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

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Summary

Background Seasonal malaria chemoprevention (SMC) with sulfadoxine–pyrimethamine plus amodiaquine prevents millions of clinical malaria cases in children younger than 5 years in Africa's Sahel region. However, *Plasmodium falciparum* parasites partially resistant to sulfadoxine–pyrimethamine (with quintuple mutations) potentially threaten the protective effectiveness of SMC. We evaluated the spread of quintuple-mutant parasites and the clinical consequences.

Methods We used an individual-based malaria transmission model with explicit parasite dynamics and drug pharmacological models to identify and quantify the influence of factors driving quintuple-mutant spread and predict the time needed for the mutant to spread from 1% to 50% of inoculations for several SMC deployment strategies. We estimated the impact of this spread on SMC effectiveness against clinical malaria.

Findings Higher transmission intensity, SMC coverage, and expanded age range of chemoprevention promoted mutant spread. When SMC was implemented in a high-transmission setting (40% parasite prevalence in children aged 2–10 years) with four monthly cycles to children aged 3 months to 5 years (with 95% initial coverage declining each cycle), the quintuple mutant required 53·1 years (95% CI 50·5–56·0) to spread from 1% to 50% of inoculations. This time increased in lower-transmission settings and reduced by half when SMC was extended to children aged 3 months to 10 years, or reduced by 10–13 years when an additional monthly cycle of SMC was deployed. For the same setting, the effective reduction in clinical cases in children receiving SMC was 79·0% (95% CI 77·8–80·8) and 60·4% (58·6–62·3) during the months of SMC implementation when the quintuple mutant was absent or fixed in the population, respectively.

Interpretation SMC with sulfadoxine–pyrimethamine plus amodiaquine leads to a relatively slow spread of sulfadoxine–pyrimethamine-resistant quintuple mutants and remains effective at preventing clinical malaria despite the mutant spread. SMC with sulfadoxine–pyrimethamine plus amodiaquine should be considered in seasonal settings where this mutant is already prevalent.

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Introduction

Plasmodium falciparum malaria is a leading cause of morbidity and mortality in African children.[1] In Africa's Sahel region, *P falciparum* transmission is seasonal, with most clinical cases occurring over a 3–5-month period.[2] Since 2012, WHO has recommended implementation of seasonal malaria chemoprevention (SMC) in this region,[2] and recent guidelines recommend flexible SMC implementation (ie, varying the number of cycles and targeted age groups).[3] SMC has been implemented as monthly sulfadoxine–pyrimethamine plus amodiaquine for children aged 3 months to 5 years during the transmission season.[2] A large implementation study reported that SMC prevented over 88% of uncomplicated malaria cases within 28 days of administration.[4] This high effectiveness is partly attributable to sulfadoxine–pyrimethamine, which remains at a concentration sufficient to inhibit development of successful blood-stage infections for long periods post-treatment. Evidence suggests that this prophylactic period is roughly 42 days against sulfadoxine–pyrimethamine-sensitive parasites, but shorter for less sensitive parasites.[5–7]

Accumulation of mutations in *dihydropteroate synthase* (*dhps*) and *dihydrofolate reductase* (*dhfr*) *P falciparum* genes leads to reduced sensitivity to sulfadoxine and pyrimethamine, respectively.[8] In many Sahelian countries, the quadruple mutant (*dhfr*-51I, *dhfr*-59R, *dhfr*-108N, and *dhps*-437G) is already highly prevalent.[4,9,10] It is challenging to estimate the prophylactic period conferred by sulfadoxine–pyrimethamine against a specific mutant in the real world due to the presence of other mutants, geographical variation in mutant frequency, and individual variations. However, in west Africa, where the quadruple mutant is highly prevalent, sulfadoxine–pyrimethamine has been shown to provide protection for approximately

Research in context

Evidence before this study

On March 22, 2021 we performed a literature search for modelling studies that assessed the impact of seasonal malaria chemoprevention (SMC) deployment on the spread of sulfadoxine–pyrimethamine-resistant malaria parasites. PubMed was used with the keywords: malaria AND model* AND resistance AND seasonal malaria chemoprevention OR intermittent preventive treatment (IPT). There were no date restrictions on the search. We found six studies focused on the impact of IPT on the spread of resistance but no studies focusing on the impact of SMC on resistance spread. These studies assumed that the drug was continuously administered to the targeted population. Thus, it remains unknown how SMC implementation strategies (such as the number of cycles administered per year and the target age group(s)) affect quintuple-mutant spread in seasonal settings. Four of these six studies assumed that parasites were fully IPT-drug resistant, and did not model partial resistance, as is the case for the quintuple mutant. Consequently, these studies ignored sulfadoxine–pyrimethamine's important residual prophylactic effect on the quintuple mutant. Five of the six studies assumed that the resistant genotype was resistant to both drug regimens used for IPT and first-line treatment. This assumption does not correspond to the use of sulfadoxine–pyrimethamine for SMC in the Sahel where different first-line treatments are used (mainly artemether–lumefantrine).

