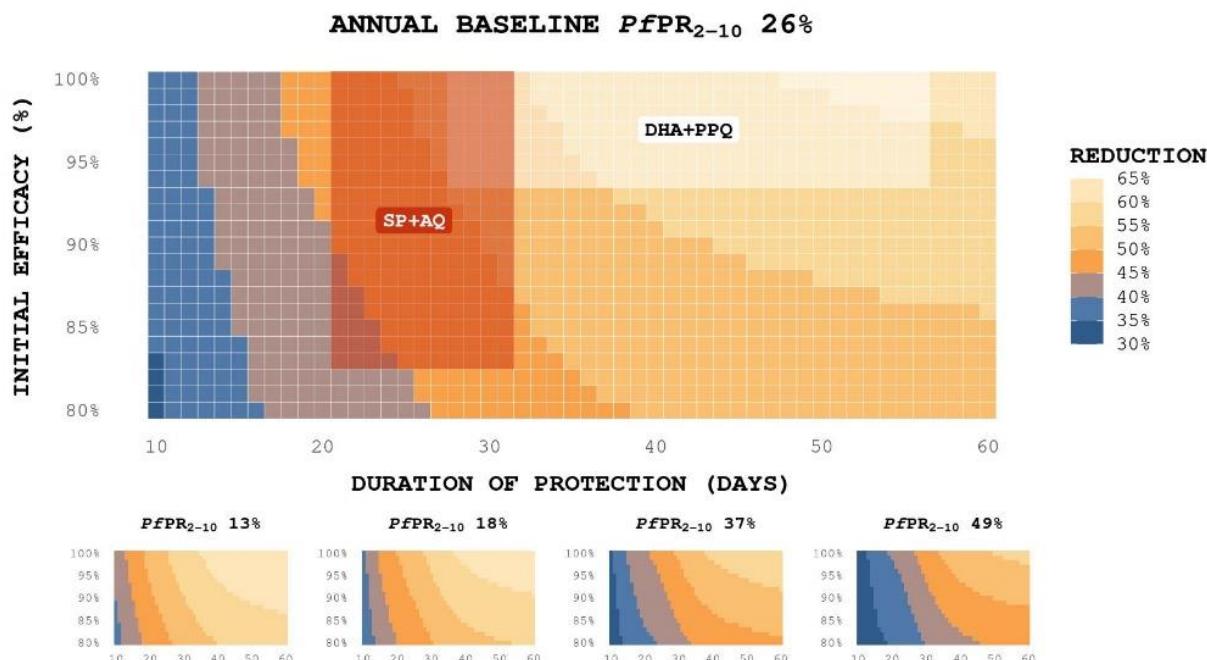


Figure 3. Predicted relative reduction in clinical incidence from SMC, measured in implementation settings compared to a no-intervention counterfactual. Each square in the grid indicates the predicted percentage reduction in clinical incidence over a five month intervention period if an intervention with the given initial efficacy and duration of chemoprotection were deployed. The intervention is modelled as a drug with liver stage chemoprotection (based on a previous analysis [1]). The highlighted red and cream segments indicate the likely range of outcomes for SP+AQ- and DHA+PPQ-like interventions, 40% to 55% and 50% to 65% reduction respectively. Results are shown for children aged three to 59 months who reside in a setting with a six-month seasonal profile, where access to treatment is high and where SMC is deployed four times a year at monthly intervals with a program coverage of 95% and round coverage of 85%, corresponding to a 50% likelihood that a child receives all four rounds of SMC. Each lower panel represents results for a different annual baseline $PfPR_{2-10}$. For guidance on interpreting this figure, refer to Section 8.3.

Initial chemoprotection efficacy

Modelling evidence suggests that **an intervention's initial liver or blood stage activity is a less important driver of burden reduction than the intervention's protection duration**. Our analysis of trade-offs between performance characteristics indicates that increasing duration is more important than focusing on increasing initial efficacy, provided the intervention's liver stage efficacy is greater than the minimum modelled value of 80% (Figure 4). While these results indicate that efficacy properties are lower-priority performance characteristics, **care should be taken to clearly specify the efficacy criteria for iTPP3's base and upside case and, in particular, should define a clear evaluation period and outcome measure**.

SMC coverage

Modelling confirms that, of the key performance properties evaluated in this study, **the proportion of children reached by an SMC program is the most important determinant of impact for a next-generation intervention**. As coverage increases, a larger impact on SMC's ability to reduce the burden of both clinical cases and severe malaria in children is predicted (Figure 4). Modelling also illustrates trade-offs between coverage and product characteristics; in a moderate transmission setting with 26% $PfPR_{2-10}$, where SMC is deployed four times annually in monthly intervals to children aged three to 59 months, an intervention with 90% initial efficacy and with a duration of protection of 21 days is predicted to achieve a 40% to 45% reduction in severe disease when the likelihood that a child receives all rounds of SMC is 44% (Figure 5.3.3.2). Deploying the same intervention with a higher coverage of 50% could lead to an increase in the expected severe disease reduction of up to 10%. Thus, increasing the number of children reached, by reducing the number of doses required, improving safety beyond that of the standard of care or improving community acceptability, may lead to greater burden reduction than improving an intervention's initial clinical efficacy.

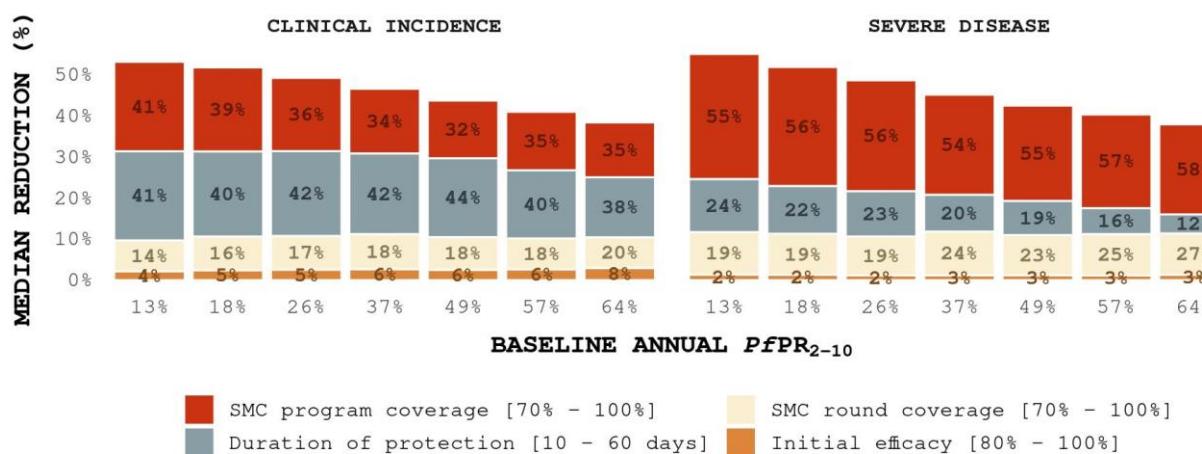


Figure 4. Drivers of impact on predicted levels of reduction of clinical incidence and severe disease for an SMC program in children aged three to 59 months, measured in implementation settings in comparison to the counterfactual of no intervention. Bars indicate the total Sobol effect indices (explaining the variance in predictions) for each of the four key performance properties – program coverage (70% to 100%), round coverage (70% to 100%), duration of protection (10 to 60 days) and initial efficacy (80% to 100%) – for an intervention modelled as a drug with liver stage chemoprotection. These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across prevalence settings (x-axis, annual baseline $PfPR_{2-10}$) for one archetypal scenario: high access to treatment with a six-month seasonal profile, where SMC is deployed in monthly intervals four times a year. For guidance on understanding this figure, refer to Section 8.2.

Target population

Modelling results indicate that **key performance characteristics of next-generation SMC are similar for children aged three to 59 months old, and children aged three to 119 months old**. SMC coverage remains the most important driver of impact for both target populations, followed by the intervention's duration of protection. A recent modelling study by Masserey et al. (available in Appendix A.5) suggests we may, however, expect an increased spread of partial sulfadoxine-pyrimethamine resistance when SMC is extended to children between three and 119 months. Despite this, the modelling also suggests that even with partial SP resistance (quintuple mutations with SP prophylaxis of less than 21 days), SP+AQ delivered as SMC is likely to remain effective at averting clinical disease, albeit at slightly lower levels. Evidence of a next-generation drug's ability to kill partially SP-resistant parasites, combined with a prophylaxis period longer than partially resistant SP, will be critical for both age groups targeted.

Access to treatment

In scenarios where clinical cases have less access to treatment, SMC coverage is the main driver of the intervention's impact; efficacy properties play a greater role when access to treatment is high. As a result, modelling shows that **reaching more children by optimizing an intervention's implementation or coverage is particularly important in settings where access to treatment for malaria is limited**.

INTRODUCTION

Novel seasonal interventions are needed to provide children with protection from malaria. Seasonal Malaria Chemoprevention, known as SMC, is a cornerstone of malaria control in regions with seasonal, intense malaria transmission. This intervention is deployed to children at monthly intervals and provides protection against new infections for the duration of the malaria season. However, resistance to sulfadoxine-pyrimethamine (SP), which in combination with amodiaquine (AQ) is the current standard of care for SMC, threatens the effectiveness of this important intervention [2, 3]. Alternative interventions are needed.

A clinical pipeline of novel SMC interventions is currently being developed and tested. The Bill and Melinda Gates Foundation, World Health Organisation (WHO) and Medicines for Malaria Venture (MMV) have proposed a three-pillar strategy for development:



Pillar One, 2020-2024: Re-purpose existing, first-generation drugs for SMC.

Pillar Two, 2024-2029: Re-combine existing, first-generation drugs for a novel tool.

Pillar Three, 2030+: Develop new, next-generation interventions for SMC.

A number of candidates have been shortlisted for this purpose (Figure 5). However, in these early stages of product development, we are uncertain as to which intervention characteristics will be critical for determining SMC's public health impact in implementation. Evidence-informed guidance is necessary to ensure that funders and developers prioritize those candidates most likely to be effective.

Modelling evidence can provide guidance to refine next-generation seasonal interventional Target Product Profiles (iTTPPs) for SMC. Through the combination of stakeholder engagement and established techniques from malaria transmission modelling, we present initial recommendations for updating each of the BMFG's iTPP3's criteria¹. The evidence presented in this report is based on four sources of information:



Stakeholder Feedback: In June 2021, our convening *Malaria Prevention: Shaping Next-Gen Medical Interventions* brought together experts to discuss target product profiles for *Plasmodium falciparum* malaria prevention. The draft iTPP3 criteria were reviewed with experts in global health and implementation, malaria program funding and research and development.



Priority Questions: Feedback from stakeholders was used to shape research questions for iTPP3, which formed the basis of evidence generation (see Appendix A.4).



Literature Review: We reviewed available evidence for candidate SMC regimens to identify known properties: the likely mechanism of action, dosing regimen, efficacy, prophylaxis period, coverage, synergisms and antagonisms, and the presence of resistance.



Modelling Evidence: An individual-based, stochastic model for malaria transmission was used to simulate public health outcomes for a generic SMC intervention over a range of scenarios. By modelling a generic drug with a range of performance characteristics, including efficacy and duration, we could map results back to the pharmacokinetics and pharmacodynamics of existing or new candidates (Figure 4). From this, we identified the relative importance of initial efficacy, duration of protection and coverage in determining the intervention's likely burden reduction. Following this evidence, we used modelling to identify the plausible range of property values for a chemoprevention intervention to achieve higher burden reduction.

Together, this body of evidence supports a first round of suggested updates to iTPP3.



Figure 5. Seasonal Malaria Chemoprevention candidate interventions.

¹ Document version 20210913-v0.2.

SCENARIO, INTERVENTION AND OUTCOME ASSUMPTIONS

Over the past ten years, modellers have used a range of approaches to explore the likely impact of SMC with SP+AQ beyond that observed in clinical trials, built on a range of assumptions about the intervention's likely mechanism of action. Many early efforts to model SMC [4-6] link back to Okell and colleagues' pharmacodynamics chemoprotection model [7], which assumes that treatment acts to reduce the likelihood of establishing blood stage infection. More recent cost-effectiveness modelling [8-10], while unclear in specifying how the effects of SMC are captured, are likely to have followed a simplified approach – calibrated to clinical data [11] – by modelling drug pharmacokinetics and pharmacodynamics as a protective effect over time. In 2015, Pemberton-Ross and colleagues similarly modelled SP+AQ's action as a prophylactic effect against infection over time [12]. This model for SP+AQ was recently updated by Burgert et al. [1], who calibrated a model for the drug combination's time-course to the same clinical trial data as used in [4-6]. Each of these approaches models the combined impact of SP+AQ as a single intervention, as opposed to a combination of two separate drugs, recognising that its prophylactic effect is driven primarily by the longer-acting drug SP.

Following early efforts to model SMC, three very different approaches to modelling SMC we developed. However, these approaches either did not capture effect decay over time or did not offer a model for SP+AQ, SMC's standard of care. In 2017, Hamilton and colleagues modelled the protective effect of SMC without decay, as blood stage parasite clearance for ten days following the intervention's administration [13]. In 2018 and 2019, Selvaraj et al made use of the EMOD model to explore the impact of SMC with DHA+PPQ [14, 15]. While the assumptions behind this intervention are, again, not clearly specified, the authors link to Gerardin et al's model for the impact of a drug on asexual parasite concentration [16]. Finally, diverging from earlier approaches to modelling SMC, Sauboin et al modelled SMC's impact as a direct reduction in the force of infection [17].

To explore next-generation SMC's impact across a range of likely scenarios, we build on this body of work by using an established, individual-based malaria transmission model coupled with a model of intervention dynamics and effects based on Burgert et al's recent calibration of SP+AQ [1], the SMC standard-of-care. To capture next-generation SMC's likely protective effect, we model the intervention's pharmacokinetics and pharmacodynamics as a probability of preventing liver stage infection that decays over time, in combination with five days of blood stage parasite clearance from the time of administration, referred to in this report as next-generation SMC with **liver stage chemoprotection**. This model has two key parameters: duration of protection, driven by the drug's concentration half-life and half maximal inhibitory concentration (IC₅₀), and; initial probability of preventing infection, driven by the drug's maximal effect (Emax) (Figure 6, Table 8.4). By modelling the intervention's prophylactic effect over time, we can translate a drug's pharmacokinetics or pharmacodynamics to its likely public health impact. As the likely efficacy and duration of protection of new oral SMC are not known, we model a range of likely values for these key characteristics. A range of possible deployment rounds are also modelled (three, four or five rounds of SMC, summarized in Figure 7), as well as varying levels of SMC coverage.

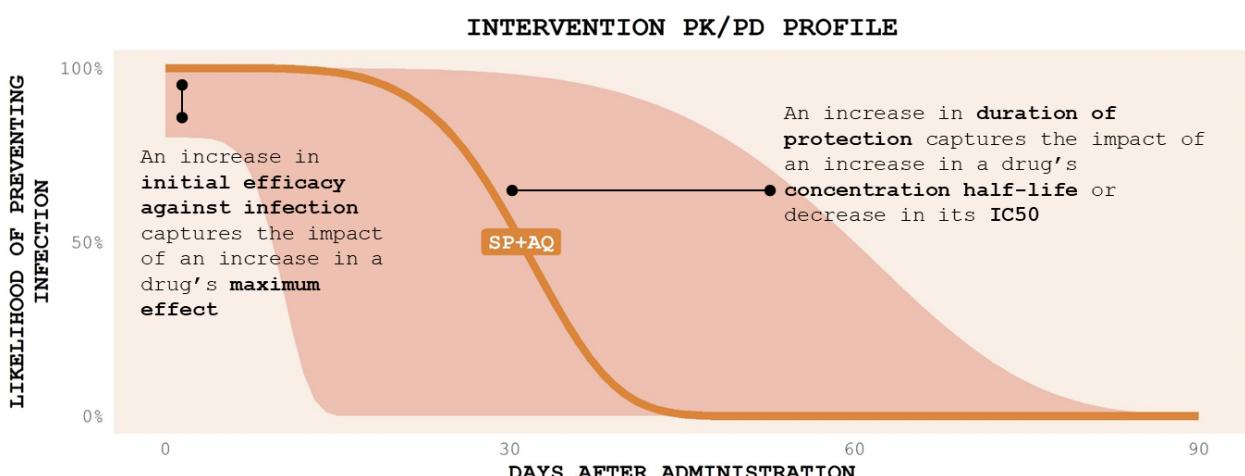


Figure 6. Schematic diagram of modelling assumptions for next-generation SMC's prophylactic effect. SMC is modelled as a drug with **liver stage chemoprotection**, a highly efficacious liver stage drug with a probability of preventing infection that decays over time (shaded region) in combination with five days of blood stage parasite clearance from the time of administration.

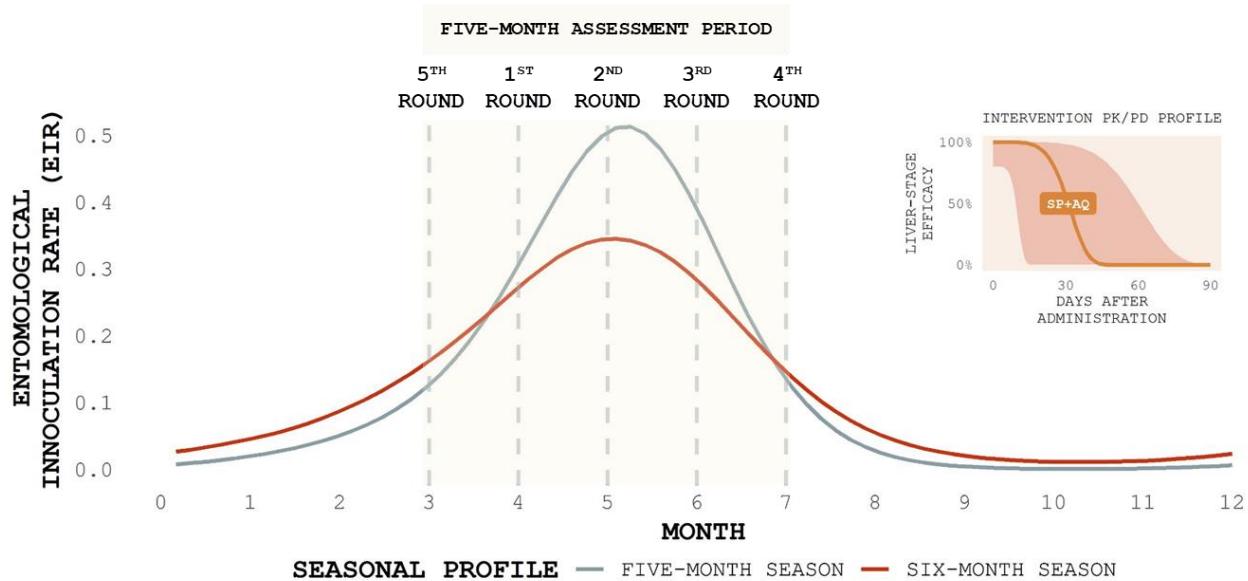


Figure 7. Schematic diagram representing the number of rounds and decay of the modelled next-generation SMC. SMC is modelled primarily as a drug with liver stage chemoprotection, with a range of decay profiles represented by the shaded region in the top right panel. SMC is deployed in three, four or five monthly rounds, starting one month prior to peak malaria transmission or, in the case of five rounds of SMC, two months prior to peak transmission. All public health outcomes are assessed over the same, five-month intervention period. Two types of seasonality are explored, a six-month and five-month seasonal profile, with approximately 70% of new cases occurring in six and five months, respectively.

In a second modelling step, using an individual-based malaria transmission model combined with a full PK/PD model, we explored outcomes for an SMC intervention with **blood stage chemoprotection**. In line with previous efforts to model SMC, our approach to modelling SMC assumes that a next-generation's activity is predominantly against liver stage parasites. However, the mechanism of action of both first- and next-generation interventions has yet to be fully understood, and SMC drug candidates may also have activity against blood stage parasites. As a result, modelers should also seek to understand the likely impact of an intervention with blood stage or mixed liver and blood stage activity. Following a first round of evidence generation, we explored the drivers of impact and key performance characteristics for an intervention with dominant activity against blood stage parasites. For reference, this intervention's effect was modelled as the rate at which a drug kills blood stage parasites, captured with a one-compartment PK/PD model without absorption or conversion, with a piperaquine-like treatment schedule and with varying concentration half-life (five to 40 days), maximum parasite killing rate (E_{max} , two to 30 units) and PD slope (one to eight). An important step for future modelling work will then be to explore likely public health outcomes for next-generation SMC candidates with both blood and liver stage activity (Figure 8).

All modelling results are analyzed across a range of scenarios, where each scenario consists of a unique combination of the different settings summarized in Table 1. By analyzing a range of scenarios, we capture a range of dynamics across the complexity of malaria-endemic geographies and health systems. Public health outcomes are evaluated over the same five-month intervention period regardless of the number of rounds of SMC deployed, chosen to enable comparison across deployments. As a result, the reported level of reduction may be lower than observed in clinical or observational studies, where the evaluation period is often matched to the number of months in which SMC is deployed. Detailed definitions of intervention properties and outcomes are available in Table 8.4.

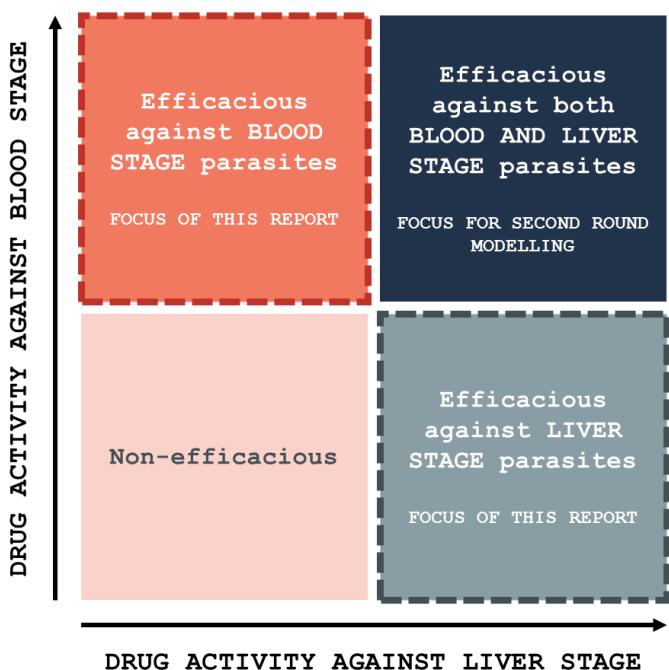


Figure 8. Overview of likely drug activity for first- and next-generation SMC. First- and next-generation drugs for SMC are expected to be efficacious against blood or liver stage malaria parasites, or both. Modelling results in this report focus on the outlined quadrants: interventions with blood and liver stage chemoprotection.

TABLE OF SCENARIO AND INTERVENTION ASSUMPTIONS

Term	Scenario
Access to Treatment	Results for two levels of health system access for 1 st line treatment of malaria are captured: <ul style="list-style-type: none"> A low probability of seeking care for clinical illness (10% over 14 days). A high probability of seeking care for clinical illness (50% over 14 days).
Seasonality	Differences in SMC's performance are captured across types of seasonal transmission by reporting results for two archetypal seasonal profiles: <ul style="list-style-type: none"> A Senegal-like season where approximately 70% of cases occur within five months. A Mali-like season where approximately 70% of cases occur within six months.
Setting	We capture differences between SMC's likely impact in phase two and three clinical trials in comparison to post-market implementation studies with two modelled settings: <ul style="list-style-type: none"> Clinical trial setting: A high level of case management (50% probability of seeking care over 14 days) with high SMC coverage (95% program and 100% round coverage, corresponding to an 81% likelihood that a child receives all rounds of SMC when four rounds are deployed). Implementation setting: A range of levels of case management and coverages.
SMC Coverage	A range of operational coverages of SMC are modelled, where coverage is specified with two different approaches: <ul style="list-style-type: none"> Program coverage, the operational coverage of SMC in a given population, ranging from 70% to 100% of eligible children receiving SMC. Round coverage, the operational coverage of a single round of SMC in a given population, ranging from 70% to 100%. In combination, the two forms of coverage determine the likelihood that an eligible child receives all or no rounds of SMC. For example, if program coverage is 95% and round coverage is 85% and four rounds of SMC are deployed: <ul style="list-style-type: none"> The probability that a child receives all rounds of SMC is approximately 50%. The probability that a child receives no round of SMC is approximately 5%.
SMC Rounds	The importance of covering the full length of a region's highest risk period to malaria infection is evaluated by varying the number of rounds of SMC: <ul style="list-style-type: none"> Three rounds of SMC, where the first round is deployed one month prior to peak malaria transmission, with additional rounds deployed in four-week intervals for the two months following. Four rounds of SMC, where the first round is deployed one month prior to peak malaria transmission, with additional rounds deployed in four week intervals for the three months following. Five rounds of SMC, where the first round is deployed two months prior to peak malaria transmission, with additional rounds deployed in four week intervals for the three months following.
SMC Efficacy and Duration of Protection	As there is uncertainty regarding the likely mechanism of action and full PK/PD of first-generation SMC, we follow a two-step approach to modelling SMC. SMC is modelled, firstly, as a drug- and dose-agnostic combination with liver stage chemoprotection . The blood stage component is modelled as a highly efficacious blood stage drug that acts to clear an individual of all infections for five days from the time of administration. The liver stage component is modelled as likelihood of preventing infections that decays with time, with the following properties: <ul style="list-style-type: none"> Weibull decay profile (shape parameter k = 5.34, indicating rapid, sigmoidal decay). Initial efficacy ranging from 80% to 100%. Duration of protection ranging from 10 to 60 days. In a second step, using an individual-based malaria transmission model combined with a full PK/PD model, SMC was modelled as a drug-agnostic intervention with blood stage chemoprotection . The rate at which the drug kills blood stage parasites was modelled with a one-compartment PK/PD model without absorption or conversion, with a piperaquine-like treatment schedule and with varying concentration half-life (five to 40 days), parasite maximum killing rate (Emax, two to 30 units) and PD slope (one to eight).
Target Population	SMC is evaluated in two target populations: <ul style="list-style-type: none"> Children between three and 59 months of age, for whom SMC is currently recommended. Children between three and 119 months of age, the target of age-extension.
Transmission Intensity	SMC's performance is explored across a range of malaria-endemic regions by providing results across a range of transmission intensities, from low-moderate (12%) to very high (73%) annual baseline <i>PfPR₂₋₁₀</i> (annual <i>Plasmodium falciparum</i> prevalence rate of patent infections in children two to ten years of age under the counterfactual of no SMC).

Table 1. Summary of simulation scenario and intervention.

RESULTS

1. Product

1.1. CURRENT CRITERIA

Variable	Base Case	Upside Case	Annotations
Product	Combination <u>no more than two active components</u> that kill the blood stage of dominant circulating <i>Plasmodium falciparum</i> strains.	Same as base	If the product contains two components, the efficacy of each component may have to be demonstrated separately.

Table 1.1. Current product criteria for iTPP3.

1.2. SUGGESTED UPDATES

Variable	Base Case	Upside Case	Annotations
Product	Combination <u>no more than two active components</u> that kill the blood stage of dominant circulating <i>Plasmodium falciparum</i> strains.	Same as base	If the product contains two components, the efficacy of each component may have to be demonstrated separately. Protection can be achieved by an intervention with either blood stage or liver stage activity. However, given that modelling indicates the critical importance of a favorable prophylaxis period, the PK/PD should be fully understood for both types of intervention.

Table 1.2. Suggested updates to product criteria for iTPP3.

1.3. KEY RESULTS

A number of SMC candidate interventions have been shortlisted by the Bill and Melinda Gates Foundation, the WHO and MMV. These candidates, shown in Figure 5 above, all contain at least one component that acts to kill the blood stage of dominant circulating *Plasmodium falciparum* strains [literature review].

1.3.1. All shortlisted SMC candidates contain a component that acts to kill the blood stage of dominant circulating *Plasmodium falciparum* strains [literature review].

1.3.1.1. All shortlisted candidate interventions, many of which are a combination of two or more active components, show evidence of activity against the blood stage of dominant circulating *Plasmodium falciparum* strains. Most shortlisted candidate interventions also show evidence of activity against the liver stage of dominant circulating *Plasmodium falciparum* strains (Table A.2).

1.3.1.2. However, a number of these shortlisted candidates consist of combinations of more than two active components and, therefore, do not meet the current base case product criteria for iTPP3 (Table A.2).

2. Impact on epidemiological outcomes

2.1. CURRENT CRITERIA

Variable	Base Case	Upside Case	Annotations
Impact on Parasite Prevalence ($PfPR$)	To be determined	To be determined	Pending on modeling studies and policy standards discussion with WHO to determine what community benefit would be necessary for a recommendation on the product.

Table 2.1. Current $PfPR$ criteria for iTPP3.

2.2. SUGGESTED UPDATES

Variable	Base Case	Upside Case	Annotations
Impact on Parasite Prevalence ($PfPR$) and clinical incidence	<p>To be determined</p> <p>In clinical trial settings with high deployment coverage:</p> <ul style="list-style-type: none"> • Prevalence reduction (at end of season) of 80% • Clinical incidence reduction (over 5 months from beginning of season) of: 55% for very high transmission (baseline $PfPR_{2-10}$ greater than 50%); 60% for moderate to high transmission (baseline $PfPR_{2-10}$ between 30% and 50%); 65% for low to moderate transmission (baseline $PfPR_{2-10}$ between 10% and 30%) 	<p>To be determined</p> <p>In clinical trial settings with high deployment coverage:</p> <ul style="list-style-type: none"> • Prevalence reduction (at end of season) of 85% • Clinical incidence reduction (over 5 months from beginning of season) of: 60% for very high transmission (baseline $PfPR_{2-10}$ greater than 50%); 65% for moderate to high transmission (baseline $PfPR_{2-10}$ between 30% and 50%); 70% for low to moderate transmission (baseline $PfPR_{2-10}$ between 10% and 30%) 	<p>Pending on modeling studies and policy standards discussion with WHO to determine what community benefit would be necessary for a recommendation on the product.</p> <p>Modelling results indicate that SMC is likely to achieve its highest impact in clinical trials conducted in low transmission settings. Across all settings, duration of protection drives the majority of impact when SMC coverage and access to treatment are high.</p>

Table 2.2. Suggested updates to $PfPR$ criteria for iTPP3.

2.3. KEY RESULTS

In June 2021, stakeholders – including funders, researchers, product developers, implementation specialists and global health representatives – identified reduction in uncomplicated malaria as the key public health outcome of interest for next-generation SMC [**stakeholder feedback**]. While specific, minimal targets for this and other epidemiological outcomes have not yet been identified, the modelling evidence presented in this report provides guidance on the likely burden reduction for a range of SMC performance characteristics and scenarios. In particular, in **clinical trial settings**, a next-generation intervention would be expected to exceed the following targets to demonstrate equivalent impact to SP+AQ:

- Prevalence reduction at the end of the season of approximately 80%.
- A five-month clinical incidence reduction of approximately 55% for very high transmission (baseline $PfPR_{2-10}$ greater than 50%) 60% for moderate to high transmission (baseline $PfPR_{2-10}$ between 30% and 50%) and 65% for low to moderate transmission (baseline $PfPR_{2-10}$ between 10% and 30%).

Modelling results in **clinical trial settings**, where both deployment coverage and access to treatment are high, indicate that an intervention's duration of protection is the clear driver of impact [**modelling evidence**]. This suggests that a sufficiently long duration of protection must be prioritized for next-generation SMC to be likely to show high protective efficacy in phase two or three clinical trials.

Interestingly, results for an intervention with blood stage chemoprotection suggest that a drug's maximum effect, rather than its duration, is critical for impact on prevalence reduction. This result points to the importance of adherence to SMC's dosing regimen for prevalence reduction and should be explored in further modelling.

2.3.1. Impact on uncomplicated malaria, rather than impact on prevalence, is a key outcome measure for iTPP3 [stakeholder feedback].

2.3.1.1. During the June 2021 convening ‘Malaria Prevention: Shaping Next-Gen Medical Interventions’, participants identified a reduction in uncomplicated malaria as the key public health outcome of interest for next-generation SMC. Reduction in uncomplicated malaria was considered to be a proxy for SMC’s impact on severe malaria and mortality. Impact on prevalence was understood to be less important.

2.3.1.2. Participants also identified clinical endpoint translation across transmission settings as a priority question. Understanding how trial results in, for example, a low transmission setting could translate to high transmission settings was thought to be a priority topic for modelling.

2.3.1.3. Participants did not, however, identify specific targets to measure public health impact.

2.3.2. In clinical trial settings, the impact of a next-generation intervention on clinical incidence, severe disease or mortality reduction is likely to be highest when transmission is low [modelling evidence].



Figure 2.3.2. Predicted relative reduction in prevalence, clinical incidence, severe disease and mortality for an SMC program with SP+AQ, measured in clinical trial settings in comparison to the counterfactual of no intervention. Each point indicates the predicted outcome when SP+AQ is deployed in three (triangle), four (square) and five (circle) rounds in low-moderate (light red) to high (dark red) transmission settings. SP+AQ is modelled as in previous work [1], as a drug with liver stage chemoprotection with an initial efficacy of 100% and a duration of protection of 31 days. Results are shown for two seasonal profiles in a clinical trial setting, where access to treatment is 50% and where coverage is assumed to be high, with an 81% likelihood that an eligible child receives all four rounds of SMC.

2.3.2.1. In clinical trial settings, the predicted clinical incidence, severe disease and mortality reduction for SP+AQ decreases with increasing transmission. In clinical trial settings, next-generation SMC should exceed a target five-month clinical incidence reduction of approximately 55% for very high transmission (baseline $PfPR_{2-10}$ greater than 50%) 60% for moderate to high transmission (baseline $PfPR_{2-10}$ between 30% and 50%) and 65% for low to moderate transmission (baseline $PfPR_{2-10}$ between 10% and 30%) in order to demonstrate non-inferiority to SP+AQ (Figure 2.3.2).

2.3.2.2. In clinical trial settings, we observe both higher outcomes for and less variation in SP+AQ’s predicted prevalence reduction. For example, SP+AQ’s predicted prevalence reduction for four rounds of SMC in a five-month seasonal setting ranges from 79% for high transmission (58% $PfPR_{2-10}$) to 85% for low to moderate transmission (12% $PfPR_{2-10}$). In the same setting, SP+AQ’s predicted incidence reduction ranges from 12% to 58%. These results indicate that, to demonstrate equivalent impact on prevalence to SP+AQ, next-generation SMC should exceed target prevalence reductions of approximately 80% and 85% for base and upside criteria respectively. Note that lower

prevalence reductions are achieved when three rounds of SMC are deployed, because three rounds of SMC is insufficient to provide protection for the modelled five- and six-month seasonal profiles.

2.3.2.3. Outcomes for clinical incidence, severe disease and mortality reduction are also higher when SMC is deployed in five rounds (Figure 2.3.2), partially resulting from the fact that all outcomes are measured across the same five-month intervention period, in five- and six-month seasonal profiles. A smaller difference is observed between three and four rounds of SMC. Importantly, these estimates are based on a fixed set of assumptions regarding SP+AQ's action and should be interpreted with care, as they do not incorporate uncertainty regarding SP+AQ's likely efficacy profile.

2.3.2.4. In clinical trial settings, SP+AQ's impact on clinical incidence translates to a similar impact on severe disease and mortality. Figure 2.3.2 indicates that the predicted relative reduction in clinical incidence for SP+AQ in a clinical trial setting, where both coverage and access to treatment are high, is associated with a slightly lower impact on severe disease and similar impact on mortality.

2.3.3. When both access to treatment and coverage are high, duration of protection is the dominant driver of impact for next-generation SMC [modelling evidence].

