Effect of mass drug administration on malaria incidence in southeast Senegal during 2020–22: a two-arm, open-label, cluster-randomised controlled trial

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Summary

Background In Africa, the scale-up of malaria-control interventions has reduced malaria burden, but progress towards elimination has stalled. Mass drug administration (MDA) is promising as a transmission-reducing strategy, but evidence from low-to-moderate transmission settings is needed. We aimed to assess the safety, coverage, and effect of three cycles of MDA with dihydroartemisinin–piperaquine plus single, low-dose primaquine on *Plasmodium falciparum* incidence and prevalence in southeast Senegal.

Methods We conducted a two-arm, open-label, cluster-randomised controlled trial in villages in the Tambacounda health district of southeast Senegal. Eligible villages had a population size of 200–800, were within a health-post catchment area with an annual malaria incidence of 60–160 cases per 1000 people, and had an established or planned Prise en Charge à Domicile Plus model. We randomly assigned villages (1:1) using a stratified, constrained randomisation approach to receive either three cycles of MDA with oral dihydroartemisinin–piperaquine plus single, low-dose primaquine administered at 6-week intervals (intervention) or to standard of care, which included three cycles of seasonal malaria chemoprevention (SMC) with oral sulfadoxine–pyrimethamine plus amodiaquine administered at 4-week intervals (control). Participants, the field team, and all investigators, including those who assessed outcomes and analysed data, were unmasked to allocation assignment. Laboratory technicians were masked to intervention assignment. The primary outcome was village-level, *P falciparum*-confirmed malaria incidence in the post-intervention year (ie, July to December, 2022). Secondary outcomes included malaria incidence during the intervention year (ie, July to December, 2021), coverage and safety of MDA, and adverse events. We conducted analyses using an intention-to-treat approach. The trial is registered with ClinicalTrials.gov (NCT04864444) and is completed.

Findings Between Sept 1 and Oct 25, 2020, 523 villages were geolocated and screened for eligibility; 111 met the inclusion criteria. Of these, 60 villages were randomly selected and assigned to the intervention arm or control arm. Distribution coverage of all three doses of dihydroartemisinin–piperaquine was 6057 (73·6%) of 8229 participants in the first cycle, 6836 (78·8%) of 8673 participants in the second cycle, and 7065 (81·3%) of 8690 participants in the third cycle. Distribution coverage of single, low-dose primaquine was 6286 (78·6%) of 7999 participants in the first cycle, 6949 (82·1%) of 8462 participants in the second cycle, and 7199 (84·0%) of 8575 participants in the third cycle. Distribution coverage of all three doses of SMC was 3187 (92·2%) of 3457 children aged 3–120 months in the first cycle, 3158 (91·8%) of 3442 children aged 3–120 months in the second cycle, and 3139 (91·4%) of 3434 children aged 3–120 months in the third cycle. In the intervention year (ie, July to December, 2021), the adjusted effect of MDA was 55% (95% CI 28 to 71). In the post-intervention year (ie, July to December 2022), the adjusted MDA effect was 26% (–17 to 53). Malaria incidence during the transmission season of the post-intervention year was 126 cases per 1000 population in the intervention arm and 146 cases per 1000 population in the control arm. No serious adverse events were reported.

Interpretation In southeast Senegal, a low-to-moderate transmission setting where malaria-control measures have been scaled up, three cycles of MDA with dihydroartemisinin–piperaquine plus single, low-dose primaquine was safe and reduced malaria burden during the intervention year. However, its sustained effect was weak and continuation of MDA or another transmission-reducing strategy could be required.

Funding US President's Malaria Initiative.

Research in context

Evidence before this study

Current WHO guidelines recommend that malaria programmes consider mass drug administration (MDA) for reduction of *Plasmodium falciparum* transmission in low-to-very-low transmission settings, broadly defined as parasite prevalence less than 10% or annual malaria incidence of less than 250 cases per 1000 population. In moderate-to-high transmission areas, MDA is recommended for rapid reduction of disease burden but not transmission reduction, due to few published studies showing its short-term or long-term benefits. Among the numerous studies that contributed to this recommendation, five evaluated the antimalarial combination of dihydroartemisinin–piperaquine plus single, low-dose primaquine. However, none of the studies were conducted in countries implementing seasonal malaria chemoprevention (SMC) as part of their routine malaria-control strategy.

We searched PubMed from database inception to Oct 11, 2024, using the search terms "mass drug administration" AND "dihydroartemisinin-piperaquine". There were no language restrictions, inclusion criteria, or exclusion criteria. We found one cluster-randomised controlled trial conducted in The Gambia, a moderate transmission setting and an SMC-implementing country, that evaluated MDA with the antimalarial combination dihydroartemisinin–piperaquine plus ivermectin. This trial, which evaluated MDA during two transmission seasons, found that MDA was safe and associated with an odds ratio of 0·30 (95% CI 0·16–0·59) regarding PCR-confirmed malaria 2 months after the final round of MDA. However, the trial did not evaluate whether the effects of MDA were sustained in the post-intervention year.

Added value of this study

Our trial adds to the current evidence base of the use of MDA for malaria burden reduction and transmission. Combined with results from a trial in The Gambia, we showed that MDA with dihydroartemisinin–piperaquine plus a transmission-reducing drug is safe and rapidly reduces malaria burden in both low-transmission and moderate-transmission settings. However, when monitoring malaria incidence for an additional follow-up year, we found that the effect was substantially reduced.

Implications of all the available evidence

As countries in sub-Sahelian and Sahelian Africa progressively scale up their malaria-control interventions, they will reach a stage at which no further gains can be made. In low-transmission and moderate-transmission settings aiming for malaria elimination, MDA with dihydroartemisinin–piperaquine plus single, low-dose primaquine can be considered, with the caution that the effects of MDA are time-limited and will likely need to be continued for several years to advance malaria elimination.

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Introduction

Malaria is a major public health concern in Africa. In regions where transmission is highly seasonal, seasonal malaria chemoprevention (SMC) has been widely implemented to prevent morbidity and mortality in children at risk of severe malaria. SMC involves administration of sulfadoxine–pyrimethamine plus amodiaquine at 4-week intervals, given during the peak transmission season to clear existing parasitaemia and prevent new infections.[1] Since its recommendation by WHO in 2012, SMC has expanded to 18 African countries, treating 1·2 million children during 2013–14 and a total of 53·0 million children by 2023,[2,3] resulting in reductions in incidence of childhood malaria of 60–88%.[1,4]

High coverage of SMC, strong vector control, and rapid case management have enabled countries in Sahelian and sub-Sahelian Africa to substantially advance malaria control, prompting many to establish new goals for elimination. However, progress towards goals during the past 5 years has stalled,[3] requiring enhanced coverage of core interventions and new interventions to accelerate transmission reduction. One promising approach is mass drug administration (MDA), which involves administering antimalarials to all individuals in a defined geographical area at a frequency and duration adapted to the local malaria epidemiology and goals. To effectively affect transmission, MDA needs to achieve high coverage of the target population (ie, ≥80%),[5] which requires optimised delivery methods and strong community engagement.[6] These requirements might be more achievable in countries already implementing SMC, where there is existing infrastructure of door-to-door delivery and community and health-system acceptance of chemoprevention.[7,8]