Added value of this study

To our knowledge, our study is the first to estimate the potential rate of spread of sulfadoxine–pyrimethamine-resistant quintuple mutants under selection by SMC with sulfadoxine–pyrimethamine plus amodiaquine. Our mechanistic model captures sulfadoxine–pyrimethamine's residual prophylactic effect on quintuple mutants, as informed by previous studies, and allows us to estimate its spread under SMC deployment for a range of settings. Clinical and observational studies remain the gold-standard evidence; however, evidence on the rate of spread of sulfadoxine–pyrimethamine resistance and why it spreads is scarce. The added value of our study, informed by sulfadoxine–pyrimethamine pharmacokinetic data and limited clinical evidence on quintuple pharmacodynamics, is that we can extrapolate and explore dynamics of sulfadoxine–pyrimethamine resistance spread under pressure from SMC to a large range of different epidemiological and clinical settings. For the first time, we estimate the dynamics of sulfadoxine–pyrimethamine resistance spread and determine that a relatively long period is required to reach fixation (100% frequency) of the quintuple mutant. Moreover, our approach allows us to assess the protective effectiveness of SMC against malaria clinical cases in a parasite population composed solely of quintuple mutants.

Implications of all the available evidence

We found that the rate of spread of the quintuple mutant with partial resistance to sulfadoxine–pyrimethamine is relatively slow if the target population for SMC is aged 3 months to 10 years or aged 3 months to 5 years, and this rate strongly depends on the implementation strategy of SMC with sulfadoxine–pyrimethamine plus amodiaquine. Our results support the continued implementation of SMC, as it will continue to prevent millions of clinical cases in Sahelian children despite the spread of the quintuple mutant. Our findings also highlight that in seasonal settings where the quintuple mutant is already highly prevalent, and clinical and severe malaria remains high, implementing SMC with sulfadoxine–pyrimethamine plus amodiaquine could still have a marked clinical benefit.

35 days (figure 1A) in clinical trials of SMC with sulfadoxine–pyrimethamine plus amodiaquine[11] and in a prospective study of intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine.[5]

A bigger threat comes from emergence of a quintuple mutant in multiple Sahelian countries.[4] This mutant carries an additional mutation (*dhps*-540E) conferring higher sulfadoxine–pyrimethamine resistance, leading to high treatment failure rates with the use of sulfadoxine–pyrimethamine monotherapy.[8] However, clinical trial data of intermittent preventive treatment in infancy with sulfadoxine–pyrimethamine[6,8] and a prospective study of intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine[5] suggest that sulfadoxine–pyrimethamine prevents successful development of quintuple-mutant infections (due to reinfection or recrudescence) for 21 days post-treatment (figure 1A). Quintuple mutants can establish blood-stage infections more rapidly post-treatment than more sensitive parasites, so implementation of SMC might drive their spread (figure 1A). This selection occurs even when sulfadoxine–pyrimethamine is used in combination with amodiaquine because amodiaquine provides an approximately 17-day prophylactic period; therefore, amodiaquine is eliminated before the selection window caused by sulfadoxine–pyrimethamine (the period during which quintuple mutants can develop successful blood-stage infections in SMC-treated children, but quadruple mutants cannot) occurs (figure 1A).[12] Markers of low degrees of amodiaquine resistance (*Pfcrt-CIVET*, *pfmdr1-86 Tyr*, and *184 Tyr*), which can slightly reduce amodiaquine's prophylactic period, have been observed in the Sahel at a low prevalence (0·5% in 2018).[4,12] However, this is unlikely to change the selection window caused by sulfadoxine–pyrimethamine or the prophylactic period conferred by SMC.

Clinical studies investigating the impact of SMC on quintuple-mutant spread have shown contradictory results.[13] Mathematical models have assessed the effect of intermittent preventive treatment on resistance spread in perennial settings.[14–19] However, to our knowledge, no model has assessed the impact of SMC on the spread of

quintuple mutants, nor investigated factors driving their spread. Moreover, it remains uncertain how the spread of quintuple mutants will reduce the effectiveness of SMC against clinical malaria. Here, we used an individual-based model of malaria transmission[20] to address these questions. We assessed the rate of spread of the quintuple mutant and systematically quantified which factors drive its spread under various deployment strategies and seasonality settings. Finally, we estimated the impact of the quintuple-mutant spread on SMC effectiveness against clinical malaria.

Methods

Model calibration

OpenMalaria simulates *P falciparum* dynamics in mosquitoes and humans,[21–23] tracks multiple parasite genotypes, models their intra-host dynamics, and allows genotypes to have different sensitivities to drugs as specified in the pharmacokinetic and pharmacodynamic model components.[24] The model has been previously described[21–24] and is briefly described in the appendix (p 4).

Using this model, we tracked quintuple-mutant spread in a parasite population composed of quadruple mutants attributable to implementation of SMC. For simplicity, we assumed that the quadruple mutant is the only competitor of the quintuple mutant because it is its most important competitor for two reasons (appendix p 44). First, the quadruple mutant is highly prevalent in the Sahel.[4,9,10] Second, there is no fitness cost associated with resistance to sulfadoxine–pyrimethamine,[9,25] implying that all other genotypes (sensitive, single, double, and triple mutants) behave similarly to the quadruple mutant in individuals who did not receive SMC, although the quadruple mutant can develop a successful blood-stage infection a few days earlier than these genotypes in children who received SMC. As the quintuple mutant is already present in the Sahel, we ignore de novo mutation, which will have a negligible effect on the mutant spread to high frequency.