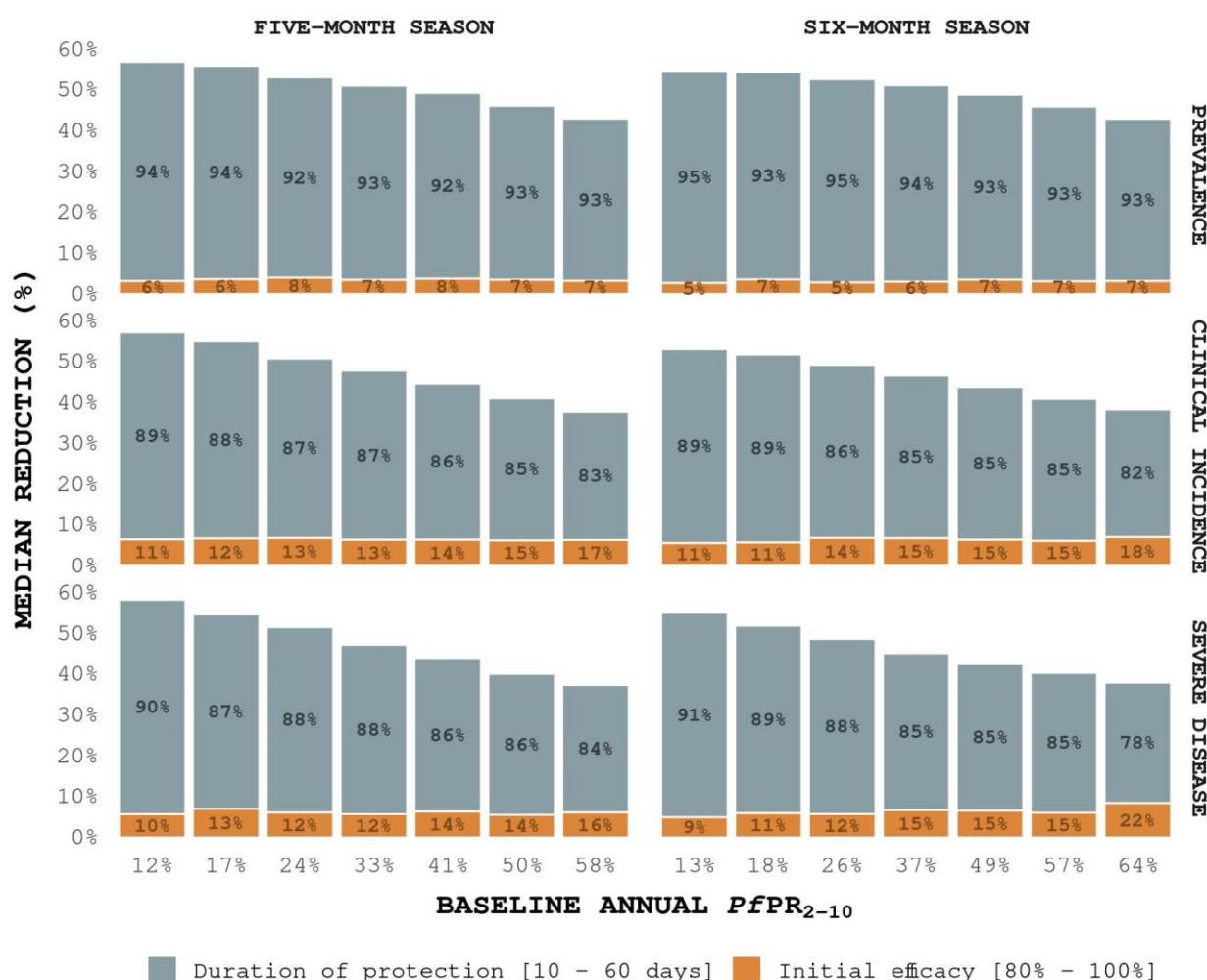


Figure 2.3.3.1. Drivers of impact on predicted prevalence, clinical incidence and severe disease reduction for SMC in children between three and 59 months of age in a clinical trial setting compared to a no-intervention counterfactual. Bars indicate the Sobol total effect indices (explaining the variance in predictions) for two key performance properties – duration of protection and initial efficacy – for an intervention modelled as a drug with liver stage chemoprotection. These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across transmission settings (x-axis, annual baseline $PfPR_{2-10}$) for a six-month seasonal profiles in an archetypal clinical trial setting, where access to treatment is high and where SMC is deployed in monthly intervals four times a year. Coverage is assumed to be high, with an 81% likelihood that an eligible child receives all four rounds of SMC. For guidance on understanding this figure, refer to Section 8.2.

2.3.3.1. For an intervention with liver stage chemoprotection, duration of protection is the most important driver of next-generation SMC's impact on prevalence, clinical incidence and severe disease reduction in clinical trial settings. This intervention property, represented by the blue segments in Figure 2.3.3.1, consistently explains a majority of outcome variation across different transmission intensities. This result suggests that, for next-generation SMC to be likely to show high efficacy in phase two or three clinical trials, a sufficiently long duration of protection must be prioritized.

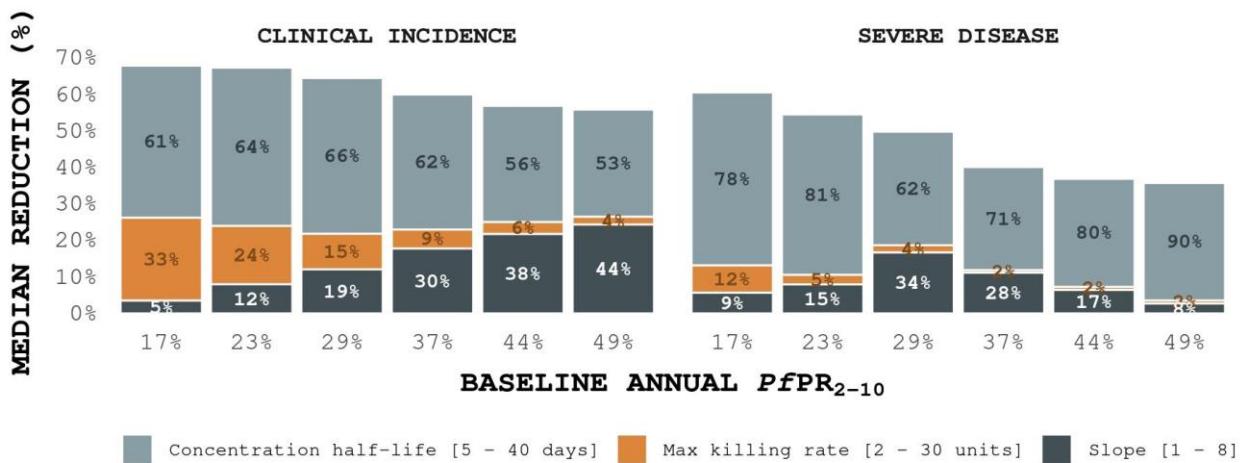


Figure 2.3.3.2. Drivers of impact on predicted clinical incidence and severe disease reduction for an SMC program in children between three and 59 months of age in a clinical trial setting compared to a no-intervention counterfactual. Bars indicate the Sobol total effect indices (explaining the variance in predictions) for an intervention modelled as a drug with long-acting chemoprotection against blood stage parasites. These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across transmission settings (x-axis, annual baseline $PfPR_{2-10}$) for two seasonal profiles in an archetypal clinical trial setting, where access to treatment is high and where SMC is deployed in monthly intervals four times a year. Coverage is assumed to be high, with an 81% likelihood that an eligible child receives all four rounds of SMC. For guidance on understanding this figure, refer to Section 8.2.

2.3.3.2. Similarly, for an intervention with blood stage chemoprotection, concentration half-life is the most important driver of impact on clinical incidence and severe disease reduction in clinical trial settings. This characteristic, which is represented by the blue segments in Figure 2.3.3.2 and which influences the intervention's duration, explains more than 50% of variation in clinical incidence and severe disease reduction. The slope of the model capturing the intervention's pharmacodynamics (dark blue segments) also plays an important role; as transmission increases, so does the importance of the parasite killing effect's decay.

2.3.4. Results suggest that blood stage chemoprotection is critical for impact on prevalence in clinical trial settings [modelling evidence].

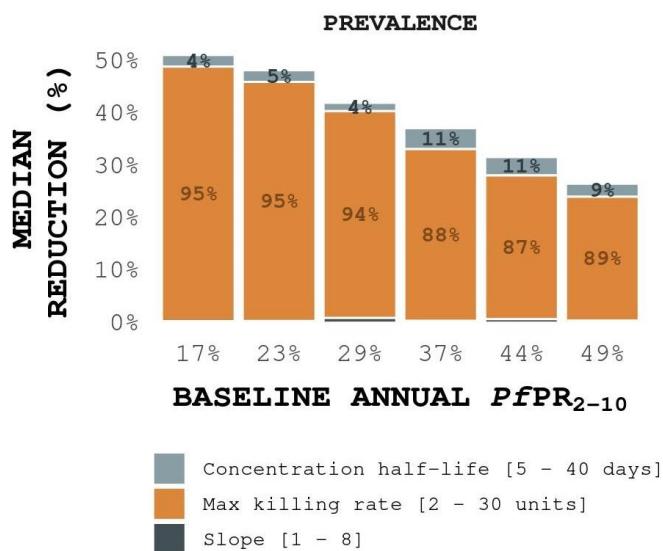


Figure 2.3.4. Drivers of impact on predicted prevalence reduction for an SMC program in children between three and 59 months of age in a clinical trial setting compared to a no-intervention counterfactual. Bars indicate the Sobol total effect indices (explaining the variance in predictions) for an intervention modelled as a drug with long-acting chemoprotection against blood stage parasites. These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across transmission settings (x-axis, annual baseline $PfPR_{2-10}$) for two seasonal profiles in an archetypal clinical trial setting, where access to care is high and where SMC is deployed in monthly intervals four times a year. Coverage is assumed to be high, with an 81% likelihood that an eligible child receives all four rounds of SMC. For guidance on understanding this figure, refer to Section 8.2.

2.3.4.1. A blood stage intervention's maximum parasite killing effect, rather than its half-life or slope, is the most important driver of impact on prevalence reduction in clinical trial settings. This performance characteristic, which describes a chemoprotection drug's ability to clear blood stage parasites, explains more than 85% of variation in prevalence reduction across baseline transmission settings (Figure 2.3.4).

2.3.4.2. The importance of an intervention's maximum killing effect suggests that it is the effectiveness with which a drug clears blood stage parasites that is critical for reducing prevalence, rather than the duration over which the drug is able to prevent new infections from taking hold.

Importantly, this result points to the need for good adherence to the dosing regimen at each round of SMC to see a reduction in malaria prevalence; reduced adherence to treatment means that a child may not benefit from the full effect of SMC. For next-generation SMC, it may be critical to prioritize drug adherence factors to see an impact on prevalence in a clinical trial: the number of doses, ease of administration and the availability of a pediatric formulation.

3. Indication (duration of protection)

3.1. CURRENT CRITERIA

Variable	Base Case	Upside Case	Annotations
Indication	Prevent infection by <i>Plasmodium falciparum</i> (Pf) for at least four weeks post-administration.	Same as base	This interventional TPP describes a second-generation product with minimum criteria for malaria burden control in seasonal transmission settings. The first round of administration to occur before the onset of the high-transmission season.

Table 3.1. Current indication criteria for iTPP3.

3.2. SUGGESTED UPDATES

Variable	Base Case	Upside Case	Annotations
Indication	Prevent infection by <i>Plasmodium falciparum</i> (Pf) for at least four weeks post-administration.	Same as base Prevent infection by <i>Plasmodium falciparum</i> (Pf) for at least five weeks post-administration.	This interventional TPP describes a second-generation product with minimum criteria for malaria burden control in seasonal transmission settings. The first round of administration to occur before the onset of the high-transmission season. The duration of the intervention's prophylaxis period against either liver or blood stage infection is an important property for achieving adequate burden reduction in seasonal settings, in both clinical trials and in implementation, and generating evidence of duration at both the blood and liver stages is critical: <ul style="list-style-type: none">Modelling evidence suggests that, for adequate burden control in seasonal settings, an intervention should provide protection across as much of the period between SMC rounds as possible. For example, to achieve a target clinical incidence and severe disease reduction of >50% for monthly SMC in high transmission settings (>40% annual PIPR₂₋₁₀), duration of protection should be >28 days.Modelling evidence suggests that a longer duration of protection is advantageous. For example, a >70% reduction in both clinical incidence and severe disease is likely only with duration of protection >35 days.

Table 3.2. Suggested updates to the indication criteria for iTPP3.

3.3. KEY RESULTS

There is limited evidence regarding a next-generation SMC candidate's duration of protection from infection by *Plasmodium falciparum*. Crucially, these properties are also not clearly defined for existing SMC drugs – SP+AQ and DHA+PPQ. For next-generation SMC to achieve its desired public health outcomes, this property should be better understood and optimised for each candidate intervention. In particular:

- Substantial uncertainty surrounds the duration of protection for each shortlisted iTPP3 candidate [literature review].
- As in clinical trial settings, duration of protection is a critical driver of impact in **implementation settings** [modelling evidence].
- When duration of protection is less than 28 days, only a limited reduction in clinical incidence is likely in **implementation settings** (Figure 3.3) [modelling evidence].
- Substantial gain is likely to be made by deploying an intervention with duration of protection greater than 35 days, particularly in settings where the SMC program may not cover the full duration of the malaria transmission season (Figure 3.3) [modelling evidence].

These results have the following **implications for decision makers**:

- For **product developers**, generating evidence for an intervention's duration of protection from infection by *Plasmodium falciparum* will be critical to achieving adequate burden control in seasonal settings; an understanding of the intervention's duration at both the blood and liver stages should be pursued.
- **Funders** should consider whether next-generation SMC is likely to provide protection across the full four weeks between monthly administrations of SMC. A longer duration of protection is likely to be advantageous and should be prioritized, particularly in settings where the number of rounds of SMC does not cover the length of the high-transmission season or where coverage decreases between rounds.

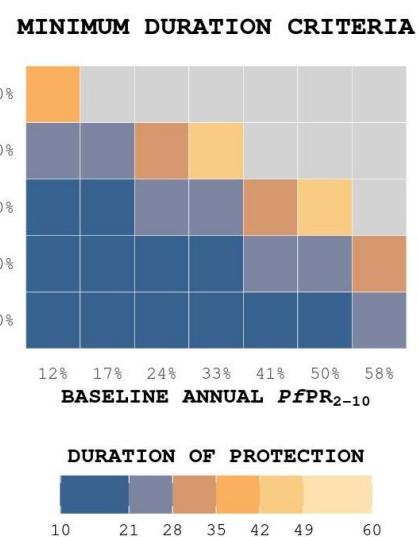


Figure 3.3. Summary of the predicted minimum duration of protection criteria for next-generation SMC towards achieving a target clinical incidence and severe disease reduction across SMC deployment rounds and target populations compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum duration of protection required to achieve a given target reduction in clinical incidence and severe disease (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. This minimum is then aggregated by calculating the most conservative (maximum) criteria across outcomes (clinical incidence and severe disease reduction), SMC rounds (three, four and five rounds of SMC), and target populations (children aged three to 59 months, and three to 119 months). Results are shown for a five-month seasonal profile in a setting with high access to treatment, and the intervention is modelled as a drug with liver stage chemoprotection. See Section A.1 for the full range of modelled scenarios.

3.3.1. Substantial uncertainty surrounds the duration of protection for each shortlisted iTPP3 candidate [literature review].

3.3.1.1. Evidence for the likely duration of protection is available for only a small number of candidate interventions, reflecting a gap in the clinical evidence for those combinations or novel drugs that have not yet been widely used in practice. For example, a literature search conducted in December 2021 identified no evidence for the combined use of Pyronaridine + Piperaquine, a leading first-generation combination candidate for SMC, against *Plasmodium falciparum* (Table A.2).

3.3.1.2. Of the two interventions with evidence for the likely duration of the prophylaxis period – Atovaquone-Proguanil and Dihydroartemisinin + Piperaquine – only Dihydroartemisinin + Piperaquine's 28 to 56 days of protection falls well within the iTPP3 base case indication criteria. Atovaquone-Proguanil's duration of protection, which ranges between 14 and 29 days only just meets the 28 day base case requirement (Table A.2). However, the evidence for these interventions spans different measures of duration; iTPP3's indication criteria must clearly specify what is meant by prevention of infection.

3.3.2. As in clinical trial settings, duration of protection is a critical driver of impact in implementation settings [modelling evidence].

3.3.2.1. For an intervention with a dominant liver stage action, duration of protection is one of the most important drivers of impact on clinical incidence reduction in implementation settings. This key intervention property, represented by the blue segments in Figure 3.3.2.1, consistently explains a large proportion of variation in public health impact; for some scenarios, up to 48% of variation in the predicted clinical incidence reduction can be attributed to duration of protection (Table A.3). These results suggest that, for next-generation SMC to achieve a high impact on the clinical incidence of malaria in seasonal settings, a sufficiently long duration of protection must be prioritized.

3.3.2.2. An SMC intervention's duration of chemoprotection against liver stage infection is, however, of lesser importance when considering its likely impact on severe disease. For severe disease, coverage is consistently the largest driver of impact. And for some scenarios, duration of protection explains as little as 1% of variation in severe disease reduction (Table A.3).

3.3.2.3. Concentration half-life, linked to an intervention's duration of protection, also drives impact for an intervention with blood stage chemoprotection. Of the PK/PD performance characteristics evaluated for this intervention – half-life, maximum effect and slope – concentration half-life is the only characteristic to have a significant impact on public health outcomes in implementation settings (Figure 3.3.2.2). This suggests that, while SMC program coverage is the dominant driver of variation in both clinical incidence and severe disease reduction for a blood stage intervention, concentration half-life has an important role to play in next-generation SMC's public health impact.

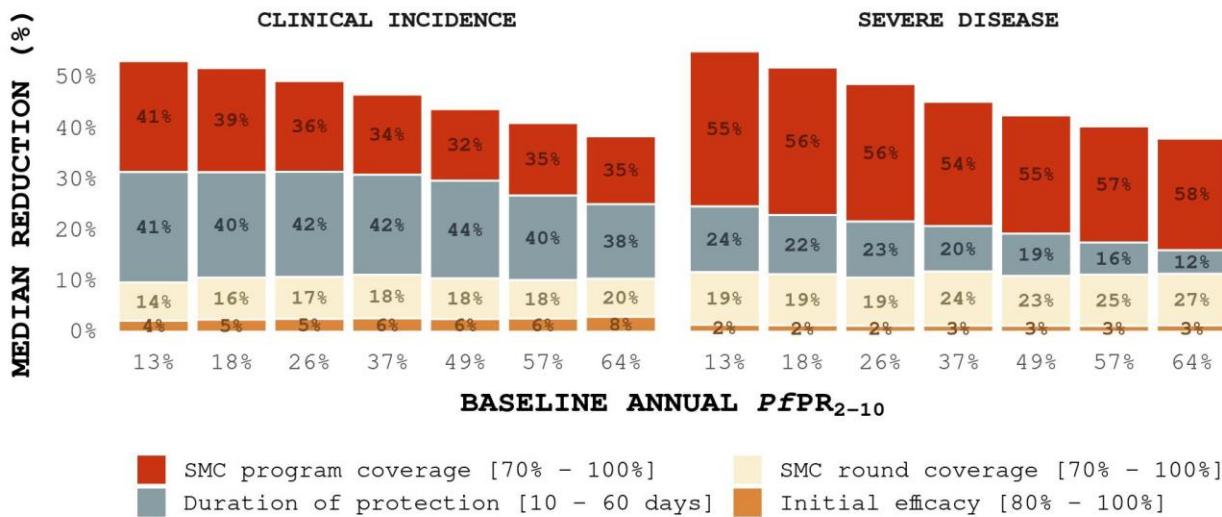


Figure 3.3.2.1. Drivers of impact on predicted clinical incidence and severe disease reduction for an SMC program in children between three and 59 months of age, measured in implementation settings in comparison to the counterfactual of no intervention. Bars indicate the Sobol total effect indices (explaining the variance in predictions) for each of the four key performance properties – program coverage (70% to 100%), round coverage (70% to 100%), duration of protection (10 to 60 days) and initial efficacy (80% to 100%) – for an intervention modelled as a drug with liver stage chemoprotection. These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across prevalence settings (x-axis, annual baseline $PfPR_{2-10}$) for one archetypal scenario: high access to treatment with a six-month seasonal profile, where SMC is deployed in monthly intervals four times a year. For guidance on understanding this figure, refer to Section 8.2.

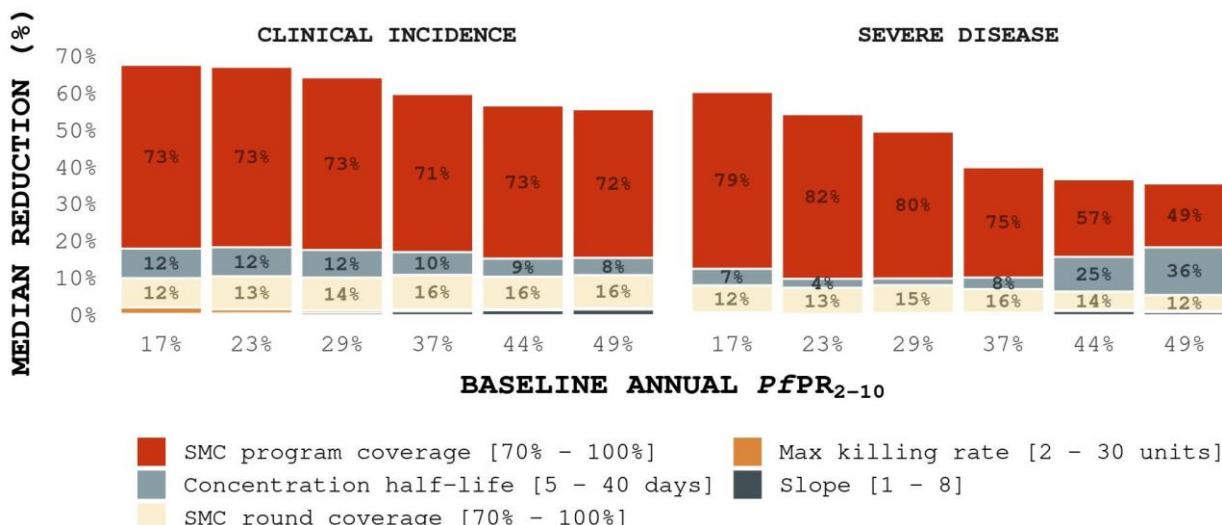


Figure 3.3.2.2. Drivers of impact on predicted clinical incidence and severe disease reduction for an SMC program in children between three and 59 months of age, measured in implementation settings in comparison to the counterfactual of no intervention. Bars indicate the Sobol total effect indices (explaining the variance in predictions) for each of the four key performance properties – program coverage (70% to 100%), round coverage (70% to 100%), duration of protection (10 to 60 days) and initial efficacy (80% to 100%) – for an intervention modelled as a drug with long acting chemoprotection against blood stage parasites. These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across prevalence settings (x-axis, annual baseline $PfPR_{2-10}$) for one archetypal scenario: high access to treatment with a six-month seasonal profile, where SMC is deployed in monthly intervals four times a year. For guidance on understanding this figure, refer to Section 8.2.

3.3.3. A duration of protection of at least 28 days is a key performance criterion in implementation settings [modelling evidence].

3.3.3.1. When duration of protection against liver stage infection is less than four weeks, or 28 days, only a limited reduction in clinical incidence is likely to be achieved in implementation settings. For example, the modelling results for an annual baseline $PfPR_{2-10}$ of 26% (Figure 3.3.3) indicates that an intervention deployed with a duration of protection of less than 28 days is likely to achieve a less than 55% reduction in clinical incidence in children between three and 59 months of age, assuming that initial efficacy is more than 80%. Table A.1 further supports this result; across scenarios, a minimum duration of protection of approximately four weeks is required for next-generation SMC to achieve a target clinical incidence and severe disease reduction comparable with that of SP+AQ.

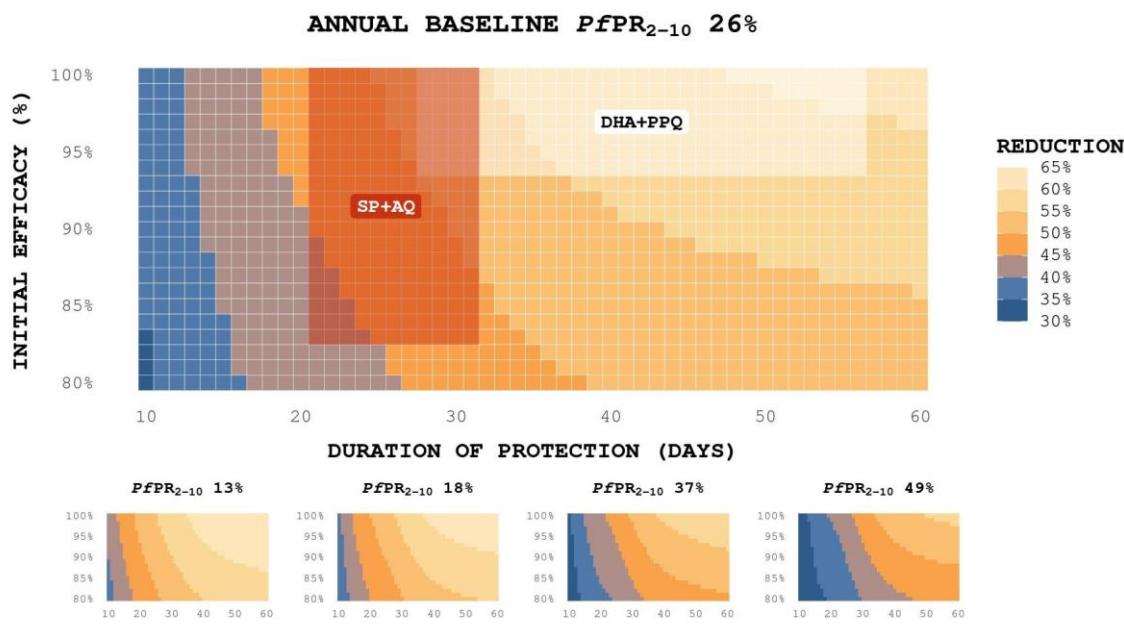


Figure 3.3.3. Predicted relative reduction in clinical incidence from SMC, measured in implementation settings compared to a no-intervention counterfactual. Each grid square indicates the predicted five-month clinical incidence reduction if an intervention with the given initial efficacy and duration of protection were deployed. SMC is modelled as a drug with liver stage chemoprotection (based on a previous analysis [1]). The highlighted red and cream segments indicate the likely range of outcomes for SP+AQ- and DHA+PPQ-like interventions, a 40% to 55% and 50% to 65% reduction respectively. Results are shown for children aged three to 59 months who reside in a setting with a six-month seasonal profile, where access to treatment is high and where SMC is deployed four times a year at monthly intervals with a program coverage of 95% and round coverage of 85%, corresponding to a 50% likelihood that a child receives all SMC rounds. Each lower panel represents results for a different annual baseline $PfPR_{2-10}$. For guidance on interpreting this figure, refer to Section 8.3.

3.3.4. Substantial gain may be made by deploying an intervention with duration of protection greater than 28 days, particularly in settings where the SMC program does not cover the full duration of the malaria transmission season [modelling evidence].

3.3.4.1. When duration of protection against liver stage infection is greater than four weeks, a larger clinical incidence reduction is likely. For example, as shown in Figure 3.3.3, when duration of protection is 35 days (five weeks), a potential clinical incidence reduction of up to 60% is likely.

3.3.4.2. When the number of rounds of SMC is not sufficient to cover the full length of the malaria transmission season, an intervention's duration of protection is one of the most important drivers of public health impact. As indicated in Figure 3.3.4, duration of protection explains a greater proportion of variation in clinical incidence reduction than any other parameter when only three rounds of SMC are deployed. This importance decreases when four or five rounds are given, indicating the critical importance of prioritizing an intervention's duration of protection in settings where the SMC program may not cover the full malaria transmission season.

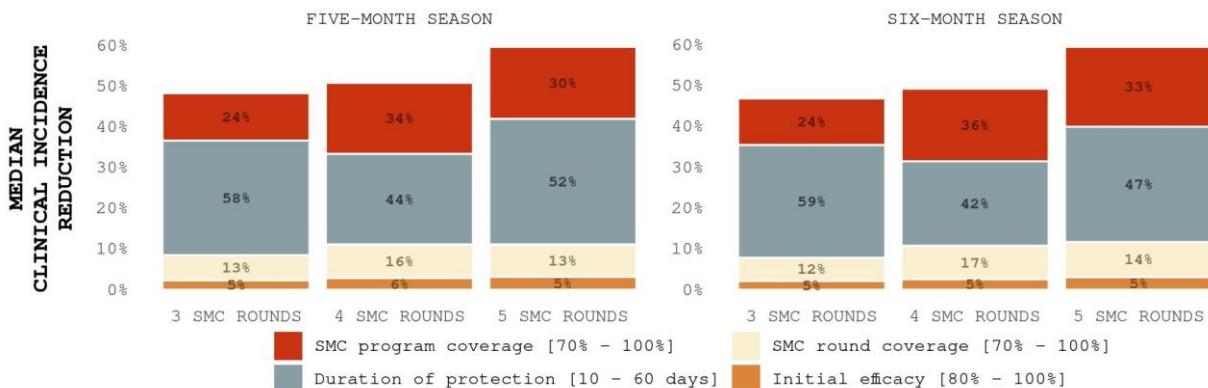


Figure 3.3.4. Drivers of impact on predicted reduction in clinical incidence for an SMC program deployed with three, four or five rounds a year, measured in implementation settings compared to the counterfactual of no intervention. Bars indicate the Sobol total effect indices, the proportion of variation in the outcome attributable to each of the four key performance properties – program coverage (70% to 100%), round coverage (70% to 100%), duration of protection (10 to 60 days) and initial efficacy (80% to 100%) – for an intervention modelled as a drug with liver stage chemoprotection. Results are shown for an SMC program in children between three and 59 months of age for two seasonal profiles in one archetypal scenario, a setting with high access to treatment and an annual baseline $PfPR_{2-10}$ of 24% (left panel) and 26% (right panel). For guidance on understanding this figure, refer to Section 8.2.

4. Efficacy

4.1. CURRENT CRITERIA

Variable	Base Case	Upside Case	Annotations
Clinical efficacy	Preventive efficacy: 87% trial efficacy to achieve non-inferiority to SMC	Preventive efficacy: 98% to achieve non-inferiority to Malarone (atovaquone/proguanil)	Target reduction goals are preliminary; modeling necessary to ensure targets meet elimination goals (herd protection). An ongoing monitoring program for efficacy will be required

Table 4.1. Current efficacy criteria for iTPP3.

4.2. SUGGESTED UPDATES

Variable	Base Case	Upside Case	Annotations
Clinical efficacy	Preventive efficacy: 87% trial efficacy to achieve non-inferiority to SMC Note that the iTPP should specify if preventative efficacy is the maximum clinical efficacy of the drug or over a time period of evaluation (four week period, two week period, over a season, etc.).	Preventive efficacy: 98% to achieve non-inferiority to Malarone (atovaquone/proguanil)	Target reduction goals are preliminary; modeling necessary to ensure targets meet elimination goals (herd protection). An ongoing monitoring program for efficacy will be required. Modelling evidence indicates that initial efficacy is a lower impact driver of burden reduction than an intervention's coverage or duration of protection (if efficacy is >80%). Equivalence to SP+AQ is likely to be achievable with a lower efficacy. For example, a clinical incidence and severe disease reduction as high as 70% can be achieved with an intervention with initial efficacy as low as 80%. While these results suggest that initial efficacy is a lower-priority performance property, the efficacy criteria in the iTPP's base and upside criteria should be clearly defined. The evaluation time period and measure of efficacy should be specified, along with the phase of product development in which this evidence should be generated.

Table 4.2. Suggested updates to efficacy criteria for iTPP3.

4.3. KEY RESULTS

As for iTPP3's indication criteria, there is limited evidence regarding a next-generation SMC candidate's likely protective efficacy against infection by *Plasmodium falciparum*. Yet, a desirable public health outcome may be achieved with a range of efficacies:

- As in clinical trial settings, an intervention's initial efficacy against liver stage parasites is a low impact driver of burden reduction in **implementation settings**. A clinical incidence and severe disease reduction as high as 70% can be achieved with an intervention with initial efficacy of 80% (Figure 4.3) **[modelling evidence]**.
- A favorable efficacy is likely to lead to a favorable burden reduction only when the intervention's duration of protection is greater than four weeks, so long as the intervention's efficacy is greater than the minimum modelled 80% **[modelling evidence]**.

These results have the following **implications for decision makers**:

- **Product developers** should be aware that increasing a drug's duration of protection is more important than increasing its initial efficacy. However, once a duration sufficient to provide protection across the full period between monthly administrations of SMC has been reached, an increase in initial efficacy is likely to lead to greater impact.
- While our results suggest that initial efficacy is a lower-priority performance property, **funders** should clarify what is meant by preventative efficacy in the iTPP's base and upside criteria. The evaluation time period and measure of efficacy should be specified, along with clear guidance given regarding the phase of product development in which this evidence should be generated.

- Following clarification, **modellers** can translate a product's efficacy to its likely effectiveness in **implementation settings**.

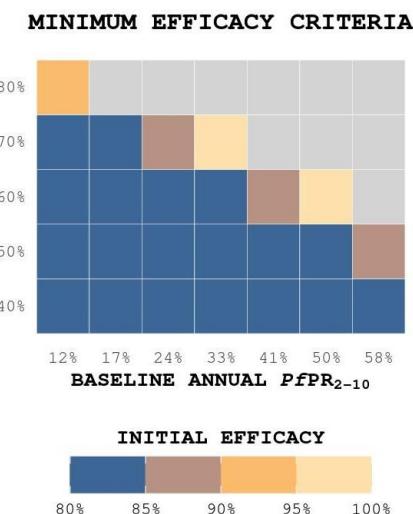


Figure 4.3. Summary of the predicted initial efficacy criteria for next-generation SMC towards achieving a target clinical incidence and severe disease reduction across SMC deployment rounds and target populations compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum initial efficacy required to achieve a given target reduction in clinical incidence and severe disease (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. This minimum is then aggregated by calculating the most conservative (maximum) criteria across outcomes (clinical incidence and severe disease reduction), SMC rounds (three, four and five rounds of SMC), and target populations (children aged three to 59 months, and three to 119 months). Results are shown for a five-month seasonal profile in a setting with high access to treatment, and the intervention is modelled as a drug with liver stage chemoprotection. See Section A.1 for the full range of modelled scenarios.

4.3.1. An intervention's initial efficacy is a low impact driver of burden reduction for an SMC program in **implementation settings** [modelling evidence].

4.3.1.1. For the modelled liver stage intervention, initial efficacy is consistently the least important driver of impact across outcome measures in **implementation settings** (Figure 3.2.2.1). Across scenarios, an SMC candidate's initial efficacy accounts for up to a maximum of only 8% of variation in the achievable clinical incidence reduction and 3% of variation in severe disease reduction (Table A.3). This result suggests that SMC's initial efficacy should not be prioritized over coverage or duration of protection, so long as this efficacy falls within the modelled 80% to 100% range.

4.3.1.2. Similarly, for next-generation SMC with blood stage activity, the drug's maximum parasite killing effect is consistently the least important driver of impact on both clinical incidence and severe disease in **implementation settings** (Figure 3.3.2.2).

4.3.2. A favorable initial efficacy is likely to lead to a favorable burden reduction only when the intervention's duration of protection is more than 28 days [modelling evidence].

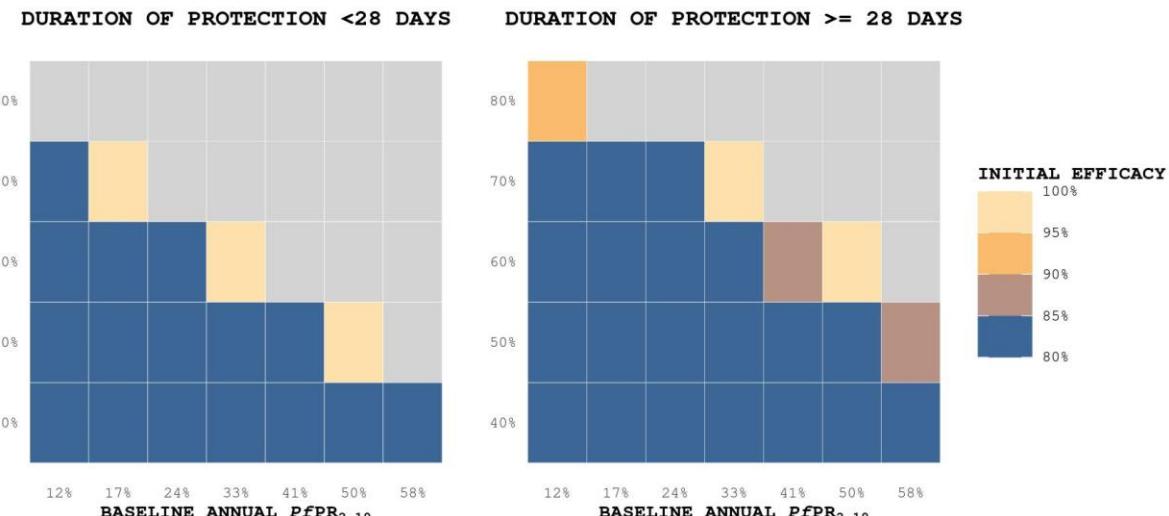


Figure 4.3.2. Summary of the predicted minimum efficacy criteria for next-generation SMC to achieve a target clinical incidence and severe disease reduction across SMC deployment rounds and target populations, shown when duration of protection is less than or greater than 28 days compared to a no-intervention counterfactual over a five-month intervention period. The results show the estimated minimum initial efficacy required to achieve a given target reduction (y-axis), with grey indicating that the target is outside the parameter range. This minimum is then aggregated by calculating the most conservative (maximum) criteria across outcomes (clinical incidence and severe disease reduction), SMC rounds (three, four and five rounds of SMC), and target populations (children aged three to 59 months and three to 119 months). Results are shown for a five-month seasonal profile with high access to treatment, and the intervention is modelled as a drug with liver stage chemoprotection.