The effectiveness of MDA depends on the antimalarial regimen used. In regions with dominant *Plasmodium falciparum*, dihydroartemisinin–piperaquine is an attractive choice due to its good safety profile, its long prophylactic period, and low prevalence of artemisinin resistance in Africa.[9,10] However, dihydroartemisinin–piperaquine is not effective against mature gametocytes,[11,12] the parasites responsible for human-to-mosquito transmission. Single, low-dose primaquine, a gametocytocidal agent, is safe and associated with the near-complete prevention of human-to-mosquito transmission.[13–15] Although empirical data on whether the human-to-mosquito transmission-blocking activity of primaquine translates into population-level effects on transmission is scarce, its addition to dihydroartemisinin–piperaquine could offer greater benefits than dihydroartemisinin–piperaquine alone, including the potential to reduce the spread of drug-resistant parasites.[16,17]

In 2022, WHO updated their guidelines recommending MDA in areas with high coverage of standard malaria interventions and low malaria-importation risk.[1] The guidelines recommend MDA for transmission reduction

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See Online for appendix

in settings with very-low-to-low transmission, broadly defined by WHO as parasite prevalence less than 10% or annual malaria incidence of less than 250 cases per 1000 population on the basis of eight cluster-randomised controlled trials showing a substantial but short-term effect.[1,18,19] In settings with moderate-to-high transmission, defined by WHO as parasite prevalence 10% or more or annual malaria incidence of more than 250 cases per 1000 population,[1] MDA is recommended for rapid reduction of disease burden but not for transmission reduction due to scarce evidence on its short-term or long-term benefits.

In southeast Senegal, malaria transmission ranges from low to high (ie, 50–500 cases per 1000 population per year) and is highly seasonal, with most cases occurring between July and December. In this region, the national malaria programme Programme National de Lutte contre le Paludisme (PNLP) implements standard malaria-control interventions, including routine distribution of insecticide-treated bednets; health-facility case management; and SMC to children aged 3–120 months, except those with reported acute illness or fever, known hypersensitivity to SMC drugs, history of antimalarials in the previous 3 weeks, or history of sulfonamide-containing drugs in the previous 10 days. In many remote villages in southeast Senegal, there have been ongoing efforts to scale up proactive community case management of fever through the Prise en Charge à Domicile Plus (PECADOM+) model. In the PECADOM+ model, community health workers, known as dispensateur de soins à domiciles (DSDOMs), conduct household visits once per week to test people with suspected malaria and treat those with a positive diagnosis during the high transmission season, regardless of age. Despite scale-up of these interventions, progress in transitioning southeast Senegal to pre-elimination, defined by the PNLP as an annual incidence of less than 5 cases per 1000 population, has been slow. Therefore, the programme needs an accelerator intervention to aggressively increase elimination margins and meet the national malaria-elimination goal by 2030.

We aimed to assess the safety, coverage, and effect of three cycles of MDA with dihydroartemisinin–piperaquine plus single, low-dose primaquine on *P falciparum* incidence and prevalence in southeast Senegal, a setting with highly seasonal, low-to-moderate transmission where malaria-control measures have been scaled up.

Methods

Trial design

We conducted a two-arm, open-label, cluster-randomised controlled trial in villages in the Tambacounda health district of southeast Senegal. In 2020, the district contained 523 villages, with an estimated overall population size of 297761.

Ethical approval was provided by the Comité National d'Ethique pour la Recherche en Santé (Dakar, Senegal) and the University of California, San Francisco Human Research Protection Program (San Francisco, CA, USA). The US Centers for Disease Control and Prevention and Population Services International agreed to rely on the Institutional Review Board of the University of California, San Francisco for ethical oversight of the trial. The protocol is available (appendix pp 19–71).

Participants

We randomly selected 60 villages for participation using a random number generator. Eligible villages had a population size of 200–800, were within a health-post catchment area with an annual malaria incidence of 60–160 cases per 1000 population, and had an established or planned PECADOM+ model. Villages were selected with centroids 2·5 km apart or more.

The eligibility of participants in each of the 30 villages was assessed before each MDA cycle. Residents of intervention villages were eligible if they were aged 3 months or older and were either personally or through parental approval were willing to comply with trial procedures and provide informed consent. Exclusion criteria were self-reported severe or chronic illness; known hypersensitivity to trial drugs; currently pregnant, confirmed by urine test; currently taking or had taken drugs that could influence cardiac function or extend the corrected QT interval in the previous 4 weeks; or had received antimalarials in the previous 3 weeks. Participants younger than 2 years or who were breastfeeding were excluded from receiving single, low-dose primaquine. No SMC was provided in intervention villages during the intervention year (ie, July to December, 2021).

Written informed consent was obtained from participants before the first MDA cycle and the cross-sectional surveys. Parental consent was obtained from participants younger than 18 years; assent was obtained from children aged 13–17 years. Informed consent forms were prepared in English and translated into French. Trained study staff (not authors of this Article) administered the consent process in French, Wolof, or the local language, as appropriate. For participants who were unable to read or write in French, a witness was present to ensure the accuracy and integrity of the informed consent process. The witness verified that the information explained verbally was consistent with the written consent form and signed the form to confirm their role in validating the process.

Randomisation and masking

We randomly assigned villages (1:1) to the intervention arm or the control arm using a stratified, constrained randomisation approach. Villages were stratified by presence of DSDOM at baseline; in each stratum we balanced health post of village; distance to health post; baseline microscopy-confirmed malaria prevalence, assessed during the baseline survey; village population

size; and population size of children younger than 10 years. A trial investigator (MER) randomly generated intervention assignment using the cvcrand module in Stata version 16.0.[20] 50 000 randomisation schemes were generated and one was randomly sampled from the top 1% (n=500 schemes), with the lowest balance scores calculated with l^2. Participants; the field team; and all investigators, including those who assessed outcomes and analysed data, were unmasked to allocation assignment. Laboratory technicians were masked to intervention assignment; the success of masking was not assessed. Villages were randomly selected by an independent investigator (MER) and enrolled by study staff.

Procedures

Upon village selection, study staff held meetings with administrative, health, and religious leaders of Tambacounda health district to discuss trial aims, planned activities, and to obtain consent for trial implementation. Community-sensitisation materials, including social media campaigns, local community radio announcements, and television advertisements, were developed by the trial team and implemented by local health staff before each MDA cycle (eg, May to August, 2020), which coincided with the peak of the COVID-19 pandemic. Before each MDA cycle, town hall meetings were held and household visits were made by study staff to ensure that the community was well informed.

Before implementation of the intervention, all trial villages received door-to-door distribution of pyrethroid–piperonyl butoxide bednets and all-year PECADOM+. During the intervention year (ie, July to December, 2021), participants in the intervention arm received three cycles of MDA with dihydroartemisinin–piperaquine plus single, low-dose primaquine, administered 6 weeks apart to individuals aged 3 months or older. MDA was initiated approximately 1 month before the expected start of the transmission season to maximise its effect on clearing the infectious reservoir, as per WHO recommendations (figure 1).[6,21,22] The decision to implement MDA at 6-week intervals was made jointly by the trial team and the Tambacounda District Medical Office to align its coverage of the transmission season with SMC, as MDA started earlier, and considered results from a consensus modelling study,[23] piperaquine's long half-life,[24] and assumed reduction in side-effects by extending intervals between cycles. In the control arm, standard-of-care chemoprevention, consisting of three cycles of SMC with sulfadoxine–pyrimethamine plus amodiaquine, was administered to children aged 3–120 months at 4-week intervals, initiated at the expected start of the transmission season. In the post-intervention year (ie, July to December, 2022), MDA was stopped and SMC was resumed in both arms.