We deployed SMC in two archetypal seasonality settings for a range of parasite prevalence in children aged 2–10 years modelled via inputs with a range of entomological inoculation rates (EIRs), in which approximately 85% of transmission occurs over 3 months (reflecting high seasonality, such as in Senegal) or 4 months (moderate seasonality, such as in Burkina Faso; appendix p 5). SMC in high-seasonality settings was deployed three times (one cycle per month) during the transmission season (as typically implemented in practice), or four times, with the additional cycle administered before or after the typical deployment period (appendix p 5). Similarly, SMC in moderate-seasonality settings was deployed four times (one cycle per month) during the transmission season or five times, with the additional cycle administered before or after the typical deployment period (appendix p 5). We deployed SMC to two different target age groups, children aged 3 months to 5 years (as typically implemented in practice), or 3 months to 10 years. For each strategy, we simulated scenarios where SMC coverage was constant or decreased by 10% from the previous cycle (eg, if cycle one is 80%, then subsequent cycles are 72%, 65%, etc).[4,11]

At each SMC cycle, children received one sulfadoxine–pyrimethamine dose and three daily amodiaquine doses, dosed according to their age (appendix p 6)[2,26] and were assumed to fully adhere to the regimen. Pharmacokinetic and pharmacodynamic models were used to model amodiaquine and its active metabolite (appendix pp 12–16). We assumed that amodiaquine and its metabolites were effective against both mutants and provided a 17-day prophylactic period. Sulfadoxine–pyrimethamine is a synergistic two-drug combination, making it challenging to simulate across a population.[27] There are currently no pharmacodynamic data that report the blood-stage activity of sulfadoxine–pyrimethamine against either the quadruple or quintuple mutant. Therefore, we made some simplifications and represented sulfadoxine–pyrimethamine

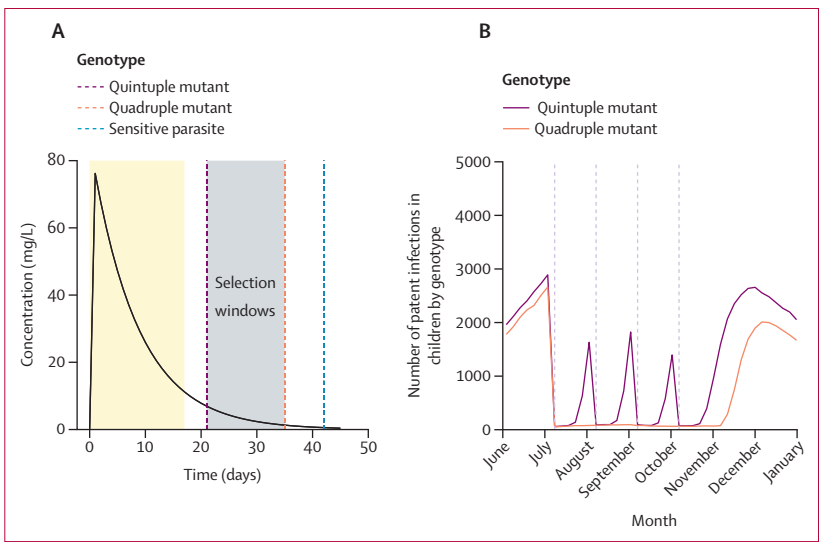

Figure 1: **Illustrations of sulfadoxine–pyrimethamine resistance calibration and dynamics modelling**
(A) Within-host plasma concentration of sulfadoxine–pyrimethamine* (the single long-acting drug with a similar duration of action as the expected synergetic combination of sulfadoxine and pyrimethamine) was modelled as a single long-acting drug with a one-compartment pharmacokinetic and pharmacodynamic model with first-order absorption (appendix pp 8–11). Sulfadoxine–pyrimethamine* mimicked the synergic effect of sulfadoxine–pyrimethamine combinations on the blood-stage (appendix pp 8–11). The purple, orange, and blue dashed lines represent the end of the prophylactic period for a quintuple mutant, quadruple mutant, and a sensitive parasite, respectively (obtained from empirical studies).[5–7,11] Half-maximal effective concentration values of 24·0 mg/L for the quintuple mutant and 2·4 mg/L for the quadruple mutant confer these clinically observed prophylactic periods (appendix pp 8–11). The yellow region represents the prophylactic period conferred by amodiaquine and its active metabolite against all genotypes.[12] Amodiaquine and its active metabolite were modelled separately using two two-compartment models with first-order absorption (appendix pp 12–16). The grey region between the orange and purple lines highlights the selection window caused by sulfadoxine–pyrimethamine (period during which the quintuple mutant can develop a successful blood-stage infection in SMC-treated children, but the quadruple mutant cannot). (B) Example of the predicted number of patent infections (defined as infections detectable by microscopy) in children aged 3 months to 5 years in a population consisting of 50% quadruple mutants (orange line) and 50% quintuple mutants (purple line) in a setting with a transmission intensity of 390 inoculations per person per year occurring mainly over 4 months (representing the seasonality pattern of Burkina Faso) and with a 35% probability of symptomatic cases receiving treatment within 2 weeks from symptom onset (defined as the level of access to treatment). Dashed lines indicate timing for cycles of SMC administered. In this example, four cycles of SMC were administered (once cycle per month) with a coverage of 98% to children aged 3 months to 10 years with no reduction of coverage between cycles. SMC=seasonal malaria chemoprevention.

