

# Effect of population-wide repeated dihydroartemisinin–piperazine mass drug administration in Ghana: a cluster-randomised trial

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## Research Article

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# Abstract

## Background

Persistent asymptomatic malaria infections remain a major obstacle to malaria elimination in sub-Saharan Africa by sustaining transmission and contributing to malaria-associated anaemia despite widespread implementation of vector control and case management interventions. We evaluated the effectiveness of repeated community-wide mass drug administration (MDA) with dihydroartemisinin–piperaquine (DHAP) in reducing malaria parasite prevalence and improving haemoglobin outcomes in a moderate-to-high transmission setting in Ghana.

## Methods

We conducted an open-label, two-arm cluster-randomised controlled trial involving 18 communities (nine intervention and nine control clusters) in the Pokrom sub-district of Ghana between November 2023 and November 2024. Intervention communities received five rounds of community-wide DHAP-based MDA, while control communities received standard malaria prevention and case management. Cross-sectional household surveys were conducted at baseline ( $n = 1,785$ ) and endline ( $n = 1,878$ ). The primary outcome was cluster-level prevalence of rapid diagnostic test (RDT)-confirmed malaria infection at endline. Secondary outcomes included haemoglobin concentration, anaemia prevalence, and reinfection risk. Analyses followed the intention-to-treat principle using mixed-effects Poisson regression models with robust standard errors to account for clustering and were adjusted for baseline malaria status, age, sex, and insecticide-treated net use.

## Results

Baseline demographic and epidemiological characteristics were comparable between study arms. At endline, RDT-confirmed malaria prevalence was substantially lower in intervention than in control communities (1.5% [15/976] vs 28.0% [236/902]), representing a 94% relative reduction (adjusted prevalence ratio [aPR] 0.07, 95% confidence interval [CI] 0.02–0.10;  $p < 0.001$ ). Protective effects were observed in both children and adults ( $p < 0.001$ ). Reinfection risk was significantly lower in intervention communities (PR 0.052, 95% CI 0.046–0.061;  $p < 0.001$ ). Mean haemoglobin concentration increased by 0.74 g/dL (95% CI 0.51–1.00), with the greatest improvement among participants in the lowest baseline haemoglobin quartile. Anaemia prevalence declined substantially, and no cases of severe anaemia were detected in intervention communities at endline. No serious adverse events related to MDA were reported.

## Conclusions

Repeated, high-coverage DHAP-based mass drug administration substantially reduced malaria parasite prevalence, lowered reinfection risk, and improved haemoglobin and anaemia outcomes in a moderate-to-high transmission setting. These findings support the integration of structured, high-coverage MDA into comprehensive malaria elimination programmes in settings where asymptomatic infections continue to sustain transmission.

## Background

Malaria remains one of the leading causes of morbidity and mortality in sub-Saharan Africa, with persistent transmission driven by both symptomatic and asymptomatic infections despite substantial gains from vector control and case management strategies [1, 2]. In 2024, the WHO estimated that global progress has stalled, with high-burden countries continuing to account for the majority of malaria cases and deaths, underscoring the need for intensified and context-specific elimination strategies [3–6].

A growing body of evidence indicates that persistent transmission is increasingly sustained by asymptomatic and sub-microscopic *Plasmodium falciparum* infections, which constitute a large but largely undetected parasite reservoir [7–9]. Individuals with asymptomatic infections frequently harbour transmissible parasites without seeking treatment because they lack clinical symptoms. Consequently, these infections are rarely detected through routine case management, allowing continued transmission within communities despite widespread implementation of conventional malaria control measures [10–12].

Current malaria control strategies—including insecticide-treated nets (ITNs), indoor residual spraying (IRS), prompt diagnosis and treatment with artemisinin-based combination therapies, intermittent preventive treatment (IPT), seasonal malaria chemoprevention (SMC), and test–treat–track (TTT) approaches—have substantially reduced malaria burden across endemic regions [3, 13–17]. In Ghana, these interventions have contributed to important gains in malaria control over the past decade [18–20]. Nevertheless, in moderate- and high-transmission settings, these approaches alone are often insufficient to interrupt transmission because they primarily target symptomatic infections and fail to adequately address the extensive reservoir of asymptomatic and low-density parasitaemia [9, 21, 22]. This persistent parasite reservoir remains a major barrier to achieving malaria elimination.