MDA was delivered via a door-to-door approach by DSDOMs with directly observed therapy of all three doses, similar to the delivery method for SMC. For each MDA cycle, dihydroartemisinin–piperaquine (Sigma-Tau, Rome, Italy) was given orally for 3 consecutive days via an age-based dosing strategy as per the manufacturer's instructions (appendix p 3). Single, low-dose primaquine (Remedica, Limassol, Cyprus) was given orally with the first dihydroartemisinin–piperaquine dose. SMC was administered directly by the national malaria programme using an age-based dosing strategy (appendix p 3). For each SMC cycle, amodiaquine (Fosun Pharma, Shanghai, China) was given orally for 3 consecutive days and sulfadoxine–pyrimethamine (Fosun Pharma, Shanghai, China) was given with the first amodiaquine dose. For participants unable to swallow tablets (eg, young children), tablets were crushed

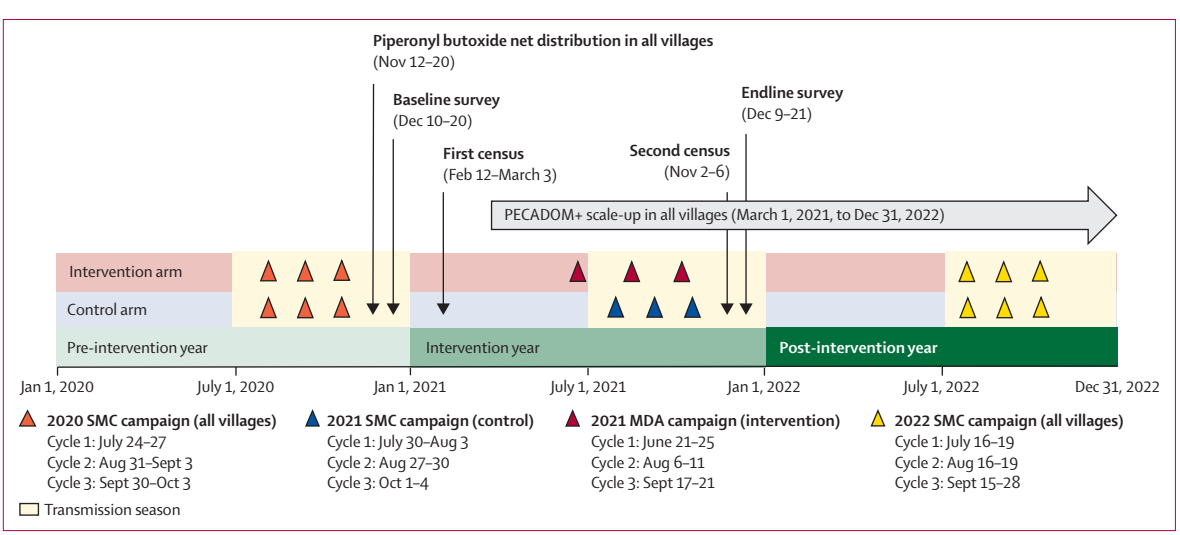

Figure 1: **Trial timeline**
MDA=mass drug administration. PECADOM+=*Prise en Charge à Domicile Plus*. SMC=seasonal malaria chemoprevention.

and mixed with water. If vomiting occurred within 30 min of administration, the full dose was re-administered. If vomiting occurred again within 30–60 min, half of the dose was given.

During drug administration, people with suspected malaria were confirmed by a histidine-rich protein 2-based rapid diagnostic test (RDT; ParaHIT f, ARKRAY Healthcare, Surat, India). People with confirmed malaria were treated with artemether–lumefantrine (Novartis, Basel, Switzerland) and did not receive chemoprevention until the subsequent cycle.

An interim safety analysis, conducted after the first MDA cycle, found no statistically significant differences in the incidence of severe or serious adverse events or immuno-allergic reactions between arms, allowing the trial to proceed as planned.

For each chemoprevention campaign, we used a pre-intervention census conducted by study staff to generate a registry with unique participant identifiers to establish who would be targeted for each cycle. Data on adherence and dose were recorded for each person per day. The registry was updated throughout the campaign to identify new residents, deaths, and emigrants. We evaluated crude and distribution coverage, as defined by WHO.[6] Crude coverage was defined as the proportion of residents who received chemoprevention among all known trial residents, the denominator of which included absences, refusals, and ineligible individuals. Distribution coverage was defined as the proportion of residents who received chemoprevention among all eligible residents, the denominator of which included absences and refusals. Both metrics excluded deaths and emigrants.

People with RDT-confirmed malaria were captured through health-facility and PECADOM+ registries. To ensure high-quality capture of incident malaria, PECADOM+ was expanded in all trial villages and throughout the year, and was scaled up by March 1, 2021. We collected data from paper-based registries and abstracted them into electronic databases, removing duplicates between registries. We estimated village-level population size by taking the mean of two trial-implemented censuses before and after intervention implementation (figure 1).

To measure parasite prevalence, we conducted cross-sectional surveys at the end of the transmission season before and after intervention implementation (ie, Dec 10–20, 2020, and Dec 9–21, 2021). We conducted a two-stage, cluster-sampling strategy to randomly select households and participants from all villages. Participants were asked about their demographic characteristics, malaria-prevention measures, and history of fever. Participants self-reported sex data; the options were male or female. We obtained blood smears and dried blood spots (DBS) from a fingerprick blood sample to confirm parasitaemia by microscopy and PCR and to detect markers of drug resistance.

Microscopy slides and DBS from surveys were transported and analysed at the Université Iba Der Thiam de Thiès (Thiès, Senegal). Slides were stained with 6% Giemsa for 20 min and read by two microscopists. A third reviewer settled any discrepant findings. Parasite DNA was extracted from DBS via the Chelex 100 extraction method[25] and tested for malaria parasitaemia by real-time PCR via species-specific primers based on the 18s rRNA gene.[26] PCR-positive samples were genotyped for point mutations in the *PfK13*, *pfdhps*, *pfdhfr*, *PfCRT*, and *PfMDR1* genes via high-resolution melting analysis.[27]

Outcomes

The primary outcome was village-level, *P falciparum*-confirmed malaria incidence in the post-intervention year (ie, July to December, 2022). Village-level malaria incidence was defined as the number of people with RDT-confirmed, symptomatic *P falciparum* malaria detected through health post and PECADOM+ surveillance divided by mean village population size (figure 1).

Secondary outcomes assessed in this trial were malaria incidence during the intervention year (ie, July to December, 2021), the proportion of clusters that reached the pre-elimination threshold (ie, annual incidence of less than 5 cases per 1000 population), parasite prevalence by microscopy and PCR, coverage and safety of MDA, and prevalence of drug-resistance markers.