See Online for appendix

	Definition	Parameter range
Coverage at the first cycle of SMC	Percentage of individuals from the target age group who received sulfadoxine–pyrimethamine plus amodiaquine during the first cycle of SMC (%)	70–100
Entomological inoculation rate	Mean number of infective bites received by an individual during a year (inoculations per person per year)	5–500
Level of access to first-line treatment	Percentage of symptomatic cases who received treatment within 14 days of symptom onset (%)	10–80
Half-life of the partner drug for first-line ACT	Time for the drug concentration of the partner drug for first-line ACT to fall by 50% (days)	6–22

The range of SMC coverage at the first cycle reflects that reported by the largest SMC implementation study in the Sahel.[4] The entomological inoculation rate (EIR) range reflects the setting varying from low to high malaria transmission intensity. SMC is not recommended in settings with malaria prevalence below 10% in children aged 2–10 years. An EIR of below five inoculations per person and per year would result in a lower prevalence than 10% in settings with high access to treatment and therefore was not investigated. The range for access to first-line treatment includes low to high access to treatment to cover a large spectrum of health system strengths. Children in the targeted groups could still contract malaria and obtain first-line treatment (an ACT) through the formal health sector, the same as individuals not targeted by SMC. The modelled ACT combined dihydroartemisinin with a partner drug whose elimination half-life was varied in the sensitivity analysis and captured the range of half-lives of lumefantrine, piperaquine, and mefloquine (appendix p 21). The partner drug was assumed to not be sulfadoxine–pyrimethamine or amodiaquine following WHO recommendations.[2] ACT was fully effective against quintuple and quadruple infections. A *Latin Hypercube* Sampling algorithm was used to sample from the ranges (appendix p 24). ACT=artemisinin-based combination therapy. SMC=seasonal malaria chemoprevention.

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

pharmacokinetics as a single, long-acting drug, denoted sulfadoxine–pyrimethamine*, and calibrated the half-maximal effective concentration of each genotype to match the prophylactic period reported by the literature (appendix pp 8–11).[5–7,11] This parameterisation demonstrated the same epidemiological properties as sulfadoxine–pyrimethamine—ie, (1) the ability, in combination with amodiaquine, to clear existing quadruple-mutant or quintuple-mutant infections, and (2) the ability to prevent quadruple-mutant and quintuple-mutant infections for 35 days and 21 days post-treatment, respectively (figure 1A).[5–7,11] Our calibration predicted that the quintuple mutant, but not the quadruple mutant, could develop a blood-stage infection before the next SMC cycle (figure 1B), and we successfully replicated a randomised clinical trial (appendix pp 17–20).

Children who received SMC could still be infected and access first-line treatment, which was an artemisinin-based combination therapy effective against both mutants (see table legend, and appendix p 21).

Identification of factors increasing sulfadoxine–pyrimethamine resistance spread

For each seasonality setting and SMC deployment strategy, we systematically varied and quantified the influence of epidemiological, pharmacokinetic and pharmacodynamic, health system, and deployment factors (table) on the quintuple-mutant spread using global sensitivity analyses (appendix pp 24–25).[24] We estimated the quintuple-mutant spread through the selection coefficient, which measures the rate at which the logit of the resistant-genotype frequency increases each parasite generation (appendix p 24).[24] We used Sobol's method of variance decomposition (appendix p 25), which allowed estimation of first-order indices for each factor and represented their influence on the spread. The 25th, 50th, and 75th quantiles of the predicted rate of spread were reported for each parameter range. To illustrate results in a time frame, we translated the selection coefficient to the time needed for the quintuple mutant to spread from 1% to 50% of inoculations (T_{50}) for a set of parameter combinations representing the Sahel (appendix p 34).

Impact of the quintuple mutant on SMC effectiveness

To estimate the impact of sulfadoxine–pyrimethamine resistance on SMC effectiveness, we estimated the protective effectiveness of SMC against parasite populations composed of 100% of the same genotype for which we varied the prophylactic period conferred by SMC across simulations: 5, 10, 15, and 21 days (mean prophylactic period against quintuple mutants), 25, 30, and 35 days (mean prophylactic period against quadruple mutants), and 42 days (mean prophylactic period against sensitive parasites; appendix p 41). When sulfadoxine–pyrimethamine plus amodiaquine provided a prophylactic period lower than 17 days, we modelled some degree of resistance to amodiaquine. We assessed the protective effectiveness as the relative reduction in the incidence of clinical malaria in children aged 3 months to 5 years during the months of SMC implementation compared with the same population before SMC (appendix pp 39–40).[4] The protective effectiveness was assessed for a set of parameter combinations (appendix pp 39–40).

Role of the funding source

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

Results

Global sensitivity analyses indicate that the extent of malaria transmission and SMC coverage affect the spread of the *P falciparum* quintuple mutant over all SMC deployment strategies and seasonality patterns (figure 2A, appendix pp 30–31). Here we provide results for the deployment of four SMC cycles per year at constant coverage to children aged 3 months to 5 years in the moderate-seasonality setting (figure 2). High transmission and high SMC coverage increased the rate of spread (appendix p 44). For example, when the EIR increased from 10 to 50 inoculations per person per year, the median selection coefficient increased by 64·0 % (figure 2B). When the coverage increased from 70% to 80%, the median selection coefficient increased by 17·9% (figure 2C). The impact of coverage was stronger for SMC targeting children aged 3 months to 10 years versus those aged 3 months to 5 years (figure 2A).