4.3.2.1. When duration of protection is less than four weeks, or 28 days, high public health impact is unlikely to be achieved regardless of the intervention's efficacy profile (Figure 4.3.2).

4.3.2.2. When duration of protection is greater than or 28 days, however, a favorable initial efficacy may contribute to an increased reduction in clinical incidence. For example, in Figure 4.3.2, an initial efficacy of greater than 90% can contribute to achieving an 80% target reduction in a setting with low to moderate transmission (12% annual $PfPR_{2-10}$) when duration of protection is greater than 28 days. Furthermore, in Figure 3.3.3, when duration of protection is fixed at 35 days (five weeks), deploying an intervention with an efficacy of 90% instead of 80% leads to a 5% increase in the associated clinical incidence reduction. As a result, should a group of candidate interventions show a highly favorable duration of protection, much may be gained from prioritizing the development of a favorable initial efficacy.

4.3.3. For the SMC candidate interventions with a known preventative efficacy, all exhibit an efficacy likely to achieve a favorable public health outcome in comparison to SMC with SP+AQ [literature review, modelling evidence].

4.3.3.1. Efficacy evidence is only available for a small number of candidates, reflecting a gap in the evidence available for those combinations or novel drugs that have not yet been widely used in practice. For example, as discussed in Section 3, no literature was identified on efficacy for the first-generation combination Pyronaridine + Piperaquine (Table A.2).

4.3.3.2. Of the three interventions with a known duration of protection – Atovaquone-Proguanil, Dihydroartemisinin + Piperaquine and Ganaplacide – all three indicate a preventative efficacy likely to meet this iTPP's current base-case requirement. As discussed above, a novel intervention may achieve equivalent impact to SP+AQ with an initial efficacy as low as 80%, so long as the intervention's duration of protection is approximately four weeks or more. KAF156 (Ganaplacide)'s lower efficacy range of 67% to 99% and Atovaquone-Proguanil's lower duration of protection of 14 to 29 days, however, indicate a risk of not meeting these cut-off criteria (Table A.2).

5. Coverage Requirement

5.1. CURRENT CRITERIA

Variable	Base Case	Upside Case	Annotations
Coverage requirement	To be determined	To be determined	To achieve community effect compatible with achieving herd immunity consistent with interruption of transmission during the protection window (in the absence of SMC). Based on modeling studies.

Table 5.1. Current coverage criteria for iTPP3.

5.2. SUGGESTED UPDATES

Variable	Base Case	Upside Case	Annotations
Coverage requirement	To be determined More than 40% of children receiving all rounds of SMC	To be determined Same as base case	To achieve community effect compatible with achieving herd immunity consistent with interruption of transmission during the protection window (in the absence of SMC). Based on modeling studies. Modelling confirms that the proportion of children reached by an SMC program is the most important determinant of impact. Thus, increasing coverage may lead to greater burden reduction than improving an intervention's clinical efficacy profile by, for example, reducing the number of doses required, improving high safety profiles and developing pediatric formulations. Coverage is particularly important for an intervention's ability to decrease severe disease burden; as coverage increases, a larger impact on the SMC intervention's ability to reduce the burden of severe malaria in children is predicted (in comparison to the corresponding reduction in clinical cases). In particular, the highest likely clinical incidence and severe disease reductions are only likely when the likelihood of a child receiving all SMC rounds is greater than 40%.

Table 5.2. Suggested updates to coverage criteria for iTPP3.

5.3. KEY RESULTS

Regardless of its efficacy profile, a novel SMC intervention's impact is limited if it cannot reach its target population. In particular:

- Of the four key performance properties evaluated in this report, SMC program coverage is the most important determinant of impact for a next-generation intervention. This property is particularly important for reducing severe disease [modelling evidence].
- Round coverage, however, is less important in implementation settings; a high impact can be achieved with a reduced level of coverage of each round of SMC [modelling evidence].
- But regardless of the source, as coverage decreases, so too does SMC's ability to reduce the burden of severe malaria in children and, hence, to save children's lives. In particular, the highest likely clinical incidence and severe disease reductions is only likely when the likelihood of a child receiving all SMC rounds is greater than 40% [modelling evidence].

These results have the following **implications for decision-makers**:

- For **product developers**, our results highlight the importance of optimizing product characteristics likely to impact an intervention's coverage, such as the dosing regimen, safety profile and formulation, in parallel to the intervention's efficacy and duration of protection.
- For **funders**, the critical importance of coverage in reducing severe disease highlights the need to look beyond an intervention's clinical performance to evaluate its likely effectiveness. The intervention's community acceptability will, for example, be key to its ability to reduce child mortality.

5.3.1. In implementation settings, SMC program coverage is the most important determinant of impact for a next-generation intervention [modelling evidence].

5.3.1.1. Program coverage is the primary driver of impact on clinical incidence and severe disease in implementation settings. This key intervention property, represented by the red segments in Figures 3.3.2.1 and 3.3.2.2, consistently explains either a majority or near majority of variation in clinical incidence. Across modelled scenarios, program coverage accounts for up to 57% of variation in the predicted clinical incidence reduction. Program coverage is even more critical for reducing severe disease; up to a clear majority of 72% of variation in severe disease reduction can be attributed to the proportion of children with access to the SMC program (Table A.3).

5.3.2. Round coverage, however, is less important in implementation settings; a high impact can be achieved with a reduced level of coverage of each round of SMC [modelling evidence].

5.3.2.1. The coverage of each round of SMC was consistently the third most important driver of impact on clinical incidence reduction. This property, represented with the cream segments in Figures 3.3.2.1 and 3.3.2.2, accounts for between 13% and 24% of variation in the achievable clinical incidence reduction across scenarios (Table A.3).

5.3.2.2. Round coverage does, however, play a greater role in determining the likely reduction in severe disease (Figure 3.3.2.1). Depending on the scenario, between 15% and 29% of variation in severe disease reduction can be attributed to SMC round coverage (Table A.3).

5.3.3. Regardless of the source, as coverage decreases, so too does SMC's ability to reduce the burden of severe malaria in children [modelling evidence].

5.3.3.1. When SMC coverage is low, so too is the maximum achievable impact on severe disease. For example, in the scenario shown in Figure 5.3.3.1, when the likelihood of a child receiving all rounds of SMC is less than 40%, an intervention is unlikely to achieve the highest reductions in either clinical incidence or severe disease, regardless of its initial efficacy and duration of protection. When this likelihood is less than 20%, a reduction of less than 40% is likely. This result is emphasised in Figure 5.3.3.2, which indicates that an increase in either initial efficacy or duration of protection only contributes to a substantial gain in impact on severe disease when coverage is very high. This result highlights the critical importance of providing SMC to as many children as possible if the intervention is to reduce burden and, in turn, save lives.

5.3.3.2. On the other hand, an increase in coverage can lead to a substantial increase in public health impact. For example, an intervention with 90% initial efficacy and a duration of protection of 21 days is predicted to achieve a 40% to 45% severe disease reduction when both SMC program and round coverage are 85%. Deploying the same intervention with a higher program coverage of 95% could lead to an increase in the expected severe disease reduction of up to 10% (Figure 5.3.3.2). This result suggests that an intervention with a poor efficacy profile could still achieve a substantial impact, should it have characteristics that favor a high coverage.

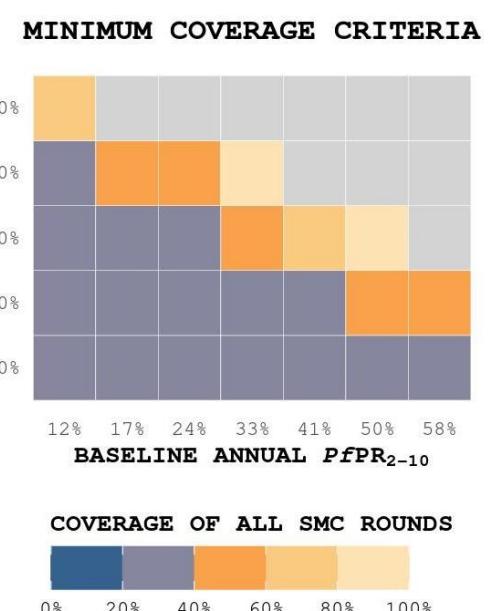


Figure 5.3.3.1. Summary of the predicted minimum coverage criteria for next-generation SMC towards achieving a target clinical incidence and severe disease reduction across SMC deployment rounds and target populations compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum coverage required to achieve a given target reduction in clinical incidence and severe disease (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. This minimum is then aggregated by calculating the most conservative (maximum) criteria across outcomes (clinical incidence and severe disease reduction), SMC rounds (three, four and five rounds of SMC), and target populations (children aged three to 59 months, and three to 119 months). Results are shown for a five month seasonal profile in a setting with high access to care, and the intervention is modelled as a drug with liver stage chemoprotection. See Section A.1 for the full range of modelled scenarios.

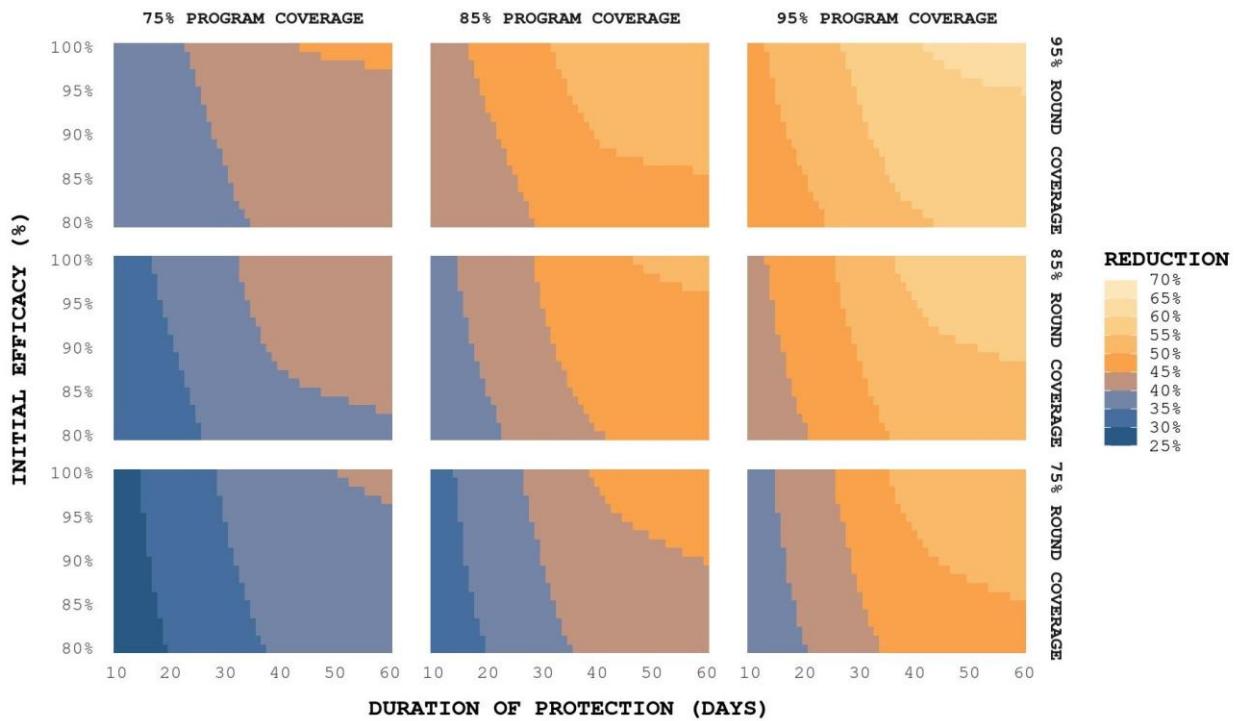


Figure 5.3.3.2. The impact of a change in coverage on the predicted relative reduction in severe disease for an SMC program, measured in implementation setting in comparison to the counterfactual of no intervention. Each square in the grid indicates the predicted relative reduction in clinical incidence if an intervention with the given initial chemoprotection efficacy and duration of chemoprotection were deployed, where the intervention is modelled as a drug with liver stage chemoprotection. Results are shown in children between three and 59 months for a six-month seasonal profile with an annual baseline P/PR_{2-10} of 26%, where access to treatment is high and where SMC is deployed four times a year at monthly intervals. Each panel represents results for a different level of program coverage (x-axis) and round coverage (y-axis). For guidance on interpreting this figure, refer to Section 8.3.

6. Target Population

6.1. CURRENT CRITERIA

Variable	Base Case	Upside Case	Annotations
Target population	Children 3- to 59-months of age	Children 3- to 119-months of age	WHO policy recommendation for SMC today covers only children 3- to 59-month-old in eligible countries (West Africa). Age-extension to 119-month-old currently being studied in Senegal. Applies to all children who aren't in case management (SME question: is it safe to administer to febrile children?).

Table 6.1. Current target population criteria for iTPP3.

6.2. SUGGESTED UPDATES

Variable	Base Case	Upside Case	Annotations
Target population	Children 3- to 59-months of age	Children 3- to 119-months of age	WHO policy recommendation for SMC today covers only children 3- to 59-month-old in eligible countries (West Africa). Age-extension to 119-month-old currently being studied in Senegal. Applies to all children who aren't in case management (SME question: is it safe to administer to febrile children?). A recent modelling study by Masserey et al. suggests we may expect an increased speed of spread of partial sulfadoxine-pyrimethamine resistance when SMC is extended to children between three and 119 months. Despite this, the study also suggests that even with partial SP resistance (quintuple mutant with prophylaxis less than 21 days), SP+AQ delivered as SMC is likely to remain effective at averting clinical disease, albeit at lower levels. Evidence of a next-generation drug's ability to kill partially SP-resistant parasites, combined with a prophylaxis period longer than partially resistant SP, will be critical for all age targeting.

Table 6.2. Suggested updates to target population criteria for iTPP3.

6.3. KEY RESULTS

While the WHO recommends SMC only for children between three and 59 months of age [18], SMC's age-extension to children up to 119 months of age is currently being studied in Senegal. Results indicate that the key performance properties required for the success of next-generation SMC are similar across these two target populations [**modelling evidence**]. A recent modelling study by Masserey et al. (available in Appendix A.5) suggests we may, however, expect an increased speed of spread of partial sulfadoxine-pyrimethamine resistance when SMC is extended to children between three and 119 months [**modelling evidence**]. Despite this, the modelling also suggests that even with partial SP resistance (with prophylaxis less than 21 days), SP+AQ delivered as SMC is likely to remain effective at averting clinical disease, albeit at lower levels than fully sensitive SP. Evidence of a next-generation drug's ability to kill partially SP-resistant parasites combined with a prophylaxis period longer than that of partial resistant SP will be critical for a next-generation drug deployed in settings where SMC has been extended to older children.

6.3.1. The key performance properties required for the success of next-generation SMC are similar when the intervention is deployed in children between three and 59 months of age, and between three and 119 months [**modelling evidence**].

6.3.1.1. Duration of protection and SMC program coverage remain the most important drivers of impact on clinical incidence and severe disease reduction across target age groups. These key intervention characteristics, represented by the blue and red segments respectively in Figure 6.3.1, consistently explain the majority of variation in public health impact across scenarios. SMC round coverage and the intervention's initial efficacy consistently play a lesser role. For example, when *PfPR*₂-

¹⁰ is 37% (moderate to high transmission), round coverage explains 54% and 57% of variation in severe disease reduction in children between three and 59 months and three and 119 months respectively.

6.3.1.2. Key performance criteria for duration of protection and initial efficacy are also consistent across age groups. As discussed in Section 3 and as shown in Figure A.3.1, when SMC is implemented in either target population, an intervention deployed with a duration of protection of less than 28 days is unlikely to achieve more than a moderate reduction in clinical incidence. Similarly, for both target populations, when duration of protection is greater than 28 days, a larger range of clinical incidence reduction is plausible.

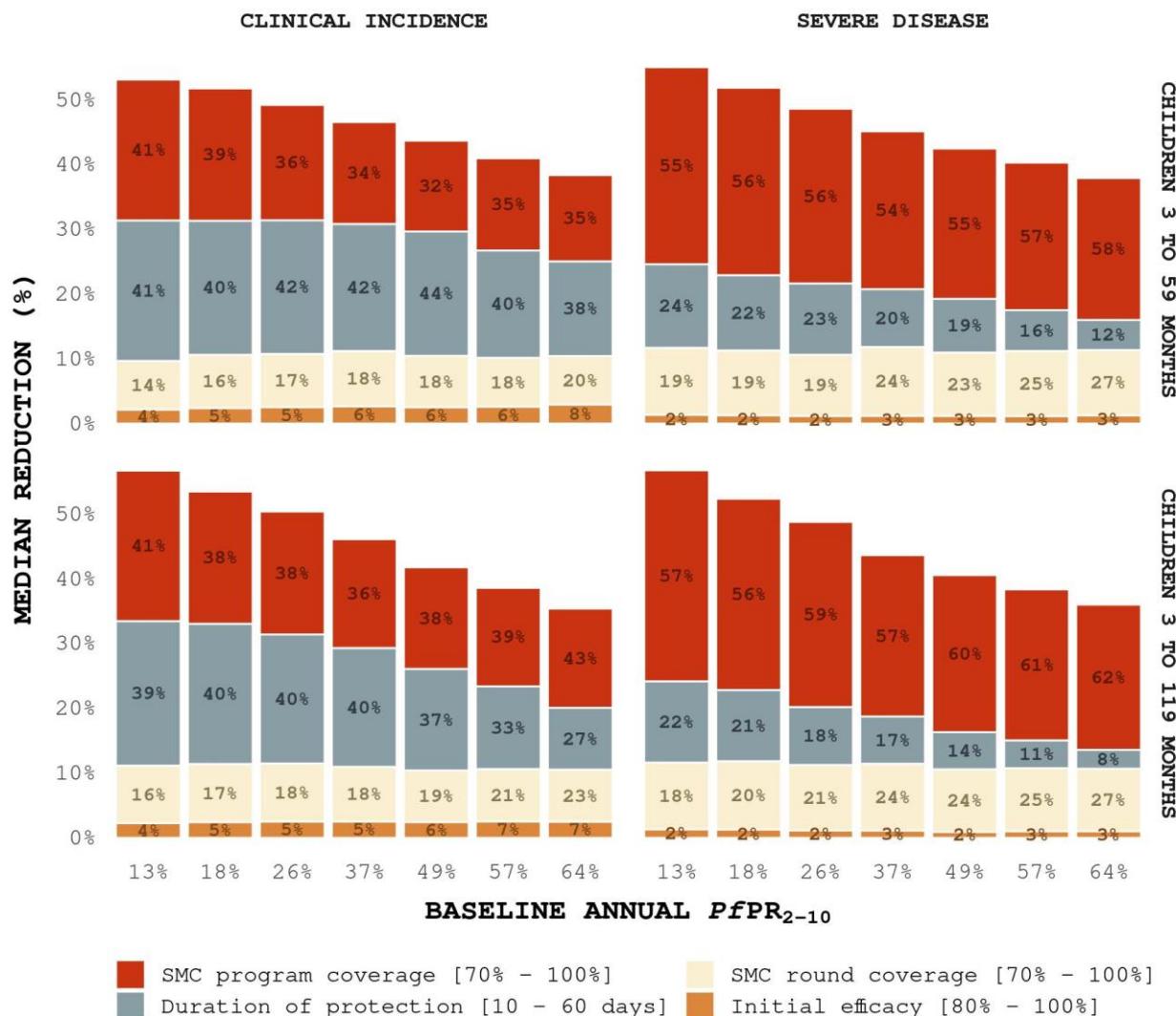


Figure 6.3.1. Drivers of impact on predicted clinical incidence and severe disease reduction for SMC in two target age groups – children aged three to 59 months, and children aged three to 119 months- measured in implementation setting in comparison to the counterfactual of no intervention. Bars indicate the Sobol total effect indices, the proportion of variation in the outcome attributable to each of the four key performance properties – program coverage (70% to 100%), round coverage (70% to 100%), duration of protection (10 to 60 days) and initial efficacy (80% to 100%) – for an intervention modelled as a drug with liver stage chemoprotection. Results are shown across prevalence settings (x-axis, annual PfPR₂₋₁₀) for an archetypal scenario: high access to treatment with a six-month seasonal profile, where SMC is deployed four times a year. For guidance on understanding this figure, refer to Section 8.2.

6.3.2. Modelling suggests that while SMC's age-extension may lead to a more rapid spread of resistance to SP, SP+AQ is likely to remain effective [modelling evidence].

6.3.2.1. SP resistance is estimated to spread twice as quickly when SMC is deployed to children aged three to 119 months in comparison to deployment in children aged three to 59 months. Masserey et al. performed a modelling study (available in Appendix A.5) of the estimated time required for a SP partially resistant genotype (quintuple mutant with dhfr-51I, dhfr-59A, dhfr-108A, dhps-437G and dhps-540G mutations) to spread from 1% to 50% of malaria inoculations under different rounds of SMC. Expanding the target population to include children under ten years old halved this time; in moderate transmission settings where transmission occurred mainly over a four month period, the time to 50% inoculations carrying the quintuple mutant was 53.1 years when SMC was administered in four rounds to children under five, in comparison to 26.4 years when administered to

children under ten. Although this result pertains only to SMC's standard of care, it suggests that evidence of a next-generation drug's ability to kill partially SP-resistant parasites will be critical should SMC be deployed to children aged three to 119 months.

6.3.2.2. However, SP+AQ is likely to remain effective even with partial SP resistance.

Modelling results explored a reduced prophylactic period of 15 days, capturing a setting with greater SP resistance than that of the quintuple mutant and with a degree of resistance to AQ. In this setting, SP+AQ's protective efficacy was found to decrease from 59% to 40%, highlighting that protection against protection remains.

7. Target Settings

7.1. CURRENT CRITERIA

Variable	Base Case	Upside Case	Annotations
Target settings	Geographies with moderate to high transmission in eligible endemic countries experiencing seasonal malaria transmission patterns (West, East and South Africa)	Same as base	The second-generation SMC product will be broadly applicable to West Africa in case resistance to SP or AQ is becoming prevalent. The product will offer seasonal protection in East and South Africa.

Table 7.1. Current target settings criteria for iTPP3.

7.2. SUGGESTED UPDATES

Variable	Base Case	Upside Case	Annotations
Target settings	Geographies with moderate to high transmission in eligible endemic countries experiencing seasonal malaria transmission patterns (West, East and South Africa)	Same as base	The second-generation SMC product will be broadly applicable to West Africa in case resistance to SP or AQ is becoming prevalent. The product will offer seasonal protection in East and South Africa. Modelling confirms that second-generation SMC's coverage is likely to be the most important driver of burden reduction in settings where access to treatment for malaria is limited.

Table 7.2. Suggested updates to target settings criteria for iTPP3.

7.3. KEY RESULTS

Use of SMC is expanding and next-generation SMC must be widely applicable across geographies with very different healthcare systems and seasonal malaria transmission patterns. The focus of this report has, until now, been on representative results from archetypal scenarios. However, important differences in the key performance characteristics emerge across scenarios:

- In scenarios with low access to treatment, SMC coverage is the dominant driver of SMC's impact; intervention performance properties play a greater role when access to treatment is high [modelling evidence].
- Cut-off criteria, however, remain similar across scenarios [modelling evidence].

These results have the following **implications for decision-makers**:

- For **product developers**, optimizing coverage will be key to demonstrating effectiveness for a product intended for settings where access to treatment for malaria is limited.
- During development, both **funders** and **product owners** will need to evaluate an intervention's performance with respect to its intended setting. Tolerability, acceptance and ease of deployment are likely to be more important drivers of burden reduction than an optimized efficacy profile in regions with limited access to treatment for malaria.

7.3.1. In scenarios with low access to treatment, SMC deployment characteristics are the dominant drivers of SMC's impact; intervention performance properties play a greater role when access to treatment is high.

7.3.1.1. In the ideal scenario of high access to treatment for clinical cases, duration of protection is consistently one of the most important drivers of impact on clinical incidence (Figure 7.3.1). When access to treatment is low, however, coverage consistently plays the most important role in driving clinical incidence reduction.

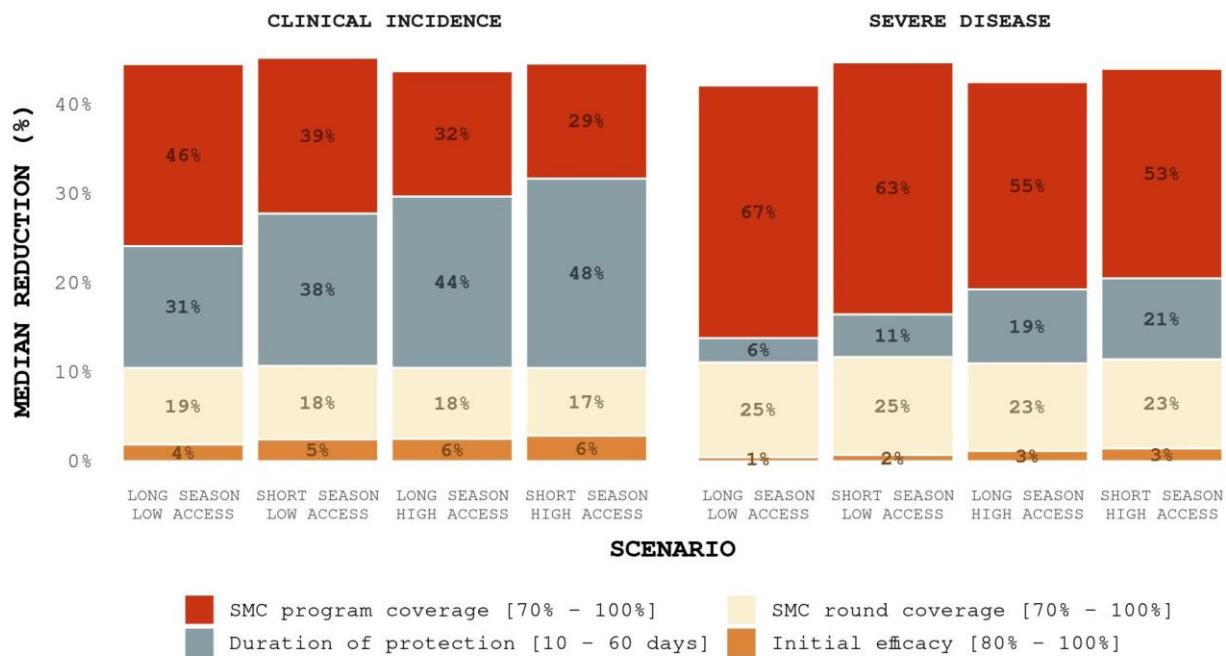


Figure 7.3.1. Drivers of impact on predicted clinical incidence and severe disease reduction for an SMC program in four scenarios – low and high levels of case management for treatment of malaria, and long (six-month) and short (five-month) seasonal profiles – measured in implementation setting in comparison to the counterfactual of no intervention. Bars indicate the Sobol total effect indices, the proportion of variation in the outcome attributable to each of the four key performance properties – program coverage (70% to 100%), round coverage (70% to 100%), duration of protection (10 to 60 days) and initial efficacy (80% to 100%) – for an intervention modelled as a drug with liver stage chemoprotection. Results are shown for a scenario where SMC is deployed four times a year at monthly intervals in children aged three to 59 months, and where the baseline annual $PfPR_{2-10}$ is high. For guidance on understanding this figure, refer to Section 8.2.

7.3.1.2. Across levels of access and seasonal profiles, the combination of SMC program and round coverage drive all but a small proportion of impact on severe disease. For example, Figure 7.3.1 shows that the combined variation in SMC program and round coverage explains more than 85% of the impact on severe disease reduction when access to treatment is low, and more than 75% when access to treatment is high.

7.3.2. Cut-off criteria for an intervention's initial efficacy and duration of protection remain similar across levels of access and across seasonal profiles.

7.3.2.1. A gain in either duration of protection or initial efficacy provides a similar gain in the achievable clinical incidence reduction across seasonal profiles and across levels of access to treatment. For example, the shape of the contour lines shown in Figure A.3.2 are similar regardless of whether access is high or low and regardless of whether the seasonal length is five or six months.

8. Methods

8.1. MODELLING CRITERIA FOR TARGET PRODUCT PROFILES

The development of next-generation medical interventions is guided by Target Product Profile documents, which help to prioritize candidates and ensure health targets are reached. Swiss TPH has developed an evidence generation framework that uses mathematical modelling to support the identification of minimum necessary product requirements. This framework, which uses established techniques from malaria disease modelling, consists of the following elements:

- **Disease and Intervention Modelling:** Simulation with a comprehensive and well-established mathematical model for the progression and transmission of malaria (OpenMalaria²) [19]. This model is applied on a discrete, uniformly sampled set of input parameters that capture key intervention properties.
- **Machine Learning:** Training of a Gaussian Process regression model on a dataset constructed from the sampled set of input parameters and their corresponding, simulated outcomes. This model captures the complex dynamics of malaria transmission without large computational cost.
- **Sensitivity Analysis:** Determination of an intervention property's impact through the use of a variance-based sensitivity analysis.
- **Optimization:** Identification of minimal intervention properties through the use of optimization techniques, which explore optimal intervention properties to achieve a target public health outcome.

The techniques employed within this framework were recently deployed in a proof-of-concept study of long acting injectables [1]. Golumbeanu et al. have also provided a detailed description of the methodology [20]. We provide guidance on interpreting the results of each component of the method in the following sections.

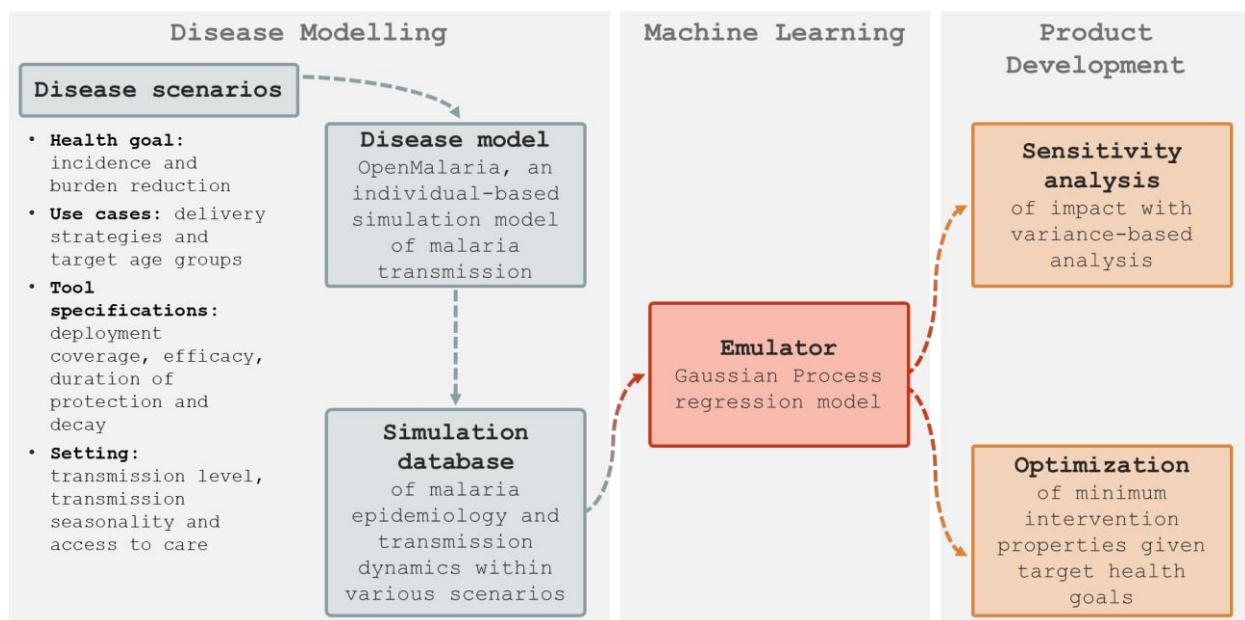


Figure 8.1. Schematic diagram of the evidence-generation framework to support the identification of minimum necessary product characteristics.

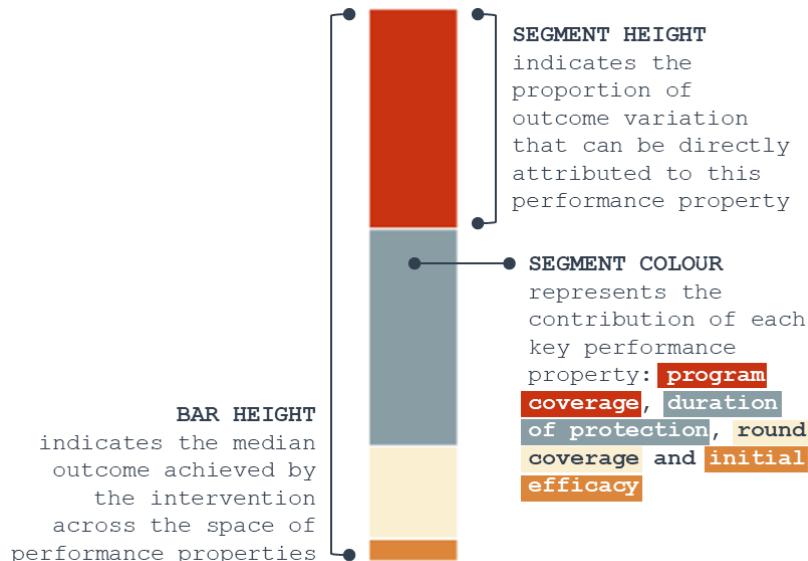
² OpenMalaria individual-based model of malaria <https://github.com/SwissTPH/openmalaria/wiki>

8.2. MEASURING DRIVERS OF IMPACT

We undertook a **global sensitivity analysis** of our model results to identify the most important drivers of impact for a new intervention. This method studies how the uncertainty in a mathematical model can be attributed to different sources of uncertainty in the model's inputs. We perform this analysis with the Sobol method, reporting the total effect indices.

In this report, we use a global sensitivity analysis to measure the extent to which a small change in an intervention's key performance properties corresponds to a change in the intervention's impact, as shown in Figure 8.2. For example, we may see that an increase in a drug's initial efficacy, from say 81% to 82%, leads to a larger change in the achievable clinical incidence reduction than a small increase in the intervention's duration of protection.

Figure 8.2. Understanding the measurement of drivers of impact.



8.3. IDENTIFYING KEY PERFORMANCE CRITERIA

To identify the key performance criteria for a novel intervention, we link a desired public health outcome with its required intervention properties. Following an optimization technique called a **grid search**, we use a machine learning emulator of our malaria transmission model to predict the likely public health outcome of a large combination of different values for the intervention's key performance characteristics.

For example, suppose that an intervention had three likely levels of duration of protection, low (15 days), medium (30 days) and high (45 days). To link these properties with their likely impact, we run the malaria transmission model emulator three times, varying the level of duration of protection each time, and recording the resulting reduction in malaria clinical incidence (Figure 8.3).

After predicting the likely public health outcome of a large combination of different property values, the results of a grid search can be used to identify optimal intervention properties. For example, given a target clinical incidence reduction, we can identify the smallest duration of protection needed for the intervention to achieve the target.

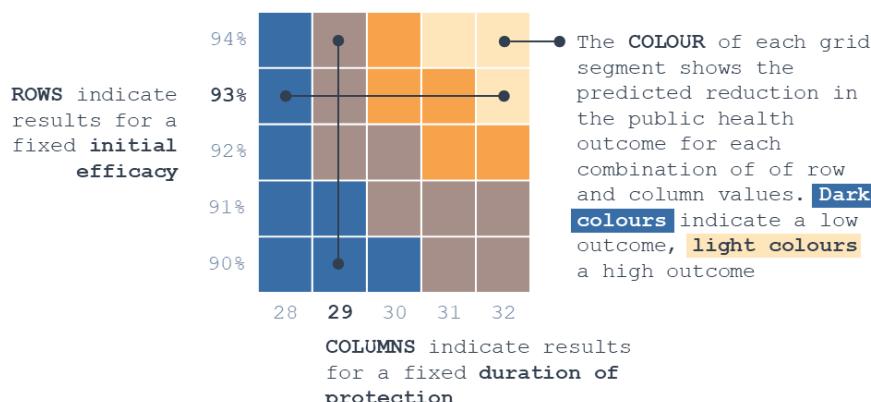


Figure 8.3. Understanding the identification of key performance criteria.