For the primary analysis, we assessed incidence outcomes during the transmission season (ie, July to December) to allow consistent comparisons between the intervention and post-intervention years, as MDA was implemented mid-year.

Additional secondary outcomes, including cost-effectiveness analyses, acceptability of MDA, and its effects on seroprevalence and parasite genetics, will be reported separately.

We used passive and active pharmacovigilance systems to comprehensively assess MDA safety. For passive surveillance, participants were encouraged to report adverse events to health or trial staff within 1 month of drug intake. Adverse events were documented in standardised case-report forms, graded as mild, moderate, or severe by a trial clinician (AD) and managed for free. To capture potentially under-reported adverse events, we implemented an active-surveillance system to proactively identify them, in which trial staff surveyed 220 randomly selected households per trial arm on the day after the final drug dose. We surveyed all villages, and household sampling was based on village population size (ie, five households were sampled from villages with fewer than 300 residents and ten households were sampled from villages with 300 residents or more). In intervention villages, we randomly sampled three participants per household

from three age groups (ie, younger than 5 years, aged 5–15 years, and aged 15 years or older) using a random number generator. In control villages, we used the same method to randomly sample three children who were age-eligible for SMC per household. We asked survey participants to report any adverse events, including the type, onset date, and duration.

Statistical analysis

Sample size calculations were based on detecting a 50% relative reduction in RDT-confirmed malaria incidence in the MDA arm in the post-intervention year (ie, July to December, 2022). We assumed a coefficient of variation of 0·80; a mean cluster size of 250; and that the combined effect of pyrethroid–piperonyl butoxide bednets, SMC, and scale-up of PECADOM+ would reduce incidence from 100 to 50 cases per 1000 population. With these assumptions, 60 clusters provided 80% power at a 5% significance level to detect a 50% relative difference using a two-tailed test.

We conducted analyses using an intention-to-treat approach based on a prespecified statistical analysis plan. We assessed the effect of the intervention on incidence using mixed-effects Poisson regression with village-level random intercepts, robust SEs, and an offset term for village population size. The unadjusted model included an MDA variable equal to 1 in intervention villages during the intervention year (ie, July to December, 2021) and 0 otherwise, a second indicator variable testing the sustained effect of MDA equal to 1 in intervention villages in the post-intervention year (ie, July to December, 2022) and 0 otherwise, and a time variable for each trial year. PECADOM+ was not scaled up until after the pre-intervention year (ie, July to December, 2020), resulting in differential capture of people with malaria in villages with and without DSDOMs at baseline (ie, proactive detection in villages with DSDOMs and passive detection in villages without). Thus, the model included a binary indicator equal to 1 during periods when DSDOMs were present in the village and 0 otherwise. Adjusted analyses included covariates used in the stratified, constrained randomisation approach.

The effect of the intervention was defined as the percentage reduction in incidence in the intervention arm compared with the control arm (1–incidence rate ratio [$IRR_{intervention}$]*100%). We estimated the effect of the intervention on cluster-level parasite prevalence using a mixed-effects Poisson regression with village-level random intercepts and robust SEs, incorporating survey weights accounting for the number and size of households.

We conducted prespecified subgroup analyses by age group (ie, aged 10 years or older *vs* younger than 10 years), transmission intensity (ie, low *vs* moderate, defined by WHO as parasite prevalence less than 10% for low and parasite prevalence 10% or more for moderate),[1] and baseline presence of DSDOMs by including two-way interaction terms between treatment and subgroup variables.

All analyses were conducted in Stata version 17.0 or R version 4.2.2. The trial is registered with ClinicalTrials.gov (NCT04864444) and is completed. Trial oversight was provided by an independent data safety monitoring board and external monitor.

Role of the funding source

The funder of the trial participated in trial design, data interpretation, and writing of the manuscript. The funder had no role in data collection or analysis.

Results

Between Sept 1 and Oct 25, 2020, 523 villages were geolocated and screened for eligibility; 111 met the inclusion criteria (figure 2). Of these 111, 60 villages were randomly selected and assigned to the intervention arm or control arm. Baseline malaria incidence was highly

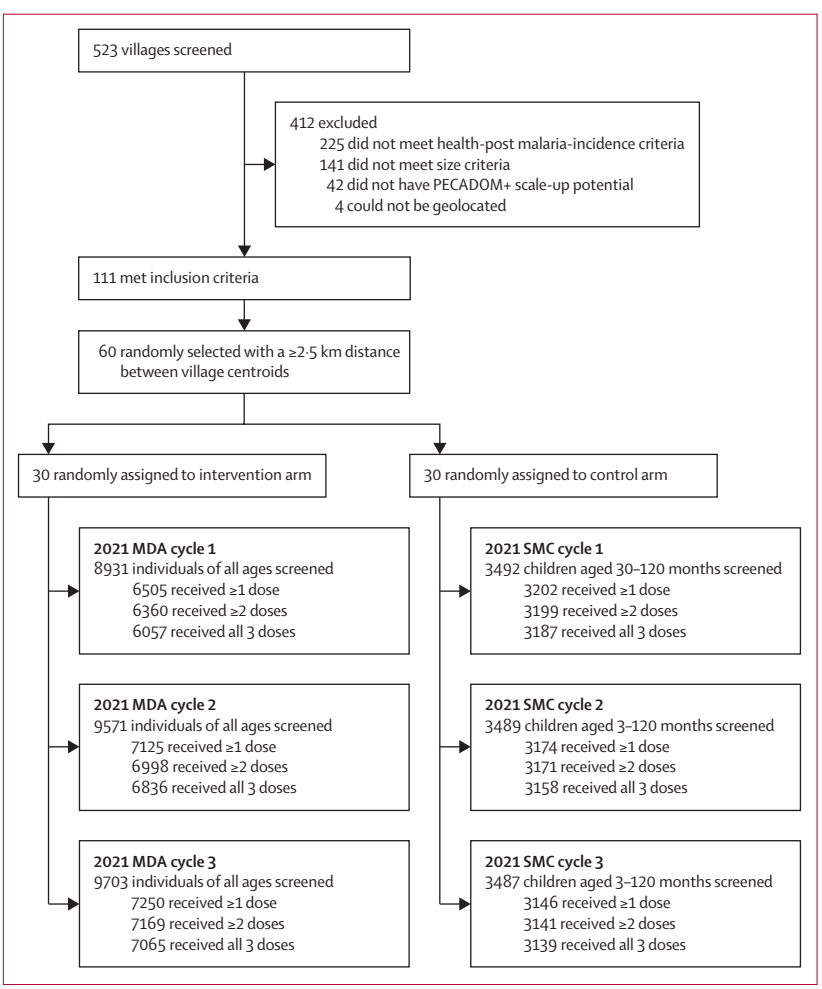

Figure 2: **Trial profile**
MDA=mass drug administration. PECADOM+=*Prise en Charge à Domicile Plus*. SMC=seasonal malaria chemoprevention.

variable across villages (coefficient of variation 1·04). Village-level factors included in the stratified, constrained randomisation approach were balanced between arms (table 1). Overall, coverage of pyrethroid–piperonyl butoxide bednets was high and similar between arms (table 1). Overall, 687 (80·3%) of 856 children younger than 10 years reported receiving the most recent cycle of SMC during the pre-intervention year and 610 (71·1%) of 858 children younger than 10 years reported receiving all three cycles during the pre-intervention year. 459 (19·9%) of 2305 participants reported sleeping away from their home in the past 15 days.