The level of access to first-line treatment (the percentage of symptomatic cases who received treatment within 14 days of symptom onset) also slightly increased the rate of spread. Individuals not targeted by SMC can be infected by the quadruple and quintuple mutants, whereas individuals protected by SMC are more likely to be infected by quintuple

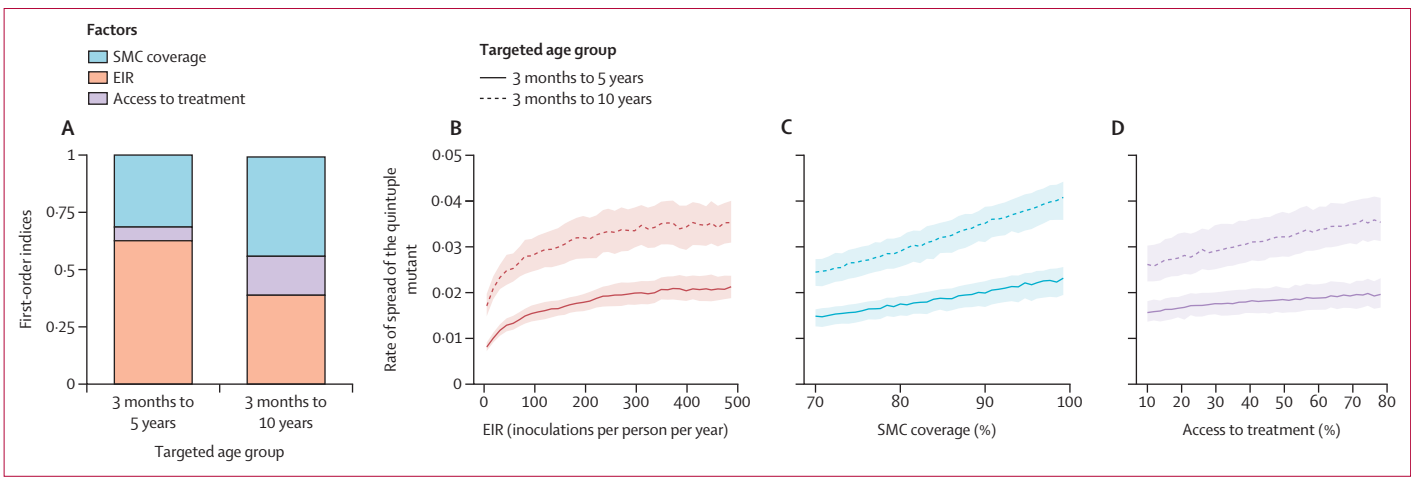

Figure 2: **Influence of different factors on the rate of spread of sulfadoxine–pyrimethamine-resistant quintuple mutants**

(A) First-order indices of coverage (blue bar areas), EIR (orange), and level of access to treatment (purple) estimated during the global sensitivity analyses of the deployment of four cycles of SMC per year at constant coverage to children aged 3 months to 5 years or 3 months to 10 years in the setting with moderate seasonality. First-order indices for each factor are proportional to their area within the bars and represent their influence on the rate of spread. Parameter ranges explored were as follows: SMC coverage 70–100%; EIR 5–500 inoculations per person per year; and level of access to treatment 10–80%. The prophylactic periods for the quadruple and quintuple mutants were 35 days and 21 days, respectively. (B, C, D) Curves and shaded areas represent the median and IQR of the rate of spread (selection coefficient) of the quintuple mutant estimated from the global sensitivity analyses over the ranges of key parameters—ie, transmission level represented by EIR (B), SMC coverage at cycle one (C), and level of access to first-line treatment for symptomatic infections (D). The median and IQR were calculated during the global sensitivity analyses for deployment of four SMC cycles per year at constant coverage to children aged 3 months to 5 years (solid curves) or 3 months to 10 years (dashed curves) in a setting with moderate seasonality. The elimination half-life of the first-line artemisinin-based combination therapy partner drug (range 6–22 days) is not displayed as it did not impact the rate of spread. Results for different seasonality settings, number of cycles deployed per year, and assumptions around SMC coverage reduction between cycles can be found in appendix pp 30–31. EIR=entomological inoculation rate. SMC=seasonal malaria chemoprevention.

mutants (appendix p 33). Settings with higher levels of access to treatment have significantly lower levels of parasite prevalence in individuals not targeted by SMC (older than 5 years or older than 10 years) but negligible prevalence reduction in children receiving SMC as they are already protected (appendix p 32; with SMC coverage of 95%). Thus, a rise in access to treatment disproportionally targets the quadruple mutants in the non-SMC group, causing a slight increase in the frequency of quintuple mutants (appendix p 33), favouring its spread. For example, in settings with access to treatment of 30%, the estimated median selection coefficient increased by 12·4% (figure 2D) compared with a setting with access to treatment of 10%.

The T_{50} depends strongly on the SMC deployment strategy (figure 3, appendix p 35). To illustrate this, we compared T_{50} for various strategies in settings with medium transmission (EIR=75 inoculations per person per year, parasite prevalence of 40·3% before SMC in children aged 2–10 years; appendix p 36) and low access to treatment (25%), and an initial SMC coverage of 95% that decreased by 10% from each previous cycle (figure 3). With standard deployment of SMC (four cycles for children aged 3 months to 5 years) in settings with moderate seasonality, it took the quintuple genotype 53·1 years (95% CI 50·5–56·0) to reach 50% of inoculations (T_{50}). In contrast, it took 67·1 years (63·2–71·5) with the standard SMC regimen (three cycles for children aged 3 months to 5 years) in highly seasonal settings. T_{50} likely increases in high-seasonality settings because it has one less SMC cycle, which reduces selection pressure.

