# Impact of directly observed treatment and extended age range of seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine in Burkina Faso: a three-group, open-label, cluster-randomised, controlled trial

*Jean Baptiste Yaro*, Alphonse Ouedraogo*, Marta Moreno*, Simon Koele, Samuel Sermé Sindie, Aissata Barry, Seyi Soremekun, Markus Gmeiner, Kjerstin Lanke, Isabel Byrne, Jordache Ramjith, Liusheng Huang, Florence Marzan, Emilie S Badoum, Issiaka Soulama, Lynn Grignard, Amidou Z Ouedraogo, Jean Sawadogo, Issa Nebie Ouedraogo, Denise Hien, John Bradley, Rob Ter Heine, Sodiomon Bienvenu Sirima, Teun Bousema†, Chris Drakeley†, Alfred B Tiono†*

## Summary

**Background** Seasonal malaria chemoprevention (SMC) currently targets children younger than 5 years but can be extended to wider age ranges to reduce clinical burden in older populations. We aimed to evaluate the effect of programmatic SMC versus SMC via directly observed treatment (DOT) and the effect of extending SMC to children younger than 10 years on malaria clinical incidence, parasite carriage, and gametocyte carriage in individuals targeted and untargeted by SMC.

**Methods** We conducted a three-group, open-label, cluster-randomised trial in Saponé (Burkina Faso) with three study groups: (1) programmatic SMC in children younger than 5 years; (2) SMC in children younger than 5 years with DOT (DOTu5); and (3) SMC in children younger than 10 years with DOT (DOTu10). The trial involved 61 programmatic SMC and 62 (each DOT group) clusters of three compounds. Eligible compounds had at least one child younger than 5 years and aged 5–9 years who had not participated in recent vaccine trials. Clusters were randomised (approximately 1:1:1) to the study groups by computer generation. Eligible children received four cycles of SMC with sulfadoxine-pyrimethamine and amodiaquine. The primary endpoint was *Plasmodium falciparum* parasite prevalence at the end of the transmission season in SMC-targeted age groups and compared between study groups. No formal missing data strategy was conducted; a modified intention-to-treat analysis was used based on those assessed during the endline survey. Secondary endpoints included drug plasma concentrations after the fourth cycle of SMC and incidence of clinical malaria during the entire malaria season. The trial is registered with ClinicalTrials.gov, NCT05878366, and is completed.

**Findings** Between 13 July and 29 Aug 2023, 3467 participants of all ages were enrolled, including 980 SMC-targeted individuals (236 in the programmatic SMC group, 231 in the DOTu5 group, and 513 in the DOTu10 group). The parasite prevalence at the end of transmission season in children younger than 5 years was 24·9% (52 of 209 participants) in the programmatic SMC group compared with 19·7% (40 of 203 participants) in the DOTu5 group (rate ratio [RR] 0·84, 95% CI 0·55–1·30; p=0·4419). Parasite prevalence in children aged 5–9 years was lower in the DOTu10 group (28·1% [63 of 224 participants]) compared with the DOTu5 group (47·1% [98 of 208 participants]; RR 0·56, 95% CI 0·43–0·74; p<0·0001). The incidence of clinical malaria in children younger than 5 years was lower in the DOTu5 group compared with the programmatic SMC group (protective efficacy 0·57, 95% CI 0·29–0·74; p=0·0009) and lower in children aged 5–9 years in the DOTu10 group compared with the DOTu5 group (0·72, 0·54–0·83; p<0·001). Clinical incidence after the 4th cycle of SMC was also lower in individuals who were scored as adherent based on plasma drug concentrations compared with those who were scored as non-adherent (incidence rate ratio 0·21, 95% CI 0·09–0·51; 0·0006).

**Interpretation** We observed no significant difference in parasite prevalence between programmatic SMC and SMC delivered through DOT in children younger than 5 years. Extending SMC to children aged 5–9 years reduced parasite carriage and incidence of clinical malaria in this age group. Although these findings support extending the SMC age range to older children, potential logistical and financial barriers need to be examined.

**Funding** Gates Foundation.

**Copyright** © 2026 The Author(s). Published by Elsevier Ltd. This is an Gold Open Access article under the CC BY 4.0 license.

*Lancet Infect Dis* 2026

Published Online July 29, 2026 https://doi.org/10.1016/S1473-3099(26)00305-1

*Contributed equally

†Contributed equally

**Groupe de Recherche Action en Santé, Ouagadougou, Burkina Faso** (J B Yaro PhD, A Ouedraogo PhD, S S Sindie PhD, E S Badoum PhD, A Z Ouedraogo MSc, J Sawadogo MD, I N Ouedraogo PhD, D Hien MSc, Prof S B Sirima PhD, A B Tiono PhD)**; Department of Infection Biology; London School of Hygiene & Tropical Medicine, London, UK** (M Moreno PhD, S Soremekun PhD, I Byrne PhD, L Grignard PhD, Prof J Bradley PhD, Prof C Drakeley PhD)**; Department of Pharmacy, Pharmacology and Toxicology** (S Koele PhD, R Ter Heine PhD) **and Department of Medical Microbiology** (M Gmeiner MSc, K Lanke BSc, J Ramjith PhD, Prof T Bousema PhD)**, Radboud University Medical Center Nijmegen, Netherlands** (S Koele PhD, R Ter Heine PhD)**; Secretariat Permanent pour l'élimination du paludisme, Ouagadougou, Burkina Faso** (A Barry PhD)**; Department of Clinical Pharmacy, University of California, San Francisco, CA, USA** (L Huang PhD, F Marzan BSc)**; Institut de Recherche en Sciences de la Santé, Ouagadougou, Burkina Faso** (I Soulama PhD)

Correspondence to:
Dr Alfred B Tiono, Groupe de Recherche Action en Santé, Ouagadougou, Burkina Faso
**a.tiono@gras.bf**

or

Prof Teun Bousema, Department of Medical Microbiology, Radboud University Medical Center, 6525 GA Nijmegen, Nijmegen, Netherlands
**teun.bousema@radboudumc.nl**

## Research in context

### Evidence before this study

Seasonal malaria chemoprevention (SMC) is a malaria preventive strategy that involves administering monthly doses of antimalarial drugs to children aged 3–59 months during the period of high malaria transmission. In 2024, almost 54 million children were covered by SMC, and WHO reported an estimated protective efficacy of 88·2% (95% CI 78·7–93·8). The prevalence of non-adherence and its effect on SMC efficacy are currently unknown. Additionally, updated WHO guidelines include adaptation of the number of SMC cycles and targeted age range to local malaria epidemiology. We searched PubMed on Nov 24, 2025, using the search terms ("malaria", OR "falciparum", OR "Plasmodium falciparum") AND ("SMC" OR "seasonal malaria chemoprevention") AND ("adherence" OR "compliance" OR "pharmacokinetics" OR "drug levels"). We searched studies assessing both SMC effect and compliance, with no restrictions on publication date or language. Of the 37 results retrieved with this initial research, nine studies were clinical trials. A randomised control trial in two areas of high malaria transmission in Burkina Faso showed that the prevalence of parasitaemia at the end of the transmission season was higher in children aged 3–59 months who missed SMC. An observational cohort study of SMC-eligible children in Burkina Faso showed that children with malaria were less likely to have any detectable sulfadoxine with pyrimethamine or amodiaquine and have lower drug concentrations compared with concurrently recruited malaria-free children. No studies systematically determined plasma concentrations of SMC drugs in relation to parasite prevalence or incidence of clinical malaria. Additionally, a search on the same date for studies on the community effect of SMC and extended SMC, using the search terms ("malaria", OR "falciparum", OR "Plasmodium falciparum") AND ("SMC" OR "seasonal malaria chemoprevention") AND ("population" OR "community") AND ("extended" OR "school-aged children, SAC" OR "5-9, 5-10, 5-14, 5-15"), yielded 24 results. In Senegal, a stepped-wedged cluster-randomised trial indicated that the introduction of extended SMC was associated with a reduction of 60% in the incidence of malaria in treated children and of 26% in untreated age groups. Similarly, the hazard of clinical malaria in non-recipients of SMC in The Gambia was reduced in households with children receiving SMC.