8.4. TABLE OF DEFINITIONS

Term	Definition	Example
Clinical incidence reduction	A primary clinical trial and implementation outcome , the % reduction in clinical incidence compared to a no intervention counterfactual, where incidence is defined as the number of new, uncomplicated malaria cases detectable by rapid diagnostic test across a five-month period ³ in the fifth year after deployment.	In a population of 1000 children monitored over a five-month intervention period, deploying SMC with four rounds led to a reduction in the number of new cases of uncomplicated malaria from 400 to 200, i.e. to a clinical incidence reduction of 50%.
Decay profile	The decrease in protective efficacy over time, resulting in the reduction of the intervention's initial efficacy. This decay curve can have multiple shapes, such as a strong decrease shortly after administration (exponential), or a high efficacy after administration with a sharp decrease (sigmoidal).	SP+AQ's efficacy decays with a sigmoidal decay profile.
Duration of protection	A key performance characteristic , the number of days until the intervention's initial efficacy has decayed to half its original value.	An individual receives an intervention with an initial efficacy of 90% and a 30 day duration of protection. 30 days after the intervention was given, the individual is protected against 45% of infections.
Initial efficacy	A key performance characteristic , the intervention's average initial efficacy as the percentage of the maximum intended efficacy against liver stage infection in the target age group before decay, with or without inter-individual variation.	An individual receives an intervention with a 90% initial efficacy. The individual is protected from 90% of infections at this time.
Mortality reduction	A secondary clinical trial outcome , the % reduction in the number of malaria deaths compared to a no intervention counterfactual, where the number of deaths is evaluated across a five-month period ² in the fifth year after deployment.	In a population of 1000 children monitored over a five-month intervention period, deploying SMC with four rounds led to a reduction in the number of malaria deaths from 10 to 5, i.e. to a mortality reduction of 50%.
Annual baseline PfPR ₂₋₁₀	The annual <i>Plasmodium falciparum</i> parasite rate in children between two and ten years old, a measure of prevalence in a given year.	In 2021, the annual PfPR in children between two and ten years old was 25%.
Prevalence reduction	A primary clinical trial outcome , the % reduction in prevalence compared to a no intervention counterfactual, where prevalence is defined as the proportion of all malaria infections per target population at the end of a five-month period in the fifth year after deployment.	In a population of 1000 children surveyed at the end of a five-month intervention period, deploying SMC with four rounds led to a reduction in the number of malaria infections from 1200 to 600, i.e. to a prevalence reduction of 50%.
Program coverage	A key performance characteristic , the operational coverage of the SMC program in a given target population.	SMC is available to children between three and 59 months old with 80% program coverage. Each child has an 80% chance of being included in the SMC program.
Round coverage	A key performance characteristic , the operational coverage of a single round of the intervention in a given target population.	SMC is given to a population of children with 90% round coverage. For each round of SMC, each child has a 90% chance of receiving the intervention.
Seasonal profile	A mathematical equation that captures the shape and length of a region's highest risk period to malaria infection.	A four-month seasonal profile has the most intense transmission of malaria during a four-month consecutive period.
Severe disease reduction	A primary clinical trial and implementation outcome , the % reduction in the number of severe malaria cases compared to a no intervention counterfactual, where severe cases of malaria are evaluated across a five-month period ² in the fifth year after deployment.	In a population of 1000 children monitored over a five-month intervention period, deploying SMC with four rounds led to a reduction in the number of severe malaria cases from 30 to 10, i.e. to a severe disease reduction of 67%.

Table 8.4. Summary of definitions.

³ All outcome reductions were evaluated over the same five-month intervention period regardless of the number of rounds of SMC deployed, chosen to enable comparison across deployments. As a result, the reported level of reduction may be lower than observed in clinical or observational studies, where the evaluation period is often matched to the number of months in which SMC is deployed.

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APPENDIX

A.1 Predicted minimum performance criteria for next-generation SMC

A.1.1 Predicted minimum clinical incidence criteria for next-generation SMC

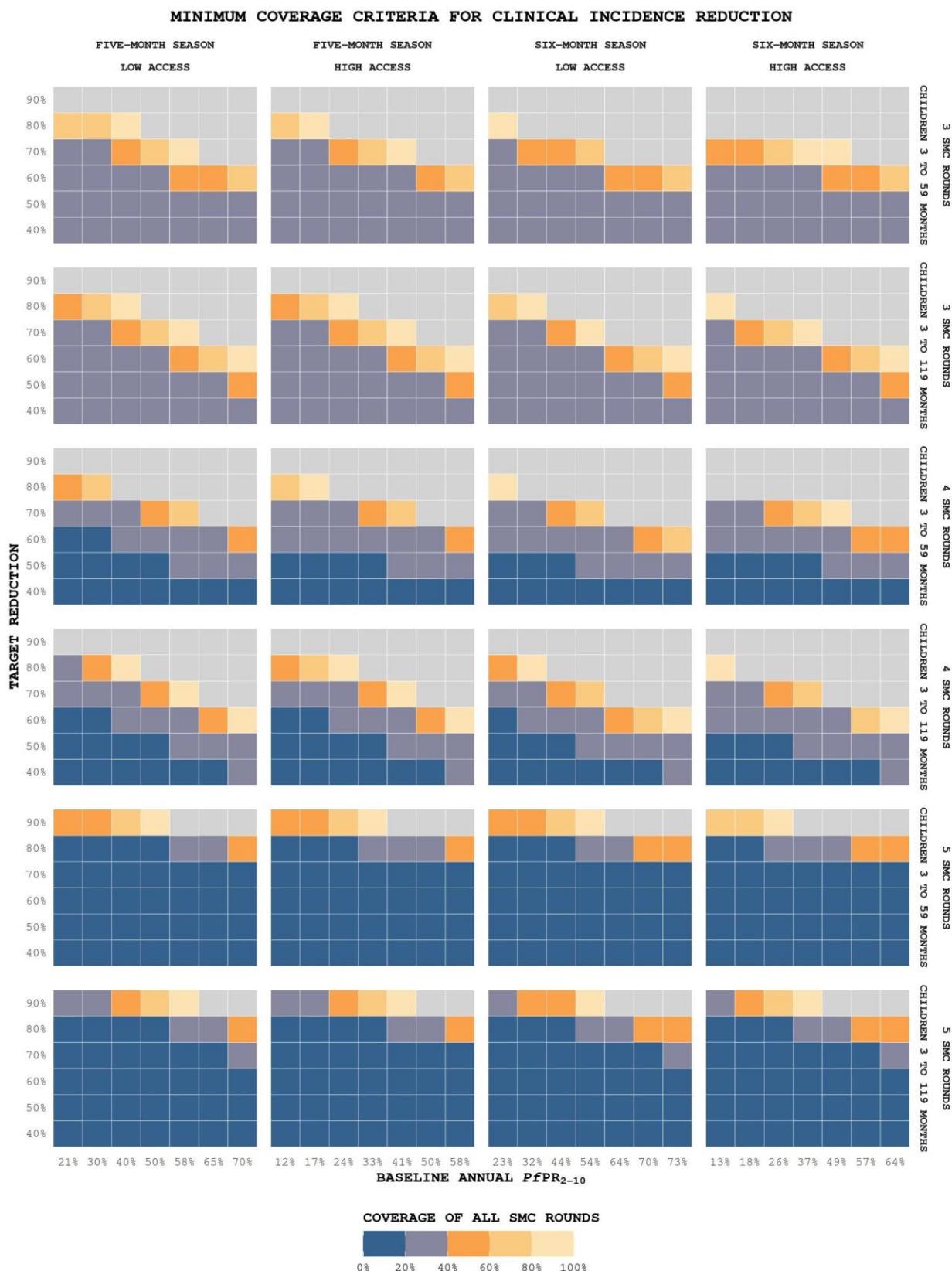


Figure A.1.1.1. Predicted minimum coverage criteria for next-generation SMC towards achieving a target clinical incidence reduction compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum values for the coverage required to achieve a given target reduction in clinical incidence (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. Results are shown for different seasonal profiles and numbers of SMC rounds, as well as for different levels of access to treatment, where the intervention is modelled as a drug with liver stage chemoprotection.

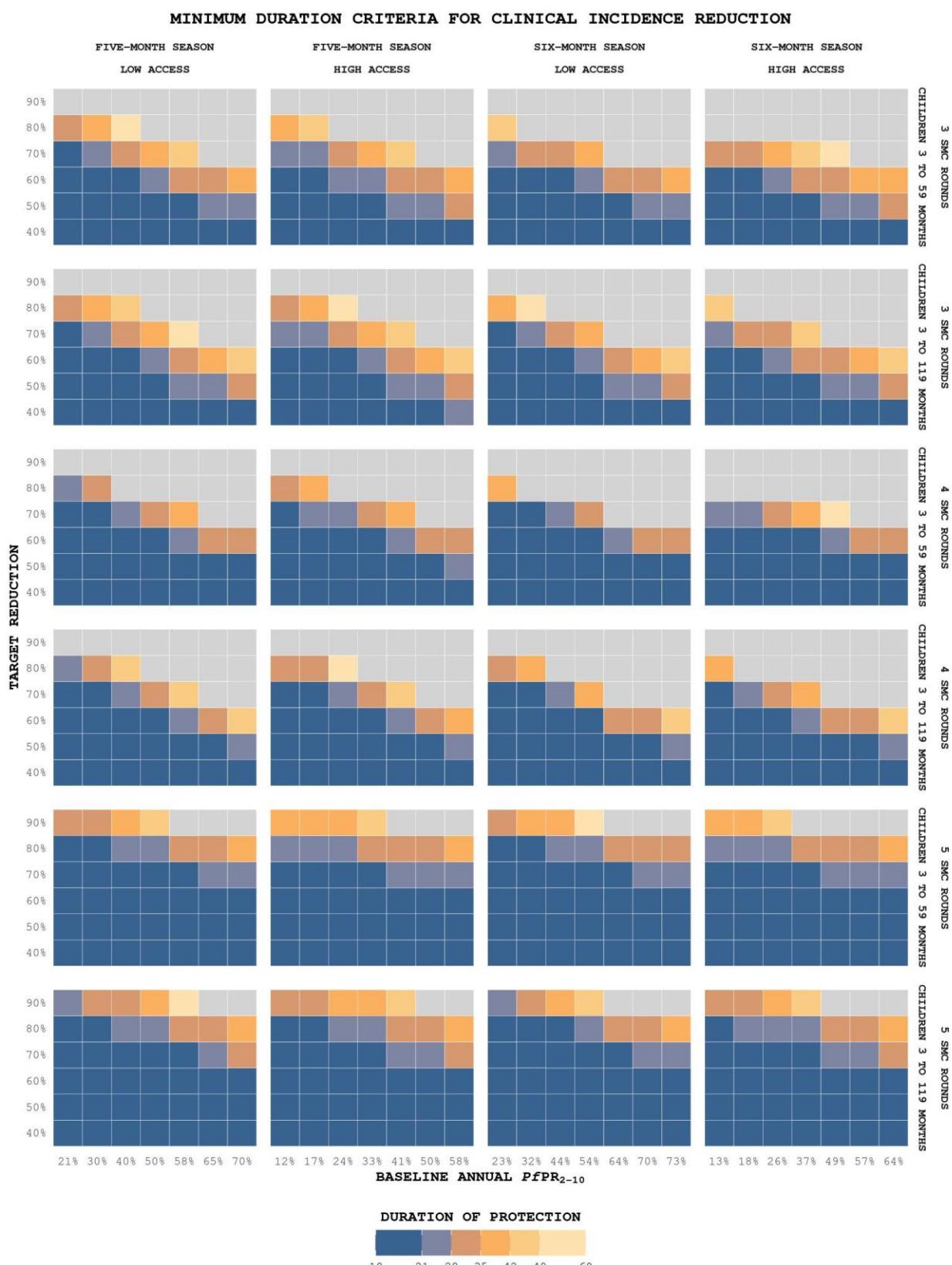


Figure A.1.1.2. Predicted minimum duration of protection criteria for next-generation SMC towards achieving a target clinical incidence reduction compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum values for the duration of protection required to achieve a given target reduction in clinical incidence (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. Results are shown for different seasonal profiles and numbers of SMC rounds, as well as for different levels of access to treatment, where the intervention is modelled as a drug with liver stage chemoprotection.

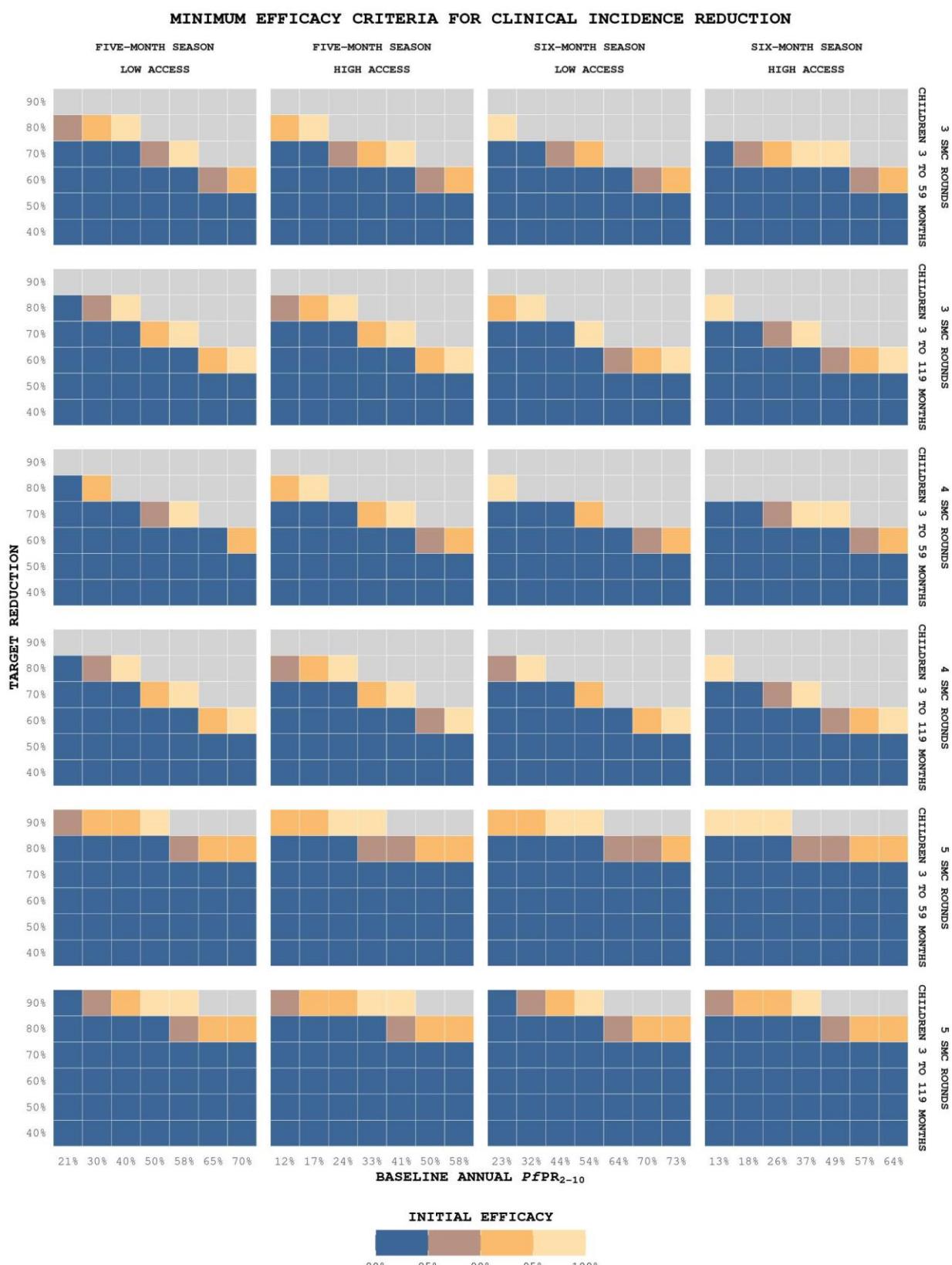
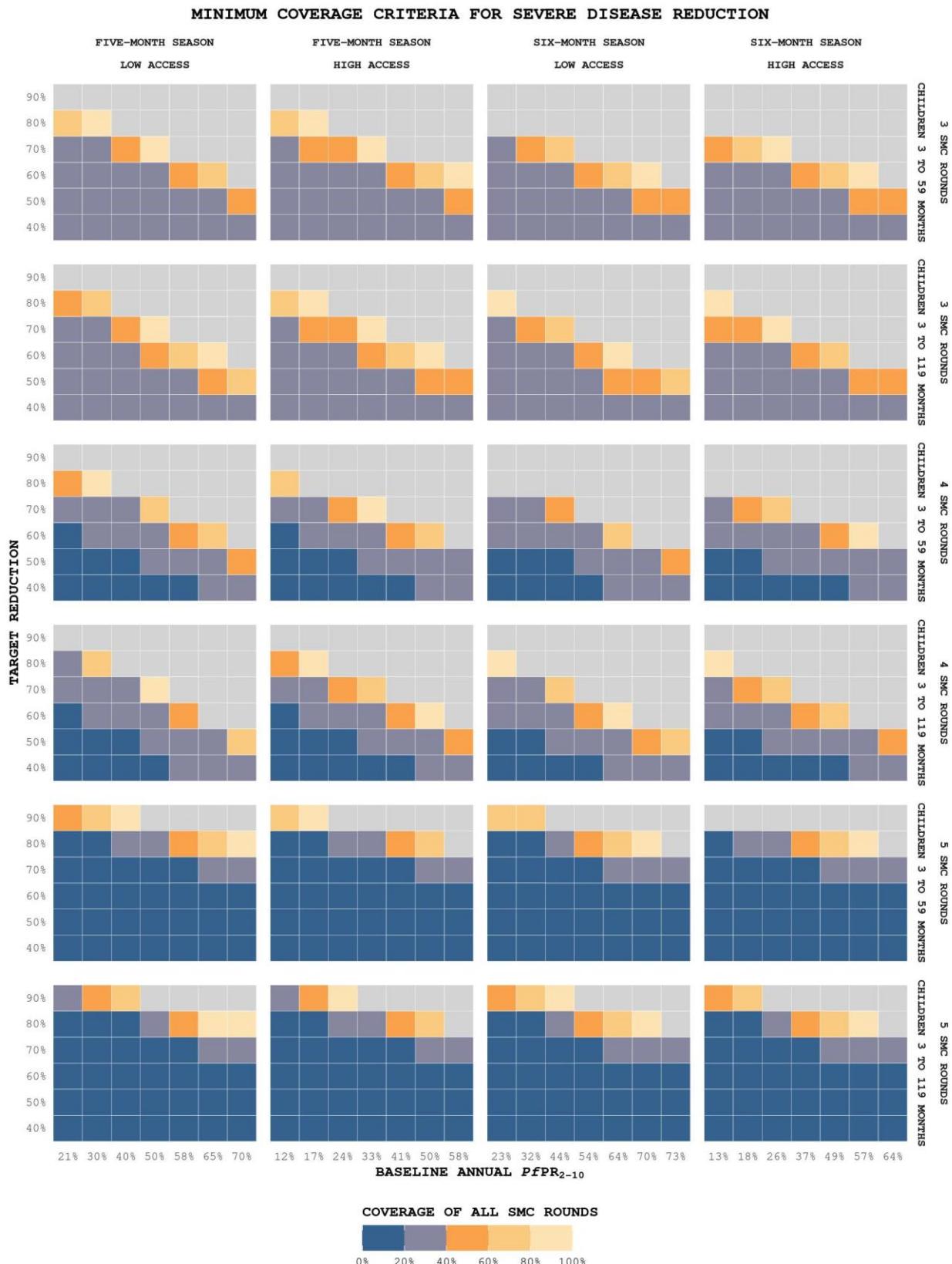
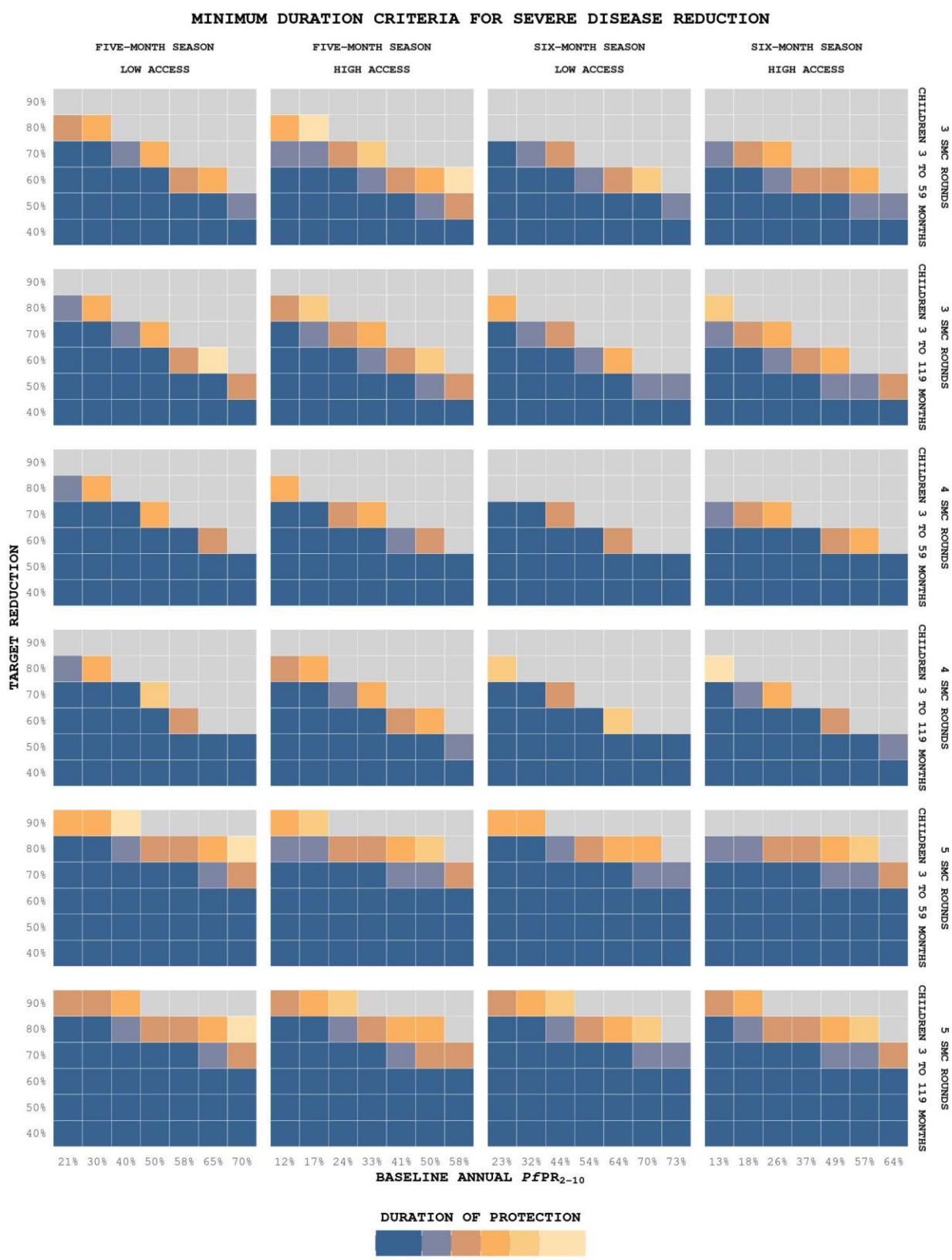


Figure A.1.1.3. Predicted minimum initial efficacy criteria for next-generation SMC towards achieving a target clinical incidence reduction compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum values for the initial efficacy required to achieve a given target reduction in clinical incidence (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. Results are shown for different seasonal profiles and numbers of SMC rounds, as well as for different levels of access to treatment, where the intervention is modelled as a drug with liver stage chemoprotection.

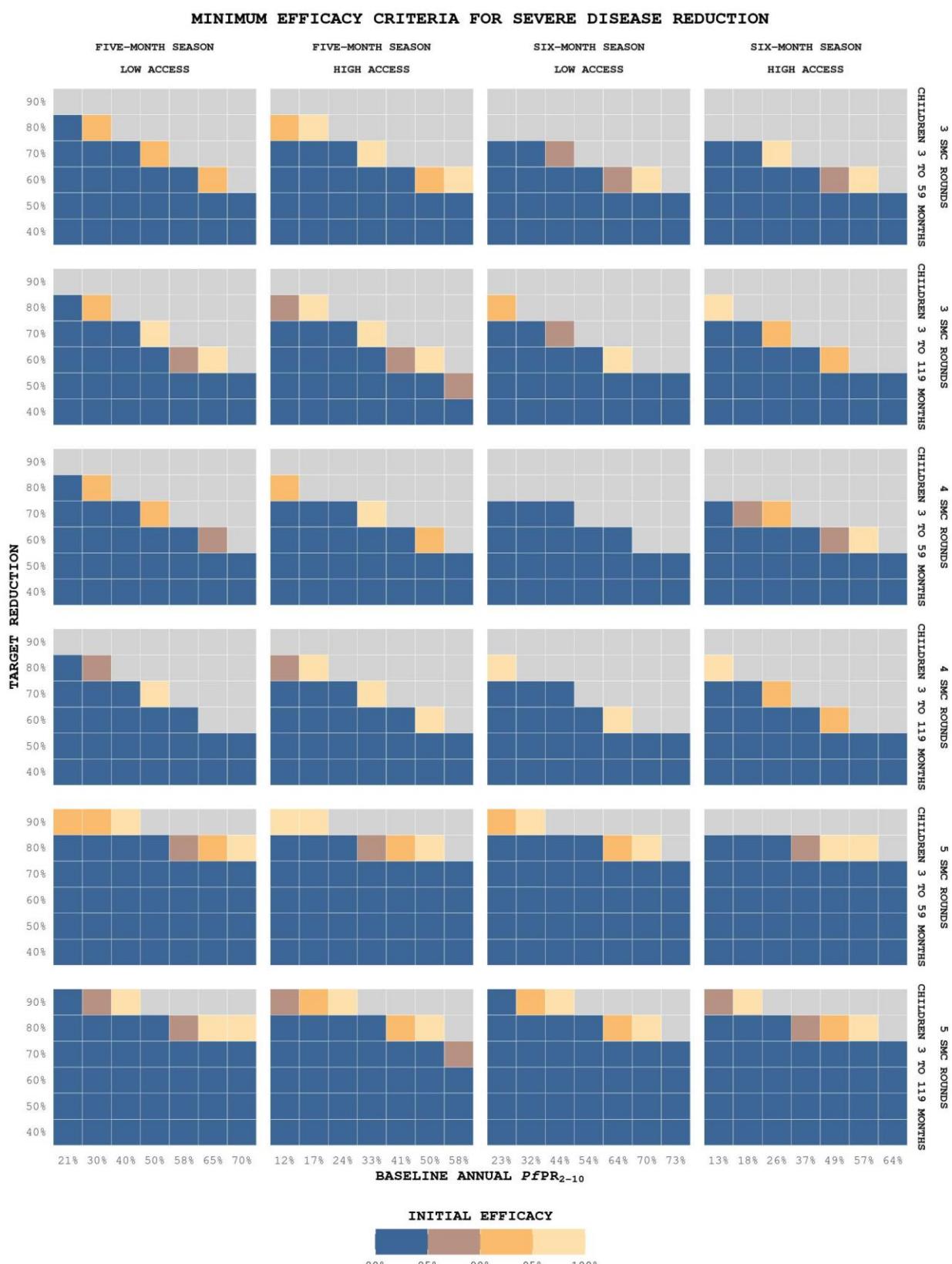
A.1.2 Predicted minimum severe disease criteria for next-generation SMC



A.1.2.1. Predicted minimum coverage criteria for next-generation SMC towards achieving a target severe disease reduction compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum values for the coverage required to achieve a given target reduction in severe disease (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. Results are shown for different seasonal profiles and numbers of SMC rounds, as well as for different levels of access to treatment, where the intervention is modelled as a drug with liver stage chemoprotection.



A.1.2.2. Predicted minimum duration of protection criteria for next-generation SMC towards achieving a target severe disease reduction compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum values for the duration of protection required to achieve a given target reduction in severe disease (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. Results are shown for different seasonal profiles and numbers of SMC rounds, as well as for different levels of access to treatment, where the intervention is modelled as a drug with liver stage chemoprotection.



A.1.2.3. Predicted minimum initial efficacy criteria for next-generation SMC towards achieving a target severe disease reduction compared with a no intervention counterfactual over a five-month period. Results show the estimated minimum values for the initial efficacy required to achieve a given target reduction in severe disease (y-axis). Grey shaded boxes indicate that the target is outside the parameter range. Results are shown for different seasonal profiles and numbers of SMC rounds, as well as for different levels of access to treatment, where the intervention is modelled as a drug with liver stage chemoprotection.

Scenario	PfPR ₂₋₁₀	Reduction in endpoint	Target Impact (over 5 months)	Minimum criteria for key performance properties			
				Program Coverage	Round Coverage	Duration of Protection	Initial Efficacy
SMC deployed 3 times a year to children aged 3 to 59 months, in a setting with a five-month seasonal profile and high access to treatment	12%	Clinical incidence	74%	90%	76%	29 days	82%
		Severe disease	75%	91%	79%	28 days	80%
	17%	Clinical incidence	70%	86%	72%	28 days	80%
		Severe disease	70%	90%	77%	27 days	80%
	24%	Clinical incidence	66%	85%	72%	28 days	80%
		Severe disease	67%	90%	76%	28 days	80%
	33%	Clinical incidence	62%	84%	71%	29 days	81%
		Severe disease	62%	89%	75%	28 days	80%
	41%	Clinical incidence	58%	82%	70%	29 days	80%
		Severe disease	57%	87%	76%	28 days	80%
	50%	Clinical incidence	54%	80%	70%	29 days	80%
		Severe disease	53%	86%	75%	28 days	80%
SMC deployed 3 times a year to children aged 3 to 119 months (expanded ages), in a setting with a five-month seasonal profile and high access to treatment	58%	Clinical incidence	50%	78%	70%	30 days	81%
		Severe disease	49%	85%	74%	27 days	80%
	12%	Clinical incidence	75%	88%	73%	28 days	80%
		Severe disease	76%	92%	77%	29 days	81%
	17%	Clinical incidence	72%	87%	72%	28 days	81%
		Severe disease	72%	91%	78%	29 days	80%
	24%	Clinical incidence	68%	86%	73%	29 days	81%
		Severe disease	68%	91%	78%	29 days	80%
	33%	Clinical incidence	62%	84%	72%	29 days	80%
		Severe disease	62%	90%	78%	28 days	81%
	41%	Clinical incidence	57%	82%	71%	29 days	80%
		Severe disease	56%	88%	77%	28 days	80%
	50%	Clinical incidence	52%	81%	71%	29 days	81%
		Severe disease	51%	88%	77%	28 days	80%
	58%	Clinical incidence	47%	80%	70%	29 days	81%
		Severe disease	48%	87%	78%	29 days	82%
SMC deployed 4 times a year to children aged 3 to 59 months, in a setting with a five-month seasonal profile and high access to treatment	12%	Clinical incidence	75%	90%	76%	26 days	82%
		Severe disease	76%	93%	79%	27 days	80%
	17%	Clinical incidence	73%	89%	77%	27 days	83%
		Severe disease	72%	91%	78%	25 days	80%
	24%	Clinical incidence	70%	90%	78%	28 days	85%
		Severe disease	69%	93%	80%	27 days	80%
	33%	Clinical incidence	66%	88%	75%	28 days	85%
		Severe disease	65%	93%	81%	28 days	80%
	41%	Clinical incidence	62%	87%	75%	28 days	84%
		Severe disease	60%	91%	80%	25 days	80%
	50%	Clinical incidence	59%	86%	76%	29 days	85%
		Severe disease	56%	91%	82%	27 days	80%
	58%	Clinical incidence	55%	85%	75%	28 days	85%
		Severe disease	52%	90%	81%	25 days	80%
SMC deployed 4 times a year to children aged 3 to 119 months (expanded ages), in a setting with a five-month seasonal profile and high access to treatment	12%	Clinical incidence	78%	91%	78%	28 days	83%
		Severe disease	77%	92%	79%	25 days	80%
	17%	Clinical incidence	75%	89%	77%	27 days	83%
		Severe disease	74%	92%	79%	26 days	80%
	24%	Clinical incidence	71%	90%	78%	27 days	83%
		Severe disease	69%	93%	80%	26 days	80%
	33%	Clinical incidence	66%	88%	76%	28 days	84%
		Severe disease	64%	92%	80%	27 days	80%
	41%	Clinical incidence	61%	88%	76%	28 days	84%
		Severe disease	59%	92%	81%	28 days	80%
	50%	Clinical incidence	56%	87%	75%	28 days	84%
		Severe disease	54%	92%	82%	27 days	80%
	58%	Clinical incidence	51%	87%	76%	28 days	85%

Scenario	$PfPR_{2-10}$	Reduction in endpoint	Target Impact (over 5 months)	Minimum criteria for key performance properties			
				Program Coverage	Round Coverage	Duration of Protection	Initial Efficacy
SMC deployed 5 times a year to children aged 3 to 59 months, in a setting with a five-month seasonal profile and high access to treatment	12%	Severe disease	49%	91%	81%	24 days	80%
		Clinical incidence	84%	89%	73%	28 days	83%
	17%	Severe disease	83%	90%	74%	27 days	80%
		Clinical incidence	83%	89%	72%	27 days	83%
	24%	Severe disease	81%	90%	73%	27 days	80%
		Clinical incidence	81%	88%	72%	28 days	84%
	33%	Severe disease	79%	91%	75%	29 days	80%
		Clinical incidence	79%	87%	73%	29 days	85%
	41%	Severe disease	76%	90%	75%	28 days	80%
		Clinical incidence	75%	86%	71%	28 days	83%
	50%	Severe disease	72%	89%	75%	27 days	80%
		Clinical incidence	74%	86%	73%	29 days	85%
	58%	Severe disease	70%	90%	76%	28 days	80%
		Clinical incidence	70%	83%	70%	28 days	84%
SMC deployed 5 times a year to children aged 3 to 119 months (expanded ages), in a setting with a five-month seasonal profile and high access to treatment	12%	Severe disease	86%	90%	74%	27 days	80%
		Clinical incidence	87%	90%	71%	28 days	82%
	17%	Severe disease	84%	91%	74%	28 days	80%
		Clinical incidence	86%	89%	73%	28 days	84%
	24%	Severe disease	80%	91%	75%	28 days	80%
		Clinical incidence	83%	88%	71%	28 days	83%
	33%	Severe disease	77%	91%	75%	29 days	80%
		Clinical incidence	80%	88%	72%	28 days	84%
	41%	Severe disease	73%	90%	76%	28 days	80%
		Clinical incidence	77%	87%	73%	29 days	85%
	50%	Severe disease	70%	91%	76%	29 days	80%
		Clinical incidence	73%	86%	71%	29 days	84%
	58%	Severe disease	67%	90%	76%	29 days	81%
		Clinical incidence	69%	84%	71%	29 days	84%

Table A.1. Summary of the predicted minimum performance criteria for next-generation SMC to achieve a target clinical incidence and severe disease compared to a no-intervention counterfactual. Results show the estimated minimum values of each key performance characteristic required to achieve a target reduction comparable with the predicted impact of SP+AQ, where the intervention is modelled as a drug with liver stage chemoprotection. SP+AQ is parameterised as in previous work [1], with an initial efficacy of 100% and a duration of protection of 31 days. Results are shown for an SMC program deployed three, four or five times a year to two target populations, in a setting with a five-month seasonal profile and high access to treatment.

A.2 Targeted literature summary of shortlisted SMC candidate interventions

A targeted literature review was performed to identify known PK/PD and observed efficacy properties of each shortlisted SMC candidate. We reviewed a selection of key evidence and modelling studies to identify the following properties: mechanism of action, dosing regimen, efficacy, prophylaxis period, coverage, synergisms and antagonisms, and existing resistance (Table A.2). A detailed summary of the literature on each of these interventions, including citations, is available on request.