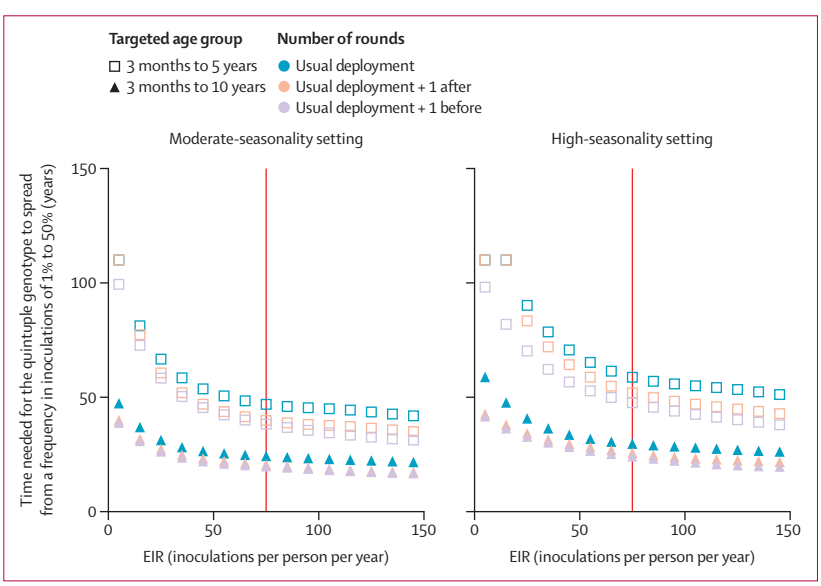

Figure 3: **Predicted impact of SMC deployment strategies on spread of the sulfadoxine–pyrimethamine-resistant quintuple mutant**

Estimated time needed for the quintuple genotype to spread from 1% to 50% of inoculations (T_{50}) when SMC was deployed to different age groups (children aged 3 months to 5 years [squares] or children aged 3 months to 10 years [triangles]) in moderate-seasonality and high-seasonality settings with various numbers of cycles deployed per year (high-seasonality setting: three cycles [blue shapes] or four cycles with the additional cycle deployed before [purple] or after [orange] the current deployment period; moderate-seasonality setting: four cycles [blue] or five cycles with the additional cycle deployed before [purple] or after [orange] the current SMC deployment). T_{50} was predicted for various transmission levels (ranging from 5 to 150 inoculations per person per year), assuming that SMC was deployed at an initial coverage of 95%, which was decreased by 10% from each previous cycle in a setting with high access to treatment (50%). Predictions at different levels of initial coverage and access to treatment can be found in appendix p 35. Red lines highlight points of interest which are discussed in the Results section.

In moderate-seasonality settings, deploying an additional cycle of SMC at the beginning or end of transmission season decreased T_{50} by approximately 13 years and 10 years, respectively. Similarly, in high-seasonality settings, deploying an additional cycle before or after the typical deployment reduced this time by 16 years and 15 years, respectively.

Increasing the SMC target population from children aged 3 months to 5 years to children aged 3 months to 10 years means almost twice the number of individuals received SMC; accordingly, the T_{50} was halved. For example, in moderate-transmission settings, T_{50} decreased from 53·1 years (95% CI 50·5–56·0) to 26·4 years (25·6–27·3) when administering four cycles of SMC to children aged 3 months to 10 years, compared with administering to children aged 3 months to 5 years. Similarly, in high-transmission settings, T_{50} decreased from 67·1 years (63·2–71·5) to 35·9 years (33·6–26·7).

As expected, the protective effectiveness of SMC was strongly dependent on the length of the prophylactic period (figure 4, appendix p 42). Protective effectiveness decreased with shorter prophylactic periods, but remained important in a parasite population composed only of quintuple mutants (appendix p 42). For example, with standard SMC deployment with 95% coverage (decreasing by 10% from each cycle) in a moderate-seasonality setting with low access to treatment (25%), SMC prevented 79·0% (95% CI 77·8–80·8) and 60·4% (58·6–62·3) of malaria episodes across all transmission intensities when the parasite population was composed of 100% quadruple mutants (resulting in a 35-day prophylactic period; figure 4) or 100% quintuple mutants (resulting in a 21-day prophylactic period; figure 4), respectively. This suggests that SMC will retain some effectiveness even if the quintuple mutant becomes fixed (ie, reaches 100% frequency) in the population.

If a genotype acquires a higher degree of resistance to sulfadoxine–pyrimethamine and some degree of resistance to amodiaquine, the prophylactic period conferred by SMC with sulfadoxine–pyrimethamine plus amodiaquine will be shorter than 21 days. Evidence suggests the prophylactic period of amodiaquine against partially amodiaquine-resistant genotypes to be slightly longer than 10 days.[12] However, even if SMC provides a prophylactic period of 10 days, SMC could still prevent 36·0% (95% CI 34·5–37·5) of clinical cases for the same deployment and setting as above (figure 4). In addition, for the same deployment, this genotype would still require 26·5 years (20·8–32·2) on average to spread from 1% to 50% frequency across settings with an EIR of 50 inoculations per person per year (appendix p 43).