### Added value of this study

To our knowledge, this is the first trial to evaluate the effect of extended SMC in children younger than 10 years that systematically incorporates quantification of SMC drug concentrations and metabolites in targeted populations, and specifically assesses gametocyte carriage and transmission to mosquitoes. This cluster-randomised trial during one malaria season in a high-transmission setting in Burkina Faso reports no significant difference in parasite prevalence at the end of the transmission season between children younger than 5 years receiving SMC under programmatic conditions versus those who received SMC drugs under directly observed treatment (DOT). The incidence of malaria was higher in children younger than 5 years in the programmatic delivery group, and we found that amodiaquine and desethylamodiaquine drug concentrations in this group were lower. Children with lower drug concentrations were more likely to acquire asymptomatic infections or develop clinical malaria in the period following SMC delivery. We observed a marked reduction in the prevalence of malaria and clinical incidence in children aged 5–9 years when SMC was extended to these older children.

### Implications of all the available evidence

Our primary endpoint, *Plasmodium falciparum* parasite prevalence at the end of the transmission season, did not show significant differences between the groups receiving either programmatic SMC or SMC under DOT. Our findings of lower drug concentrations under programmatic conditions and the association of inferred treatment adherence with improved protection from both clinical malaria and asymptomatic parasite carriage align with earlier findings that higher SMC adherence and drug plasma concentrations are associated with reduced parasite carriage and clinical incidence. Our findings further highlight the effect of extending SMC to include all children younger than 10 years on reducing malaria burden in this age group.

## Introduction

Seasonal malaria chemoprevention (SMC), involving administration of sulfadoxine–pyrimethamine and amodiaquine monthly during the peak transmission season, is highly effective in reducing clinical malaria burden in children younger than 5 years.[1-3] Despite SMC being highly efficacious, reducing the incidence of malaria by more than 70%[1,2] could lead to the efficacy being considerably lower when delivered programmatically.[3-5] In programmatic SMC, the first doses of each SMC cycle are typically provided by a health worker, with the remaining doses being given to the caregiver to administer to children on subsequent days. Measurements of plasma concentrations of amodiaquine and its metabolite desethylamodiaquine suggest that up to 80% of SMC-treated children could have plasma concentrations indicative of non-adherence and highlight the need for studies that directly examine potential benefits of directly observed treatment (DOT) for enhancing the benefits of SMC.[6]

In areas of intense malaria transmission, parasite carriage is also high in school-age children who carry high parasite densities and transmissible gametocytes,[7–9] and experience a considerable clinical malaria burden[10] and, could therefore benefit from age-extended SMC.[11] In a large stepped-wedge study in Senegal, SMC administered to children younger than 10 years achieved reductions of 30–84% in parasite prevalence.[12] Burkina

Faso is a country with a high malaria burden that is also considering extending the age range for SMC to include all children younger than 10 years. Although SMC safety is firmly established with more than 54 million children covered by SMC in 2024,[13] evidence for direct clinical benefits in children younger than 10 years and the potential community benefits of extended SMC, are needed to support policy recommendations.

We conducted a cluster-randomised trial in Burkina Faso and aimed to evaluate the effect of programmatic SMC versus SMC via DOT and the effect of extending SMC to children younger than 10 years on clinical incidence, parasite carriage, and gametocyte carriage in individuals targeted and untargeted by SMC. As we hypothesised SMC adherence to be a key determinant of impact, we determined drug plasma concentrations in relation to clinical study outcomes and infectivity to mosquitoes.

## Methods

### Study design and participants

We performed a three-group, open-label, cluster-randomised, controlled trial with masked laboratory evaluators and three intervention groups. The study area in Saponé, Burkina Faso, is characterised by intense, seasonal malaria transmission. Eligible compounds had at least one child aged 3–59 months and one child aged 5–9 years. The unit of randomisation was the cluster, which consisted of three compounds, as described elsewhere.[14] To account for spatial differences in malaria exposure, distance from health facilities, treatment-seeking behaviour, and neighbouring clusters were grouped before randomisation.

Randomisation to clusters, rather than individual compounds, was performed for logistical feasibility and to reduce the chance that compounds randomised to DOT would influence SMC adherence in compounds randomised to programmatic SMC. Efficacy was assessed at the level of the individual with cluster-adjusted standard errors. The three study groups were: (1) programmatic SMC (61 clusters, 183 compounds); (2) DOT SMC in children younger than 5 years (DOTu5; 62 clusters, 186 compounds); and (3) DOT SMC in children younger than 10 years (DOTu10; 62 clusters, 186 compounds). To examine possible behavioural contamination, a control zone was identified more than 2 km from the nearest study compound. For this zone, a single cross-sectional survey was conducted 7 days after the last (fourth) cycle of SMC to assess treatment adherence; there were no other interactions during the study. Before the study, its design and procedures were discussed with local stakeholders (ie, National Malaria Elimination Programme, village leaders and local health providers) without input on study design.

Residents of all ages of enrolled compounds were eligible for inclusion in the study procedures and evaluation of the intervention; children were excluded from the intervention if they had any illness requiring continuous care, were participating in a malaria drug trial or vaccine trial within the last 2 years, or were ineligible for SMC according to the National Malaria Elimination Programme guidelines.[14,15]

The protocol was approved by the London School of Hygiene & Tropical Medicine's Ethics Committee (number: 29193) and the Burkina Faso National Medical Ethics Committee (number: 2023-05-104) and was published previously.[14] Informed consent was obtained from the parents or guardians of all participating children. This study is registered with ClinicalTrials.gov, NCT05878366, before the study initiation (May 18, 2023) including a statistical analysis plan, and is completed. No data safety and monitoring board was installed given extensive evidence of SMC safety.

### Randomisation and masking

Allocation of clusters to the study groups was computer-generated in STATA (version 19.5) by the study statistician (JB). All eligible clusters were randomised in an approximate 1:1:1 ratio to the study groups. SMC drugs were administered by unmasked National Malaria Elimination Programme workers; all individuals conducting laboratory analyses were masked to the study groups.

### Procedures

Four cycles of SMC were implemented in all study groups during the peak malaria season (July–October, 2023) approximately 30 days apart. In group 1, SMC-eligible children younger than 5 years (59 months at the first cycle of SMC) received the treatment as normally delivered by the National Malaria Elimination Programme with the first dose given under DOT and other doses being given to caregivers to administer to children on subsequent days. In group 2, a research team accompanied staff from the National Malaria Elimination Programme to administer all SMC drug doses under DOT. Group 3 administered SMC drugs under direct supervision to all children younger than 10 years (119 months at the first cycle of SMC). SMC drugs were provided by the National Malaria Elimination Programme. For children aged 3–11 months, a fixed dose of 262·5 mg sulphadoxine with pyrimethamine and 76·5 mg amodiaquine were used, whereas from 12–60 months, a fixed dose of 525 mg sulphadoxine with pyrimethamine and 153 mg amodiaquine were used (appendix 1 p 11). Children aged 5–9 years received two tablets of sulphadoxine with pyrimethamine and two tablets of amodiaquine per day during the first SMC cycle. Side-effects were not systematically recorded; tolerability was verbally assessed at caregiver level at each cycle. To comply with national pharmacovigilance, caregivers were instructed to report to local health facilities in case of adverse events. Complaints from caregivers on side-effects (notably somnolence),

See Online for appendix

prompted us to reduce the dose in children aged 5–9 years to a previously used dose of 229·5 mg (1·5 tablets) of amodiaquine for subsequent SMC cycles 2, 3 and 4;[12] sulphadoxine with pyrimethamine was still given at two tablets.