Candidate intervention	Target (blood stage, liver stage)	Initial efficacy (min - max %)	Duration of protection (min - max days)	Decay profile	Coverage (min - max %)	Risk of resistance (high, medium, low, none)
Atovaquone-Proguanil (ATV-PG)	Blood + liver stages	87% - 100%	14 - 29 days	Unknown	Unknown	High prevalence of PG resistance with high likelihood of selection for resistance
Atovaquone-Proguanil + Chloroquine (ATV-PG+CQ)	Blood + liver stages	Unknown	Unknown	Unknown	Unknown	High prevalence of PG and CQ resistance with high likelihood of selection for resistance
Atovaquone-Proguanil + Piperaquine (ATV-PG+PPQ)	Blood + liver stages	Unknown	Unknown	Unknown	Unknown	High prevalence of PG resistance, low prevalence of PPQ resistance
Atovaquone-Proguanil + Pyronaridine (ATV-PG+PYN)	Blood + liver stages	Unknown	Unknown	Unknown	Unknown	High prevalence of PG resistance with high likelihood of selection for resistance
Dihydroartemisinin + Piperaquine (DHA+PPQ)	Blood stage	94% - 100%	28 - 56 days	Sigmoidal or exponential	81% - 98%	Medium prevalence of resistance
Dihydroartemisinin + Piperaquine + Sulfadoxine-Pyrimethamine (DHA+PPQ+SP)	Blood stage	Unknown	Unknown	Unknown	Unknown	Medium prevalence of DHA+PPQ resistance, medium prevalence of SP resistance
KAF156 (Ganaplacide)	Blood + liver stages	67% - 99%	Unknown	Unknown	Unknown	None
MMV370/MMV371 (previously mCBE161)	Blood + liver stages	Unknown	Unknown	Unknown	Unknown	None
Pyronaridine + Amodiaquine (PYN+AQ)	Blood + liver stages	Unknown	Unknown	Unknown	Unknown	Low
Pyronaridine + Chloroquine (PYN+CQ)	Blood + liver stages	Unknown	Unknown	Unknown	Unknown	High prevalence of CQ resistance
Pyronaridine + Piperaquine (PYN+PPQ)	Blood + liver stages	Unknown	Unknown	Unknown	Unknown	Low prevalence of PPQ resistance
Sulfadoxine-Pyrimethamine + Amodiaquine (SP+AQ)	Blood + liver stages	83% - 100%	21 - 31 days	Exponential	53% - 100%	Medium prevalence of SP resistance

Table A.2. Summary of the likely ranges of each shortlisted SMC candidates' key performance properties against *Plasmodium falciparum* infection. These properties were identified from a targeted literature review of evidence and modelling studies, and summarize the maximum and minimum values identified across use-cases, settings and clinical outcomes. A detailed summary of the literature on each of these interventions, including citations, is available on request.

A.3 Supplementary evidence for iTPP3 criteria

Key performance property	Range of attributable outcome variation (min - max %)	
	Clinical incidence reduction	Severe disease reduction
SMC program coverage [70% - 100%]	29% to 57%	52% to 72%
Duration of protection [10 - 60 days]	19% to 48%	1% to 26%
SMC round coverage [70% - 100%]	13% to 24%	15% to 29%
Initial efficacy [80% - 100%]	2% to 8%	0% to 3%

Table A.3. Contribution of key performance properties to health outcomes. Results show the minimum to maximum Sobol total effect indices evaluated across all modelled scenarios (varying baseline prevalence, seasonality and access to treatment), indicating the variation in predicted clinical incidence and severe disease reduction that can be attributed to each key performance property: program coverage (ranging from 70% to 100%), duration of protection (10 to 60 days), round coverage (70% to 100%) and initial efficacy (80% to 100%).

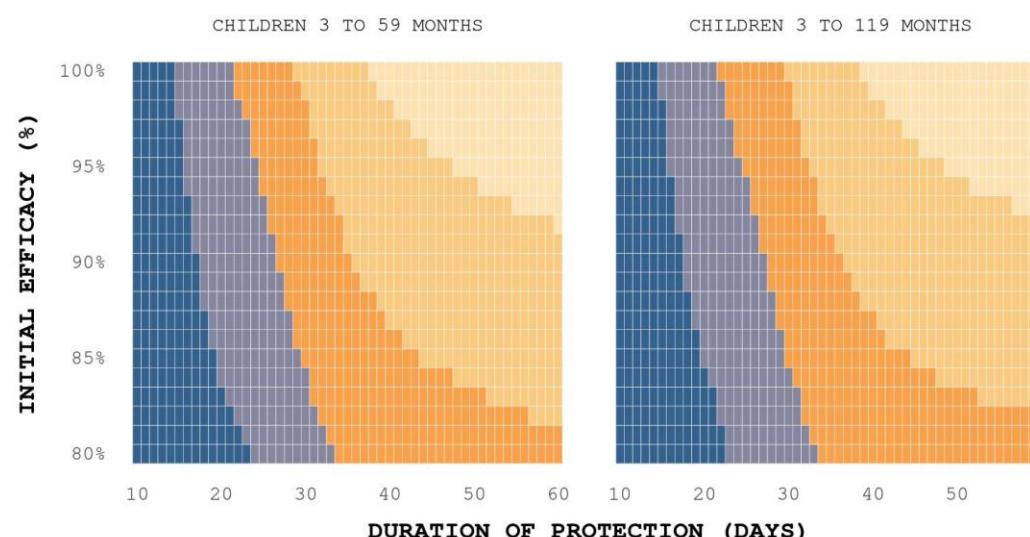


Figure A.3.1. Predicted relative reduction in clinical incidence for an SMC program deployed in two target age groups – children aged three to 59 months (left panel), and children aged three to 119 months (right panel) – measured in implementation settings in comparison to the counterfactual of no intervention. Each square in the grid indicates the predicted relative reduction in clinical incidence if an intervention with the given initial chemoprotection efficacy and duration of protection were deployed, where the intervention is modelled as a drug with liver stage chemoprotection. Results are shown for an SMC program in one archetypal scenario: high access to treatment with a six-month seasonal profile and moderate to high transmission intensity (37% annual baseline $PfPR_{2-10}$), where SMC is deployed four times a year in monthly intervals with a moderate program and round coverage of 95% and 85% respectively, corresponding to a 50% likelihood that a child receives all SMC rounds. For guidance on interpreting this figure, refer to Section 8.3.

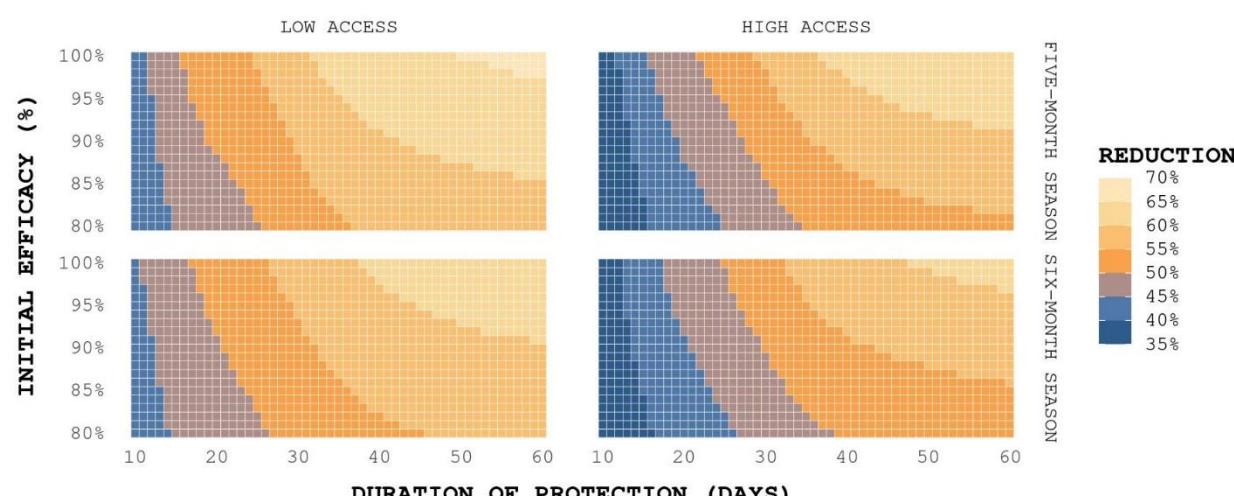


Figure A.3.2. Predicted relative reduction in clinical incidence for an SMC program deployed across seasonal profiles and across levels of access to treatment, measured in implementation settings in comparison to the counterfactual of no intervention. Each square in the grid indicates the predicted relative reduction in clinical incidence if an intervention with the given initial chemoprotection efficacy and duration of protection were deployed, where the intervention is modelled as a drug with liver stage chemoprotection. Results are shown for a scenario where transmission intensity is moderate and where SMC is deployed four times a year at monthly intervals to children aged three to 59 months, with a moderate program and round coverage of 95% and 85% respectively, corresponding to a 50% likelihood that a child receives all SMC rounds. For guidance on interpreting this figure, refer to Section 8.3.

A.4 Priority questions for iTPP3: Second-generation Seasonal Malaria Chemoprophylaxis

A.4.1 Questions identified as higher priority

- Duration of protection: what would happen if it could extend to 8 weeks? And impact of resistance? i.e. many countries are considering extending to five months next year.
- Effect of transmission-blocking potential to lead to optimized impact.
- How do we define when resistance burden becomes too high that we urgently need a replacement strategy? i.e. when to stop SMC and start new interventions? Impact of imperfect adherence for resistance?
- How do we optimize coverage to increase impact? i.e. dosing vs. intervals and if we can extend protection duration and reduce dosing.
- Interventions strategies to optimize tolerance and acceptability by the end-user (linked to adherence and resistance but alone less important).
- Key drivers of efficacy (with current sulfadoxine-pyrimethamine + amodiaquine)? Key feature (i.e. expanding target ages, duration, etc.) that a new product needs to improve the impact with current tools? Is new tool ambitious enough?
- What is the impact of the new intervention on drug resistance? i.e. mosaic strategy.
- What levels of transmission do we stop using SMC? Rely only on transmission or costs.

A.4.2 Questions identified as lower priority

- Acceptable threshold of safety for this intervention is higher. What strategy balances safety with key performance characteristics?
- Comparing clinical trials and strategy to bridging from regulatory endpoints to policy makers criteria.
- Evaluate time to introduction of new drugs.
- Expanding second-generation SMC to other regions (perennial and other seasonal settings)?
- Should we completely rethink the SMC strategy/definition with a novel medicine?
- What happens if we stop SMC or if we stop a new intervention? What is the effect? Benefit of leaky intervention (sulfadoxine-pyrimethamine + amodiaquine) or protection of new intervention?
- Which coverage definition matters more: pharmacokinetic coverage vs. population coverage?

A.5 Seasonal malaria chemoprevention and the spread of *Plasmodium falciparum* parasites resistant to sulfadoxine-pyrimethamine: a mathematical modelling study

Seasonal malaria chemoprevention and the spread of *Plasmodium falciparum* parasites resistant to sulfadoxine-pyrimethamine: a mathematical modelling study

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DRAFT

Summary

Background Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine prevents millions of clinical malaria cases in the Sahel. However, a genotype with five mutations causing partial resistance to sulfadoxine-pyrimethamine has emerged. We estimated the rate of spread of this mutant following SMC, assessed factors promoting its spread, and evaluated its impact on the effectiveness of SMC against clinical malaria.

Methods Using an individual-based malaria transmission model, we systematically quantified the influence of multiple factors on the spread of the mutant and predicted the time needed for the mutant to spread from 1% to 50% of inoculations in different settings and for several SMC deployment strategies. We further estimated the reduction in SMC effectiveness against clinical *Plasmodium falciparum* malaria expected due to the mutant spread.

Findings High coverage, transmission intensity, and access to treatment promoted the mutant spread. With SMC implementation of four rounds to children under five (with 95% initial coverage declining each round), the mutant took 53·1 years (95% CI 50·5–56·0) to spread from 1% to 50% of inoculations in a medium transmission intensity setting with seasonal transmission mostly occurring over four months, and access to clinical treatment relatively low. This time was reduced by half when SMC targeted children under ten, and reduced by 13 and 10 years when an additional round of SMC was deployed at the beginning and the end of the transmission season, respectively. For the same setting, the mean percentage of clinical malaria averted during the four months of SMC implementation was 79·0% (95% CI 77·8–80·8) when the mutant was absent in the population and still high at 60·4% (95% CI 58·6–62·3) when the quintuple was fixated.

Interpretation SMC with SP-AQ leads to a relatively slow spread of SP resistant quintuple mutants and remains an effective prophylactic intervention to prevent child clinical malaria in the Sahel despite quintuple mutants spread. Given the prophylactic period of SP-AQ, SMC could be considered in seasonal settings where the quintuple mutant is already prevalent.

Introduction

Plasmodium falciparum malaria is a leading cause of morbidity and mortality in African children.¹ In the Sahel, malaria transmission is highly seasonal, with most of the burden occurring during three to five months (between August and December).² The World Health Organization (WHO) recommends implementation of seasonal malaria chemoprevention (SMC) to reduce disease burden in this region. SMC involves monthly administration of sulfadoxine and pyrimethamine (SP) plus amodiaquine (AQ) to children under five years during the transmission seasons.² A recent implementation study in the Sahel reported that SMC prevents more than 88% of uncomplicated malaria cases within 28-days of administration.³ This high effectiveness is partly attributable to the fact that SP remains at a concentration sufficient to inhibit development of successful blood-stage infections for a long time post-treatment.⁴ Current evidence suggests that this prophylactic period is roughly 42-days against SP sensitive parasites but is reduced for parasites with lower sensitivity to SP.^{5,6}

Accumulation of mutations in *dhps* and *dhfr* genes of the *P. falciparum* parasite leads to reduced sensitivity to SP.^{7,8} Previous use of SP as first-line treatment has caused worldwide spread of malaria parasites with multiple mutations in these genes.^{9,10} In many Sahelian countries, the quadruple mutant genotype (with *dhfr*-51I, *dhfr*-59A, *dhfr*-108A, and *dhps*-437G mutations) is already the most prevalent genotype.^{3,11} Nevertheless, SMC remains efficient in this region because SP still provides a prophylactic period of approximately 35-days against this genotype (figure 1A) as reported by clinical trials of SMC with SP+AQ, and intermittent preventive treatment in infancy (IPTi) with SP and a prospective study of intermittent preventive treatment in pregnancy (IPTp) with SP.^{5,12,13} A more significant threat comes from the emergence of a quintuple mutant,³ which carries an additional mutation (*dhps*-540G) that has higher resistance to SP. The use of SP in monotherapy against this mutant is associated with increased treatment failure rates.¹⁴ However, current data from clinical trials of IPTi with SP and a prospective study of IPTp with SP suggest that SP still prevents the successful development of quintuple mutant blood-stage infection (due to reinfection or recrudescence) for a period of 21-days post-treatment (figure 1A).^{5,6} Given the chance quintuple mutants can develop blood-stage infections before more sensitive parasites, including the quadruple mutant, the implementation of SMC may favour its spread. Selection is possible even though AQ provides a prophylactic period of 17-days because this prophylactic period cannot prevent the selection of the quintuple mutant (figure 1A).¹⁵

It is unknown at which rate the quintuple mutant will spread in a population due to implementation of SMC, nor which factors including target age group, number of rounds administered per year, or transmission intensity will favour or delay its spread. Moreover, it is uncertain how strongly spread of the quintuple mutant will reduce SMC effectiveness against clinical cases, and thus whether SMC with SP+AQ will remain a valuable preventive tool or if alternatives are urgently needed. In this study, we used an individual-based model of malaria transmission, OpenMalaria,¹⁶ to assess the rate of spread of the SP resistant quintuple mutant. We assessed this rate of spread in a parasite population predominantly composed of quadruple mutants because the quadruple mutant is the most prevalent genotype in the Sahel^{3,11} and the quadruple mutant is the most prominent competitor of the quintuple mutant as there is no fitness cost associated with resistance to SP¹⁷ (other genotypes (sensitive, single, double,

triple mutants) behave similarly to the quadruple mutant in individuals who did not receive SMC, but the quadruple mutant can develop a successful blood-stage infection a few days earlier than these genotypes in children who received SMC). In addition, we systematically quantified which factors are more likely to drive the spread in various deployment strategies and seasonality settings. Finally, we estimated the potential decrease in the effectiveness of SMC against clinical malaria expected with the spread of the quintuple mutant.

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Research in context

Evidence before this study

In March 2021 we performed a literature search for studies that modelled the impact of SMC deployment on the spread of malaria parasites less sensitive to SP. We accomplished this search using PubMed for the following keywords: malaria AND model* AND resistance AND seasonal malaria chemoprevention OR intermittent preventive treatment". We found five modelling studies focusing on intermittent preventive treatment but no studies focusing on SMC. Consequently, these studies assumed that SP was administered at a constant rate in the targeted population in settings with perennial malaria transmission. Thus, it remains unknown how seasonality and SMC implementation strategies affect the quintuple mutant's spread, such as the number of rounds administered per year and target age group. In addition, three of these studies assumed that the parasite was fully resistant to the drug used in IPT, ignoring the remaining drug effect on the parasite. Moreover, four of these studies modelled that the resistant genotype was resistant to both the drug used for IPT and first-line treatment. This assumption does not correspond to the use of SP for SMC and first-line treatments used in the Sahel.

Added value of this study

To the best of our knowledge, our study is first to estimate the impact of SMC on the spread of the quintuple mutant and assess the mutant's impact on SMC effectiveness. Our model captures the remaining effect of SP on partially resistant parasites and allows examination of the impact of different deployment strategies and seasonality settings on the rate of spread. The results show that with current SMC implementation (four rounds for children under five years with 95% initial coverage declining by 10% each round), the mutant need 53·1 years (95% CI 50·5–56·0) to spread from 1% to 50% of inoculations in a typical setting of the Sahel (medium transmission intensity mostly occurring over four months, with low access to treatment). However, the spread accelerates with additional rounds of SMC deployed at the beginning or end of the transmission season and when SMC targets children under ten. Nevertheless, our results demonstrate that even in the worst-case scenario of the quintuple mutant reaching fixation, current SMC implementation is likely to prevent 60·4% (95% CI 58·6–62·3) of clinical malaria in children in the Sahel.

Implications of all available evidence

We found that the rate of spread of the quintuple mutant with partial resistance to SP strongly depends on the implementation strategy of SMC with SP+AQ. Nevertheless, our results suggest that SMC will continue to prevent millions of clinical cases in Sahelian children despite the spread of the quintuple mutant. Our results also highlight that in seasonal settings where the quintuple mutant is already the most prevalent genotype, and clinical and severe malaria burden remains high, there is cause to consider implementing SMC with SP+AQ.

Methods

Model calibration

In this study we calibrated and used our existing individual-based model of malaria transmission, known as OpenMalaria, that simulates the dynamics of *P. falciparum* in mosquitoes and humans.¹⁸⁻²⁰ This model tracks multiple parasite genotypes, models their dynamics within the host, and captures that genotypes have different sensitivity to drugs using pharmacokinetic (PK) and pharmacodynamics (PD) model components. The model was previously described in¹⁸⁻²¹ and is briefly described in appendix p 4.

With this model, we tracked the spread of the quintuple mutant (*dhfr*-51I, *dhfr*-59A, *dhfr*-108A, and *dhps*-437G, *dhps*-540G) in a parasite population composed of predominantly quadruple mutants (*dhfr*-51I, *dhfr*-59A, *dhfr*-108A, and *dhps*-437G) due to the implementation of SMC with SP+AQ. We deployed SMC in two seasonality settings, one in which approximately 85% of transmission occurs over three months (high seasonality), and another over four months (moderate seasonality) (appendix p 6 figure S1.1). For the high seasonality settings, SMC was deployed three times per year (as currently recommended by WHO), or four times per year, with the additional round administered before or after the recommended deployment period (appendix p 6 figure S1.2). Similarly, for moderate seasonality settings, SMC was deployed four times per year, or five times per year, with the additional round administered before or after the recommended deployment period (appendix p 6 figure S1.3). We deployed SMC to two different target age groups: children aged three months to five years or three months to ten years. For each deployment strategy, we investigated scenarios for which SMC coverage was constant across rounds or decreased by 10% each round (e.g., if the first round is 80%, then subsequent rounds are 72%, 65%, etc.).^{3, 12}

At each SMC round, children received one dose of SP and three daily doses of AQ with the dosage adapted to their age as recommend by WHO (appendix p 7 table S1.1).^{2, 22} We modelled AQ using two-compartment PK/PD models with first-order absorption (appendix p 11-13 table S1.3 and S1.4) and assumed that both mutants were sensitive to AQ. We modelled that SP conferred a blood-stage prophylactic period of 35-days against the quadruple mutant and 21-days against the quintuple mutant as suggested by the literature (figure 1A).^{5, 6, 12, 13} To do that, we modelled SP as one long-acting drug with a one-compartment PK/PD model with first-order absorption (appendix p 8-10 table S1.2), and we used a higher half-maximal effective concentration (EC50) for the quintuple mutant than for the quadruple mutant. The increased EC50 of the quintuple mutant captures the mutant is less sensitive to SP at lower drug concentrations and could thus reinfect the host sooner than the quadruple mutant. To determine the EC50 of each mutant, we first established the link between the prophylactic period and the EC50 (figure 1B, appendix p 8-10 figure S1.2) and calibrated the EC50 to match the prophylactic period reported in IPTi, IPTp, and SMC studies.^{5, 6, 12, 13} With this calibration against clinical data, in our model we predict the quintuple genotype could develop a blood-stage infection before the next SMC round and not the quadruple mutant (figure 1C).

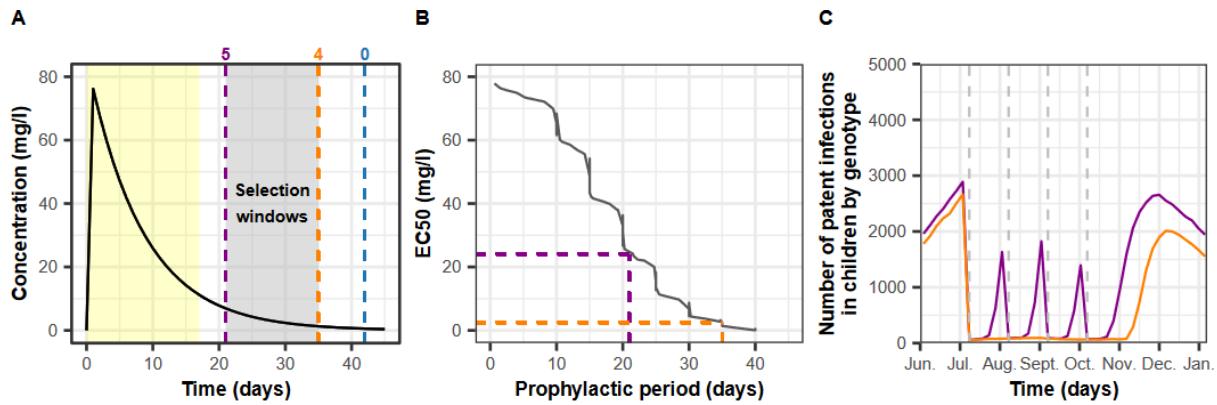


Figure 1: Schematics of SP resistance calibration and dynamics in our model

(A) Within-host plasma concentration of SP was modelled as a single long-acting drug with a one-compartment PK/PD model with first-order absorption (appendix p 8-10 table S1.2). The blue, orange, and purple dashed lines represent the end of the prophylactic period for a sensitive parasite, quadruple mutant, and quintuple mutant, respectively. The grey region between the orange and purple lines highlights the selection window (period during which the quintuple mutant can develop a successful blood-stage infection in treated children but not the quadruple mutant). The yellow region represents the prophylactic period conferred by AQ against all genotypes. AQ was modelled separately with two-compartment models with first-order absorption (appendix p 11-13 table S1.3 and S1.4). (B) The predicted relationship between the EC50 and the prophylactic period conferred by SP was estimated by our model (appendix p 8-10). The orange and purple dashed lines represent the estimated EC50 for the quadruple and quintuple mutants to confer the wished prophylactic periods, respectively, as reported by SMC, IPTi, IPTp studies.^{5, 6, 12, 13} (C) Example of the predicted number of patent infections in children under five years caused by the quadruple (orange line) or quintuple (purple line) mutant in a setting with a transmission intensity of 390 inoculations per person per year occurring mainly over four months and a 35% probability of symptomatic cases receiving treatment within two weeks from symptom onset (level of access to treatment). The grey dashed lines indicate timing for rounds of SMC administered. In this example, four rounds of SMC were administered with a coverage of 98% to children under ten years.

Identification of factors increasing SP resistance and quintuple mutant spread

For each seasonality setting and SMC deployment strategy we systematically quantified the level of influence of multiple epidemiological, PKPD properties, resistance and setting factors (table 1) on the spread of the quintuple mutant using global sensitivity analyses.²¹ We estimated the rate of spread of the quintuple genotype through the selection coefficient defined as the proportion by which the relative frequency of the quintuple mutant increases each parasite generation (appendix p 14).²³ Given the computational requirements of our individual-based model to be efficient with our global sensitivity analysis, we used emulators trained on our model simulations (appendix p 14-15). Emulators are predictive models that can approximate the relationship between input and output parameters of complex models and run much faster than complex models. For the global sensitivity analysis, we used Sobol method of variance decomposition (appendix p 15) which allowed us to estimate the first-order indices of each factor, representing their influence on the rate of spread, and the 25th, 50th, and 75th quantiles of the predicted rate of spread over each parameter range.

We further estimated the impact of SMC deployment strategies and seasonality settings on spread of the quintuple mutant by comparing the T_{50} , the time needed by the quintuple mutant to spread from a relative frequency of 1% (its current frequency in the Sahel)³ to 50% in inoculations (threshold above which ITP in infancy is not recommended).²⁴ For each SMC deployment strategy and seasonality setting, we first predicted the selection coefficient for various levels of coverage, transmission, and access to treatment with the trained emulators. We then converted the predictions to T_{50} (appendix p 22).

Table 1: Parameters and their ranges investigated in the global sensitivity analyses of the spread of the quintuple mutant

ACT: artemisinin-based combination therapy; AQ: amodiaquine SMC: seasonal malaria chemoprevention, SP: sulfadoxine-pyrimethamine

Determinant	Definition	Parameter range
Coverage of SMC	Percentage of individuals from the target age group that received SP+AQ during the first round of SMC (%)	[70,100]
Entomological inoculation rate (EIR)	Number of infective bites received by an individual during a year (inoculations per person per year)	[5, 500]
Level of access to treatment	Probability of symptomatic cases receiving treatment within two weeks from symptom onset (%)	[10, 80]
Half-life of the ACT partner drug	Time at which half the initial drug concentration remains (days)	[6, 22]

The impact of the quintuple mutant on SMC effectiveness

To estimate the impact of high-frequency quintuple mutant in the population on model estimates of the effectiveness of SMC, we varied the length of the prophylactic period offered by SMC with SP+AQ (between 5 and 40 days) for a range of settings. We assessed the protective effectiveness (PE) of SMC as the relative reduction in incidence of clinical malaria due to SMC during the months of SMC implementation (appendix p 25-26).³ We estimated the PE against parasite populations composed of only one genotype for which SP+AQ provide a prophylactic period of different length (5-, 10-, 15-, 21-, 25-, 30-, 35-, and 40-days, appendix p 27 table S2.1). For each parasite population, we assessed the PE of the recommended deployment of SMC (four rounds of SMC deployed per year to children under five years in the moderate seasonality setting with a coverage reduction of 10% from the previous round) for different levels of transmission, SMC coverage, and access to treatment.

DRAFT

Results

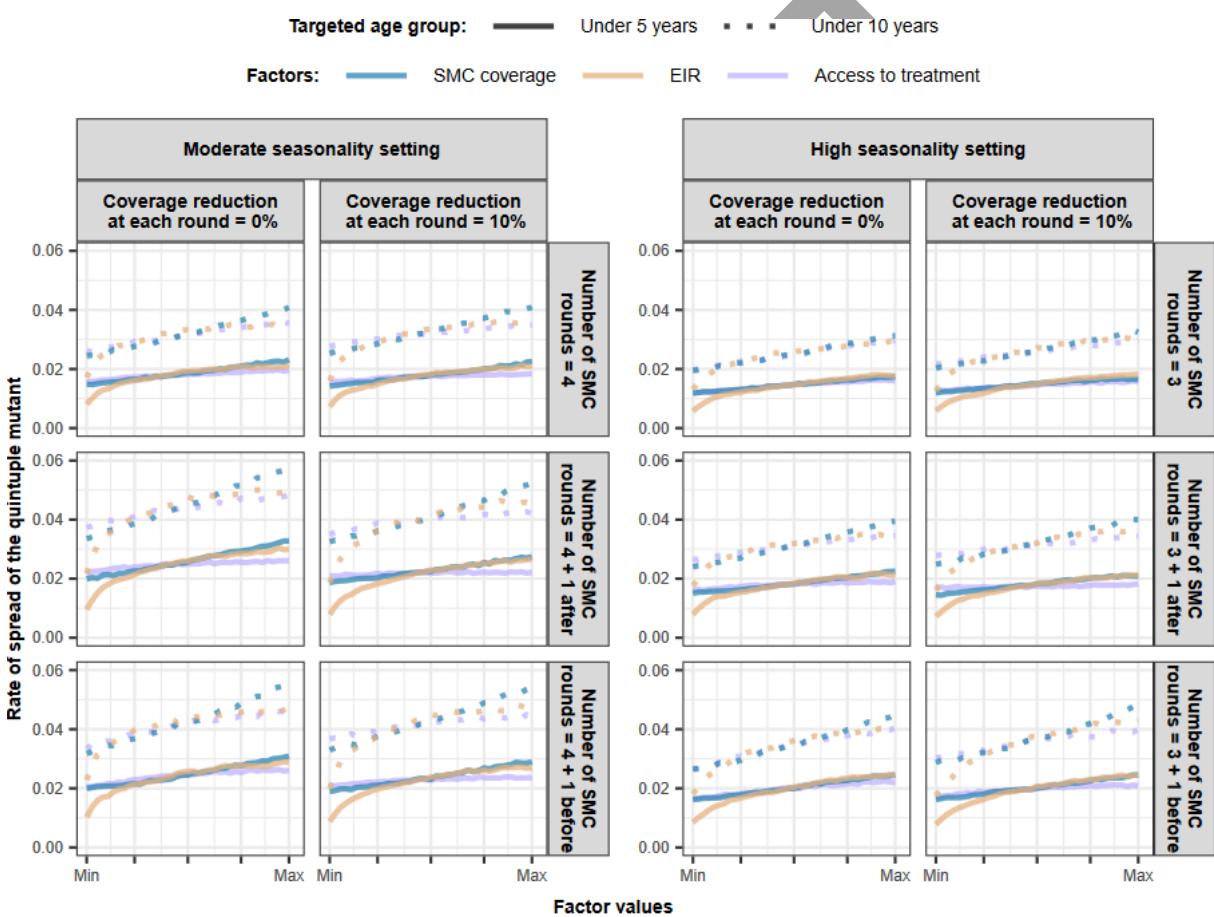
Factors driving the spread of SP quintuple mutant resistance

Our global sensitivity analysis of epidemiological, drug, and setting parameters on estimates of selection coefficients indicates that the levels of malaria transmission and SMC coverage play a crucial role in the predicted spread of the quintuple mutant resistant to SP (appendix p 19 figure S2.5). We found that high transmission levels increased the rate of spread (figure 2). Spread of SP resistance is faster in higher transmission settings due to the quintuple genotype being more likely to infect children during the selection window (period during which the quintuple genotype can develop a blood-stage infection in treated children but not the quadruple mutant). High SMC coverage levels also increased the rate of spread (figure 2), because more children receive SP increasing the selection pressure on the quintuple mutant.

The level of access to treatment of clinical cases also slightly increased the rate of spread in many settings (figure 2). Improving access to treatment reduces the parasite prevalence in individuals who do not receive SMC but not in children that receive SMC (appendix p 20 figure S2.6). Individuals who do not receive SMC are equally likely infected by the quadruple and quintuple mutants, whereas individuals that received SMC are more likely infected by quintuple mutants while protected by SP (appendix p 21 figure S2.7). Thus, a rise in access to treatment causes a slight increase in the relative frequency of quintuple mutant (appendix p 21 figure S2.7), favouring its spread.

Figure 2: The influence of different factors on the rate of spread of the quintuple mutant SP resistance

The lines represent the predicted median rate of spread (selection coefficient) of the quintuple mutant estimated from the global sensitivity analysis over the parameter ranges of each epidemiological, setting, SMC or drug properties factor when SMC is delivered to children under five years (plain lines) or children under ten years (dashed lines). The explored factors and their parameter ranges were as follows: SMC coverage at round one during the season [70%, 100%] (blue lines); transmission level as EIR [5, 500] inoculations per person per year (orange lines); and the level of access to treatment [10%, 80%] (purple lines). Results are for different seasonality settings (moderate or high seasonality), for various numbers of rounds deployed per year (high seasonality setting: three rounds or four rounds with the additional round deployed before or after the recommended deployment of SMC, moderate seasonality setting: four rounds or five rounds with the additional round deployed before or after the recommended deployment of SMC), and different assumptions about the reduction of the SMC coverage across each round (0% (constant coverage) or 10% reduction (e.g., if the first round is 80%, then subsequent rounds are 72%, 65%, etc.).



Predicted time till 50% frequency of SP resistant quintuple mutations

We observed that the predicted T_{50} from our model depends strongly on the SMC deployment strategies (figure 3, appendix p 23 figure S2.8 for results related to baseline parasite prevalence in 2-10 year olds). As an illustration, we compared T_{50} for various deployment strategies in a setting with a medium transmission intensity (EIR = 70 inoculations per person per year) and a low access to treatment (25%) when SMC had an initial coverage of 95%, which decreased by 10% each round (e.g. 100%, 90%, 81%) (figure 3, red lines). With the standard deployment of SMC (four rounds for children under five years) in settings with moderate seasonality, the quintuple genotype took 53·1 years (95% CI 50·5– 56·0) to reach a relative frequency of 50% in inoculations (T_{50}). Time was equal to 67·1 years (95% CI 63·2– 71·5) with a standard SMC regimen (three rounds for children under five years) in settings with high seasonality. T_{50} increases in high seasonality settings probably because it has one less round of SMC, which reduces the selection pressure on the quintuple genotype.

In the moderate seasonality setting, deploying an additional round of SMC at the beginning or the end of the transmission season decreased the T_{50} by approximately 13 and 10 years (39·6 (95% CI 38·0–41·3) and 42·8 (95% CI 41·0–44·7) years), respectively. Similarly, in the high seasonality setting, deploying an additional round before or after the recommended SMC deployment reduced this time by 16 and 15 years (50·5 (95% CI 48·0–53·4) and 51·6 (95% CI 48·7–54·8) years), respectively. Adding a round of SMC at the beginning of the transmission season accelerates the spread of the quintuple mutant more than adding one at the end probably because the quintuple mutant is more likely to reinfect children at the beginning of the transmission season as the EIR is rising.

Increasing the target age range from children under five years to children under ten means almost twice the number of individuals will receive SMC, accordingly, the T_{50} gets halved. For example, for moderate transmission settings, T_{50} decreased from 53·1 to 26·4 years (95% CI 25·6–27·3) when four rounds of SMC were administered to children under ten years, compared with children under five. Similarly, in high transmission settings, the T_{50} decreased from 67·1 years to 35·9 years (95% CI 33·6–26·7).

In our simulations, we deployed SMC to the same children across rounds, mimicking poor or in-equitable SMC delivery, with a proportion of children systematically missed for SMC. We assessed how the T_{50} changed if SMC was deployed more equitably, that is all children in the eligible population have the same probability of receiving SMC each round within a season. The spread of the quintuple mutant accelerated when SMC was deployed equitably (appendix p 24 figure S2.9). This result is because, with a more equitable coverage, children reinfected by the quintuple mutant do not have necessarily their infection with the quintuple mutant treated at the next SMC round in opposition to when the same children receive SMC each round (in-equitable delivery).