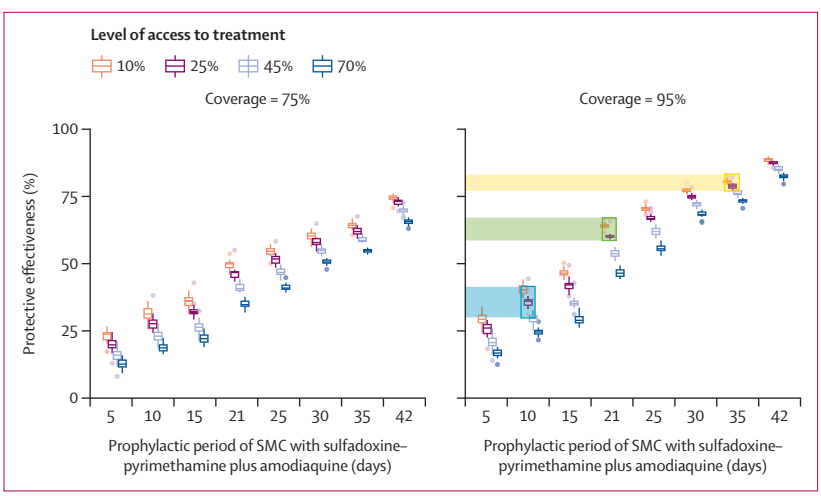

Figure 4: **Protective effectiveness of SMC for a range of prophylactic periods**
The protective effectiveness of SMC (the relative reduction in the number of clinical malaria cases in children aged 3 months to 5 years during the months of SMC implementation) when four cycles of SMC were delivered to these children at different coverage levels (75% and 95% with coverage decreased by 10% from each cycle), in settings with diverse transmission intensities (from 5 to 150 inoculations per person per year), and at levels of access to treatment from 10% (orange boxplot) to 70% (dark blue boxplot). The protective effectiveness was assessed against parasite populations composed of 100% of the same genotype for which we varied the prophylactic period conferred by SMC with sulfadoxine–pyrimethamine plus amodiaquine across simulations: 5, 10, 15, and 21 days (mean prophylactic period against quintuple mutants); 25, 30, and 35 days (mean prophylactic period against quadruple mutants); and 42 days (mean prophylactic period against sensitive parasites; appendix p 41). Note that when sulfadoxine–pyrimethamine plus amodiaquine provided a prophylactic period lower than 17 days, we modelled some degree of resistance to amodiaquine. The x-axis is not equally spaced in order to illustrate the assumed prophylactic period against each genotype. The circles represent outliers. The results for different SMC coverage levels can be found in appendix p 42. Boxes and shaded areas identify examples described in the main text when SMC was deployed with an initial coverage of 95%. The yellow, green, and blue boxes and shaded areas highlight the protective effectiveness of SMC against a population of parasites composed of 100% quadruple mutants, 100% quintuple mutants, and 100% mutants fully resistant to sulfadoxine–pyrimethamine and partially resistant to amodiaquine, respectively. SMC=seasonal malaria chemoprevention.

Discussion

To our knowledge, this is the first modelling study that estimates the impact of SMC on the spread of the *dhfr* and *dhps* quintuple mutants resistant to sulfadoxine–pyrimethamine, and assesses the consequence of the quintuple-mutant spread on the ability of SMC to prevent malaria cases. In our model, the current implementation of SMC (four cycles for children aged 3 months to 5 years assuming 95% initial coverage declining by 10% from each cycle) resulted in a relatively slow spread of the quintuple mutant (over 50 years to spread from a frequency of 1% to 50%) in typical Sahelian settings. We predicted that the spread of the quintuple mutant could accelerate if additional cycles of SMC were deployed per year and if older children (aged 3 months to 10 years) were targeted. Nevertheless, the time to fixation was still relatively long. Our study further shows that SMC with sulfadoxine–pyrimethamine plus amodiaquine will remain a valuable tool to prevent uncomplicated malaria despite the slow spread of the quintuple mutant with reduced sensitivity to sulfadoxine–pyrimethamine. Our model predicts that SMC will remain effective at preventing malaria morbidity, even with a high frequency of quintuple mutations. For example, the typical SMC delivery to children prevented 60·4% (95% CI 58·6–62·3) of clinical cases in typical Sahelian settings with 100% frequency of quintuple mutations. Implementation of SMC in seasonal settings where the quintuple mutant is already prevalent should be considered, as it could considerably reduce malaria-related morbidity.

Multiple factors explain this relatively slow spread of quintuple mutants. First, only a minority of individuals in the population receive SMC and can potentially select the quintuple genotype. Second, sulfadoxine–pyrimethamine creates a short selection opportunity for the quintuple mutant among treated children. The selection window was equal to 14 days (ie, 21 days to 35 days post-SMC) and reduced to 9 days (ie, 21 days to 30 days post-SMC) when children received a subsequent SMC cycle. Finally, individuals who receive SMC and become infected by the quintuple mutant can have their infection cleared by the next SMC cycle, further limiting spread. Our findings for slow spread of the quintuple mutant agree with previous studies, which reported that SMC leads to a slow or no marked increase in the quintuple mutant's frequency.[4,13,28]

We demonstrated that deploying SMC to children aged 3 months to 10 years compared with deploying it to children aged 3 months to 5 years almost doubled the rate of quintuple-mutant spread. This is presumably because the number of individuals receiving SMC approximately doubles. In addition, deploying one additional cycle of SMC per year reduced the time needed for the quintuple mutant to reach 50% frequency by approximately 10 years. Nevertheless, previous studies have highlighted that extending SMC to children younger than 10 years (rather than providing it only to children younger than 5 years) or adding extra cycles of SMC per transmission season could provide substantial health benefits.[11,26]