During a baseline survey in all age groups conducted in July, 2023, parasite carriage was determined by microscopy.[14] An additional survey was conducted 7 days after the start of the final cycle of SMC in October, 2023, in SMC recipients only, to quantify plasma concentrations of amodiaquine and desethylamodiaquine. We further conducted a mid-study survey in all ages to assess parasite carriage by microscopy and quantitative PCR (qPCR) at weeks 3, 4, or 5 following SMC in October. At the end of the study survey between December, 2023, and January, 2024, we assessed the *Plasmodium falciparum* parasite carriage in all age groups by var acidic terminal sequence (varATS) qPCR; gametocyte densities were determined by quantitative reverse transcriptase PCR (qRT-PCR).[16,17] The endline survey was implemented in geographical units, sampling equal numbers of clusters from each group during each time-unit to avoid an effect of season in between-group comparisons.

Clinical malaria episodes were passively monitored (passive case detection) in three health facilities (Saponé Marché, Karkuidighin, and Pissy), using study identification cards to link episodes to clusters. All participants were encouraged to visit the local health facility in case of health-related events. In case of suspected malaria during passive case detection or surveys, malaria infection was diagnosed by Rapid Diagnostic Test (HRP2 Ag detection, Abbott-Bioline™ Malaria Ag Pf/Pan, Yongin, South Korea). Symptomatic malaria was defined as Rapid Diagnostic Test confirmed parasitaemia with history of fever and treated following national guidelines.

We assessed infectivity to mosquitoes in a subset of the study population; these experiments focused on determining whether presence of SMC drugs affected gametocyte infectivity.[18] To select donors, a blood smear was obtained from children aged 5–9 years before SMC cycles 2, 3, and 4. Microscopy-positive gametocyte carriers and children with at least 100 asexual parasites per µL were invited to donate venous blood within 14 days after slide collection to determine infectivity to locally reared *An gambiae* mosquitoes. Feeding assays were performed based on mosquito availability on a first-come first-served basis, using established methods.[19] To evaluate adherence in the 4th and final SMC cycle, plasma concentrations of amodiaquine and desethylamodiaquine were quantified using ultra-high performance liquid chromatography–tandem mass spectrometry, as described previously[20] with a calibration range of 0·1–100 ng/mL for amodiaquine and 0·2–200 ng/mL for desethylamodiaquine. Samples for this substudy were selected from each study group using computer-generated random tables using STATA with a predefined target number.[14] A previously published population pharmacokinetic modelling approach was used to assess adherence by comparing observed desethylamodiaquine concentrations with those expected based on dosing, age, and weight (appendix 1 pp 26–28).[6]

### Outcomes

The primary endpoint was the prevalence of *P falciparum* parasite measured by qPCR at the end of the transmission season (endline survey between Dec 11, 2023, and Jan 12, 2024) in age groups targeted by SMC and compared between groups 1 and 2 (in children aged 3–59 months) and groups 2 and 3 (in children aged 5–9 years). In the study protocol and trial registry, children aged 3–9 years were proposed for the comparison of the qPCR parasite prevalence between groups 2 and 3; in the Statistical Analysis Plan and protocol manuscript,[14] this population was changed to age 5–9 years to better evaluate the effectiveness of SMC to reduce the prevalence of malaria infection in the age group targeted by age-extended SMC. We adopted a modified intention-to-treat analysis based on participants present during the endline survey. Predefined secondary endpoints were: (1) parasite prevalence by qPCR at the end of the transmission season in all age groups; (2) parasite prevalence by qPCR at the end of the transmission season in the SMC-targeted population compared between programmatic SMC (group 1) and DOT groups (groups 2 and 3 combined); (3) parasite prevalence by microscopy before SMC cycles 2, 3, and 4 in the SMC-targeted age groups; (4) parasite prevalence and gametocytes at weeks 3, 4, and 5 after the final cycle of SMC; (5) the prevalence of gametocytes at the end of the transmission season survey in age groups targeted by SMC and all age groups (between groups, and between group 1 versus combined groups 2 and 3); (6) the incidence of clinical malaria in targeted and non-targeted SMC groups (between groups); and (7) plasma concentrations of amodiaquine and desethylamodiaquine 7 days after the fourth cycle of SMC. Exploratory endpoints were infectivity to mosquitoes in relation to gametocyte density and plasma drug concentrations. The age-distribution of the infectious reservoir, the prevalence of drug resistance markers, and social barriers to SMC uptake were defined as exploratory endpoints that will be reported in future manuscripts. Post-hoc analyses were comparisons of parasite prevalence by qPCR and the incidence of clinical malaria in SMC-targeted children who were scored as SMC adherent versus non-adherent based on desethylamodiaquine plasma concentrations. In the trial, the initial 0–9 years comparison seemed appropriate because in group 3, all children in this age range would receive SMC and it was therefore programmatically relevant. However, following discussions, the analysis of age 5–9 years was agreed to be more logical in a trial context (ie, comparing groups with and without the intervention and allowing a specific assessment of

effect in the older children). Consequentially, this comparison (age 5–9 years) was included in the protocol and the Statistical Analysis Plan as supplementary documentation submitted in November, 2023, and published in February, 2024.

### Statistical analysis

For the sample size calculation, we used previous data on end of transmission season qPCR parasite prevalence of 40% in children aged 5–9 years without SMC and 16% in children younger than 5 years under the programmatic SMC.[21] Assuming a reduction to 25% for the parasite prevalence at the end of the transmission season in children aged 5–9 years when SMC was extended to include this age group, a sample size of 55 clusters per group and an estimated total of 330 children in this age range per group was estimated to provide 87% power to detect this difference at an alpha of 0·05 and a between-cluster coefficient of variation of 0·3.[19,21] This sample size also gave more than 80% power to detect a reduction in parasite prevalence in children younger than 5 years from 16% to 7% as a result of DOT. As we were concerned about dropouts due to research fatigue, the total number of clusters per group was increased by approximately 10% to 61 or 62 clusters per group. Parasite prevalence by qPCR was used as a binary variable with parasite densities of at least 100 parasites per mL, classified as parasite positive.[14] Parasite prevalence was compared between groups by logistic regression; models accounted for clustering by including a cluster as a random intercept and adjusted for the village, bed net use, and baseline parasite prevalence. In the Statistical Analysis Plan, random effects per compound were mentioned, but our analyses included cluster-level random effects; a cluster was also the unit of randomisation. The same regression approach was used to compare percentage coverage of SMC in programmatic SMC group 1 versus DOT group 2 for children aged 0–4 years (only group 3 provided SMC to children aged 5–9 years). Analyses that were not adjusted for baseline characteristics are given in the appendix 1 (pp 14–15). Risk ratios were calculated directly from the model margins and 95% CIs were estimated using the Delta method. Odds ratios (ORs) from the logistic models and unadjusted analyses are presented in the appendix 1 (pp 15–16). Geometric mean parasite densities were compared between the groups at endline by linear regression of the natural log densities with cluster as a random effect. Effect sizes (the difference in log means) were exponentiated to produce the ratio of geometric means. Secondary and post-hoc analyses followed the same approaches. Anderson–Gill recurrent-event Cox regression models with robust standard errors were used to analyse time to all clinical malaria episodes recorded during passive case detection after the first cycle of SMC. Protective efficacy was calculated as 1 minus the hazard ratio (HR). Malaria episodes that were recorded within 14 days of a previous episode were classified as the same event.

The number of samples for drug level measurements assumed a median log desethylamodiaquine concentration of 6·31 (IQR 5·86–6·75; SD 0·93) in the DOT SMC groups[6] and 5·99 or less (5·30–6·55; 0·66) for programmatic SMC. 120 observations from the programmatic SMC group and 120 observations for the combined DOT groups would give 86·3% power to detect this difference using a Welch's two-sample *t*-test. The impact of drug adherence on the incidence of clinical malaria was estimated by negative binomial regression with cluster as a random effect. Data analyses were done in R (version 4.4.3) and Stata.