	Overall	Mass drug administration	Control
Village-level characteristics*			
Villages by health post			
Bohe	9/60 (15·0%)	6/30 (20·0%)	3/30 (10·0%)
Dar Salam	2/60 (3·3%)	1/30 (3·3%)	1/30 (3·3%)
Dawadi	14/60 (23·3%)	6/30 (20·0%)	8/30 (26·7%)
Koussanar	9/60 (15·0%)	5/30 (16·7%)	4/30 (13·3%)
Missirah	6/60 (10·0%)	2/30 (6·7%)	4/30 (13·3%)
Neteboulou	5/60 (8·3%)	2/30 (6·7%)	3/30 (10·0%)
Sinthiou Maleme	15/60 (25·0%)	8/30 (26·7%)	7/30 (23·3%)
Presence of *dispensateur de soins à domiciles* before the trial			
No	20/60 (33·3%)	10/30 (33·3%)	10/30 (33·3%)
Yes	40/60 (66·7%)	20/30 (66·7%)	20/30 (66·7%)
Distance to health post, km	14·8 (8·4)	14·9 (8·6)	14·6 (8·3)
Population size in 2019†	322 (168)	330 (170)	315 (168)
Population size of children younger than 10 years in 2019†	119 (62)	120 (63)	117 (62)
Proportion of population younger than 10 years in 2019	37% (5)	36% (4)	37% (6)
Baseline microscopy prevalence	8% (8)	7% (9)	9% (8)
Individual-level characteristics			
Age			
Younger than 10 years	783/2361 (33·2%)	373/1182 (31·6%)	410/1179 (34·8%)
Aged 10 years or older	1578/2361 (66·8%)	809/1182 (68·4%)	769/1179 (65·2%)
Sex			
Male	1180/2362 (50·0%)	576/1183 (48·7%)	604/1179 (51·2%)
Female	1182/2362 (50·0%)	607/1183 (51·3%)	575/1179 (48·8%)
Slept away from home in the past 15 days			
No	1846/2305 (80·1%)	910/1155 (78·8%)	936/1150 (81·4%)
Yes	459/2305 (19·9%)	245/1155 (21·2%)	214/1150 (18·6%)
Type of bednet used			
None	37/2340 (1·6%)	28/1179 (2·4%)	9/1161 (0·8%)
Pyrethroid–piperonyl butoxide	2282/2340 (97·5%)	1131/1179 (95·9%)	1151/1161 (99·1%)
Non-piperonyl butoxide	21/2340 (0·9%)	20/1179 (1·7%)	1/1161 (0·1%)
Received the most recent cycle of SMC during the pre-intervention year‡			
No	169/856 (19·7%)	94/410 (22·9%)	75/446 (16·8%)
Yes	687/856 (80·3%)	316/410 (77·1%)	371/446 (83·2%)
Completed all three cycles of SMC during the pre-intervention year‡			
No	248/858 (28·9%)	128/412 (31·1%)	120/446 (26·9%)
Yes	610/858 (71·1%)	284/412 (68·9%)	326/446 (73·1%)

Data are n/N (%) or mean (SD). SMC=seasonal malaria chemoprevention. *Used in constrained randomisation scheme. †Incidence estimates provided by Tambacounda Regional District Office. ‡Assessed in children younger than 10 years only.

Table 1: **Baseline characteristics**

In the intervention arm, 8931 residents were screened for the first MDA cycle, 9571 were screened for the second, and 9703 were screened for the third. Distribution coverage of all three doses of dihydroartemisinin–piperaquine was 6057 (73·6%) of 8229 participants in the first cycle, 6836 (78·8%) of 8673 participants in the second cycle, and 7065 (81·3%) of 8690 participants in the third cycle. Distribution coverage of all three doses of single, low-dose primaquine was 6286 (78·6%) of 7999 participants in the first cycle, 6949 (82·1%) of 8462 participants in the second cycle, and 7199 (84·0%) of 8575 participants in the third cycle. Distribution coverage of all three doses of dihydroartemisinin–piperaquine was 2618 (81·0%) of 3232 children younger than 10 years in the first cycle, 2904 (83·1%) of 3493 children younger than 10 years in the second cycle, and 3046 (85·6%) of 3560 children younger than 10 years in the third cycle versus 3438 (68·8%) of 4996 children aged 10 years or older in the first cycle, 3932 (75·9%) of 5180 children aged 10 years or older in the second cycle, and 4017 (78·4%) of 5127 children aged 10 years or older in the third cycle. Crude coverage of all three doses of dihydroartemisinin–piperaquine was 6057 (67·8%) of 8931 participants in the first cycle, 6836 (71·4%) of 9571 participants in the second cycle, and 7065 (72·8%) of 9703 participants in the third cycle.

At the village level, median distribution coverage of all three doses of dihydroartemisinin–piperaquine was 74·7% (IQR 68·9–78·8) in the first cycle, 78·6% (76·3–81·6) in the second cycle, and 81·5% (76·5–85·8) in the third cycle (appendix p 6). Six (20·0%) of 30 intervention villages in the first cycle, 12 (40·0%) in the second cycle, and 18 (60·0%) in the third cycle reached the WHO target of at least 80% coverage (appendix p 6). The main reasons for non-participation were absence (range 13·5–21·1% across doses and cycles) and illness (5·1–7·5% across doses and cycles; appendix p 7). Absences were similar by sex (1·11:1 male:female ratio) and age (median 16 years, IQR 8–26 *vs* 12 years, 6–26). Refusals were rare (range 1·4–1·8% across doses and cycles) and were mostly among male participants (218 [67·1%] of 325 participants who refused any one cycle) with a median age of 21 years (IQR 14–30; appendix p 7).

In the control arm, 3492 children aged 3–120 months were screened for the first SMC cycle, 3489 were screened for the second, and 3487 were screened for the third. Distribution coverage of all three doses of SMC was 3187 (92·2%) of 3457 children in the first cycle, 3158 (91·8%) of 3442 children in the second cycle, and 3139 (91·4%) of 3434 children in the third cycle. Crude coverage of all three doses of SMC was 3187 (91·3%) of 3492 children in the first cycle, 3158 (90·5%) of

3489 children in the second cycle, and 3139 (90·0%) of 3487 children in the third cycle. At the village level, median distribution coverage of all three doses of SMC was 93·9% (IQR 87·9–98·2) in the first cycle, 92·9% (87·2–97·4) in the second cycle, and 93·3% (85·2–96·5) in the third cycle (appendix pp 6–7). The main reasons for non-receipt were absence (range 6·7–7·5% across doses and cycles) and illness (1·0–1·7% across doses and cycles; appendix p 7). Refusals were low across cycles (0·6–0·8% across doses and cycles; appendix p 7).

Mean village-level malaria incidence during the transmission season of the pre-intervention year (ie, July to December, 2020) was 181 cases per 1000 population in the intervention arm and 204 cases per 1000 population in the control arm. Mean village-level malaria incidence during the transmission season of the intervention year was 93 cases per 1000 population in the intervention arm and 173 cases per 1000 population in the control arm. Mean village-level malaria incidence during the transmission season of the post-intervention year was 126 cases per 1000 population in the intervention arm and 146 cases per 1000 population in the control arm (table 2; appendix p 8). Analyses of incidence data (appendix pp 8–10) indicated that neither SMC or MDA were optimally timed to cover the entire transmission season.