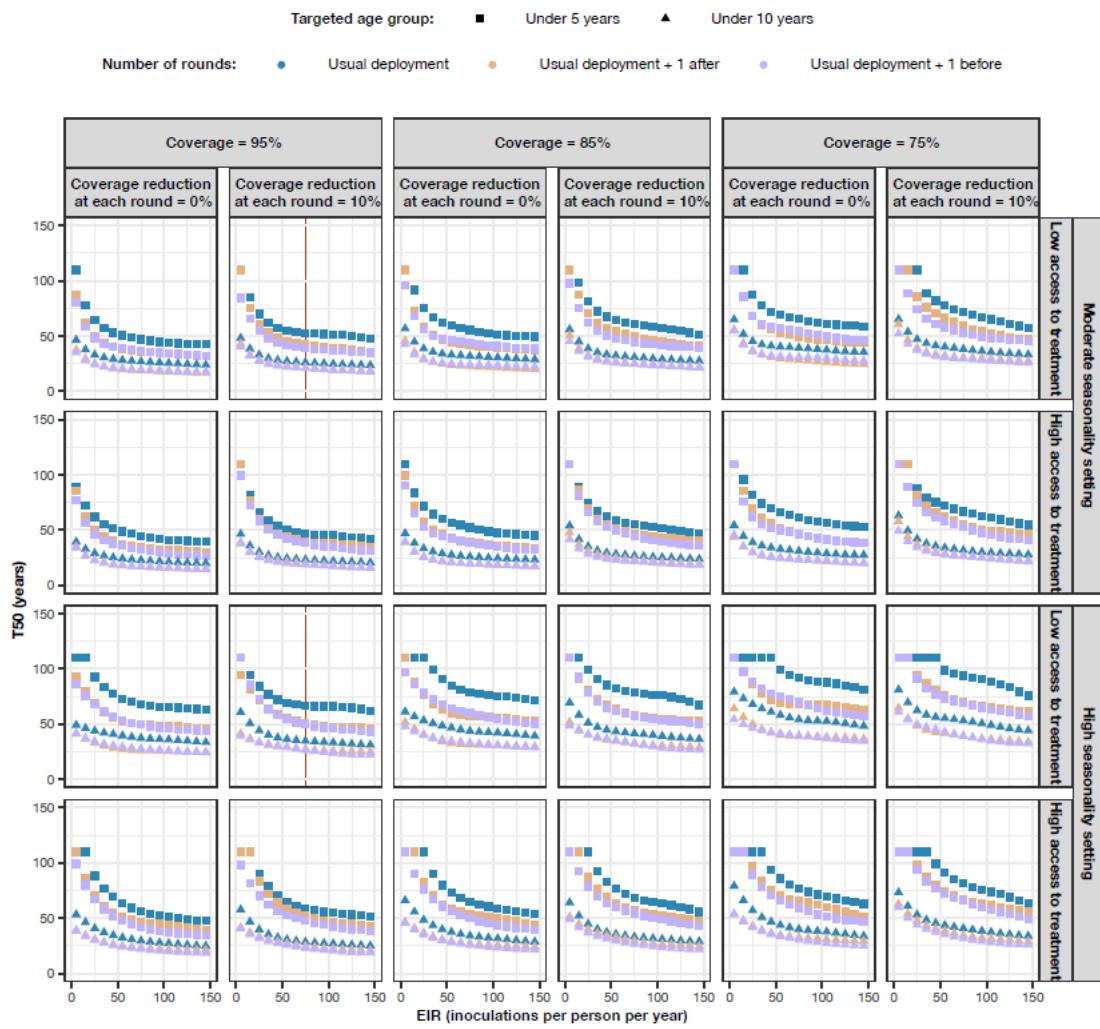


Figure 3: Predicted impact of SMC deployment strategies on the spread of the SP resistant quintuple mutant

Estimated time needed for the quintuple genotype to spread from a relative frequency in inoculations of 1% to 50%, T_{50} , when SMC was deployed to different age groups (under five (squares) or under ten years of age (triangles)) in diverse seasonality settings (moderate and high seasonality pattern) with a various number of rounds deployed per year (high seasonality: three (blue shapes) or four rounds with the additional round deployed before (purple shapes) or after (orange shapes) the standard deployment period; moderate seasonality setting: four (blue shapes) or five rounds with the additional round deployed before (purple shapes) or after (orange shapes) the standard SMC deployment period). We predicted the T_{50} for different levels of initial coverage (75%, 85%, and 95%) and coverage reduction across rounds (0% or 10% reduction since the previous round). For each setting and SMC deployment strategy, T_{50} was predicted for various transmission levels (ranging from 5 to 150 inoculations per person per year) and for two levels of access to treatment (25 and 70%). Red lines highlight points of interest which are described above.

Impact of SP quintuple mutant resistance on SMC effectiveness

As expected, the PE of SMC was strongly dependent on the prophylactic period length (figure 4). Simulations in which SMC conferred a prophylactic period of 35-days and 21-days mimicked deployment of SMC in a parasite population composed only of quadruple mutant and quintuple mutant, respectively. We observed that the PE decreased with shorter prophylactic periods, but the PE in a parasite population composed of quintuple mutant remained non-negligible (figure 4). We found that the PE range between 70·6–83·0% and 44·3–66·4% for 35-days and 21-days, respectively, at 95% SMC coverage overall simulated settings (figure 4). More specifically, in a setting with low access to treatment (25%), SMC prevented 79·0% (95% CI 77·8–80·8) of malaria episodes across all transmission intensity in a parasite population composed of quadruple mutant (figure 4, black arrow), and 60·4% (95% CI 58·6–62·3) of clinical cases across all transmission intensity in a parasite population composed of quintuple mutant (figure 4, dark grey arrow). These results suggest that SMC will conserve some effectiveness even if the quintuple mutant becomes fixated at high frequency in the population.

If the prophylactic period is reduced to 15-days, this means that the parasite population is composed of parasites that are even more resistant to SP than the quintuple mutant (e.g., if the quintuple mutant acquires an additional mutation) and also had some degree of resistance to AQ (i.e. prophylactic period of AQ reduced from 17- to 15-days).¹⁵ In this case, the PE decreased to 41·9% (95% CI 40·7–43·2) for the same setting than above (figure 4, light grey arrow). This result highlights that even if a parasite population is fully resistant to SP, some protection will remain even if there is a slight reduction in parasite sensitivity to AQ.

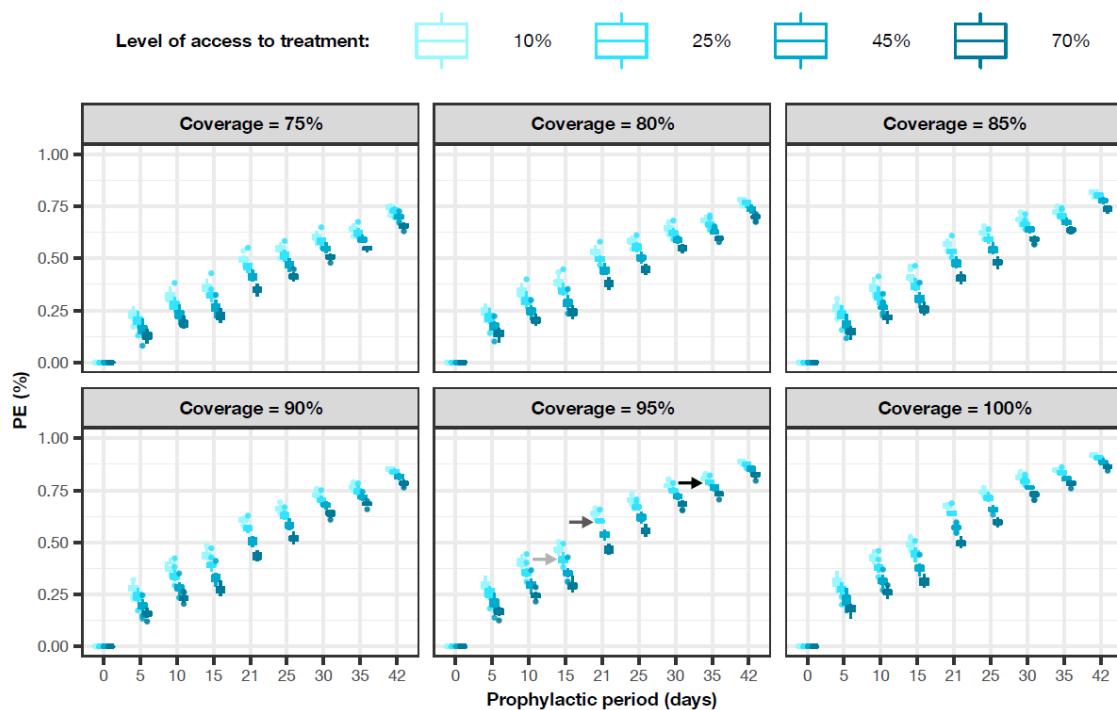


Figure 4: Protective effectiveness of SMC for a range of prophylactic periods

The protective effectiveness of SMC (the relative reduction in the number of clinical malaria cases during the months of SMC implementation) when four rounds of SMC were delivered to children under five years at different coverage levels (75%, 80%, 85%, 90%, 95%, and 100%), in settings with diverse transmission intensities (from 5 to 150 inoculations per person per year) and levels of access to treatment (from 10% (light blue boxplot) to 70% (dark blue boxplot)). The coverage was decreased by 10% each round. Arrows (second row, middle panel) highlight examples described above.

Discussion

This modelling study is the first study that estimates the rate of spread of the quintuple mutant (*dhfr*-51I, *dhfr*-59A, *dhfr*-108A, and *dhps*-437G, *dhps*-540G) with resistance to SP due to SMC implementation and assesses the impact of this spread on SMC effectiveness to prevent *Plasmodium falciparum* malaria in children. In our model, the typical implementation of SMC (four rounds for children under five years with 95% initial coverage declining by 10% each round) was predicted to result in a relatively slow spread of the quintuple mutant in typical settings of the Sahel (the quintuple mutant need always more than 50 years to spread from a relative frequency of 1% to 50% in inoculations in settings with low access to treatment). We further predicted that the spread of the quintuple mutant could accelerate due to changes in the SMC deployment, such as deploying SMC at higher coverage, with a more equitable delivery, adding additional rounds of SMC per year (preferably earlier), and targeting children under ten years. Nevertheless, even if the quintuple mutant spread, we estimated that SMC remained a valuable tool to prevent malaria morbidity, with the typical SMC delivery, SMC prevented in meaning 60·4% (95% CI 58·6–62·3) % of clinical cases in typical settings of the Sahel.

Multiple factors can explain this relatively slow spread of the quintuple mutant. First, SMC is deployed only to a minority of individuals in the population (children under five year of age represent approximately 18% of the total population in our demography), so only a minority of individuals can potentially select the quintuple genotype. We found that SMC coverage was a critical factor that influenced the predicted rate of spread, but even at a coverage of 100%, only less than 20% of the population receives SMC at each round. Second, SP creates only a short selection window within treated children. The selection window was equal to 14-days (35-21) in our model scenarios for the quintuple compared to the quadruple mutant. In settings with low to moderate malaria transmissions, the spread is limited because patients are less likely to be infected during the selection window. Finally, individuals who receive SP+AQ and become newly infected by the quintuple mutant can have their infection cleared at the next SMC round, further limiting the spread. The slow spread of the quintuple mutant is in agreement with existing studies which reported that SMC leads to a slow or no marked increase in the quintuple mutant's frequency.^{3, 12, 25, 26} Slow spread of the quintuple genotype may challenge the ability to estimate the rate of spread in the real-world.

Previous studies highlighted that extending SMC to children under ten years or adding extra rounds of SMC per transmission season could considerably reduce the burden of malaria in the Sahel.^{12, 22} We demonstrated that deploying SMC to children under ten years compared with the administration to children under five almost doubled the rate of spread of the quintuple mutant (the number of individuals receiving SMC also roughly doubles). In addition, adding one more round of SMC per year decreased by approximately ten years the predicted time needed for the quintuple mutant to reach a relative frequency of 50% in inoculations as more SP was given to the population. Thus, the health benefit of deploying more rounds of SMC or targeting SMC to children under ten years, should balance the gains made by implementing this strategy with losses sustained from an acceleration in spread of the quintuple mutant and its impact on SMC effectiveness.

We estimated that SMC retains a substantial level of protective effectiveness even if the quintuple mutant spread to saturation. There are multiple reasons that explain our finding. First, AQ administration ensures that children who receive SMC can successfully eliminate the quintuple mutant as it is still sensitive to AQ. Second, as SP inhibits development of successful blood-stage infection of the quintuple mutant for 21-days post-treatment, and children receive SP+AQ every 30-days, children are protected most of the SMC deployment period. In addition, children that develop blood-stage infections after 21-days have their infections cleared by the next round of SMC. This result highlights that SMC will remain a valuable tool to reduce malaria morbidity in the Sahel despite the spread of the quintuple mutant.

Critically, our findings on continued effectiveness of SP-AQ used as SMC in children also suggests that SMC could be implemented in seasonal regions where the quintuple mutant is prevalent, such as in some South and East Africa countries.²⁷ Currently, the WHO does not recommend SMC due to the high prevalence of the quintuple mutant in this region.² We argue that further evidence is needed to challenge or confirm our results that SMC is likely to still provide substantial health benefits in these settings, for example, further trials of SMC with SP+AQ in areas with high prevalence of quintuple mutant, such as the current ongoing trial in Mozambique.²⁸

Our recommendations and modelling results depend on several assumptions. Firstly, our results depend on our assumption that SP provides a prophylactic period of 21-days against the quintuple mutant and 35-days against the quadruple mutant as informed by available data.^{5, 6, 12} However, if the prophylactic period against the quintuple mutant is shorter than 21-days, the spread of SP quintuple mutants would likely be faster. Nevertheless, it is important to note that AQ also provides a blood-stage prophylactic period of 17-days against AQ-sensitive parasites,¹⁵ thus, SMC would still offer a prophylactic period for a minimum of 17-days. Consequently, our estimation of the rate of spread and the effectiveness of SMC would not change enormously. In addition, this means that if a parasite more resistant to SP emerge, such as the sextuple mutant (with an additional mutation: *dfps*-A581G) observed in a few settings in East Africa,²⁹ we also expect a limited spread and the protective effectiveness of SMC to be retained thanks to the prophylactic period of AQ. However, note that the spread of a parasite completely resistant to SP would probably favour the emergence of resistance to AQ, as AQ would not be protected by SP.²¹

Secondly, we did not model the potential effect of pyrimethamine on the liver stage of *P. falciparum*.³⁰ Previous studies suggest that the liver stage effect of pyrimethamine is reduced against the quadruple and quintuple mutants, as they have three mutations conferring resistance to pyrimethamine.^{31, 32} Thus, we may have slightly underestimated, rather than overestimated, the effectiveness of SMC as we did not model the remaining impact of pyrimethamine on the liver stage. However, this assumption does not affect our estimation of the spread of the quintuple mutant, as the liver stage effect of pyrimethamine is similar for both genotypes.

Finally, we assumed that both genotypes were sensitive to AQ. Markers of low degree of resistance to AQ have been observed in the Sahel (*Pfcrt*-C1VET + *pfmdr1*-86 Tyr + 184 Tyr) although at a low prevalence in 2018 (0·5% of samples in 2018).³ These mutations cause the

prophylactic period of AQ to reduce from 17-to 12-days.¹⁵ However, to the best of our knowledge, these mutations are not associated with the quintuple mutant, and their frequency is declining. Thus these mutations should not impact the spread of the quintuple mutant.³

In conclusion, our study shows that SMC will remain a valuable tool to prevent uncomplicated malaria throughout the next decade, even if its prophylactic period is likely to decrease over time with the slow spread of the quintuple mutant. Current or newer research or implementation studies could evaluate implementation of SMC in seasonal settings where the quintuple mutant is already highly prevalent, as its implementation could considerably reduce malaria-related morbidity. Our assessment of the risk of spread of the quintuple mutant and associated consequences are overall quite reassuring and should be validated with other modelling studies as well as trial or implementation studies. However, mutants with a high degree of resistance to SP and AQ could emerge at any time in the Sahel. Therefore, routine molecular surveillance alongside efficacy testing of detected mutants must continue.

Contributors

MAP conceived the study. TM, TL, and MAP designed the study. TM performed the literature searches to parameterise the model and performed the analyses. TM, TL, and MAP interpreted results and examined their implications. TM wrote the first draft of the manuscript. TL, SK, IMH and MAP revised the manuscript. All authors reviewed and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant-level data was not used in this study. Parameter values used to inform the model were extracted from the literature as referred in the main text or in the Supplementary Material. All data and codes used to create the figures will be made available.

Acknowledgments

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Seasonal malaria chemoprevention and the spread of *Plasmodium falciparum* parasites resistant to sulfadoxine-pyrimethamine: a mathematical modelling study

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Summary

Background Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine prevents millions of clinical malaria cases in the Sahel. However, a genotype with five mutations causing partial resistance to sulfadoxine-pyrimethamine has emerged. We estimated the rate of spread of this mutant following SMC, assessed factors promoting its spread, and evaluated its impact on the effectiveness of SMC against clinical malaria.

Methods Using an individual-based malaria transmission model, we systematically quantified the influence of multiple factors on the spread of the mutant and predicted the time needed for the mutant to spread from 1% to 50% of inoculations in different settings and for several SMC deployment strategies. We further estimated the reduction in SMC effectiveness against clinical *Plasmodium falciparum* malaria expected due to the mutant spread.

Findings High coverage, transmission intensity, and access to treatment promoted the mutant spread. With SMC implementation of four rounds to children under five (with 95% initial coverage declining each round), the mutant took 53·1 years (95% CI 50·5–56·0) to spread from 1% to 50% of inoculations in a medium transmission intensity setting with seasonal transmission mostly occurring over four months, and access to clinical treatment relatively low. This time was reduced by half when SMC targeted children under ten, and reduced by 13 and 10 years when an additional round of SMC was deployed at the beginning and the end of the transmission season, respectively. For the same setting, the mean percentage of clinical malaria averted during the four months of SMC implementation was 79·0% (95% CI 77·8–80·8) when the mutant was absent in the population and still high at 60·4% (95% CI 58·6–62·3) when the quintuple was fixated.

Interpretation SMC with SP-AQ leads to a relatively slow spread of SP resistant quintuple mutants and remains an effective prophylactic intervention to prevent child clinical malaria in the Sahel despite quintuple mutants spread. Given the prophylactic period of SP-AQ, SMC could be considered in seasonal settings where the quintuple mutant is already prevalent.

Introduction

Plasmodium falciparum malaria is a leading cause of morbidity and mortality in African children.¹ In the Sahel, malaria transmission is highly seasonal, with most of the burden occurring during three to five months (between August and December).² The World Health Organization (WHO) recommends implementation of seasonal malaria chemoprevention (SMC) to reduce disease burden in this region. SMC involves monthly administration of sulfadoxine and pyrimethamine (SP) plus amodiaquine (AQ) to children under five years during the transmission seasons.² A recent implementation study in the Sahel reported that SMC prevents more than 88% of uncomplicated malaria cases within 28-days of administration.³ This high effectiveness is partly attributable to the fact that SP remains at a concentration sufficient to inhibit development of successful blood-stage infections for a long time post-treatment.⁴ Current evidence suggests that this prophylactic period is roughly 42-days against SP sensitive parasites but is reduced for parasites with lower sensitivity to SP.^{5,6}

Accumulation of mutations in *dhps* and *dhfr* genes of the *P. falciparum* parasite leads to reduced sensitivity to SP.^{7,8} Previous use of SP as first-line treatment has caused worldwide spread of malaria parasites with multiple mutations in these genes.^{9,10} In many Sahelian countries, the quadruple mutant genotype (with *dhfr*-51I, *dhfr*-59A, *dhfr*-108A, and *dhps*-437G mutations) is already the most prevalent genotype.^{3,11} Nevertheless, SMC remains efficient in this region because SP still provides a prophylactic period of approximately 35-days against this genotype (figure 1A) as reported by clinical trials of SMC with SP+AQ, and intermittent preventive treatment in infancy (IPTi) with SP and a prospective study of intermittent preventive treatment in pregnancy (IPTp) with SP.^{5,12,13} A more significant threat comes from the emergence of a quintuple mutant,³ which carries an additional mutation (*dhps*-540G) that has higher resistance to SP. The use of SP in monotherapy against this mutant is associated with increased treatment failure rates.¹⁴ However, current data from clinical trials of IPTi with SP and a prospective study of IPTp with SP suggest that SP still prevents the successful development of quintuple mutant blood-stage infection (due to reinfection or recrudescence) for a period of 21-days post-treatment (figure 1A).^{5,6} Given the chance quintuple mutants can develop blood-stage infections before more sensitive parasites, including the quadruple mutant, the implementation of SMC may favour its spread. Selection is possible even though AQ provides a prophylactic period of 17-days because this prophylactic period cannot prevent the selection of the quintuple mutant (figure 1A).¹⁵

It is unknown at which rate the quintuple mutant will spread in a population due to implementation of SMC, nor which factors including target age group, number of rounds administered per year, or transmission intensity will favour or delay its spread. Moreover, it is uncertain how strongly spread of the quintuple mutant will reduce SMC effectiveness against clinical cases, and thus whether SMC with SP+AQ will remain a valuable preventive tool or if alternatives are urgently needed. In this study, we used an individual-based model of malaria transmission, OpenMalaria,¹⁶ to assess the rate of spread of the SP resistant quintuple mutant. We assessed this rate of spread in a parasite population predominantly composed of quadruple mutants because the quadruple mutant is the most prevalent genotype in the Sahel^{3,11} and the quadruple mutant is the most prominent competitor of the quintuple mutant as there is no fitness cost associated with resistance to SP¹⁷ (other genotypes (sensitive, single, double,

triple mutants) behave similarly to the quadruple mutant in individuals who did not receive SMC, but the quadruple mutant can develop a successful blood-stage infection a few days earlier than these genotypes in children who received SMC). In addition, we systematically quantified which factors are more likely to drive the spread in various deployment strategies and seasonality settings. Finally, we estimated the potential decrease in the effectiveness of SMC against clinical malaria expected with the spread of the quintuple mutant.

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Research in context

Evidence before this study

In March 2021 we performed a literature search for studies that modelled the impact of SMC deployment on the spread of malaria parasites less sensitive to SP. We accomplished this search using PubMed for the following keywords: malaria AND model* AND resistance AND seasonal malaria chemoprevention OR intermittent preventive treatment". We found five modelling studies focusing on intermittent preventive treatment but no studies focusing on SMC. Consequently, these studies assumed that SP was administered at a constant rate in the targeted population in settings with perennial malaria transmission. Thus, it remains unknown how seasonality and SMC implementation strategies affect the quintuple mutant's spread, such as the number of rounds administered per year and target age group. In addition, three of these studies assumed that the parasite was fully resistant to the drug used in IPT, ignoring the remaining drug effect on the parasite. Moreover, four of these studies modelled that the resistant genotype was resistant to both the drug used for IPT and first-line treatment. This assumption does not correspond to the use of SP for SMC and first-line treatments used in the Sahel.

Added value of this study

To the best of our knowledge, our study is first to estimate the impact of SMC on the spread of the quintuple mutant and assess the mutant's impact on SMC effectiveness. Our model captures the remaining effect of SP on partially resistant parasites and allows examination of the impact of different deployment strategies and seasonality settings on the rate of spread. The results show that with current SMC implementation (four rounds for children under five years with 95% initial coverage declining by 10% each round), the mutant need 53·1 years (95% CI 50·5–56·0) to spread from 1% to 50% of inoculations in a typical setting of the Sahel (medium transmission intensity mostly occurring over four months, with low access to treatment). However, the spread accelerates with additional rounds of SMC deployed at the beginning or end of the transmission season and when SMC targets children under ten. Nevertheless, our results demonstrate that even in the worst-case scenario of the quintuple mutant reaching fixation, current SMC implementation is likely to prevent 60·4% (95% CI 58·6–62·3) of clinical malaria in children in the Sahel.

Implications of all available evidence

We found that the rate of spread of the quintuple mutant with partial resistance to SP strongly depends on the implementation strategy of SMC with SP+AQ. Nevertheless, our results suggest that SMC will continue to prevent millions of clinical cases in Sahelian children despite the spread of the quintuple mutant. Our results also highlight that in seasonal settings where the quintuple mutant is already the most prevalent genotype, and clinical and severe malaria burden remains high, there is cause to consider implementing SMC with SP+AQ.

Methods

Model calibration

In this study we calibrated and used our existing individual-based model of malaria transmission, known as OpenMalaria, that simulates the dynamics of *P. falciparum* in mosquitoes and humans.¹⁸⁻²⁰ This model tracks multiple parasite genotypes, models their dynamics within the host, and captures that genotypes have different sensitivity to drugs using pharmacokinetic (PK) and pharmacodynamics (PD) model components. The model was previously described in¹⁸⁻²¹ and is briefly described in appendix p 4.

With this model, we tracked the spread of the quintuple mutant (*dhfr*-51I, *dhfr*-59A, *dhfr*-108A, and *dhps*-437G, *dhps*-540G) in a parasite population composed of predominantly quadruple mutants (*dhfr*-51I, *dhfr*-59A, *dhfr*-108A, and *dhps*-437G) due to the implementation of SMC with SP+AQ. We deployed SMC in two seasonality settings, one in which approximately 85% of transmission occurs over three months (high seasonality), and another over four months (moderate seasonality) (appendix p 6 figure S1.1). For the high seasonality settings, SMC was deployed three times per year (as currently recommended by WHO), or four times per year, with the additional round administered before or after the recommended deployment period (appendix p 6 figure S1.2). Similarly, for moderate seasonality settings, SMC was deployed four times per year, or five times per year, with the additional round administered before or after the recommended deployment period (appendix p 6 figure S1.3). We deployed SMC to two different target age groups: children aged three months to five years or three months to ten years. For each deployment strategy, we investigated scenarios for which SMC coverage was constant across rounds or decreased by 10% each round (e.g., if the first round is 80%, then subsequent rounds are 72%, 65%, etc.).^{3, 12}

At each SMC round, children received one dose of SP and three daily doses of AQ with the dosage adapted to their age as recommend by WHO (appendix p 7 table S1.1).^{2, 22} We modelled AQ using two-compartment PK/PD models with first-order absorption (appendix p 11-13 table S1.3 and S1.4) and assumed that both mutants were sensitive to AQ. We modelled that SP conferred a blood-stage prophylactic period of 35-days against the quadruple mutant and 21-days against the quintuple mutant as suggested by the literature (figure 1A).^{5, 6, 12, 13} To do that, we modelled SP as one long-acting drug with a one-compartment PK/PD model with first-order absorption (appendix p 8-10 table S1.2), and we used a higher half-maximal effective concentration (EC50) for the quintuple mutant than for the quadruple mutant. The increased EC50 of the quintuple mutant captures the mutant is less sensitive to SP at lower drug concentrations and could thus reinfect the host sooner than the quadruple mutant. To determine the EC50 of each mutant, we first established the link between the prophylactic period and the EC50 (figure 1B, appendix p 8-10 figure S1.2) and calibrated the EC50 to match the prophylactic period reported in IPTi, IPTp, and SMC studies.^{5, 6, 12, 13} With this calibration against clinical data, in our model we predict the quintuple genotype could develop a blood-stage infection before the next SMC round and not the quadruple mutant (figure 1C).

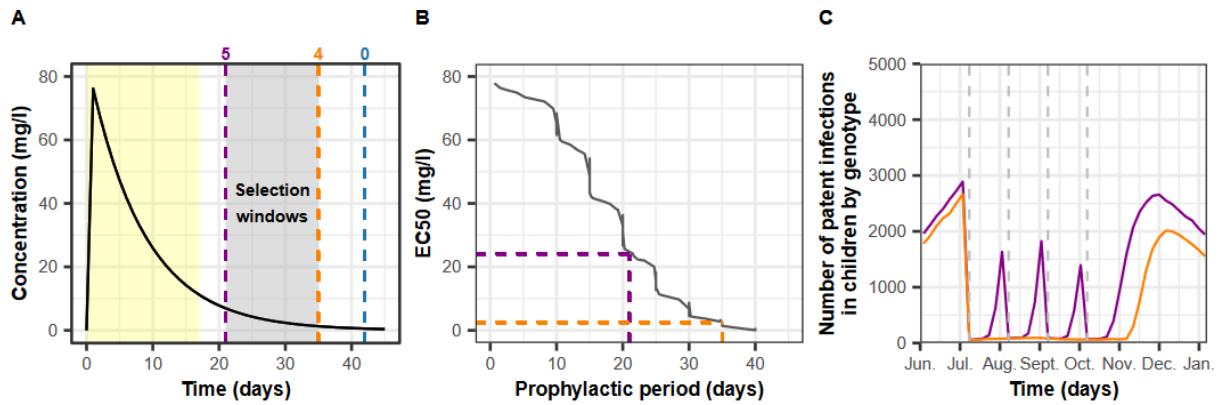


Figure 1: Schematics of SP resistance calibration and dynamics in our model

(A) Within-host plasma concentration of SP was modelled as a single long-acting drug with a one-compartment PK/PD model with first-order absorption (appendix p 8-10 table S1.2). The blue, orange, and purple dashed lines represent the end of the prophylactic period for a sensitive parasite, quadruple mutant, and quintuple mutant, respectively. The grey region between the orange and purple lines highlights the selection window (period during which the quintuple mutant can develop a successful blood-stage infection in treated children but not the quadruple mutant). The yellow region represents the prophylactic period conferred by AQ against all genotypes. AQ was modelled separately with two-compartment models with first-order absorption (appendix p 11-13 table S1.3 and S1.4). (B) The predicted relationship between the EC50 and the prophylactic period conferred by SP was estimated by our model (appendix p 8-10). The orange and purple dashed lines represent the estimated EC50 for the quadruple and quintuple mutants to confer the wished prophylactic periods, respectively, as reported by SMC, IPTi, IPTp studies.^{5, 6, 12, 13} (C) Example of the predicted number of patent infections in children under five years caused by the quadruple (orange line) or quintuple (purple line) mutant in a setting with a transmission intensity of 390 inoculations per person per year occurring mainly over four months and a 35% probability of symptomatic cases receiving treatment within two weeks from symptom onset (level of access to treatment). The grey dashed lines indicate timing for rounds of SMC administered. In this example, four rounds of SMC were administered with a coverage of 98% to children under ten years.

Identification of factors increasing SP resistance and quintuple mutant spread

For each seasonality setting and SMC deployment strategy we systematically quantified the level of influence of multiple epidemiological, PKPD properties, resistance and setting factors (table 1) on the spread of the quintuple mutant using global sensitivity analyses.²¹ We estimated the rate of spread of the quintuple genotype through the selection coefficient defined as the proportion by which the relative frequency of the quintuple mutant increases each parasite generation (appendix p 14).²³ Given the computational requirements of our individual-based model to be efficient with our global sensitivity analysis, we used emulators trained on our model simulations (appendix p 14-15). Emulators are predictive models that can approximate the relationship between input and output parameters of complex models and run much faster than complex models. For the global sensitivity analysis, we used Sobol method of variance decomposition (appendix p 15) which allowed us to estimate the first-order indices of each factor, representing their influence on the rate of spread, and the 25th, 50th, and 75th quantiles of the predicted rate of spread over each parameter range.

We further estimated the impact of SMC deployment strategies and seasonality settings on spread of the quintuple mutant by comparing the T_{50} , the time needed by the quintuple mutant to spread from a relative frequency of 1% (its current frequency in the Sahel)³ to 50% in inoculations (threshold above which ITP in infancy is not recommended).²⁴ For each SMC deployment strategy and seasonality setting, we first predicted the selection coefficient for various levels of coverage, transmission, and access to treatment with the trained emulators. We then converted the predictions to T_{50} (appendix p 22).

Table 1: Parameters and their ranges investigated in the global sensitivity analyses of the spread of the quintuple mutant

ACT: artemisinin-based combination therapy; AQ: amodiaquine SMC: seasonal malaria chemoprevention, SP: sulfadoxine-pyrimethamine

Determinant	Definition	Parameter range
Coverage of SMC	Percentage of individuals from the target age group that received SP+AQ during the first round of SMC (%)	[70,100]
Entomological inoculation rate (EIR)	Number of infective bites received by an individual during a year (inoculations per person per year)	[5, 500]
Level of access to treatment	Probability of symptomatic cases receiving treatment within two weeks from symptom onset (%)	[10, 80]
Half-life of the ACT partner drug	Time at which half the initial drug concentration remains (days)	[6, 22]

The impact of the quintuple mutant on SMC effectiveness

To estimate the impact of high-frequency quintuple mutant in the population on model estimates of the effectiveness of SMC, we varied the length of the prophylactic period offered by SMC with SP+AQ (between 5 and 40 days) for a range of settings. We assessed the protective effectiveness (PE) of SMC as the relative reduction in incidence of clinical malaria due to SMC during the months of SMC implementation (appendix p 25-26).³ We estimated the PE against parasite populations composed of only one genotype for which SP+AQ provide a prophylactic period of different length (5-, 10-, 15-, 21-, 25-, 30-, 35-, and 40-days, appendix p 27 table S2.1). For each parasite population, we assessed the PE of the recommended deployment of SMC (four rounds of SMC deployed per year to children under five years in the moderate seasonality setting with a coverage reduction of 10% from the previous round) for different levels of transmission, SMC coverage, and access to treatment.

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Results

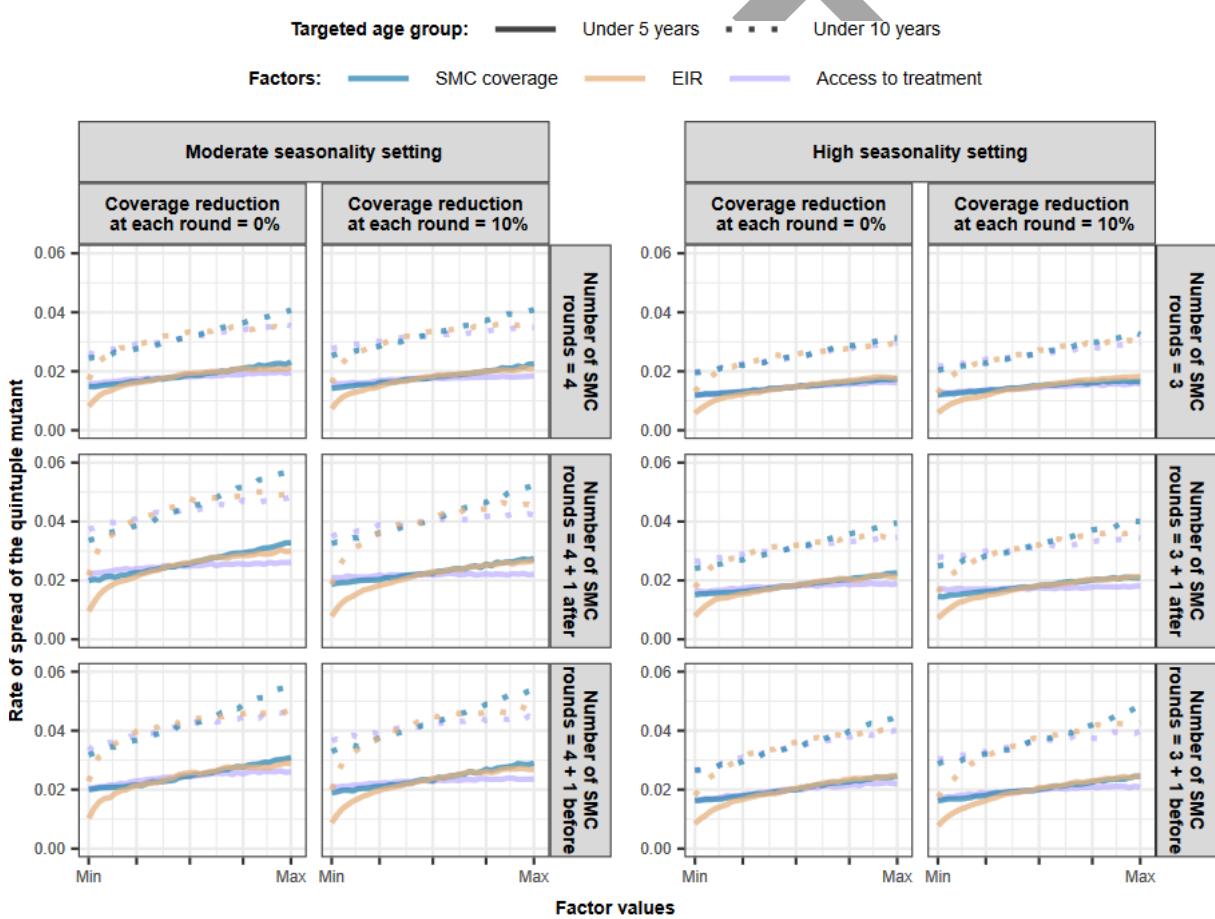
Factors driving the spread of SP quintuple mutant resistance

Our global sensitivity analysis of epidemiological, drug, and setting parameters on estimates of selection coefficients indicates that the levels of malaria transmission and SMC coverage play a crucial role in the predicted spread of the quintuple mutant resistant to SP (appendix p 19 figure S2.5). We found that high transmission levels increased the rate of spread (figure 2). Spread of SP resistance is faster in higher transmission settings due to the quintuple genotype being more likely to infect children during the selection window (period during which the quintuple genotype can develop a blood-stage infection in treated children but not the quadruple mutant). High SMC coverage levels also increased the rate of spread (figure 2), because more children receive SP increasing the selection pressure on the quintuple mutant.

The level of access to treatment of clinical cases also slightly increased the rate of spread in many settings (figure 2). Improving access to treatment reduces the parasite prevalence in individuals who do not receive SMC but not in children that receive SMC (appendix p 20 figure S2.6). Individuals who do not receive SMC are equally likely infected by the quadruple and quintuple mutants, whereas individuals that received SMC are more likely infected by quintuple mutants while protected by SP (appendix p 21 figure S2.7). Thus, a rise in access to treatment causes a slight increase in the relative frequency of quintuple mutant (appendix p 21 figure S2.7), favouring its spread.