### Role of the funding source

The Gates Foundation reviewed the draft protocol and provided general input on the study design, but had no role in data collection, analysis, interpretation, or reporting.

## Results

Between 13 July and 29 Aug, 2023, 185 clusters with 555 compounds and 3467 participants were enrolled, including 847 children younger than 5 years and 849 children younger than 10 years, providing 980 SMC-targeted individuals for the three trials groups (236 in the programmatic SMC group, 231 in the DOTu5 group, and 513 in the DOTu10 group; figure 1). Baseline parasite prevalence in children younger than 5 years before the first cycle of SMC was 7·6% (18 of 236 participants) in the programmatic SMC group, 13·9% (32 of

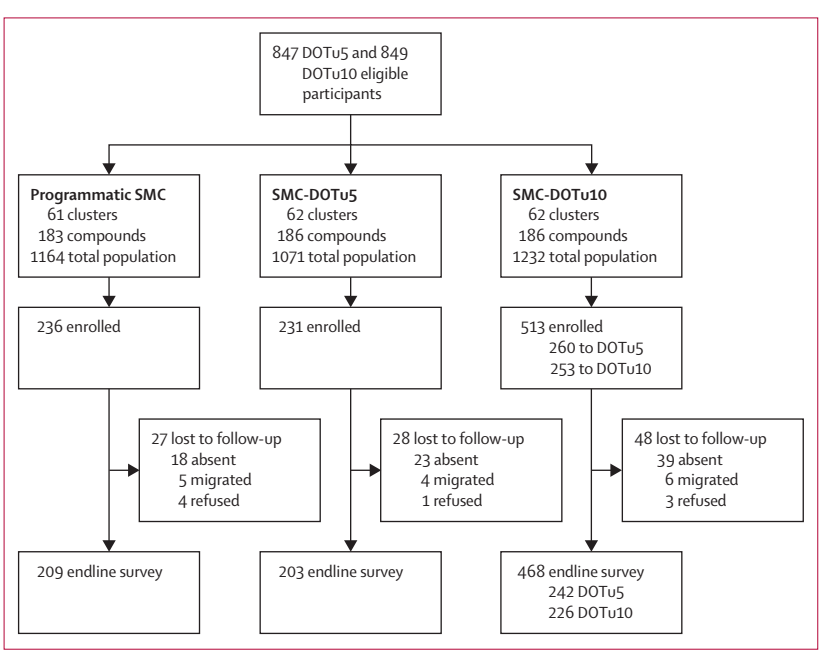


***Figure 1:*** **Trial profile**
Numbers of participants older than 10 years included in the end-of-study analysis were 508 (programmatic SMC), 467 (DOTu5), and 586 (DOTu10).

231 participants) in the DOTu5 group, and 10·0% (26 of 260) in the DOTu10 group (table 1).

The primary endpoint was qPCR parasite prevalence in the endline survey and was 24·9% (52 of 209 participants) in children younger than 5 years in the programmatic SMC group, 19·7% (40 of 203 participants) in the DOTu5 group (RR 0·84, 95% CI 0·55–1·30; p=0·4419), and 18·3% (44 of 241 participants) in the DOTu10 group (table 2, figure 2A). Parasite prevalence was not significantly different between programmatic SMC versus DOTu5 (RR 0·82, 95% CI 0·53–1·28; p=0·3879) after adjusting for village, bed net use, and baseline malaria prevalence (table 2). Parasite prevalence in children aged 5–9 years was 38·5% (84 of 218 participants) in the programmatic SMC group, 47·1% (98 of 208 participants) in the DOTu5 group, and 28·1% (63 of 224 participants) in the DOTu10 group. Parasite prevalence was significantly lower in this age group in the DOTu10 group compared with the DOTu5 group (RR 0·56, 95% CI 0·43 to 0·72; p<0·0001). This effect was also apparent when parasite prevalence in all children younger than 10 years was compared between the DOTu10 and DOTu5 groups (RR 0·66, 95% CI 0·52–0·84; p=0·0006; appendix 1 pp 16–17).

The percentage of enrolled children younger than 5 years who were absent or had migrated, or refused participation during the endline survey was 12·9% (27 of 209 participants) in the programmatic SMC group, 12·1% (28 of 231 participants) in the DOTu5 group, and 6·9% (18 of 260 participants) in the DOTu10 group. 10·7% (27 of 253 participants) of children aged 5–9 years in the DOTu10 group were absent or refused participation in the endline survey (figure 1). As the secondary endpoint, the qPCR parasite prevalence at the endline survey in children younger than 5 years was not significantly different when compared between the programmatic group versus the two DOT SMC groups combined (0·77, 95% CI 0·53–1·12; p=0·1681; table 2) or when compared between groups in other age groups as an exploratory analysis (appendix 1 pp 16–18).

During the study period (one complete transmission season), 131 episodes of clinical malaria were experienced by children younger than 5 years and 283 episodes by children aged 5–9 years (table 3). After adjusting for village, bed net use, and baseline malaria prevalence, incidence of clinical malaria in children younger than 5 years was lower in the DOTu5 group compared with the programmatic SMC group (protective efficacy 0·57, 95% CI 0·29–0·74; p=0·0009; table 3, figure 2C). Clinical incidence in children aged 5–9 years was lower in the DOTu10 group compared with the DOTu5 group that did not target this age group

| | Programmatic SMC | DOTu5 | DOTu10 |
|---|---|---|---|
| Clusters (n)* | 61 | 62 | 62 |
| Compounds (n) | 183 | 186 | 186 |
| Total population (n)† | 1164 | 1071 | 1232 |
| Sex | | | |
| Male | 508/1164 (43·6%) | 491/1071 (45·8%) | 585/1232 (47·5%) |
| Female | 656/1164 (56·4%) | 580/1071 (54·2%) | 647/1232 (52·5%) |
| Age, years | | | |
| <5 | 236/1164 (20·3%) | 231/1071 (21·6%) | 260/1232 (21·1%) |
| ≥5–9 | 252/1164 (21·6%) | 255/1071 (23·8%) | 253/1232 (20·5%) |
| 10–15 | 180/1164 (15·5%) | 150/1071 (14·0%) | 188/1232 (14·3%) |
| >15 | 496/1164 (42·6%) | 435/1071 (40·6%) | 531/1232 (43·1%) |
| Insecticide-treated net use‡ | 780/1164 (67·0%) | 690/1071 (64·4%) | 848/1232 (68·8%) |
| Microscopy parasite prevalence, years | | | |
| <5 | 18/236 (7·6%) | 32/231 (13·9%) | 26/260 (10·0%) |
| ≥5–9 | 48/252 (19·0%) | 70/255 (27·5%) | 67/253 (26·5%) |
| 10–15 | 54/180 (30·0%) | 53/150 (35·3%) | 48/188 (25·5%) |
| >15 | 38/495 (7·7%)* | 29/434 (6·7%)* | 30/531 (5·6%) |

Data are in n/N (%) and proportion (n/N), unless stated otherwise. All data are for the baseline survey that was conducted in July–August, 2023. *Number of clusters in this group, each cluster comprising three compounds. †Total population in the study group, including individuals outside the SMC age range. ‡Insecticide-treated net coverage, defined as self-reported use in the preceding night.