We observed that SMC retains a substantial protective effectiveness even if the quintuple mutant spreads to 100%. This is because sulfadoxine–pyrimethamine inhibits development of successful quintuple blood-stage infection for 21 days post-treatment, and thus, children are protected during most of the time between monthly SMC cycles. In addition, children who develop blood-stage infections after 21 days have their infections cleared by the next SMC cycle. Consequently, SMC will remain a valuable tool to reduce malaria morbidity in the Sahel despite the spread of the quintuple mutant. Critically, SMC with sulfadoxine–pyrimethamine plus amodiaquine could be implemented in seasonal regions where the quintuple mutant is already prevalent, such as in southern and eastern Africa. Currently, SMC with sulfadoxine–pyrimethamine plus amodiaquine is not implemented there due to the high quintuple-mutant prevalence.[2] Further evidence is needed to challenge or confirm our predictions. A recent SMC trial with sulfadoxine–pyrimethamine plus amodiaquine in Uganda seems to support our findings.[29]

Our recommendations depend on several assumptions. First, given scarce data on sulfadoxine–pyrimethamine's mode of action and synergism, we used clinical data to model sulfadoxine–pyrimethamine as a long-acting drug providing a prophylactic period of 21 days on average against quintuple mutants and 35 days on average against quadruple mutants.[5,6,11] Our approach captured some variation of prophylactic period among individuals due to differences in weight and dosage among children (appendix p 8). However, we did not model individual variability in pharmacokinetic parameters which would cause additional variation in prophylactic period but should not strongly impact the average rate of spread. In addition, our parameterisation of sulfadoxine–pyrimethamine depends on few studies of the prophylactic period of sulfadoxine–pyrimethamine in regions where the different mutants are prevalent.[5,6,11] Our additional analysis shows that if the prophylactic period against the quintuple mutant is shorter than 21 days, the spread of resistance will be faster (appendix p 43). However, amodiaquine provides a blood-stage prophylactic period of approximately 17 days.[12] Consequently, our estimation of the rate of spread and the effectiveness of SMC would not change dramatically due to amodiaquine. Similarly, if a parasite more resistant to sulfadoxine–pyrimethamine emerges, such as the sextuple mutant (with an additional mutation, *dhps*-A581G) observed in a few settings in east Africa,[9] we would still expect limited spread and some protective effectiveness of SMC to be retained.

Second, we assumed that both genotypes were sensitive to amodiaquine and that children were fully adherent to amodiaquine doses.[2] If we had considered a high degree of resistance or low adherence to amodiaquine, the prophylactic period conferred by SMC against each mutant should not change as sulfadoxine–pyrimethamine determines the prophylactic period. However, both considerations could lead to treatment failure of sulfadoxine–pyrimethamine plus amodiaquine, which would occur at a higher rate for quintuple mutants than quadruple mutants and favour the spread of the quintuple mutant. Nevertheless, only markers for low degrees of resistance to amodiaquine have been observed in the Sahel at low and declining prevalence.[4] Thus, these mutations should not impact the spread of the quintuple mutant. Considering the potential interaction between amodiaquine and artemisinin resistance, further modelling studies should assess how SMC implementation might impact the spread of partial artemisinin resistance.

Third, we did not model the potential effect of pyrimethamine on *P falciparum* liver-stage infection. Previous studies suggest that the liver-stage effect of pyrimethamine is reduced against quadruple and quintuple mutants having three mutations conferring pyrimethamine resistance.[30] Thus, we might have underestimated the effectiveness of SMC by ignoring these liver-stage effects. However, this assumption does not affect our estimation for quintuple-mutant spread, as the liver-stage effect of pyrimethamine is similar for both genotypes.

Lastly, we focused on the spread of the quintuple mutant favoured by SMC. However, sulfadoxine–pyrimethamine's use in the private sector or other interventions, such as intermittent preventive treatment in pregnancy,[3] could also favour the quintuple-mutant spread. In addition, other interventions could be deployed in the future, such as vector-based interventions, that could further affect the rate of spread.

In conclusion, our assessment of the risk of spread of the quintuple mutant and associated consequences are

reassuring overall but should be validated by other modelling studies and, importantly, through clinical trials or implementation studies. However, mutants with a high degree of resistance to sulfadoxine–pyrimethamine and amodiaquine could emerge at any time in the Sahel. Therefore, routine molecular surveillance alongside efficacy testing for detected mutants must continue.

Contributors

MAP conceived the study. TM, TL, IMH, and MAP designed the study. TM led and performed the literature searches to parameterise the model and performed the analyses. MAP further verified the model and analysis. TM, TL, IMH, SLK, and MAP interpreted results and examined their implications. TM wrote the first draft of the manuscript and created the tables and figures. TL, SLK, IMH, and MAP revised the manuscript. All authors reviewed and approved the final manuscript. MAP acquired the funds and managed the project. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. TM and MAP verified the underlying data.

Declaration of interests

MAP was part of the WHO Guidelines Development Group for Malaria Chemoprevention (2020–21). SLK is currently a Senior Editor at *The Lancet* but was not involved in the handling of this manuscript and joined after submission. All other authors declare no competing interests.

Data sharing

Individual participant-level data were not used in this study. Parameter values used to inform the model were extracted from the literature as described in the main text or in the appendix. All data and code used to produce the figures are available at https://zenodo.org/record/7244708. In addition, the code used to run the simulations and perform the analyses can be found at https://zenodo.org/record/7244732. The individual-based model of malaria transmission and epidemiology used in the study has an open-access code (https://github.com/SwissTPH/openmalaria) and documentation (https://github.com/SwissTPH/openmalaria/wiki).

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