During the intervention year (ie, July to December, 2021), the adjusted effect of MDA was 55% (95% CI 28 to 71). Prespecified subgroup analyses showed an interaction by age; the adjusted MDA effect was 58% (34 to 73) in participants aged 10 years or older and 45% (10 to 66) in participants younger than 10 years ($p_{interaction}$=0·012). The adjusted MDA effect was 56% (32 to 71) in low-transmission settings and 52% (–22 to 81) in moderate-transmission settings ($p_{interaction}$=0·87). Analyses restricted to villages with DSDOMs at baseline showed that the effect of MDA was 60% (36 to 76). In the post-intervention year (ie, July to December 2022), the adjusted MDA effect was 26% (–17 to 53). There was no interaction by transmission intensity ($p_{interaction}$=0·98). An interaction by age was observed ($p_{interaction}$=0·0065), although differences in effect estimates were minimal. Analyses restricted to villages with DSDOMs at baseline showed the effect of MDA was 30% (–14 to 57). Only two villages in the intervention arm reached the threshold for pre-elimination (incidence of less than 5 cases per 1000 population) during the intervention year and none in the post-intervention year. None of the control villages reached pre-elimination status in either year. We assessed incidence during the full calendar year (ie, January to December) in the post-intervention year, as specified in the protocol, and found similar results to analyses restricted to the transmission season (appendix p 11).

Surveys conducted at the end of the transmission season in the pre-intervention and intervention years (ie, December, 2020 and 2021), showed mean

	Mean village-level incidence						Mean intervention effect*			
	Mass drug administration			Control			2020 compared with 2021		2020 compared with 2022	
	2020	2021	2022	2020	2021	2022	Unadjusted	Adjusted†	Unadjusted	Adjusted†
Primary outcome										
Overall	181 (2067/10745)	93 (924/10745)	126 (1331/10745)	204 (1883/9641)	173 (1751/9641)	146 (1541/9641)	55% (28 to 71)	55% (28 to 71)	26% (–18 to 53)	26% (–17 to 53)
Subgroup analyses										
Age group										
Younger than 10 years	133 (514/4091)	84 (287/4091)	79 (319/4091)	154 (515/3598)	120 (463/3598)	96 (359/3598)	45% (11 to 66)	45% (10 to 66)	31% (–11 to 57)	31% (–12 to 57)
Aged 10 years or older	213 (1553/6637)	100 (633/6637)	158 (1012/6637)	236 (1368/5991)	206 (1287/5991)	178 (1182/5991)	58% (34 to 74)	58% (34 to 73)	24% (–22 to 53)	24% (–21 to 52)
Baseline transmission intensity‡										
<10% (low)	172 (1508/8316)	83 (658/8316)	111 (958/8316)	228 (1385/6463)	171 (1085/6463)	131 (889/6463)	56% (32 to 71)	56% (32 to 71)	27% (–16 to 54)	27% (–16 to 54)
≥10% (moderate)	214 (559/2429)	125 (266/2429)	174 (373/2429)	148 (498/3178)	178 (666/3178)	181 (652/3178)	52% (–23 to 81)	52% (–22 to 81)	23% (–89 to 69)	24% (–88 to 69)
DSDOM at baseline§										
Yes	258 (1980/7783)	87 (665/7783)	128 (1035/7783)	275 (1769/7401)	188 (1474/7401)	170 (1333/7401)	60% (35 to 75)	60% (36 to 76)	30% (–14 to 57)	30% (–14 to 57)
No	28 (87/2963)	105 (259/2963)	121 (296/2963)	62 (114/2240)	145 (277/2240)	98 (208/2240)	–14% (–278 to –65)	–15% (–248 to 62)	–48% (–423 to 58)	–49% (–387 to 54)

Data are incidence per 1000 population (events/population) or (1-incidence rate ratio) × 100 (95% CI). Variance of the γ-distributed random effect was 0·21, giving an underlying coefficient of variation of the incidence rate per cluster of 0·46. DSDOM=dispensateur de soins à domicile. PECADOM+=*Prise en Charge à Domicile Plus*. *We estimated the intervention effect using a mixed-effects Poisson regression with village-level random intercepts and robust SEs. †Adjusted for DSDOM at baseline, village population size of children younger than 10 years, distance from health post, baseline parasite prevalence by microscopy, village population size in 2019, and presence of DSDOM at time of case detection. ‡Defined as village-level, microscopy-confirmed parasite prevalence of <10% (low) and ≥10% (moderate). The low category contained 23 intervention clusters and 21 control clusters. The moderate category contained seven intervention clusters and nine control clusters. Due to delays in PECADOM+ scale-up, baseline incidence was under-reported in clusters without a DSDOM, preventing prespecified analyses based on incidence thresholds (ie, <250 or ≥250 events per 1000 population). 19 (95%) of 20 clusters without a DSDOM would have been classified as low in these analyses, which would have biased subgroup effects in this category. §Yes contained 20 clusters per arm. No contained ten clusters per arm.

Table 2: **Malaria incidence and estimated intervention effect during peak transmission seasons in 2020–22**

village-level microscopy-confirmed parasite prevalence reduced from 6·1% (95% CI 2·8 to 9·4) in 2020 to 1·8% (0·8 to 2·9) in 2021 in the intervention arm and from 6·7% (4·0 to 9·4) to 4·7% (2·5 to 6·9) in the control arm (adjusted MDA effect 62%, 95% CI 22 to 80; table 3). The effect of MDA was 76% (42 to 90) in children younger than 10 years and 51% (–14 to 79) in children aged 10 years or older ($p_{interaction}$=0·17). Post-hoc analyses showed mean village-level microscopy-confirmed gametocyte prevalence decreased from 2020 to 2021: from 3·2% to 0·6% in the intervention arm and from 3·1% to 1·0% in the control arm (adjusted MDA effect 39% [95% CI –98 to 81]).

By PCR, mean village-level parasite prevalence decreased from 17·9% (95% CI 11·3 to 24·4) to 4·5% (2·5 to 6·4) in the intervention arm and from 19·9% (11·8 to 28·1) to 8·3% (4·8 to 11·7) in the control arm (adjusted MDA effect 47%, 95% CI 3–71). The effect of MDA was 71% (35 to 87) in participants younger than 10 years and 33% (–27 to 65) in children aged 10 years or older ($p_{interaction}$=0·050). The effect of MDA on microscopy-confirmed and PCR-confirmed parasite prevalence did not differ between low-transmission and moderate-transmission settings ($p_{interaction}$=0·73; table 3).