***Table 1:*** **Baseline characteristics of the intention-to-treat population**

| | Programmatic SMC | DOTu5 | DOTu10 | DOTu5 versus programmatic SMC (RR [95% CI]; p value) | DOTu10 versus DOTu5 (RR [95% CI]; p value) | DOT (DOTu5 plus DOTu10) versus programmatic SMC (RR [95% CI]; p value) |
|---|---|---|---|---|---|---|
| **Parasite** | | | | | | |
| Age 0–4 years | 52/209 (24·9%) | 40/203 (19·7%) | 44/241 (18·3%) | 0·8 (0·5–1·2); p=0·3879 | 0·8 (0·5–1·3); p=0·5817 | 0·7 (0·5–1·1); p=0·1681 |
| Age 5–9 years | 84/218 (38·5%) | 98/208 (47·1%) | 63/224 (28·1%) | 1·2 (0·9–1·5); p=0·0581 | 0·5 (0·4–0·7); p<0·0001* | 0·9 (0·7–1·1); p=0·6230 |
| **Gametocyte** | | | | | | |
| Age 0–4 years | 6/87 (6·9%) | 3/86 (3·5%) | 5/76 (6·6%) | 0·4 (0·1–1·6); p=0·1948 | 2·4 (0·5–10·1); p=0·2329 | 0·6 (0·2–1·8); p=0·4298 |
| Age 5–9 years | 18/82 (22·0%) | 18/62 (29·0%) | 8/90 (8·9%) | 1·3 (0·8–2·3); p=0·2382 | 0·2 (0·1–0·6); p=0·0010* | 0·8 (0·4–1·3); p=0·3888 |

Data are n/N (%). The prevalence of parasites was determined by quantitative PCR and the prevalence of gametocytes by quantitative reverse transcriptase PCR at the endline survey. Comparisons were made between groups (primary endpoint) and between combined DOT groups versus the programmatic SMC group (secondary endpoint). Analyses include cluster randomisation as the random effect and are adjusted for village, bed net use, and baseline malaria prevalence. The denominator for the prevalence of parasites was the number of individuals present in the endline survey, which were: the total number of randomly assigned children aged 0–4 years was 236 (programmatic SMC group), 231 children (DOTu5 group), and 260 children (DOTu10 group). The total number of randomly assigned children aged 5–9 years was 252 (programmatic SMC group), 255 children (DOTu5 group), and 253 children (DOTu10 group). Gametocyte measurements were performed for a selection of children who were present at the endline survey. RR=risk ratio. *Significant comparisons.

***Table 2:*** **Impact of the intervention on the prevalence of parasites and gametocytes**

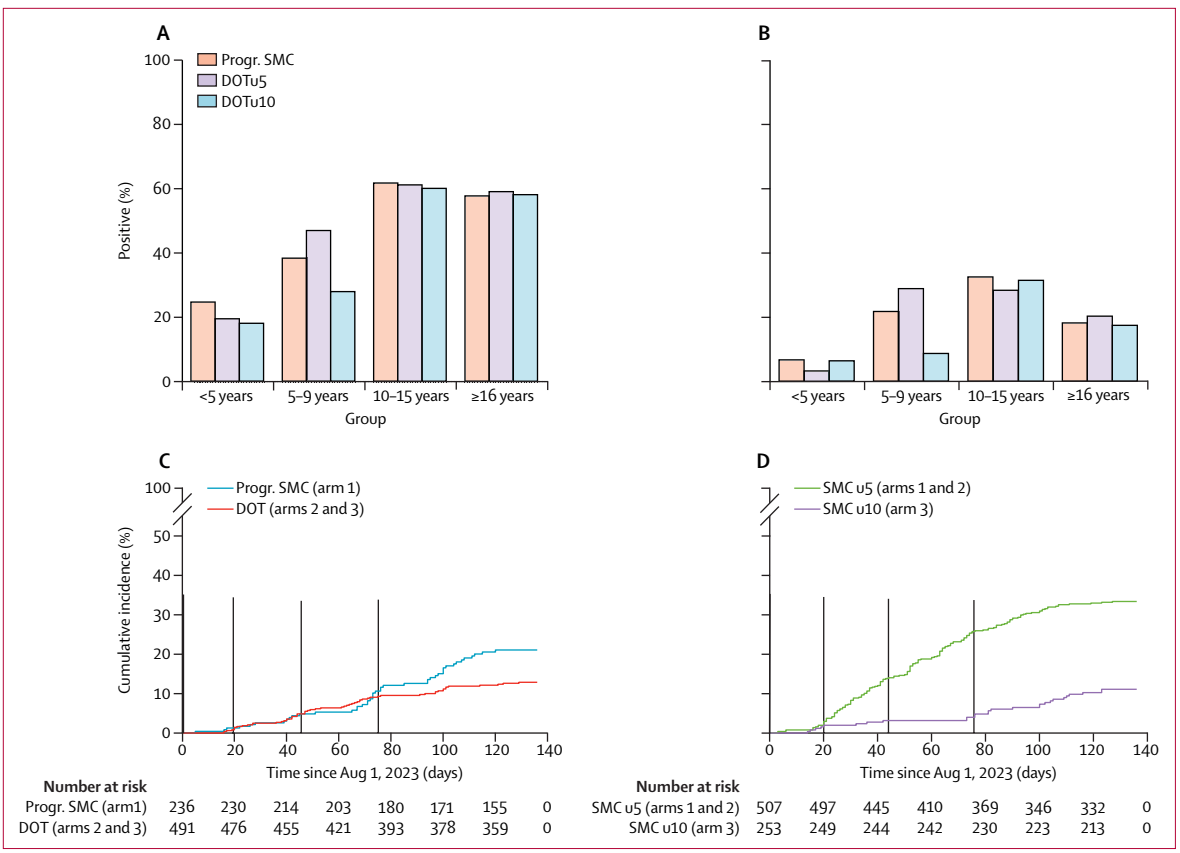


***Figure 2:*** **Prevalence of malaria parasites and gametocytes at the end-of-season surveys and the incidence of clinical malaria from passive case detection**
(A) The prevalence of *Plasmodium falciparum* parasites by quantitative PCR during the cross-sectional survey conducted at the end of the season (primary endpoint). (B) The prevalence of gametocytes by quantitative reverse transcriptase PCR at the end of the season. (C) The cumulative incidence of clinical malaria in children aged 0–4 years for programmatic SMC versus SMC with DOT in the combined groups 2 and 3. (D) The cumulative incidence of clinical malaria in children aged 5–9 years for the combined groups that only targeted children younger than 5 years (SMC u5 in the combined groups 1 and 2) versus the group that targeted children aged 5–9 years (SCM u10). Vertical grey lines represent the timing of SMC cycles. DoT=directly observed treatment. DOTu5=study group providing SMC as directly observed treatment to children younger than 5 years. DOTu10=study group providing SMC as directly observed treatment to children younger than 10 years. Progr.SMC=study group providing SMC under programmatic conditions without directly observed treatment. SMC=seasonal malaria chemoprevention.

(0·72, 0·54–0·83; p<0·0001; table 3, figure 2D). Clinical incidence in the age group outside the SMC-targeted population (individuals aged ≥10 years) was also lower in the DOTu10 group compared with the DOTu5 group (0·86, 95% CI 0·32–0·97; p=0·0149; appendix 1 pp 8, 19).

On day 7 after the first dose of the final cycle of SMC, we measured amodiaquine and its metabolite desethylamodiaquine in samples from 162 children younger than 5 years in the programmatic SMC group, 82 children in the DOTu5 group, 106 children in the DOTu10 group, and 150 children in the control zone outside the study area. In addition, we had 147 observations in children aged 5–9 years in the DOTu10 group. Crude amodiaquine and desethylamodiaquine concentrations were higher in the DOTu5 and DOTu10 groups than in the programmatic SMC group (figures 3A and B). The proportion of adherent SMC recipients was estimated based on age, weight, reported dose, and desethylamodiaquine plasma concentrations. Measured desethylamodiaquine concentrations were lower in individuals scored as non-adherent (figure 3C). Based on this analysis, we inferred that 58·0% (94 of 162 participants) were adherent in the programmatic SMC group; in groups DOTu5 and DOTu10 and in the control zone, these proportions were 84·1% (69 of 82 participants), 85·8% (91 of 106 participants), and 47·3% (71 of 150 participants), respectively (figure 3D). In a post-hoc analysis that was adjusted for village, net use, and baseline malaria prevalence, parasite prevalence at the end of the study survey was lower in children who were inferred to be treatment adherent based in the last SMC cycle, as based on desethylamodiaquine concentrations (RR 0·60, 95% CI 0·38–0·93; p=0·0237; appendix 1 p 20).