Figure 2: The influence of different factors on the rate of spread of the quintuple mutant SP resistance

The lines represent the predicted median rate of spread (selection coefficient) of the quintuple mutant estimated from the global sensitivity analysis over the parameter ranges of each epidemiological, setting, SMC or drug properties factor when SMC is delivered to children under five years (plain lines) or children under ten years (dashed lines). The explored factors and their parameter ranges were as follows: SMC coverage at round one during the season [70%, 100%] (blue lines); transmission level as EIR [5, 500] inoculations per person per year (orange lines); and the level of access to treatment [10%, 80%] (purple lines). Results are for different seasonality settings (moderate or high seasonality), for various numbers of rounds deployed per year (high seasonality setting: three rounds or four rounds with the additional round deployed before or after the recommended deployment of SMC, moderate seasonality setting: four rounds or five rounds with the additional round deployed before or after the recommended deployment of SMC), and different assumptions about the reduction of the SMC coverage across each round (0% (constant coverage) or 10% reduction (e.g., if the first round is 80%, then subsequent rounds are 72%, 65%, etc.)).



Predicted time till 50% frequency of SP resistant quintuple mutations

We observed that the predicted T_{50} from our model depends strongly on the SMC deployment strategies (figure 3, appendix p 23 figure S2.8 for results related to baseline parasite prevalence in 2-10 year olds). As an illustration, we compared T_{50} for various deployment strategies in a setting with a medium transmission intensity (EIR = 70 inoculations per person per year) and a low access to treatment (25%) when SMC had an initial coverage of 95%, which decreased by 10% each round (e.g. 100%, 90%, 81%) (figure 3, red lines). With the standard deployment of SMC (four rounds for children under five years) in settings with moderate seasonality, the quintuple genotype took 53·1 years (95% CI 50·5– 56·0) to reach a relative frequency of 50% in inoculations (T_{50}). Time was equal to 67·1 years (95% CI 63·2– 71·5) with a standard SMC regimen (three rounds for children under five years) in settings with high seasonality. T_{50} increases in high seasonality settings probably because it has one less round of SMC, which reduces the selection pressure on the quintuple genotype.

In the moderate seasonality setting, deploying an additional round of SMC at the beginning or the end of the transmission season decreased the T_{50} by approximately 13 and 10 years (39·6 (95% CI 38·0–41·3) and 42·8 (95% CI 41·0–44·7) years), respectively. Similarly, in the high seasonality setting, deploying an additional round before or after the recommended SMC deployment reduced this time by 16 and 15 years (50·5 (95% CI 48·0–53·4) and 51·6 (95% CI 48·7–54·8) years), respectively. Adding a round of SMC at the beginning of the transmission season accelerates the spread of the quintuple mutant more than adding one at the end probably because the quintuple mutant is more likely to reinfect children at the beginning of the transmission season as the EIR is rising.

Increasing the target age range from children under five years to children under ten means almost twice the number of individuals will receive SMC, accordingly, the T_{50} gets halved. For example, for moderate transmission settings, T_{50} decreased from 53·1 to 26·4 years (95% CI 25·6–27·3) when four rounds of SMC were administered to children under ten years, compared with children under five. Similarly, in high transmission settings, the T_{50} decreased from 67·1 years to 35·9 years (95% CI 33·6–26·7).

In our simulations, we deployed SMC to the same children across rounds, mimicking poor or in-equitable SMC delivery, with a proportion of children systematically missed for SMC. We assessed how the T_{50} changed if SMC was deployed more equitably, that is all children in the eligible population have the same probability of receiving SMC each round within a season. The spread of the quintuple mutant accelerated when SMC was deployed equitably (appendix p 24 figure S2.9). This result is because, with a more equitable coverage, children reinfected by the quintuple mutant do not have necessarily their infection with the quintuple mutant treated at the next SMC round in opposition to when the same children receive SMC each round (in-equitable delivery).

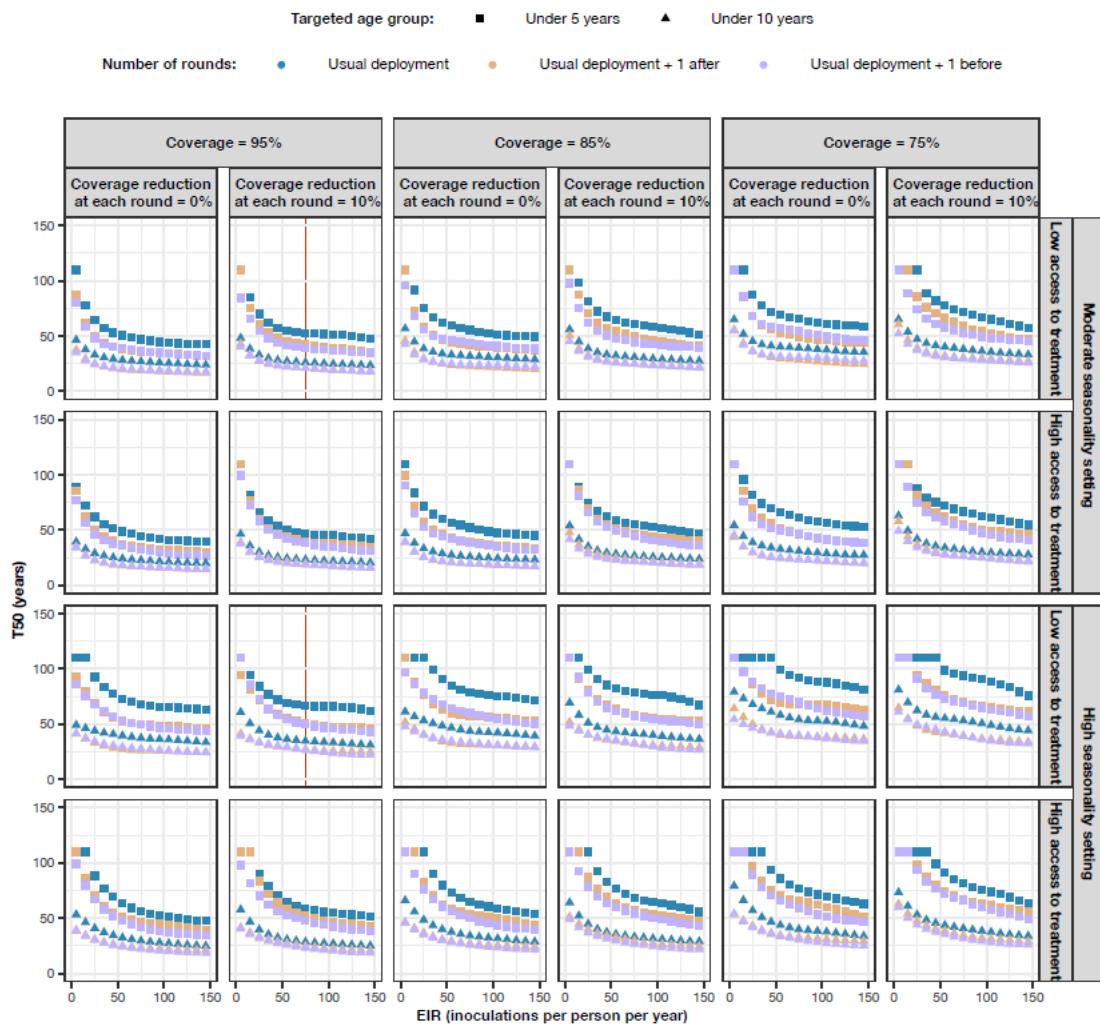


Figure 3: Predicted impact of SMC deployment strategies on the spread of the SP resistant quintuple mutant

Estimated time needed for the quintuple genotype to spread from a relative frequency in inoculations of 1% to 50%, T_{50} , when SMC was deployed to different age groups (under five (squares) or under ten years of age (triangles)) in diverse seasonality settings (moderate and high seasonality pattern) with a various number of rounds deployed per year (high seasonality: three (blue shapes) or four rounds with the additional round deployed before (purple shapes) or after (orange shapes) the standard deployment period; moderate seasonality setting: four (blue shapes) or five rounds with the additional round deployed before (purple shapes) or after (orange shapes) the standard SMC deployment period). We predicted the T_{50} for different levels of initial coverage (75%, 85%, and 95%) and coverage reduction across rounds (0% or 10% reduction since the previous round). For each setting and SMC deployment strategy, T_{50} was predicted for various transmission levels (ranging from 5 to 150 inoculations per person per year) and for two levels of access to treatment (25 and 70%). Red lines highlight points of interest which are described above.

Impact of SP quintuple mutant resistance on SMC effectiveness

As expected, the PE of SMC was strongly dependent on the prophylactic period length (figure 4). Simulations in which SMC conferred a prophylactic period of 35-days and 21-days mimicked deployment of SMC in a parasite population composed only of quadruple mutant and quintuple mutant, respectively. We observed that the PE decreased with shorter prophylactic periods, but the PE in a parasite population composed of quintuple mutant remained non-negligible (figure 4). We found that the PE range between 70·6–83·0% and 44·3–66·4% for 35-days and 21-days, respectively, at 95% SMC coverage overall simulated settings (figure 4). More specifically, in a setting with low access to treatment (25%), SMC prevented 79·0% (95% CI 77·8–80·8) of malaria episodes across all transmission intensity in a parasite population composed of quadruple mutant (figure 4, black arrow), and 60·4% (95% CI 58·6–62·3) of clinical cases across all transmission intensity in a parasite population composed of quintuple mutant (figure 4, dark grey arrow). These results suggest that SMC will conserve some effectiveness even if the quintuple mutant becomes fixated at high frequency in the population.

If the prophylactic period is reduced to 15-days, this means that the parasite population is composed of parasites that are even more resistant to SP than the quintuple mutant (e.g., if the quintuple mutant acquires an additional mutation) and also had some degree of resistance to AQ (i.e. prophylactic period of AQ reduced from 17- to 15-days).¹⁵ In this case, the PE decreased to 41·9% (95% CI 40·7–43·2) for the same setting than above (figure 4, light grey arrow). This result highlights that even if a parasite population is fully resistant to SP, some protection will remain even if there is a slight reduction in parasite sensitivity to AQ.

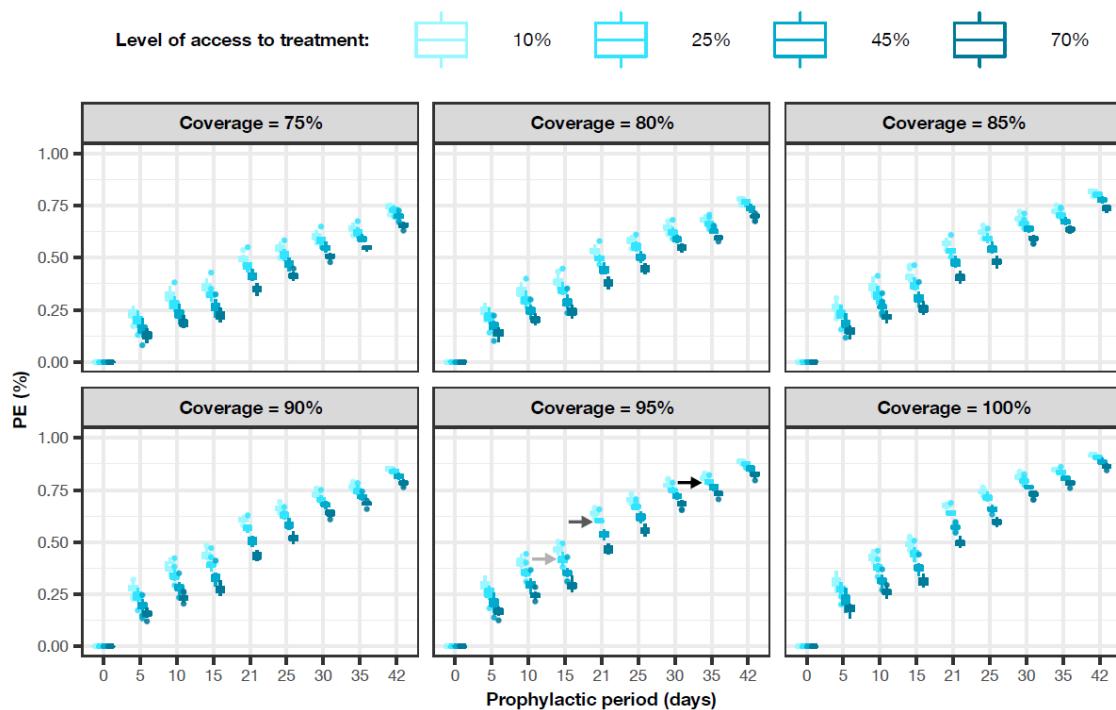


Figure 4: Protective effectiveness of SMC for a range of prophylactic periods

The protective effectiveness of SMC (the relative reduction in the number of clinical malaria cases during the months of SMC implementation) when four rounds of SMC were delivered to children under five years at different coverage levels (75%, 80%, 85%, 90%, 95%, and 100%), in settings with diverse transmission intensities (from 5 to 150 inoculations per person per year) and levels of access to treatment (from 10% (light blue boxplot) to 70% (dark blue boxplot)). The coverage was decreased by 10% each round. Arrows (second row, middle panel) highlight examples described above.

Discussion

This modelling study is the first study that estimates the rate of spread of the quintuple mutant (*dhfr*-51I, *dhfr*-59A, *dhfr*-108A, and *dhps*-437G, *dhps*-540G) with resistance to SP due to SMC implementation and assesses the impact of this spread on SMC effectiveness to prevent *Plasmodium falciparum* malaria in children. In our model, the typical implementation of SMC (four rounds for children under five years with 95% initial coverage declining by 10% each round) was predicted to result in a relatively slow spread of the quintuple mutant in typical settings of the Sahel (the quintuple mutant need always more than 50 years to spread from a relative frequency of 1% to 50% in inoculations in settings with low access to treatment). We further predicted that the spread of the quintuple mutant could accelerate due to changes in the SMC deployment, such as deploying SMC at higher coverage, with a more equitable delivery, adding additional rounds of SMC per year (preferably earlier), and targeting children under ten years. Nevertheless, even if the quintuple mutant spread, we estimated that SMC remained a valuable tool to prevent malaria morbidity, with the typical SMC delivery, SMC prevented in meaning 60·4% (95% CI 58·6–62·3) % of clinical cases in typical settings of the Sahel.

Multiple factors can explain this relatively slow spread of the quintuple mutant. First, SMC is deployed only to a minority of individuals in the population (children under five year of age represent approximately 18% of the total population in our demography), so only a minority of individuals can potentially select the quintuple genotype. We found that SMC coverage was a critical factor that influenced the predicted rate of spread, but even at a coverage of 100%, only less than 20% of the population receives SMC at each round. Second, SP creates only a short selection window within treated children. The selection window was equal to 14-days (35-21) in our model scenarios for the quintuple compared to the quadruple mutant. In settings with low to moderate malaria transmissions, the spread is limited because patients are less likely to be infected during the selection window. Finally, individuals who receive SP+AQ and become newly infected by the quintuple mutant can have their infection cleared at the next SMC round, further limiting the spread. The slow spread of the quintuple mutant is in agreement with existing studies which reported that SMC leads to a slow or no marked increase in the quintuple mutant's frequency.^{3, 12, 25, 26} Slow spread of the quintuple genotype may challenge the ability to estimate the rate of spread in the real-world.

Previous studies highlighted that extending SMC to children under ten years or adding extra rounds of SMC per transmission season could considerably reduce the burden of malaria in the Sahel.^{12, 22} We demonstrated that deploying SMC to children under ten years compared with the administration to children under five almost doubled the rate of spread of the quintuple mutant (the number of individuals receiving SMC also roughly doubles). In addition, adding one more round of SMC per year decreased by approximately ten years the predicted time needed for the quintuple mutant to reach a relative frequency of 50% in inoculations as more SP was given to the population. Thus, the health benefit of deploying more rounds of SMC or targeting SMC to children under ten years, should balance the gains made by implementing this strategy with losses sustained from an acceleration in spread of the quintuple mutant and its impact on SMC effectiveness.

We estimated that SMC retains a substantial level of protective effectiveness even if the quintuple mutant spread to saturation. There are multiple reasons that explain our finding. First, AQ administration ensures that children who receive SMC can successfully eliminate the quintuple mutant as it is still sensitive to AQ. Second, as SP inhibits development of successful blood-stage infection of the quintuple mutant for 21-days post-treatment, and children receive SP+AQ every 30-days, children are protected most of the SMC deployment period. In addition, children that develop blood-stage infections after 21-days have their infections cleared by the next round of SMC. This result highlights that SMC will remain a valuable tool to reduce malaria morbidity in the Sahel despite the spread of the quintuple mutant.

Critically, our findings on continued effectiveness of SP-AQ used as SMC in children also suggests that SMC could be implemented in seasonal regions where the quintuple mutant is prevalent, such as in some South and East Africa countries.²⁷ Currently, the WHO does not recommend SMC due to the high prevalence of the quintuple mutant in this region.² We argue that further evidence is needed to challenge or confirm our results that SMC is likely to still provide substantial health benefits in these settings, for example, further trials of SMC with SP+AQ in areas with high prevalence of quintuple mutant, such as the current ongoing trial in Mozambique.²⁸

Our recommendations and modelling results depend on several assumptions. Firstly, our results depend on our assumption that SP provides a prophylactic period of 21-days against the quintuple mutant and 35-days against the quadruple mutant as informed by available data.^{5, 6, 12} However, if the prophylactic period against the quintuple mutant is shorter than 21-days, the spread of SP quintuple mutants would likely be faster. Nevertheless, it is important to note that AQ also provides a blood-stage prophylactic period of 17-days against AQ-sensitive parasites,¹⁵ thus, SMC would still offer a prophylactic period for a minimum of 17-days. Consequently, our estimation of the rate of spread and the effectiveness of SMC would not change enormously. In addition, this means that if a parasite more resistant to SP emerge, such as the sextuple mutant (with an additional mutation: *dhps*-A581G) observed in a few settings in East Africa,²⁹ we also expect a limited spread and the protective effectiveness of SMC to be retained thanks to the prophylactic period of AQ. However, note that the spread of a parasite completely resistant to SP would probably favour the emergence of resistance to AQ, as AQ would not be protected by SP.²¹

Secondly, we did not model the potential effect of pyrimethamine on the liver stage of *P. falciparum*.³⁰ Previous studies suggest that the liver stage effect of pyrimethamine is reduced against the quadruple and quintuple mutants, as they have three mutations conferring resistance to pyrimethamine.^{31, 32} Thus, we may have slightly underestimated, rather than overestimated, the effectiveness of SMC as we did not model the remaining impact of pyrimethamine on the liver stage. However, this assumption does not affect our estimation of the spread of the quintuple mutant, as the liver stage effect of pyrimethamine is similar for both genotypes.

Finally, we assumed that both genotypes were sensitive to AQ. Markers of low degree of resistance to AQ have been observed in the Sahel (*Pfcrt*-CIVET + *pfmdr1*-86 Tyr + 184 Tyr) although at a low prevalence in 2018 (0·5% of samples in 2018).³ These mutations cause the

prophylactic period of AQ to reduce from 17-to 12-days.¹⁵ However, to the best of our knowledge, these mutations are not associated with the quintuple mutant, and their frequency is declining. Thus these mutations should not impact the spread of the quintuple mutant.³

In conclusion, our study shows that SMC will remain a valuable tool to prevent uncomplicated malaria throughout the next decade, even if its prophylactic period is likely to decrease over time with the slow spread of the quintuple mutant. Current or newer research or implementation studies could evaluate implementation of SMC in seasonal settings where the quintuple mutant is already highly prevalent, as its implementation could considerably reduce malaria-related morbidity. Our assessment of the risk of spread of the quintuple mutant and associated consequences are overall quite reassuring and should be validated with other modelling studies as well as trial or implementation studies. However, mutants with a high degree of resistance to SP and AQ could emerge at any time in the Sahel. Therefore, routine molecular surveillance alongside efficacy testing of detected mutants must continue.

Contributors

MAP conceived the study. TM, TL, and MAP designed the study. TM performed the literature searches to parameterise the model and performed the analyses. TM, TL, and MAP interpreted results and examined their implications. TM wrote the first draft of the manuscript. TL, SK, IMH and MAP revised the manuscript. All authors reviewed and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant-level data was not used in this study. Parameter values used to inform the model were extracted from the literature as referred in the main text or in the Supplementary Material. All data and codes used to create the figures will be made available.

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**Seasonal malaria chemoprevention and the spread of *Plasmodium falciparum* parasites
resistant to sulfadoxine-pyrimethamine: a mathematical modelling study**

Supplementary appendix

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1 Model description and parameterisation

1.1 Individual-based model of malaria transmission dynamics

In this study we parameterised and used our existing individual-based model of malaria transmission, known as OpenMalaria, that simulates the dynamics of *P. falciparum* in mosquitoes and humans.¹⁻³ The model was previously described in²⁻⁵. Here we briefly described the main attributes of the model with a focus on the features that allowed us to model drug resistance.

OpenMalaria is an ensemble of models that are updated every five days. The user can specify multiple parasite genotypes and their initial frequencies in the population. The human population size and age structure are maintained constant through simulations, and each individual is tracked separately. When an individual becomes infected, a model component simulates mechanistically the within-host parasite dynamics.⁶ This model simulates the parasite densities based on the parasite multiplication rate and the effect of innate, variant and acquired immunities, which reduce this multiplication rate.⁶ Each individual's immunity is developed based on their cumulative parasite exposure.⁷ Infants are also protected by maternal immunity during the first months of life.⁷ The within-host model allows for concurrent infection of multiple parasite genotypes within the same host and captures that the different parasite genotypes can indirectly compete due to immunity regulating the total parasite load. The model also allows users to specify a reduction of the within-host multiplication rate of a genotype to capture a potential fitness cost associated with the mutation that differs between the genotypes. The simulated parasite densities influence diagnostic outcomes, patient symptoms,¹ risks of severe malaria and death,^{8,9} and the probability that a feeding mosquito becomes infected.¹⁰

The parasite multiplication rate within the host is also affected by the use of drugs. A case management component describes the use of treatments of uncomplicated and severe cases based on the previous use of drugs to treat the same episode and access to health services.¹¹ In addition, the model allows the deployment of drug-based interventions at specific timings to a defined population. Pharmacokinetic (PK) models components (with one-, two- and three-compartment models possible) track the drug concentrations in individuals that have received drugs, either as a treatment or a drug-based intervention.^{12,13} The effect of the drug concentration on the parasite multiplication rate within the host is estimated using a pharmacodynamics (PD) model.^{12,13} Pharmacodynamics parameters can be parameterised individually for each genotype to model different degrees of drug susceptibility.

Malaria parasite transmission in mosquitoes is modelled with a periodically forced deterministic model component to capture vector feeding behaviour and track the infectious states of the mosquitoes.² The model periodicity allows simulating seasonality transmission patterns. The different parasite genotypes are followed in the mosquitoes but do not recombine (recombination does not apply to this study as the two mutants considered differ by only one mutation). The number of newly infected human hosts depends on the simulated entomological inoculation rate (EIR). The genotype of new infections is based on the genotype frequencies in humans at the previous five time-steps.

1.2 Parameterisation of SMC

We modelled seasonal malaria chemoprevention (SMC) as the monthly deployment of SP+AQ in target age groups during the transmission period. As explained in the main article, we deployed SMC to different age groups (under five or under ten years) in diverse seasonality settings (Figure S1.1) with various numbers of rounds deployed per year (Figure S1.1). Children under five years received the dosage regimen of SP+AQ recommended by WHO (Table S1.1).¹⁴ Children under ten years received the dosage regimen of AQ+SP used in Senegal (Table S1.1).¹⁵

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Figure S1.1: Seasonality pattern of transmission and timing of SMC deployment

The figure illustrates the entomological inoculation rate (EIR, in inoculations per person per year) across time in (A) the high (B) and the moderate seasonality setting. In the high seasonality settings, SMC was deployed three times per year (as recommended by WHO), or four times per year, with the additional round administered before or after the recommended deployment period. Similarly, for moderate seasonality settings, SMC was deployed four times per year (as recommended by WHO for this type of setting), or five times per year, with the additional round administered before or after the recommended deployment period. The blue dashed lines represent the recommended deployment of SMC. The pink dashed lines represent the additional rounds of SMC that were either deployed before or after the recommended deployment of SMC.

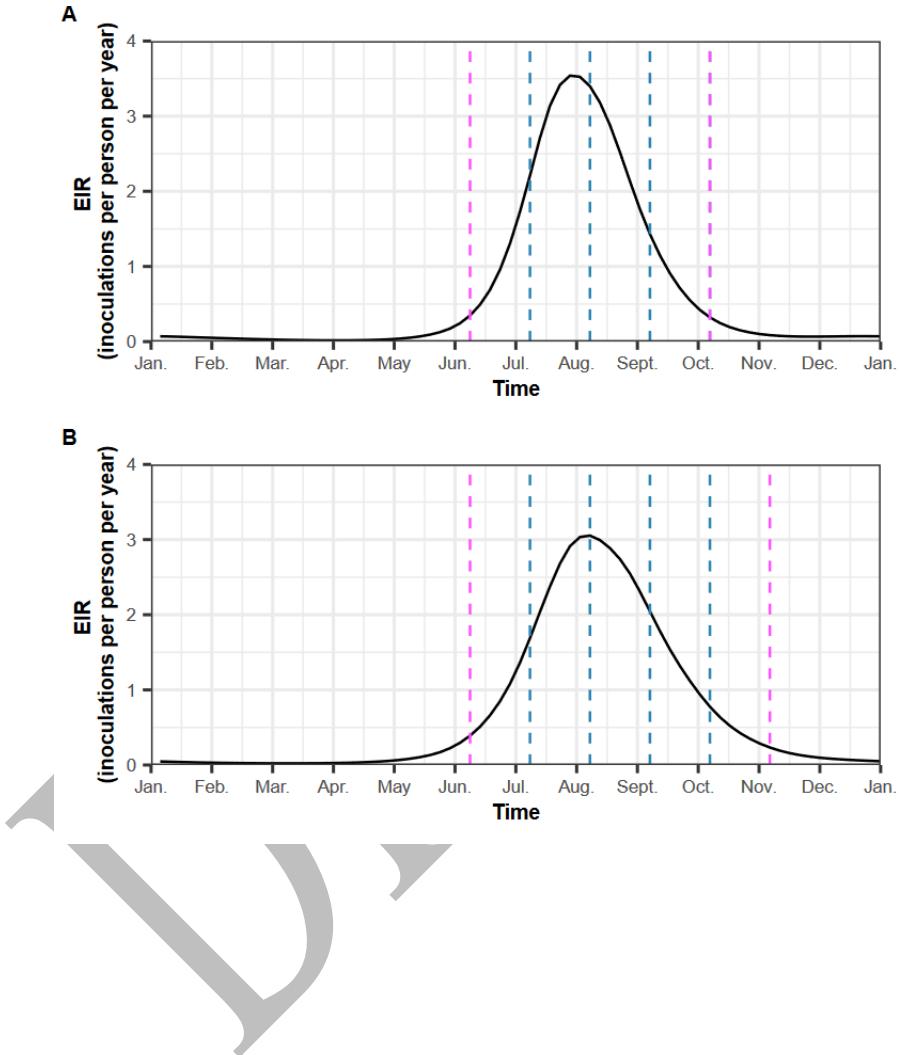


Table S1.1: The dosage regimens of sulfadoxine-pyrimethamine and amodiaquine by age groups sourced from literature

AQ: amodiaquine, SP: sulfadoxine-pyrimethamine

Age group	SP	AQ	Reference
3 months to 1 year	A single dose of 250/12·5 mg	Three daily doses of 76·5 mg	¹⁴
1 to 5 years	A single dose of 500/25 mg	Three daily doses of 153 mg	¹⁴
5 to 10 years	A single dose of 750/37·5 mg	Three daily doses of 229·5 mg	¹⁵

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1.2.1 Sulfadoxine and pyrimethamine

Sulfadoxine and pyrimethamine have a synergic effect on the blood-stage of *P. falciparum*. This synergic effect is not well understood and is challenging to capture in PD models.¹⁶ For simplicity, we modelled the two drugs as a single long-acting drug that had a similar action as the expected synergetic effect of sulfadoxine and pyrimethamine. This long-acting drug was modelled with a one-compartmental model with first-order absorption. We parameterised the drug with the PK parameters of sulfadoxine (Table S1.2) because sulfadoxine has a longer half-life than pyrimethamine, and thus we captured the maximum time until one drug component of SP was present in a patient.

For the PD model, the maximum killing rate was parameterised based on an estimate of the synergetic maximum killing rate of SP (Table S1.2).¹⁶ As informed by the literature, we modelled that the quadruple and quintuple mutants could develop a successful blood-stage infection after 21 days and 35 days, respectively.¹⁷⁻²⁰ To do that, we parameterised a higher EC50 for the quintuple mutant than the quadruple mutant capturing that the quintuple mutant was less sensitive to low drug concentrations. To determine the EC50 value of each mutant, we established the link between the prophylactic period and the EC50 of SP. To do that, we simulated the deployment of one round of SMC with only SP to all children (coverage equal to 100%) under five years in a non-seasonal setting in which children had no access to first-line treatment. We ran multiple simulations in which we varied the EC50 of SP and the transmission levels (EIR=5, 50, 100, 150 inoculations per person and per year). Each simulation started with a burn-in phase of 130 years, ran in ten seeds, and modelled 100'000 humans. In each simulation, we estimated the prophylactic period of SP as the median time before detecting a blood-stage infection in children during a follow-up period of 42 days after the deployment of SMC as Desia *et al.*¹⁹ The blood-stage infections could develop either due to treatment failure of a previous infection or reinfection as in real life.¹⁹

As expected, the prophylactic period decreased with higher EC50 (Figure S1.2). We observed that the relationship between EC50 and the prophylactic period was stable in settings having EIR ranging between 50 and 150 inoculations per person per year. However, for similar EC50 values, the prophylactic period was longer at an EIR of five inoculations per person per year than higher EIR. This result was because patients needed more time to be reinfected in a low transmission setting than a high transmission setting. Studies that assessed the prophylactic period of SP against the quintuple and quadruple mutants occurred in settings where the EIR ranged between 50 and 150 inoculations per person per year. In these settings, SP had an EC50 of 24 mg/μl against the quintuple mutant and an EC50 of 2·4 mg/μl against the quadruple mutant (Figure S1.2).

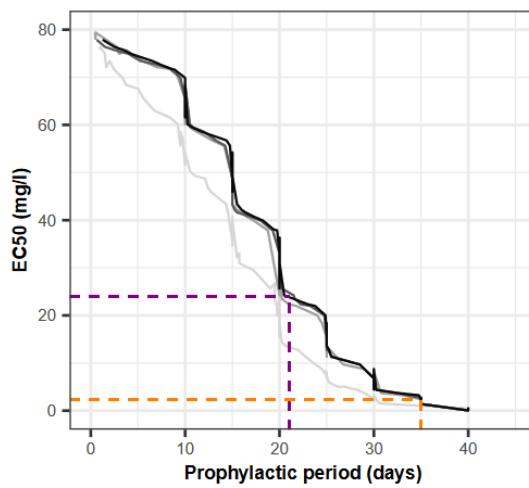
Table S1.2: The PK/PD parameters of sulfadoxine-pyrimethamine

Parameter	Value	Reference
Volume of distribution (l/kg)	0·29	²¹
Absorption rate (per day)	12·50	²¹
Elimination rate (per day)	0·12	²¹
Maximum killing rate (per day)	2·30	¹⁶
Half-maximal effective concentration (mg/l) of the quadruple mutant	2·40	Estimated
Half-maximal effective concentration (mg/l) of the quintuple mutant	24·00	Estimated
Slope of the effect curve	2·10	Assumed

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Figure S1.2: The predicted relationship between the EC50 and the prophylactic period conferred by SP in various transmission settings

The figure illustrates the predicted relationship between the EC50 and the prophylactic period conferred by SP in perineal settings that had an EIR equal to 5 (light grey line), 50 (grey line), 100 (dark grey line), 150 (black line) inoculations per person per year. The orange and purple dashed lines illustrate the relationship between the prophylactic period and the estimated EC50 of the quadruple mutant and the quintuple mutant, respectively.



1.2.2 Amodiaquine

In the human host, AQ is converted into its active metabolite, desethylamodiaquine (DEAQ). Our individual-based model does not include a conversion PK model with multiple compartments. Thus, as assumed in a previous study, we modelled AQ and DEAQ as two separate drugs.²² Each drug component was modelled with a two-compartment model with first-order absorption (Tables S1.3 and S1.4). We captured the fast metabolism of AQ into DEAQ by assuming that both drugs had a similar absorption rate and that AQ had a short elimination half-life.

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Table S1.3: The PK/PD parameters of amodiaquine

Parameter	Value	Reference
Absorption rate (per day)	2·16	²²
Elimination rate (per day)	42·00	²²
Rate at which the drugs move from the central compartment to the peripheral compartment (per day)	51·00	²²
Rate at which the drugs move from the peripheral compartment to the central compartment (per day)	1·46	²²
Volume of distribution (l/kg)	8·00	²²
Maximum killing rate (per day)	2·30	²²
Half-maximal effective concentration (mg/l)	0·0043	²²
Slope of the effect curve	7·00	²²

Table S1.4: The PK/PD parameters of desethylamodiaquine

Parameter	Value	Reference
Absorption rate (per day)	2·16	²²
Elimination rate (per day)	0·86	²²
Rate at which the drugs move from the central compartment to the peripheral compartment (per day)	1·70	²²
Rate at which the drugs move from the peripheral compartment to the central compartment (per day)	0·46	²²
Volume of distribution (l/kg)	18·40	²²
Maximum killing rate (per day)	2·30	²²
Half-maximal effective concentration (mg/l)	0·02	²²
Slope of the effect curve	7·00	²²

2 Supplementary methods and results

2.1 Assessment of the impact of factors on the rate of spread

We systematically assessed the impact of multiple factors (see main text Table 1) on the spread of the quintuple mutant through global sensitivity analyses. To perform multiple sensitivity analyses and be computationally efficient, we used a previous approach we developed to assess the impact of factors on the spread of parasites resistant to first-line treatment.⁴ This approach involved performing the global sensitivity analyses on emulators trained on our model simulations, because it was computationally infeasible to use the model directly. The steps of the approach are described in Figure S 2.1 and summarized below.

i. Randomly sample combinations of parameters

First, we (i) randomly sampled 250 parameter combinations from the parameter ranges (see main text Table 1) using a Latin hypercube sampling algorithm (LHS).²³ The parameter ranges were defined as follows. The range of SMC coverage corresponded to the range reported by an implementation study.²⁴ The variation in EIR captured settings with low transmission to those with high transmission. The range of access to treatment captured low to high 14-day effective coverage. The first-line treatments were artemisinin-based combination therapies. We varied the half-life of the long-acting partner drug in a range that captured the half-life of lumefantrine, mefloquine, piperaquine, and amodiaquine.^{22, 25-28}

ii. Model simulation and estimation of selection coefficients

For each parameter combination, (ii) we simulated and quantified the rate of spread of the quintuple mutant in our model as followed. Each parameter combination was simulated in five seeds and modelled a human population of 100,000 individuals with demographic age distribution of Tanzania, a lower-middle-income country.²⁹ Simulations started with a burn-in period of 130 years. After the burn-in period, we deployed SMC for ten consecutive years and estimated the spread of the quintuple mutant through the selection coefficient, defined as the proportion by which the quintuple mutant relative frequency increases each parasite generation (see below).³⁰ Note that simulations started with a relative frequency of the quintuple mutant in infection of 50%. We did not start with a lower relative frequency because the strength of genetic drift would have been more substantial, which would have led to stochastic extinction of the quintuple mutant in many simulations and reduced the accuracy of the estimated selection coefficient.^{4, 30} Nevertheless, as the selection coefficient is not frequency-dependent in our model, our estimates represent selection that occurs at a low frequency of the quintuple mutant.^{4, 30}

To calculate the selection coefficient, we defined the relative frequency of the quintuple genotype, p , based on the relative frequency of the quintuple mutant in inoculations (Figure S2.2). This measurement is a good representation of the spread at the population level as it tracked genotypes transmitted to the next generations and was more stable across age groups than other variables, such as the number of patients infected by each genotype (Figure S2.3). The selection coefficient, s , was defined as the slope of the logistic regression of $p(t)$,

$$s = \frac{1}{t} \left(\ln \left(\frac{p(t)}{1 - p(t)} \right) - \ln \left(\frac{p(0)}{1 - p(0)} \right) \right) = \frac{1}{60} \left(\ln \left(\frac{p(60)}{1 - p(60)} \right) - \ln \left(\frac{p(0)}{1 - p(0)} \right) \right), \quad (\text{Equation 2.1})$$

where t is the number of parasite generations after the deployment of SMC at $t = 0$. We assumed that a parasite generation is equal to 60 days (6 generations per year).³⁰ We started the regression directly at the first round of SMC ($t = 0$), and we stopped the regression ten years later at the last SMC round ($t = 60$). We stopped the regression sooner if p was higher than 90% or lower than 30% to prevent tracking one genotype at a low frequency which would have led to strong genetic drift.

iii. Model emulation and adaptive sampling

Once the selection coefficient was estimated for each parameter combination, we (iii) randomly split our data into a training and a testing dataset containing 80% and 20% of the simulations, respectively. Then, (iii) we trained a heteroskedastic Gaussian process (HGP) on the training dataset using the function *mleHetGP* from the R-package *hetGP*.³¹ To assess the accuracy of the emulator, we predicted the selection coefficient from the test dataset with the emulator and compared it to its true values. If the fit of the emulator was not satisfactory, we iteratively improved the emulator fit through adaptive sampling. To undertake adaptive sampling, we sampled 100 parameter combinations in the parameter space region where we were less confident (higher variance) in the emulator prediction, and we repeated the whole process until the emulators reached sufficient accuracy (Figure S2.4).

iv. Global sensitivity analysis

After that, (iv) we assessed the influence of each factor on the selection coefficient via global sensitivity analysis using Sobol's method of variance decomposition.³² To perform the global sensitivity analysis, we first generated two random datasets of 100'000 parameter combinations using Latin hypercube sampling. Then, we predicted the selection coefficient for each parameter combination using the emulators. Finally, we performed the global sensitivity analysis on the two datasets with 150000 bootstrap replicates using the function *soboljansen* of the R-package *Sensitivity*.³³ With the global sensitivity analysis, we estimated the first-order indices of each factor, representing their influence on the rate of spread (Figure S2.5), and assessed the 25th, 50th, and 75th quantiles of the predicted rate of spread over each parameter range (see main text Figure 2).