In both active and passive pharmacovigilance systems, the frequency of adverse events decreased with each cycle and no serious adverse events or anaemia were detected in either arm. Active surveillance showed that more participants reported any adverse event in the intervention arm than in the control arm (table 4). Among children aged 10 years or older, the proportion of participants reporting an adverse event across all cycles did not differ between arms (table 4). In the intervention arm, common adverse events were gastrointestinal issues, fever, and other (ie, dizziness, cough, skin rashes, pruritus, jaundice, muscle and joint pain, convulsions, and influenza-like illness; table 4). Of the 498 adverse events in the intervention arm, 319 (64·1%) were mild, 164 (32·9%) were moderate, and 15 (3·0%) were severe. Severe adverse events were fever (n=7), headache (n=4), drowsiness (n=1), vomiting (n=1), diarrhoea (n=1), and loss of appetite (n=1). All adverse events occurred within 3 h after drug intake, resolved within 72 h, and did not require hospitalisation. Results from passive surveillance were similar (appendix p 12).

Genotypic analysis of mutations associated with antimalarial resistance showed no differences between arms or time periods (appendix p 13). There were no *pfdhps* K540E, *pfdhps* A581G, or *PfK13* C580Y mutations (appendix p 13).

	Mean village-level prevalence*†				Mean intervention effect*‡	
	Mass drug administration		Control		Unadjusted	Adjusted§
	2020 (n=1183)	2021 (n=1109)	2020 (n=1179)	2021 (n=1086)		
Microscopy-detected infections						
Overall	6·1% (2·8 to 9·4)	1·8% (0·8 to 2·9)	6·7% (4·0 to 9·4)	4·7% (2·5 to 6·9)	61% (21 to 81)	62% (22 to 80)
Age group						
Younger than 10 years	8·2% (2·7 to 13·7)	1·3% (0·2 to 2·4)	7·3% (3·1 to 11·6)	4·5% (2·0 to 7·0)	76% (41 to 90)	76% (42 to 90)
Aged 10 years or older	5·1% (2·6 to 7·7)	2·2% (0·7 to 3·6)	6·4% (3·9 to 8·8)	4·8% (1·8 to 7·9)	50% (–16 to 79)	51% (–14 to 79)
Baseline transmission intensity¶						
<10% (low)	2·6% (1·3 to 3·9)	1·0% (0·2 to 1·8)	3·4% (2·1 to 4·8)	4·3% (1·4 to 7·2)	63% (–1 to 86)	62% (0 to 86)
≥10% (moderate)	18·8% (9·4 to 28·2)	5·0% (2·1 to 7·8)	17·1% (12·5 to 21·8)	6·0% (3·4 to 8·6)	54% (18 to 73)	56% (22 to 75)
PCR-detected infections						
Overall	17·9% (11·3 to 24·4)	4·5% (2·5 to 6·4)	19·9% (11·8 to 28·1)	8·3% (4·8 to 11·7)	46% (–3 to 70)	47% (3 to 71)
Age group						
Younger than 10 years	18·6% (10·9 to 26·4)	2·3% (0·6 to 3·9)	19·6% (9·9 to 29·4)	5·1% (2·2 to 8·0)	71% (34 to 87)	71% (35 to 87)
Aged 10 years or older	17·5% (11·0 to 24·0)	5·8% (2·9 to 8·6)	20·1% (11·7 to 28·5)	10·2% (5·2 to 15·3)	33% (–27 to 64)	33% (–27 to 65)
Baseline transmission intensity¶						
<10% (low)	14·0% (7·9 to 20·1)	3·0% (1·0 to 5·0)	14·3% (6·3 to 22·3)	4·7% (2·4 to 6·9)	48% (–4 to 74)	47% (–7 to 74)
≥10% (moderate)	32·0% (11·4 to 52·5)	9·9% (6·1 to 13·7)	38·0% (21·7 to 54·4)	18·7% (12·2 to 25·3)	37% (2 to 59)	40% (9 to 60)
Microscopy-confirmed gametocytaemia						
Overall	3·2% (1·4 to 5·1)	0·6% (0·0 to 1·2)	3·1% (1·8 to 4·4)	1·0% (0·1 to 1·9)	38% (–110 to 81)	39% (–98 to 81)

DSDOM=dispensateur de soins à domiciles. PECADOM+=*Prise en Charge à Domicile Plus*. *We estimated the intervention effect using a mixed-effects Poisson regression with village-level random intercepts and robust SEs. †Data are prevalence (95% CI). ‡Data are (1–prevalence ratio) × 100 (95% CI). §Adjusted for DSDOM at baseline, village population size of children younger than 10 years, distance from health post, and village population size in 2019. ¶Defined as village-level, microscopy-confirmed parasite prevalence of <10% (low) and ≥10% (moderate). The low category contained 23 intervention clusters and 21 control clusters. The moderate category contained seven intervention clusters and nine control clusters. Due to delays in PECADOM+ scale-up, baseline incidence was under-reported in clusters without a DSDOM, preventing prespecified analyses based on incidence thresholds (ie, <250 or ≥250 events per 1000 population). 19 (95%) of 20 clusters without a DSDOM would have been classified as low in these analyses, which would have biased subgroup effects in this category.

Table 3: **Secondary outcomes of estimated parasite prevalence**

Discussion

Our two-arm, open-label, cluster-randomised controlled trial showed that after the pre-intervention year, malaria incidence and parasite prevalence reduced in both arms, likely in part due to distribution of pyrethroid–piperonyl butoxide bednets. During the intervention year in the MDA arm, malaria incidence was reduced by 55%, microscopy-confirmed parasite prevalence by 62%, and PCR-confirmed parasite prevalence by 47%. Subgroup analyses showed reductions in incidence were observed in both low-transmission and moderate-transmission settings and in participants of any age. Consistent with other trials,[9,28,29] MDA with dihydroartemisinin–piperaquine plus single, low-dose primaquine was generally safe and well tolerated. During the post-intervention year, when villages returned to standard of care, incidence was lower in intervention villages than in control villages. However, the strength of this evidence was weak. Pre-elimination status (ie, less than 5 cases per 1000 population) was reached in only two MDA villages during the intervention year and none in the post-intervention year. Overall, our findings suggest that although MDA is effective in rapidly reducing malaria burden for a short-term reduction in transmission, its sustained effect was weak and did not accelerate areas to pre-elimination.

The direction of our estimates are consistent with a 2022 cluster-randomised controlled trial conducted in The Gambia,[29] which evaluated the effect of three MDA cycles with dihydroartemisinin–piperaquine plus ivermectin in a moderate-transmission setting across two transmission seasons. The trial showed an odds ratio of 0·78 (95% CI 0·43–1·41) regarding malaria incidence during the second transmission season and an odds ratio of 0·30 (0·16–0·59) regarding PCR-confirmed parasitaemia 2 months after the final round of MDA. Unlike our trial, The Gambia trial did not assess whether effects persisted into the post-intervention year. On the basis of our findings and a previous consensus modelling study,[23] the effects of MDA are likely transient and would eventually return to pre-MDA levels without equally aggressive follow-up measures. For MDA to accelerate malaria elimination in low-to-moderate transmission settings, it might need to be sustained for several years until malaria cases reach sufficiently low levels (ie, less than 5 cases per 1000 population), at which point more targeted interventions, such as focal MDA, could be introduced.