For comparison, caregiver-reported intervention coverage in children younger than 5 years (defined as receiving the first of three doses of SMC) was high throughout the intervention period; in the programmatic SMC group, it ranged from 87·3% to 94·1% in the four cycles whereas it ranged from 88·1% to 93·5% in the two DOT SMC groups (appendix 1 pp 5, 12–13). The proportion of children younger than 5 years reported by

| | Programmatic SMC age 0–4 years (IR per 100 population | DOTu5 (IR per 100 population) | DOTu10 (IR per 100 population) | DOTu5 versus programmatic SMC (clinical efficacy† [95% CI]; p value) | DOTu10 versus DOTu5 (clinical efficacy† [95% CI]; p value) | DOT (DOTu5 plus DOTu10) versus programmatic SMC (clinical efficacy† [95% CI]; p value) |
|---|---|---|---|---|---|---|
| Age 0–4 years | 0·2 (58·0/268·1) | 0·1 (27·0/269·5) | 0·1 (46·0/301·9) | 0·5 (0·2 to 0·7); p=0·0009 | −0·3 (−1·1 to 0·1); p=0·2396 | 0·4 (0·2 to 0·6); p=0·0015 |
| Age 5–9 years | 0·5 (153·0/281·2) | 0·3 (99·0/297·7) | 0·1 (31·0/320·1) | 0·3 (0·1 to 0·5); 0·0101 | 0·7 (0·5 to 0·8); p<0·0001 | 0·6 (0·4 to 0·7); p<0·0001 |
| Age ≥10 years | 0·01 (8·0/913·3) | 0·02 (13·0/792·0) | 0·0 (2·0/977·3) | −0·9 (−5·1 to 0·4); p=0·2767 | 0·8 (0·3 to 0·9); p=0·0149 | −0·04 (−2·2 to 0·6); p=0·9419 |

*IR is calculated as the number of malaria cases divided by total person-days of follow-up for each group (displayed per 100 days or 100 people). †Clinical efficacy (1 – hazard ratio) based on positive rapid diagnostic tests and time to all malaria episodes. Analyses include cluster randomisation as the random effect and are adjusted for village, bed net use, and baseline malaria prevalence. IR=incidence rate.

***Table 3:*** **Impact of interventions on the incidence of clinical malaria**

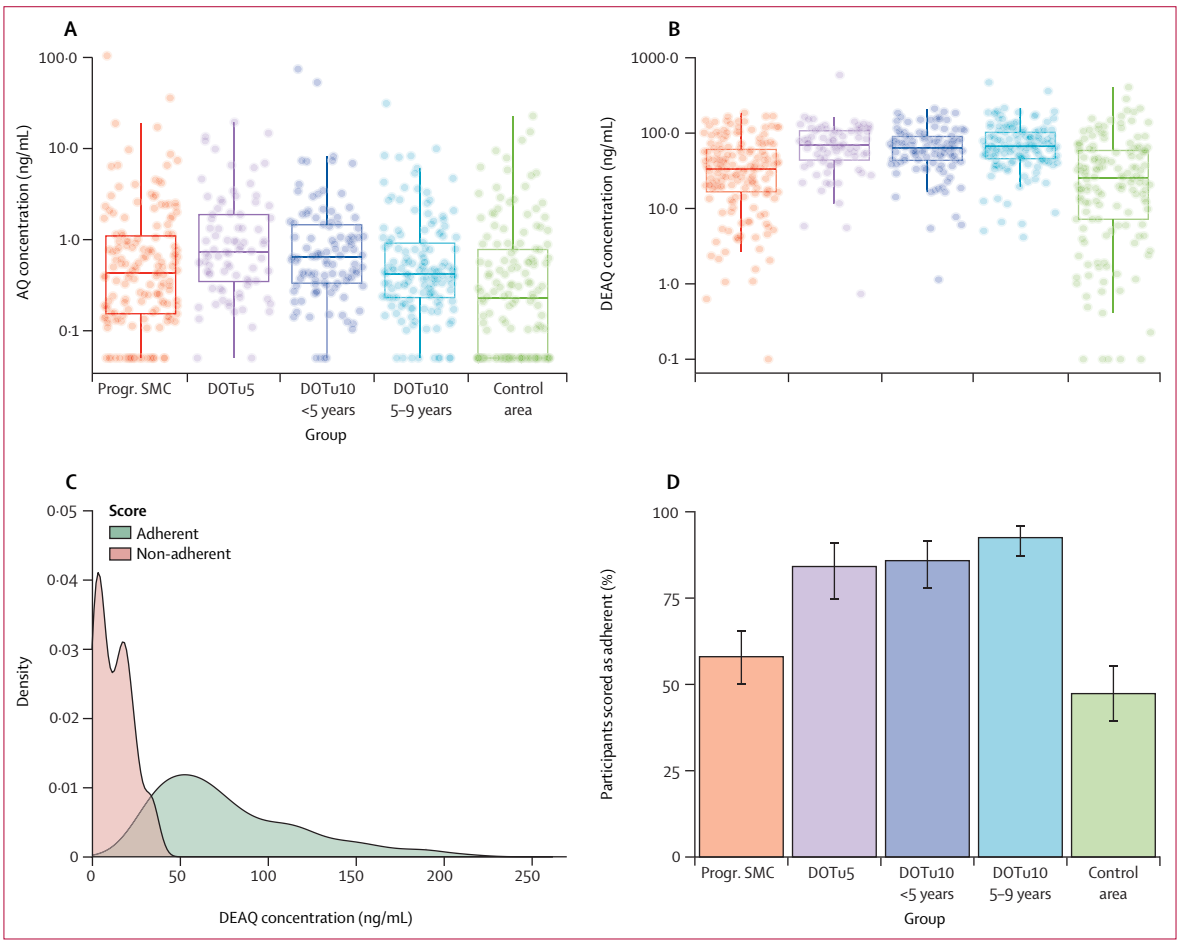


***Figure 3:*** **Plasma drug concentrations per study group and the percentage of participants scored as treatment adherent**
(A) Measured plasma concentrations of AQ with each dot presenting an individual study participant and the box indicating the upper and lower quartile and the whiskers 1·5-times the upper and lower quartile (Tukey method). (B) Measured plasma concentrations of DEAQ. Measurements are unadjusted for weight and age of participants. (C) Density plot of DEAQ concentration in individuals scored as adherent or non-adherent participants in all intervention groups and the control area combined, using a model that compared observed DEAQ concentrations with those expected based on dosing, age, and weight. (D) Percentage of children scored as adherent per study group and for the control area. Error bars indicate the 95% CIs around the proportion. AQ=amodiaquine. DEAQ=desethylamodiaquine. DOTu5=study group providing SMC as directly observed treatment to children younger than 5 years. DOTu10=study group providing SMC as directly observed treatment to children younger than 10 years. Progr.SMC=study group providing SMC under programmatic conditions without directly observed treatment. SMC=seasonal malaria chemoprevention.

the caregiver as taking all three doses ranged from 67·0% to 77·5% in the programmatic SMC group; in the DOT SMC groups, 81·0–92·1% of children received all three doses under supervision (appendix 1 pp 6, 14–15). Adherence to individual doses of SMC drugs is presented in the appendix 1 (p 7). In a post-hoc analysis that was adjusted for village, net use, and baseline malaria prevalence, clinical incidence after the 4th cycle of SMC

was lower in individuals who were scored as adherent based on their desethylamodiaquine plasma concentrations compared with those who were scored as non-adherent (incident rate ratio 0·22, 95% CI 0·09–0·52; p=0·0006; appendix 1 pp 20–21).