Figure S2.1: Schematic of our global sensitivity analysis approach

The approach aims to assess the influence of factors on the rate of spread (selection coefficient) of the quintuple mutant through global sensitivity analyses. Our approach involved: (i) randomly sampling parameters combinations; (ii) simulating and estimating the rate of spread of the quintuple mutant via the selection coefficient for each parameter combination with our model; (iii) training an emulator on the simulated data with iterative fitting improvements through adaptive sampling, and (iv) performing the global sensitivity analysis using the fitted emulator. The purple line illustrates an example of the relative frequency of the quintuple mutant in infected humans across time. HGP: Heteroskedastic Gaussian Process

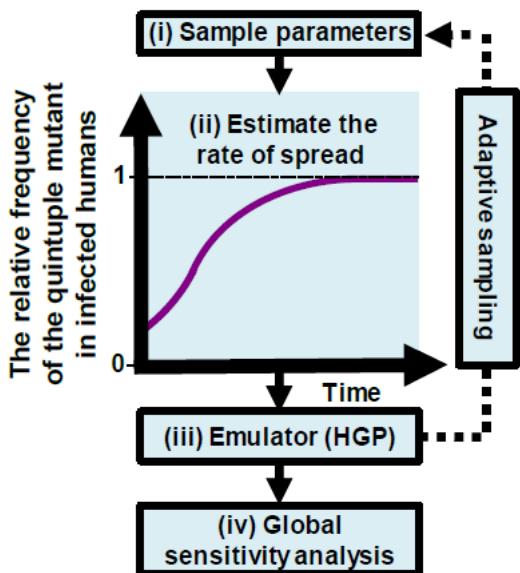


Figure S2.2: The relative frequency of each genotype in inoculations

We estimated the relative frequency of inoculations carrying the quadruple (orange line) and quintuple mutants (purple line) when we deployed SMC four times per year in the moderate seasonal setting to children under ten years. The coverage was equal to 98% at each round. The EIR was equal to 339 inoculations per person per year. The access to treatment was equal to 35%. The grey lines indicate the deployment of SMC.

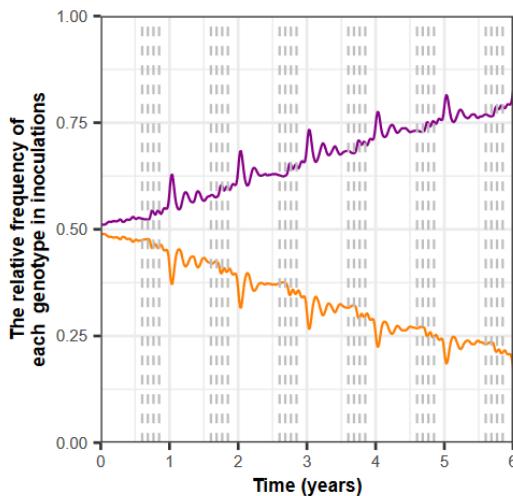


Figure S2.3: Illustration of the frequency of the quadruple and quintuple mutants in infections and inoculations in different age groups

The top row shows the number of patent infections caused by the quadruple mutant (orange lines) and the quintuple mutant (purple lines) in (A) the total population, (B) children under ten years old, and (C) individuals over ten years old. The bottom row shows the number of inoculations caused by the quadruple mutant (orange lines) and the quintuple mutant (purple lines) in (D) the whole population, (E) children under ten years old, and (F) individuals over ten years old. In each plot, we delivered SMC four times a year (grey dashed lines) in the moderate seasonal setting to children under ten years with a coverage of 98% (high coverage). The EIR was equal to 339 inoculations per person per year (high transmission). The access to treatment was equal to 35% (low access).

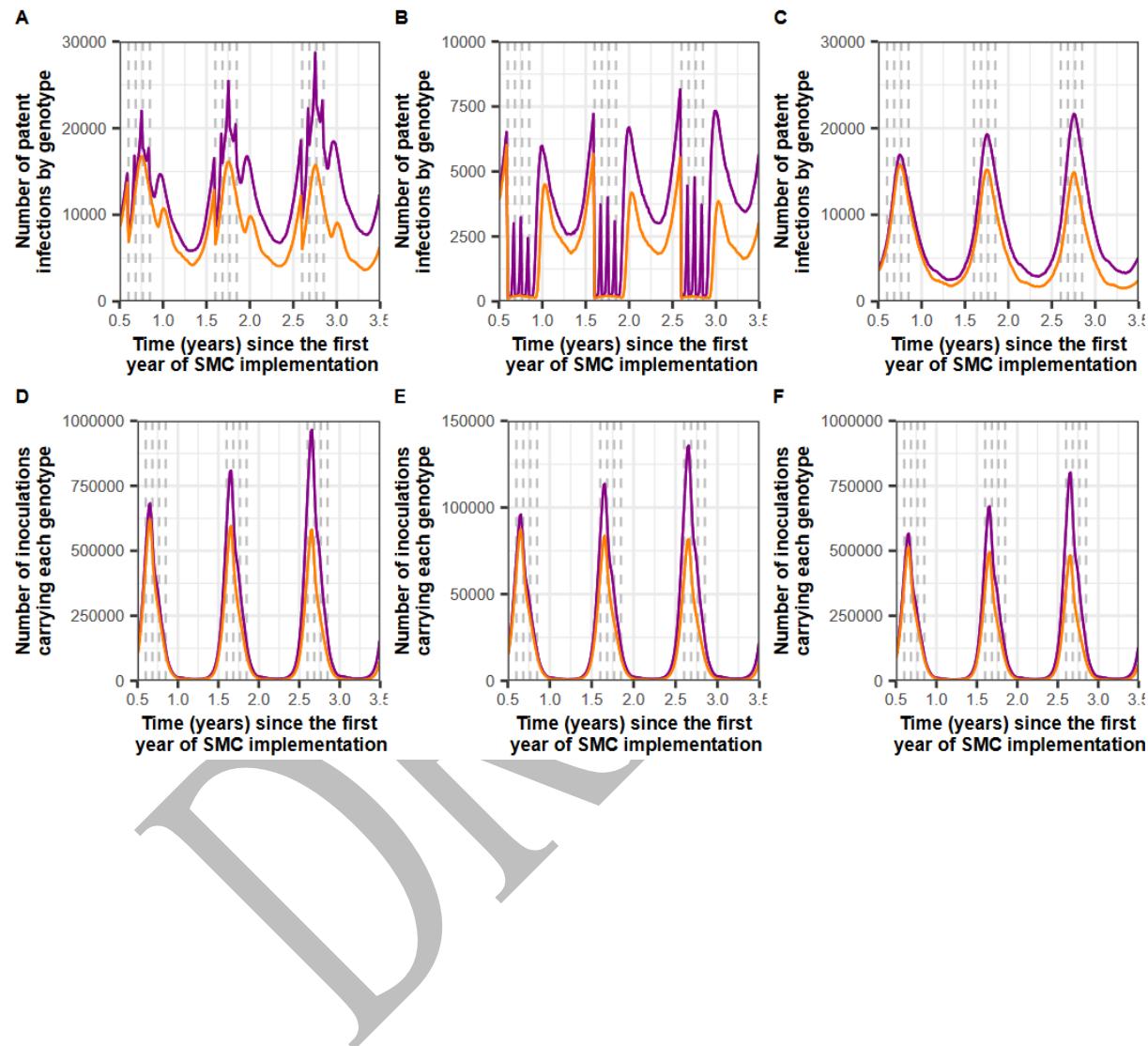


Figure S2.4: Accuracy of the emulators used for each global sensitivity analysis of the spread of quintuple mutants in each seasonality setting and for each SMC deployment strategy

The figure exhibits the observed rate of spread of the quintuple mutant estimated by our model simulations, and the rate of spread predicted with the emulators for the testing dataset at the final round of adaptive sampling for each global sensitivity analysis. We performed the global sensitivity analyses in two different seasonality settings (moderate and high seasonal), and for various SMC deployment strategies that varied by: targeted age groups (under five years or under ten years), numbers of SMC rounds deployed per year (high seasonality setting: three rounds or four rounds with the additional round deployed before or after the recommended deployment of SMC, moderate seasonality setting: four rounds or five rounds with the additional round deployed before or after the recommended deployment of SMC), and assumptions about the reduction of the coverage across each round (none (0%) or 10% from the previous round). Cor: Spearman correlation coefficient, RMSE: root mean squared error, blue lines: linear regression fit.

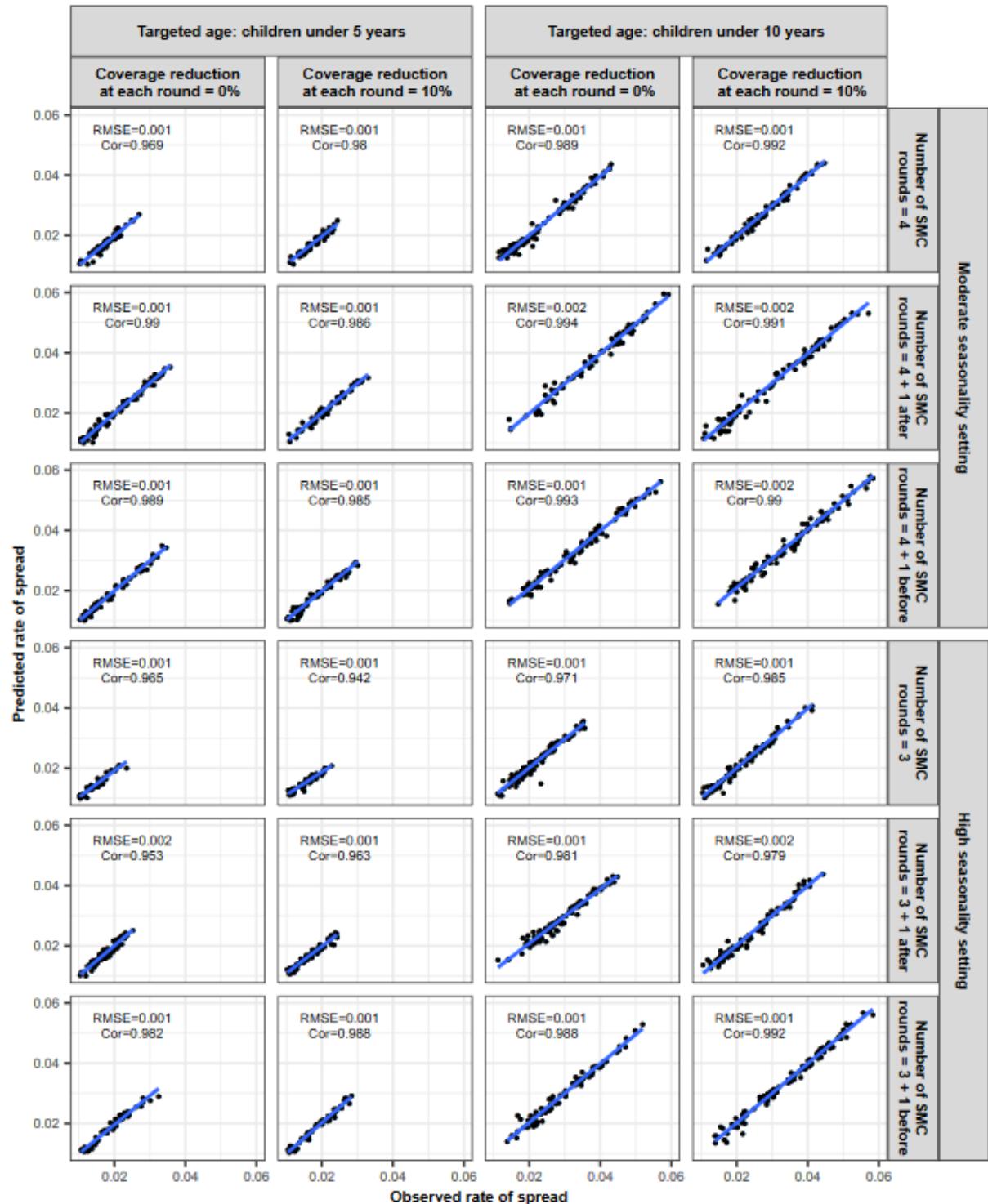


Figure S2.5: The impact of factors on the spread of the quintuple mutant

The figure displays the first-order indices of the coverage (blue), the EIR (orange), and the level of access to treatment (purple) estimated during each global sensitivity analysis. The explored parameter ranges were the following: SMC coverage [70%, 100%]; EIR [5, 500] inoculations per person per year; and the level of access to treatment [10%, 80%]. We performed the global sensitivity analyses in two different seasonality settings (moderate and high seasonal) and for various SMC deployment strategies that varied by: targeted age groups (under five years or under ten years), numbers of SMC rounds deployed per year (high seasonality setting: three rounds or four rounds with the additional round deployed before or after the recommended deployment of SMC, moderate seasonality setting: four rounds or five rounds with the additional round deployed before or after the recommended deployment of SMC), and assumptions about the reduction of the coverage across each round (none (0%) or 10% from the previous round).

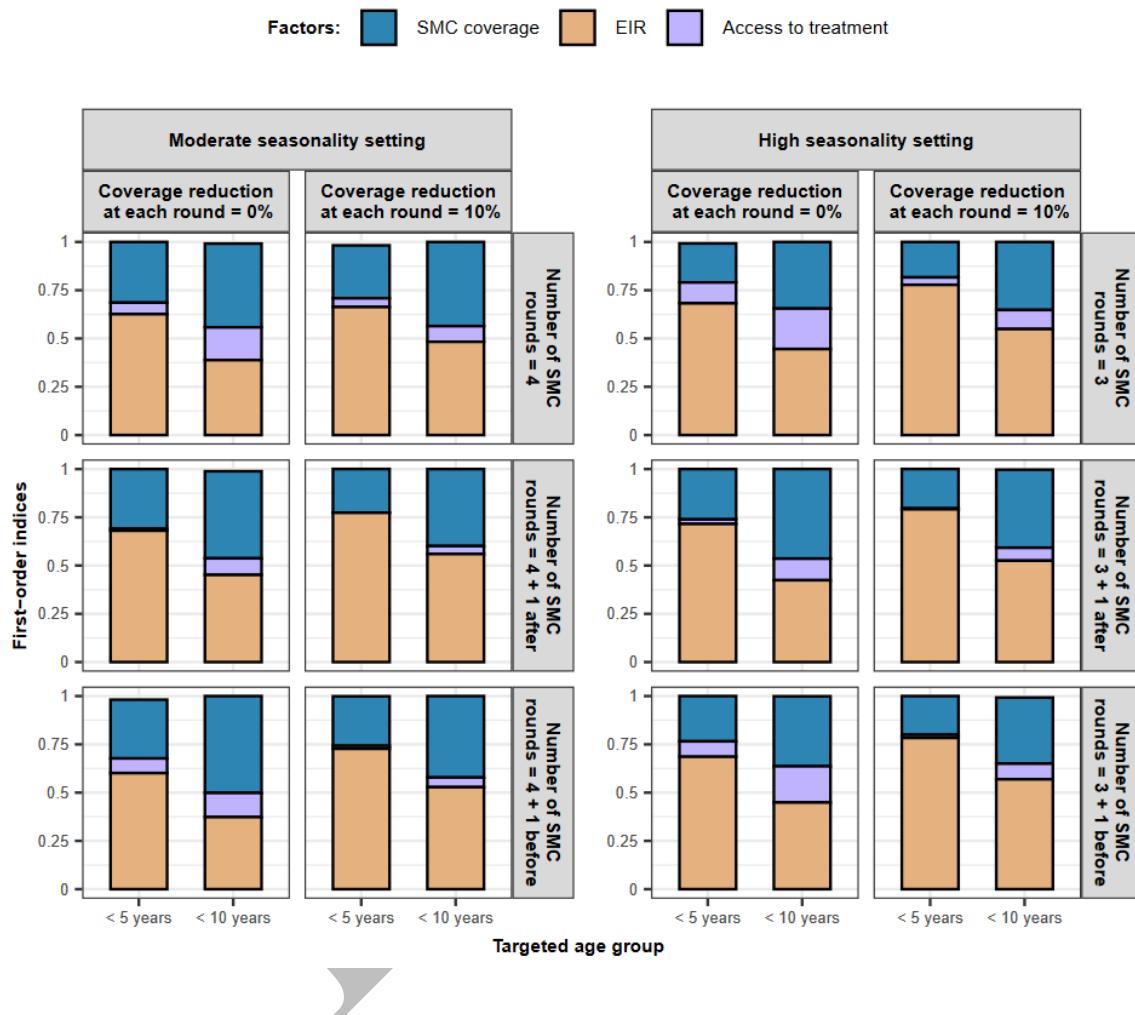


Figure S2.6: The impact of access to first-line treatment on the numbers of patent infections

The figure reports the numbers of patent infections in children under five years old who received SMC (blue) and in individuals above five years old who did not receive SMC (pink) in settings where the level of access to treatment was low (solid line, access to treatment: 10%) or high (dashed line, access to treatment: 80%). In this example, four rounds of SMC were deployed in the moderate seasonal setting to children under five years. The coverage was equal to 96% for each SMC round. The EIR was equal to 315 inoculations per person per year (high transmission).

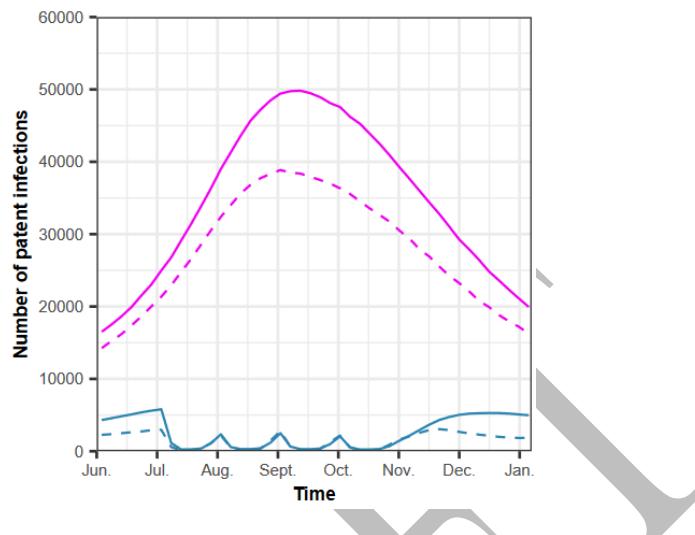
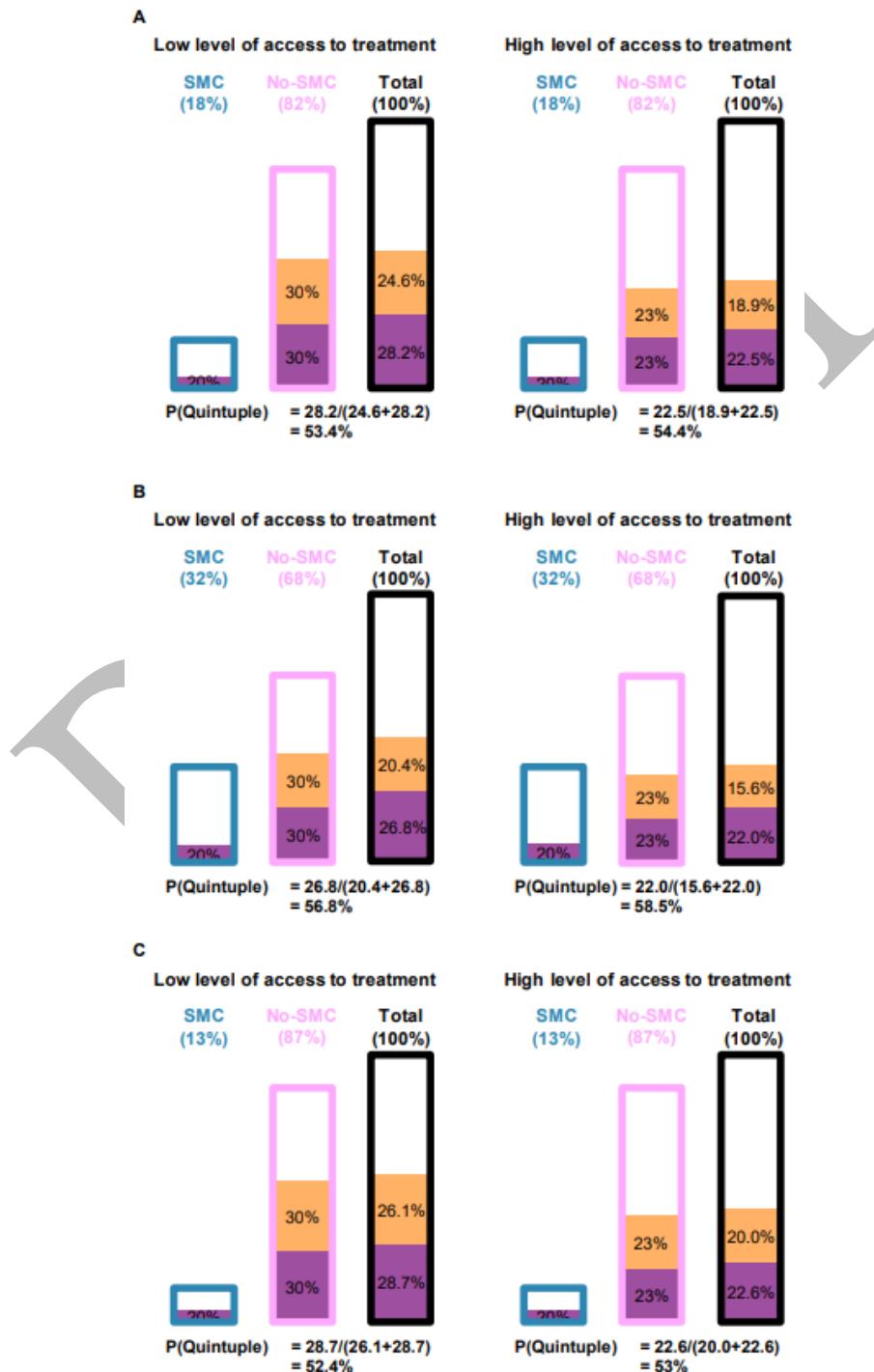


Figure S2.7: The effect of access to treatment on the relative frequency of the quintuple mutant

The figures schematically illustrate the effect of access to treatment on the relative frequency of the quintuple mutant. The relative frequencies were estimated in setting that had a low (10%) or high (80%) level of access to treatment and where we deployed four rounds of SMC to (A) children under five years with a constant coverage across rounds; (B) children under ten years with a constant coverage across rounds; (C) children under five years with a coverage reduction of 10% from the previous round. The SMC coverage was 96%. The EIR was equal to 315 inoculations per person per year (high transmission). The percentages of individuals who received SMC are in the blue bars, and the percentages of individuals who did not receive SMC are in the pink bars. The black bars represent the total population. Within each bar, individuals are separated as carrying the quadruple mutant (orange), the quintuple mutant (purple), or neither (white). The relative frequency of the quintuple mutant in infected individuals, P(Quintuple), is the number of infections caused by the quintuple mutant to the total number of infections.



2.2 Conversion from the selection coefficient into the T_{50}

To convert the selection coefficient into the time needed for the quintuple genotype to spread from a relative frequency in inoculations of 1% to 50%, T_{50} , we converted the selection coefficient into the numbers of parasite generations needed for the relative frequency of the quintuple mutant in inoculations to increase from 1% to 50% as follow, t ,

$$t = \frac{1}{s} \left(\ln \left(\frac{0.5}{1 - 0.5} \right) - \ln \left(\frac{0.01}{1 - 0.01} \right) \right). \quad (\text{Equation 2.2})$$

Then, we converted the number of parasite generations to the T_{50} in years. We assumed that a parasite generation is equal to 60 days.³⁰ For each SMC deployment strategy and seasonality setting, we assessed the T_{50} for various levels of coverage, transmission, and access to treatment (See main text Figure 3). We also illustrated the T_{50} for different levels of prevalence instead of EIR (Figure S2.8) and when we deployed SMC with an equitable delivery (deployment where each child had the same probability of receiving SMC each round) (Figure S2.9).

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Figure S2.8: Impact of SMC deployment strategies on the spread of the quintuple mutant

The time needed for the quintuple genotype to spread from a relative frequency in inoculations of 1% to 50%, T_{50} , when SMC was deployed to different age groups (under five (squares) or under ten years (triangles)) in diverse seasonality settings (moderate and high seasonality pattern) with a various number of rounds deployed per year (high seasonality: three (blue shapes) or four rounds with the additional round deployed before (purple shapes) or after (orange shapes) the standard deployment period; moderate seasonality setting: four (blue shapes) or five rounds with the additional round deployed before (purple shapes) or after (orange shapes) the standard SMC deployment period). We predicted the T_{50} for different levels of initial coverage (75%, 85%, and 95%) and coverage reduction across rounds (0% or 10% reduction since the previous round). For each setting and SMC deployment strategy, T_{50} was predicted for various transmission levels (ranging from 5 to 150 inoculations per person per year) and for two levels of access to treatment (25 and 70%). The mean annual prevalence of *P. falciparum* was estimated based on the number of patent infections in children between 2 to 10 years.

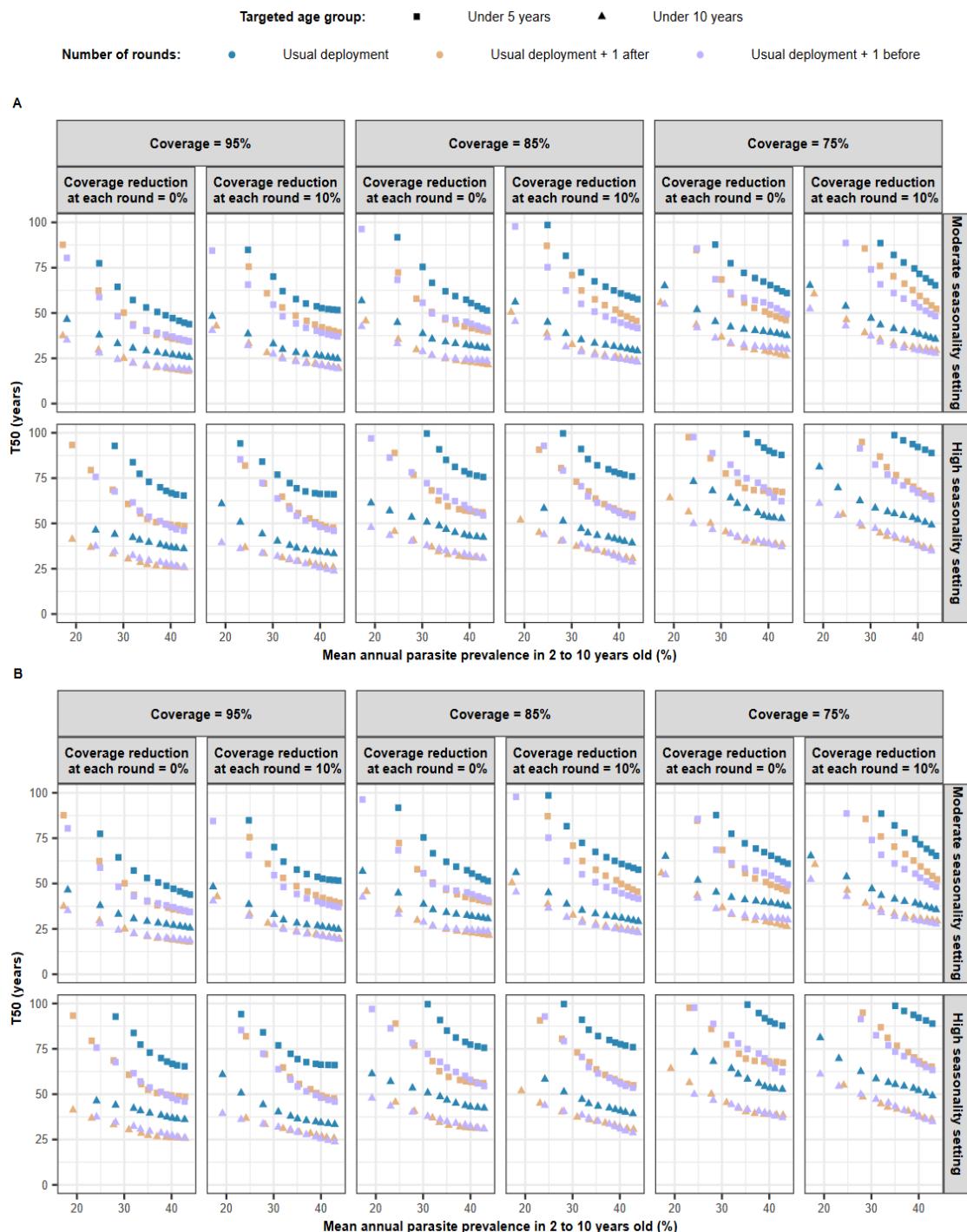
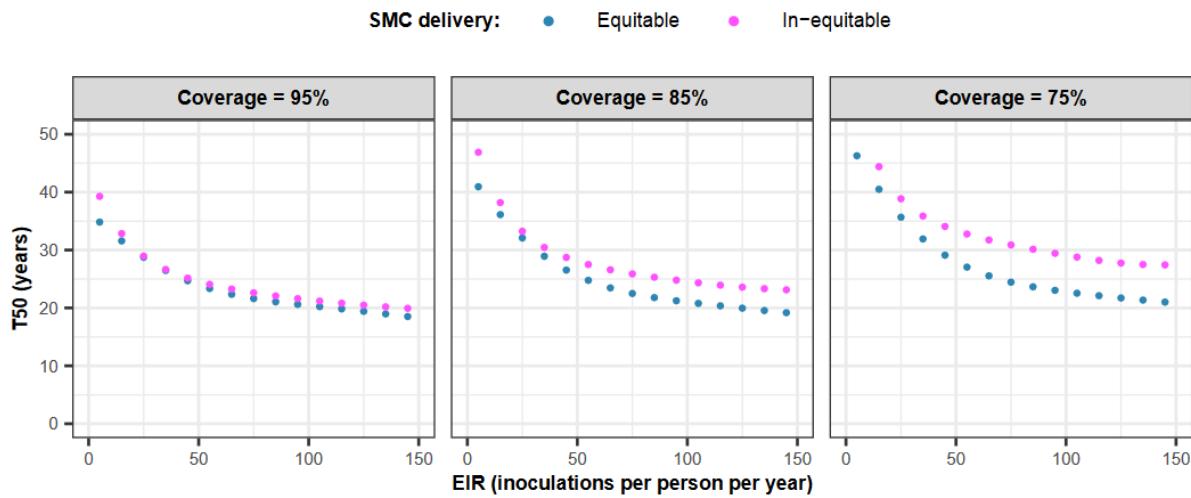


Figure S2.9: The impact of equitable and in-equitable SMC delivery on the spread of the quintuple mutant

We predicted the T_{50} when delivering SMC with an equitable (blue dots) and an in-equitable (pink dots) deployment strategy. We defined an equitable delivery as a deployment where each child had the same probability of receiving SMC each round. We defined an in-equitable delivery as a deployment where the same children received SMC each round. In this illustration, we deployed four rounds of SMC to children under ten years in a setting with a high access to treatment (70%) and a moderate seasonality pattern of transmission. In each setting and SMC deployment strategy, the T_{50} was predicted for various transmission levels (ranging from 5 to 150 inoculations per person per year) and three different SMC coverage levels (75%, 85%, 95%), which were constant across rounds.



2.3 Estimation of the protective effectiveness of SMC

We estimated the protective effectiveness (PE) of SMC against parasite populations composed of only one genotype for which SP+AQ provide a prophylactic period of different length (Table S2.1). To do that, we simulated the recommended deployment of SMC (four rounds of SMC deployed per year to children under five years in the moderate seasonality setting with a coverage reduction of 10% from the previous round) in a human population of 10'000 individuals. Each simulation was run in three seeds, started with a burn-in phase of 130 years, and then we deployed SMC and assessed the PE.

To assess the PE, we first estimated the incidence rate (per person per month) of uncomplicated malaria episodes in children between 3 months and 5 years during the months of SMC deployment (Figure S2.10). For comparison, we estimated the incidence rate of uncomplicated malaria during the same period of the year one year before SMC deployment (Figure S2.10). The incidence rates (I) were calculated as,

$$I = \frac{U}{N * t} = \frac{U}{N * 4}, \quad (\text{Equation 2.3})$$

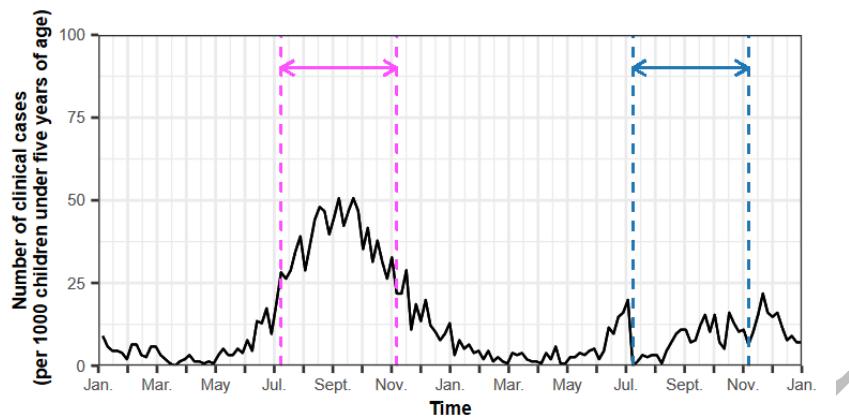
where, U is the number of uncomplicated malaria episodes that occur during the four months of SMC deployment, N is the number of children aged between 3 months and 5 years, and t is the number of months of SMC deployment (four). Then, we estimated the PE as the relative reduction of the incidence rate of clinical malaria when SMC was deployed (I_{SMC}) compared to the incidence rate the year before the deployment ($I_{Before SMC}$),¹⁹ as

$$PE = \left(1 - \left(\frac{I_{SMC}}{I_{Before SMC}} \right) \right) * 100. \quad (\text{Equation 2.4})$$

For each prophylactic period length, we assessed the PE for different levels of transmission, coverage, and access to treatment (see main text Figure 4).

Figure S2.10: An illustration of the estimation of the SMC protective effectiveness

The black line represents the incidence of malaria clinical cases per 1000 children under five years of age over time in the year before the deployment of SMC and the first year of SMC deployment in a parasite population composed only of quadruple mutants (prophylactic period of SP equal to 35 days). The orange arrow and dashed lines indicate the period during which we estimated the incidence rate of clinical malaria before the deployment of SMC. The blue arrow and dashed lines represent the period during which we estimated the incidence of clinical malaria during SMC deployment. In this example, we deployed four rounds of SMC to children under five within the period indicated by the blue arrow, with initial coverage of 95%, decreasing by 10% from the previous round. The probability of symptomatic cases receiving treatment within two weeks from symptom onset was equal to 25% (low access to treatment). The EIR was equal to 10 inoculations per person per year (medium transmission). The seasonality of the transmission pattern was moderate.



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Table S2.1: Parameterisation of the EC50 of SP and AQ to model the desired prophylactic period of SMC

AQ: amodiaquine, DEAQ: desethylamodiaquine, SP: sulfadoxine-pyrimethamine

Predicted length of the prophylactic period (days)	EC50 of SP (mg/l)	EC50 of DEAQ (mg/l)	EC50 of AQ (mg/l)
5	73·450	0·130	0·0089
10	60·120	0·094	0·0044
15	42·160	0·061	0·0044
21	24·200	0·024	0·0044
25	11·327	0·024	0·0044
30	4·372	0·024	0·0044
35	2·39	0·024	0·0044
40	0·500	0·024	0·0044

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