Mass drug administration (MDA), defined as the administration of a full therapeutic course of antimalarial treatment to an entire population irrespective of infection status, has re-emerged as a promising complementary intervention for accelerating malaria control and elimination [21, 23–25]. By simultaneously clearing symptomatic, asymptomatic, and sub-microscopic infections, MDA can rapidly reduce the human parasite reservoir and potentially interrupt transmission. Although early large-scale programmes, including the Garki Project, highlighted the difficulty of sustaining malaria interruption in high-transmission settings [26], more recent studies from Africa have shown that well-implemented, high-coverage MDA can substantially reduce malaria prevalence and transmission intensity [27–29]. Emerging evidence further suggests that repeated treatment rounds, high community participation, and integration with existing vector control interventions are essential for achieving sustained epidemiological impact [24, 30, 31].

In Ghana, community-based malaria control strategies such as mass testing, treatment, and tracking (MTTT) have demonstrated reductions in malaria prevalence and asymptomatic parasitaemia [32, 33]. However, the effectiveness of these approaches is constrained by the limited sensitivity of rapid diagnostic tests (RDTs), which fail to detect many low-density and sub-microscopic infections that continue to sustain transmission [33–35]. Unlike targeted testing strategies, MDA provides presumptive treatment to all eligible community members regardless of infection status, thereby overcoming diagnostic limitations and offering a more comprehensive strategy for reducing the parasite reservoir [23, 25]. Despite encouraging findings from previous MDA trials, important uncertainties remain regarding the durability of transmission reduction following repeated treatment rounds, the risk of reinfection and transmission rebound, and the broader public health benefits of sustained community-wide implementation [27, 30].

Beyond reducing parasite prevalence, malaria control interventions may also improve haematological health. Malaria is a major contributor to anaemia through haemolysis, ineffective erythropoiesis, and chronic inflammation, particularly among young children living in endemic settings [36, 37]. Clearance of malaria parasitaemia has been associated with improvements in haemoglobin concentration; however, relatively few community-wide MDA studies have simultaneously evaluated malaria transmission and population-level haematological outcomes [38, 39]. Generating evidence on both epidemiological and clinical benefits is essential for understanding the broader value of MDA as a public health intervention.

To address these gaps, we conducted an open-label, cluster-randomised controlled trial in Ghana to evaluate repeated community-wide mass drug administration with dihydroartemisinin–piperaquine (DHAP) in a moderate-to-high transmission setting. We assessed its impact on parasite prevalence, anaemia, haemoglobin concentration, and reinfection across age groups. We hypothesised that repeated high-coverage DHAP-based MDA would reduce the community parasite reservoir, lower reinfection risk, improve haemoglobin concentration, and decrease malaria-associated anaemia compared with standard control interventions.

## Methods

### Study design and setting

We conducted a two-arm, open-labelled, cluster-randomised controlled trial in a moderate-to-high malaria transmission area, Pokrom sub district in the Eastern Region of Ghana from November 2023 to November 2024. Each community represented a cluster. This study was designed in collaboration with the NMEP, the Municipal Directorate and the communities. The study was designed to compare the baseline to endline evaluation findings following the interventions. Eighteen geographically distinct clusters were randomly assigned (1:1) to intervention (MDA) or control (standard care), with 9 clusters per arm. Clusters were defined to minimise contamination and represented discrete village populations. The study spanned approximately 12 months, covering both dry and rainy transmission seasons. The intervention clusters included Pokrom/Nsaba, Yaw Duodu/Kwesikrom, Amamfrom, Attakrom, Dumpong, Kwame Nrow, Kwesi Dei, Nkumkrom and Obengkrom while the control clusters included Aburi Amamfrom, Agynoa, Akwakupong, Apantem, Kwamekrom, Mariakrom, Oboadaka, Obodan/Alata and Pepewani.

The Pokrom sub district which is one of five sub-districts in the Akwapim south district health directorate (DHD) in the Eastern region of Ghana. The Akwapim south district lies within the semi-equatorial climatic region, and experiences two rainfall seasons in a year, with an average rainfall of 125cm to 200cm. The first rainy season begins from May to June with the heaviest rainfall in June, whilst the second rainy season begins from September to October. According to the Ghana Statistical Service (GSS), the average household size in the Akwapim South district is estimated to be 4.0 whilst the average number of households per house or compound is estimated to be 1.6 [40]. The Pokrom sub district has an estimated population of 13,931 inhabitants with a malaria test positivity rate of 87%.