In the end of transmission season survey, the prevalence of gametocytes by qRT-PCR in SMC-targeted population (children aged <5 years) was 3·5–6·6% in the different groups (table 2, figure 3B; appendix 1 p 9). The prevalence of gametocytes in children aged 5–9 years was 8·9% (eight of 90 participants) in the DOTu10 group, which was significantly lower than in the DOTu5 group, in which this age group was not targeted (29·0% [18 of 62 participants]; RR 0·29, 95% CI 0·14–0·61; p=0·0010), after adjusting for village, bed net use, and baseline malaria prevalence.

Parasite prevalence was measured by microscopy at each SMC cycle, before administration of the first dose and, by qPCR, at weeks 3, 4, and 5 after the final cycle of the SMC in the targeted population (appendix 1 pp 22–23). At week 3, 8·2% (nine of 110 participants) in the programmatic SMC group, 3·7% (one of 27 participants) in the DOTu5 group, and 5·3% (four of 76 participants) in the DOTu10 group were parasite positive by microscopy; at week 4, these proportions were 0% (0 of 30 participants), 3·1% (three of 98 participants), and 2·6% (two of 76 participants), and at week 5, 7·0% (five of 71 participants), 3·0% (two of 66 participants), and 2·5% (two of 79 participants) in the programmatic SMC, DOTu5, and DOTu10 groups, respectively (appendix 1 p 23). A total of 203 mosquito feeding assays were performed on 173 children; 13 (6·4%) experiments resulted in at least one infected mosquito (appendix 1 p 25). Gametocyte density was positively associated with mosquito infection rates without an apparent effect of residual drug concentrations that were detected in the plasma of 109 of 203 feeding experiments (appendix 1 p 10). These analyses were descriptive only with no statistical comparisons made.

## Discussion

This cluster-randomised controlled trial evaluated the effect of SMC, delivered under programmatic conditions or under direct treatment observation, on parasite prevalence and prevalence of gametocytes, and the incidence of malaria, in an area of intense malaria transmission in Burkina Faso. For children younger than 5 years, parasite prevalence at the end of the transmission season was not significantly different between groups. In a post-hoc analysis, we found evidence that SMC adherence, assessed by plasma drug concentrations after the final cycle of SMC, was an important determinant of both parasite carriage at the end of the season and incidence of clinical malaria in the last weeks of the transmission season. We further observed a high parasite prevalence and high clinical incidence in children aged 5–9 years, both of which were considerably reduced by SMC.

SMC is a highly effective intervention, yet with variable protective efficacy under programmatic conditions. A large case–control study in five countries that implemented SMC in children younger than 5 years reported 73–98% protection against clinical malaria.[4] In 2015, data from a Malaria Indicator Survey in Mali indicated a much lower SMC-associated reduction in clinical incidence of 44%.[5] Treatment adherence is likely a prime contributor to these variations in protective effect. Self-reported treatment adherence is often high and exceeded 90% in household surveys in Nigeria, Burkina Faso, Chad, and Togo.[22] In marked contrast, a study in Niger that measured adherence by drug metabolite concentrations suggested that less than 20% of children were fully treated.[6] We observed that although more than 87% of eligible children were present at the fourth SMC cycle for treatment, desethylamodiaquine plasma concentrations indicate only approximately 58% of children were fully adherent in this cycle. Although it is impossible to differentiate between treatment adherence and absorption, differences between DOT study groups and the programmatic SMC group are likely to be due to differences in adherence, and suggest a non-negligible proportion of children might not receive all SMC drug doses. Importantly, children defined as treatment adherent had an approximate two-fold lower parasite prevalence at the end of the study season and experienced an approximate five-fold fewer clinical malaria episodes in the last weeks of the transmission season compared with children defined as non-adherent.

It is increasingly recognised that school-aged children suffer substantial malaria-related morbidity and mortality.[23] Consequently, countries, including Burkina Faso, are considering expanding the age range of the SMC-targeted population. We included children up to age 9 years and, after mild side-effects observed in cycle 1, SMC dosing was adjusted and was subsequently well tolerated.[24] We observed approximately a 40% reduction in parasite prevalence at the end of the transmission season survey in children receiving SMC in this age group. We recorded a total of 433 clinical malaria cases during the study period of which 283 (65%) occurred in children aged 5–9 years. The incidence of clinical malaria was reduced by 20% overall and in the weeks following the 4th cycle of SMC was approximately five-fold lower in children aged 5–9 years who received SMC drugs. This period reflected the peak incidence in the area and could justify extending the number of SMC cycles.[25,26,27] Our findings are in line with observations from a large trial in Senegal, in which SMC was delivered to children up to age 10 years and an approximate 60% reduction in the incidence of malaria and an approximate 45% reduction in severe malaria were reported.[12]

In addition to the substantial morbidity, school-aged children are also considered to represent the major source of mosquito infections for malaria and contribute

significantly to the human reservoir of infection.[16,19] The marked reduction in parasite prevalence in children aged 5–9 years receiving SMC in the endline survey was accompanied by a larger reduction in gametocyte carriage, suggesting that extended-age SMC could have an impact on transmission. In this study, we have showed a strong correlation between gametocyte density and mosquito infection consistent with previous studies,[28] no evidence that SMC drugs reduced gametocyte infectivity, which was previously suggested,[18] and the primary reason to perform mosquito feeding assays. Our findings suggest that the reduction in gametocyte carriage that we observed in the DOTu10 group reflects a true reduction in transmission potential.

We also observed an indication that this reduction could result in a lower clinical burden in the untargeted population. Although small numbers of events warn against over-interpretation, clinical incidence appeared reduced in individuals aged 10 years and older in the group in which SMC was given to children aged up to 9 years. This potential community effect of age-extended SMC warrants further investigation.

See Online for appendix 2

Our study has several limitations. Although most comparisons were prespecified, our primary outcome changed post enrolment and we performed a large number of comparisons and secondary and exploratory findings, which should be interpreted with caution. No formal missing data strategy was prespecified or conducted; we used a modified intention-to-treat analysis based on those assessed during the endline survey. Importantly, although adherence outcome analyses corroborate earlier findings,[20] and are consistent across parasite prevalence and clinical incidence outcome measures, the analyses were not defined a priori and should be considered post-hoc. We are unable to rule out some level of behavioural contamination in our study. To explore this, we included a control zone outside our study area in which we observed the lowest inferred SMC drug adherence (47·3%), which appeared lower than in programmatic SMC group (58·0%). This finding suggests that the presence of our study team could have resulted in higher treatment adherence than would have been observed in the absence of research activities; differences between programmatic SMC and DOT SMC could therefore underestimate true differences. Our study was designed to ensure similar transmission intensity and similar distances to health facilities between study groups, but small-scale heterogeneity in transmission is unavoidable. Another limitation is that we assessed drug plasma concentrations for treatment adherence only after the final round of SMC and did not assess the effect of drug resistance.[29] Lastly, we conducted a relatively small number of mosquito feeding assays that were sufficient to rule out a gametocyte-sterilising effect of SMC drugs but insufficient to compare infectivity between groups.

In conclusion, this study provides evidence that extending the age range of the delivery of SMC to include children aged 5–9 years reduces both the prevalence and incidence of malaria in this age group and indicates that treatment adherence is probably an important determinant of SMC impact. Future studies should further address how the evident beneficial effects of age-extended SMC, in addition to the potential benefits of DOT, compare with the additional costs for SMC delivery.