One potential reason we might not have observed a sustained effect of MDA could be insufficient statistical power, as the trial was designed to detect a 50% intervention effect in the follow-up year. Another possibility could be the unexpectedly high variability in baseline malaria incidence, which was differentially measured in villages without a DSDOM before the trial, potentially biasing effect estimates towards the null. Restricting our analysis to those with DSDOMs at baseline showed a slight increase in the intervention effect. The previous consensus modelling study[23] suggested that additional years of MDA or other

	Mass drug administration	Control	p value*
All participants			
Participants with any adverse event			
All cycles	260/1903 (13·7%)	152/1616 (9·4%)	<0·0001
First cycle	124/619 (20·0%)	93/569 (16·3%)	0·10
Second cycle	94/628 (15·0%)	51/563 (9·1%)	0·0018
Third cycle	42/656 (6·4%)	8/484 (1·7%)	<0·0001
Frequency of adverse events			
All cycles	498	310	..
First cycle	229	175	..
Second cycle	181	119	..
Third cycle	88	16	..
Most common adverse events			
Gastrointestinal issues†	205/498 (41·2%)	144/310 (46·5%)	0·16
Fever	113/498 (22·7%)	109/310 (35·2%)	0·0001
Headache	59/498 (11·8%)	20/310 (6·5%)	0·017
Drowsiness	26/498 (5·2%)	8/310 (2·6%)	0·10
Other‡	95/498 (19·1%)	29/310 (9·4%)	0·0001
Severity of adverse events			
Mild	319/498 (64·1%)	178/310 (57·4%)	0·059
Moderate	164/498 (32·9%)	118/310 (38·1%)	0·14
Severe	15/498 (3·0%)	14/310 (4·5%)	0·26
Any serious adverse event	0/498	0/310	..
Children younger than 10 years			
Participants with any adverse event			
All cycles	85/841 (10·1%)	145/1544 (9·4%)	0·57
First cycle	36/259 (13·9%)	90/547 (16·5%)	0·35
Second cycle	33/271 (12·2%)	47/529 (8·9%)	0·14
Third cycle	16/311 (5·1%)	8/468 (1·7%)	0·0066
Frequency of adverse events			
All cycles	176	296	..
First cycle	68	170	..
Second cycle	67	110	..
Third cycle	41	16	..
Most common adverse events			
Gastrointestinal issues†	87/176 (49·4%)	136/296 (45·9%)	0·52
Fever	50/176 (28·4%)	106/296 (35·8%)	0·12
Headache	10/176 (5·7%)	19/296 (6·4%)	0·90
Drowsiness	2/176 (1·1%)	8/296 (2·7%)	0·33
Other‡	27/176 (15·3%)	27/296 (9·1%)	0·0057
Severity of adverse events			
Mild	102/176 (58·0%)	169/296 (57·1%)	0·86
Moderate	69/176 (39·2%)	115/296 (38·9%)	0·94
Severe	5/176 (2·8%)	12/296 (4·1%)	0·49
Any serious adverse events	0/176	0/296	..

Data are n or n/N (%), unless otherwise specified. *Computed with χ^2 test or Fisher's exact test if frequency of any cell value was <5. †Defined as nausea, vomiting, diarrhoea, abdominal pain, or loss of appetite. ‡Other was dizziness, cough, skin rashes, pruritus, jaundice, muscle and joint pain, convulsions, and influenza-like illness.

Table 4: **Safety outcomes monitored via active surveillance**

transmission-reducing measures are needed to maintain or further reduce transmission. We were unable to secure funding for additional intervention years, reflecting the challenges that programmes might have in securing sustained funding to avoid rebound and effectively drive elimination.

Our incidence data suggest that neither SMC or MDA were optimally timed. Had both campaigns started 1 month later and been extended to four cycles, more of the transmission season would have been covered, potentially enhancing the effectiveness of both campaigns. The suboptimal delivery of MDA might also partly explain its weak sustained effect in the post-intervention year, as it likely resulted in incomplete clearance of the transmission reservoir.

Our trial had several strengths, including rigorous safety monitoring. By the final MDA cycle, 60% of villages achieved the WHO target of at least 80% coverage[6] for all three doses, despite the COVID-19 pandemic. High intervention coverage was likely attributable to community acceptance of SMC, support from key administrative and health authorities, and repeated community-sensitisation campaigns. However, absences were common during the campaign, especially among adolescents and young adults, who often go undetected but contribute substantially to transmission.[30] To further sustain MDA gains, future campaigns should consider additional strategies to reach these groups.

Beyond the potential underpowering to detect sustained effects, our trial had other limitations. First, the trial was open-label and not placebo-controlled, which could explain the higher number of adverse events in the intervention arm among participants aged 10 years or older who do not routinely receive chemoprevention. However, this likely did not bias our malaria outcomes, which were supported by diagnostic methods. Second, the superior effect of MDA over SMC in children younger than 10 years should be interpreted with caution, as SMC was not optimally timed to align with the transmission season. Third, due to budget constraints, we were unable to conduct a survey in the post-intervention year, limiting our ability to understand MDA effects on parasite prevalence during this time. Fourth, our trial was likely underpowered to detect subgroup effects. However, effect estimates were consistent across low-transmission and moderate-transmission settings with highly overlapping confidence intervals, suggesting that differences were likely minimal. Finally, the trial design did not permit separate estimation of the effect of adding single, low-dose primaquine.

Our findings might not be generalisable to most settings using SMC where the malaria burden is mostly moderate to high. However, when these settings reach low-to-moderate malaria transmission and coverage of standard malaria-control interventions is high, MDA with dihydroartemisinin–piperaquine plus single, low-dose primaquine could safely and rapidly reduce transmission. Effects are unlikely to be sustained after discontinuation, and sustained funding for additional years of transmission-reducing interventions will be required to accelerate towards and achieve elimination.

For the **Vectorlink** see https://pmivectorlink.org/

Contributors

JH conceptualised the trial and wrote the first draft of the protocol. E-hKCB, MER, ST, ID, ABG, JT, AB, RG, FB, KS-R, and JLN contributed to the protocol and approved the final version. E-hKCB, AD, TG, AS, ST, SG, ID, ACL, ED, OGB, and JLN implemented the trial. E-hKCB, MER, AD, TG, ABG, TK, MH, EE, RG, DS, FB, KS-R, MSH, and JLN oversaw the trial. ACL conducted laboratory analysis of samples. E-hKCB, AS, AF, MER, and XW had full access to and verified data. MSH, PM, AF, MER, and AB developed the statistical analysis plan. AF analysed data with input from XW, AS, E-hKCB, and MER. E-hKCB, MER, AF, XW, PM, AB, JH, KS-R, MSH, and JLN interpreted the results. E-hKCB, MER, MSH, and JLN wrote the first draft of the manuscript with input from AF, PM, JH, and KS-R. All authors reviewed and approved the final manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

MER is funded by the Eunice Kennedy Shriver National Institute Of Child Health & Human Development of the US National Institutes of Health (K99HD111572). JH, KS-R, and ABG receive or have received salary support and travel expenses from the US President's Malaria Initiative. RG has received salary support from Unitaid, consultancy fees from Population Services International and Pelumbra, and honoraria from the University of Cape Town. All other authors declare no competing interests.

Data sharing

De-identified individual participant data and corresponding data dictionaries are available with publication on reasonable request to the corresponding author and require approval from the principal investigator (JLN) via a data sharing agreement; a description of study objectives will be needed before requests are approved. The statistical analysis plan is available (appendix pp 72–107).

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