#### Contributors

ABT, TB, and CD developed and conceived the initial design of the study with contributions from JBY, AO, MM, AB, and JB. JBP, AO, SSS, AB, KL, LH, FM, ESB, IS, LG, AZO, JS, INO, DH, SBS did the data acquisition in the field and in the lab. JBY, AO, ABT, MM, and SS accessed and verified the underlying data. Statistical analysis of the drug concentrations and epidemiological outcomes were done by SK and SS, with input from IB, JD, and JB. JBY, AO, MM, SS, MG, LH, FM, and RTH contributed to the data interpretation. JBY, AO, MM, TB, CD, and ABT wrote the first draft of the manuscript. All authors have reviewed, read, and approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

#### Equitable Partnership Declaration

The authors of this paper have submitted an Equitable Partnership Declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of The Lancet Group's broader goal to decolonise global health.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

All de-identified data used in this manuscript are available on https://doi.org/10.5061/dryad.9cnp5hr0p.

#### Acknowledgements

This work is supported by the Gates Foundation grant (grant number: NV-053846). TB is further supported by a fellowship from the Netherlands Organization for Scientific Research (Vici fellowship NWO 09150182210039). The authors thank the Ministry of Health and National Malaria Control Program of Burkina Faso for their support in designing and implementing this study and for early discussions on the operational feasibility of age-extended seasonal malaria chemoprevention. We further thank staff at the study sites for support and the research nurses and laboratory and administrative staff involved in the study.

#### References

1 Ashley EA, Poespoprodjo JR. Treatment and prevention of malaria in children. *Lancet Child Adolesc Health* 2020; **4:** 775–89.
2 Thwing J, Williamson J, Cavros I, Gutman JR. Systematic review and meta-analysis of seasonal malaria chemoprevention. *Am J Trop Med Hyg* 2023; **110:** 20–31.
3 Baba E, Hamade P, Kivumbi H, et al, and the ACCESS-SMC Partnership. Effectiveness of seasonal malaria chemoprevention at scale in west and central Africa: an observational study. *Lancet* 2020; **396:** 1829–40.
4 Cairns M, Ceesay SJ, Sagara I, et al. Effectiveness of seasonal malaria chemoprevention (SMC) treatments when SMC is implemented at scale: case-control studies in 5 countries. *PLoS Med* 2021; **18:** e1003727.
5 Druetz T, Corneau-Tremblay N, Millogo T, et al. Impact evaluation of seasonal malaria chemoprevention under routine program implementation: a quasi-experimental study in Burkina Faso. *Am J Trop Med Hyg* 2018; **98:** 524–33.
6 Ding J, Coldiron ME, Assao B, et al. Adherence and population pharmacokinetic properties of amodiaquine when used for seasonal malaria chemoprevention in African children. *Clin Pharmacol Ther* 2020; **107:** 1179–88.
7 Rek J, Blanken SL, Okoth J, et al. Asymptomatic school-aged children are important drivers of malaria transmission in a high endemicity setting in Uganda. *J Infect Dis* 2022; **226:** 708–13.

8 Soumare HM, Blanken SL, Ahmad A, et al. Asymptomatic school children and adults are important for the human infectious reservoir for *Plasmodium falciparum* malaria in an area of low endemicity in The Gambia. *J Infect* 2025; **91:** 106507.

9 Yaro JB, Tiono AB, Ouedraogo A, et al. Risk of *Plasmodium falciparum* infection in south-west Burkina Faso: potential impact of expanding eligibility for seasonal malaria chemoprevention. *Sci Rep* 2022; **12:** 1402.

10 Collins KA, Ouedraogo A, Guelbeogo WM, et al. Effect of weekly fever-screening and treatment and monthly RDT testing and treatment on the infectious reservoir of malaria parasites in Burkina Faso: a cluster-randomised trial. *Lancet Microbe* 2024; **5:** 100891.

11 World Health Organisation. WHO guidelines for malaria Geneva. 2024. https://www.who.int/publications/i/item/guidelines-for-malaria (accessed July 20, 2026).

12 Cisse B, Ba EH, Sokhna C, et al. Effectiveness of seasonal malaria chemoprevention in children under ten years of age in Senegal: a stepped-wedge cluster-randomised trial. *PLoS Med* 2016; **13:** 11e1002175.

13 World Health Organization. World malaria report 2025. 2025. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2025 (accessed April 1, 2025).

14 Moreno M, Barry A, Gmeiner M, et al. Understanding and maximising the community impact of seasonal malaria chemoprevention in Burkina Faso (INDIE-SMC): study protocol for a cluster randomised evaluation trial. *BMJ Open* 2024; **14:** 3e081682.

15 Ministère de la Santé—Burkina Faso. Directives nationales de prise en charge du paludisme. Ouagadougou, 2021. https://www.ipsca.bf/fichier/20220317155932.pdf (accessed July 20, 2026).

16 Andolina C, Rek JC, Briggs J, et al. Sources of persistent malaria transmission in a setting with effective malaria control in eastern Uganda: a longitudinal, observational cohort study. *Lancet Infect Dis* 2021; **21:** 1568–78.

17 Meerstein-Kessel L, Andolina C, Carrio E, et al. A multiplex assay for the sensitive detection and quantification of male and female *Plasmodium falciparum* gametocytes. *Malar J* 2018; **17:** 441.

18 Alkema M, Reuling IJ, de Jong GM, et al. A randomized clinical trial to compare *Plasmodium falciparum* gametocytemia and infectivity after blood-stage or mosquito bite-induced controlled malaria infection. *J Infect Dis* 2021; **224:** 1257–65.

19 Collins KA, Ouedraogo A, Guelbeogo WM, et al. Investigating the impact of enhanced community case management and monthly screening and treatment on the transmissibility of malaria infections in Burkina Faso: study protocol for a cluster-randomised trial. *BMJ Open* 2019; **9:** 9e030598.

20 Roh ME, Zongo I, Haro A, et al. Seasonal malaria chemoprevention drug levels and drug resistance markers in children with or without malaria in Burkina Faso: a case-control study. *J Infect Dis* 2023; **228:** 926–35.

21 Barry A, Bradley J, Stone W, et al. Higher gametocyte production and mosquito infectivity in chronic compared to incident *Plasmodium falciparum* infections. *Nat Commun* 2021; **12:** 2443.

22 Ibinaiye T, Oresanya O, Oguoma C, et al. Predictors of caregiver adherence to administration of amodiaquine during delivery of seasonal malaria chemoprevention in Nigeria, Burkina Faso, Chad, and Togo. *Malar J* 2023; **22:** 148.

23 Morlino C, Byrne I, Achan J, et al. Barriers to uptake and implementation of malaria chemoprevention in school-aged children: a stakeholder engagement meeting report. *Front Trop Dis* 2025; **6:** 148090710.

24 Afolabi MO, Sow D, Ndiaye JLA, Greenwood B. Safety and effectiveness of delivering mass drug administration for helminths through the seasonal malaria chemoprevention platform among Senegalese children: study protocol for a randomised controlled trial. *Trials* 2022; **23:** 627.

25 Grant J, Sagara I, Zongo I, et al. Impact of seasonal RTS,S/AS01E vaccination plus seasonal malaria chemoprevention on the nutritional status of children in Burkina Faso and Mali. *Malar J* 2022; **21:** 5915.

26 Chandramohan D, Zongo I, Sagara I, et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. *N Engl J Med* 2021; **385:** 1005–17.

27 Konate D, Diawara SI, Sogoba N, et al. Effect of a fifth round of seasonal malaria chemoprevention in children aged 5–14 years in Dangassa, an area of long transmission in Mali. *Parasite Epidemiol Control* 2023; **20:** e00283.

28 Bradley J, Stone W, Da DF, et al. Predicting the likelihood and intensity of mosquito infection from sex specific *Plasmodium falciparum* gametocyte density. *eLife* 2018; **7:** 7.

29 Masserey T, Lee T, Kelly SL, Hastings IM, Penny MA. Seasonal malaria chemoprevention and the spread of *Plasmodium falciparum* quintuple-mutant parasites resistant to sulfadoxine–pyrimethamine: a modelling study. *Lancet Microbe* 2024; **5:** 100892.