## Participant recruitment and household enumeration

### Community engagement, and enrolment strategy

Participant recruitment was conducted at the community and household levels following extensive engagement with local leaders and stakeholders. Prior to study initiation, community entry meetings were held to explain the

study objectives, procedures, potential risks, and benefits. Community health volunteers (CHV) identified by the community were trained on household enumeration procedures. This was to make the volunteers familiar with the holds as they were part of the team to implement the interventions. Written informed consent was obtained from the head of each household before household recruitment and participant enrolment commenced.

## **Household enumeration**

Each study community was demarcated into neighbourhoods to facilitate systematic enumeration. A baseline household census was conducted in all clusters, during which all households were listed and assigned a unique identification code. This code linked each individual participant to their household and community, enabling longitudinal tracking across survey rounds. All consenting household members were registered during the census to establish a comprehensive community register. Recruitment was conducted at the household level through visits by trained field workers, who recorded demographic information and obtained consent.

## **Human Ethics Approval**

The study protocol was reviewed and approved by the Ethics Review Board of the Noguchi Memorial Institute for Medical Research, University of Ghana (Reference No. 068/19–20). Community permission to conduct the study was obtained from local leaders before participant recruitment.

## **Consent to Participate declaration**

Written informed consent was obtained from all adult participants ( $\geq 18$  years) prior to enrolment. For participants younger than 18 years, written informed consent was obtained from a parent or legal guardian, and written assent was obtained from children aged 12–17 years. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments [41].

## **Eligibility criteria**

### **Inclusion criteria**

All permanent residents in selected clusters were eligible for participation irrespective of age ( $\geq 3$  months) or sex. Individuals were eligible if they were aged  $\geq 3$  months and intended to reside in the study area for the duration of the study. Individuals temporarily present in the community during MDA rounds were also eligible to receive the intervention, provided they consented.

### **Exclusion criteria**

Individuals were excluded from enrolment if they had a known hypersensitivity to study medications, a life-threatening illness requiring referral at the time of recruitment or declined consent. Pregnant women were eligible for participation in survey activities, including malaria testing and follow-up, but were excluded from receiving study medications. Pregnant women in the district are routinely monitored through antenatal clinics in the health facilities.

# Recruitment outcome

All eligible and consenting individuals identified during the household census were enrolled into the study cohort. This approach enabled the inclusion of a representative population across all age groups and supported cluster-level analyses of malaria outcomes.

## Randomisation and masking

Clusters were randomised in a 1:1 ratio to intervention or control arms using a computer-generated sequence in R by an independent statistician. Simple randomisation without stratification was used. Allocation was performed at the cluster level prior to participant enrolment. Allocation concealment was maintained until clusters were assigned, after which implementation teams were informed due to the nature of the intervention.

## Procedures

Community sensitisation activities were conducted prior to each MDA round, and participation rates (coverage) were documented for each round at the cluster level. Intervention clusters received five rounds of community-wide MDA with DHAP, administered at bimonthly intervals in accordance with national malaria treatment guidelines. The dosing regimen for DHAP was administered once daily for three consecutive days and stratified by age and corresponding weight bands to ensure appropriate therapeutic exposure. Infants aged 6–11 months received one tablet containing 20 mg dihydroartemisinin and 160 mg piperaquine daily, while children aged 1–6 years were given one tablet of 40 mg/320 mg daily. For older children aged 7–13 years, the dose was increased to two tablets (60 mg/480 mg total daily dose), and adolescents aged 14–17 years received two tablets (80 mg/640 mg) daily. Adults aged 18 years and above were administered a higher dose of two and a half tablets (80 mg/640 mg) daily, also once daily for three days. This weight- and age-based dosing approach aligns with standard treatment guidelines to optimise efficacy while maintaining safety across all population groups.

The first dose of treatment was directly observed by community health volunteers (CHVs) who live in the same community moved from door-to-door by. Participants were advised to take each DHAP dose 3 hours after or before meals. Following each dose, participants were observed for 30 minutes to assess immediate tolerability; episodes of vomiting and the need for re-dosing were documented. Participants who vomited a replacement dose were not re-treated and were referred to the nearest health facility where necessary. Adherence to treatment was assessed through follow-up visits conducted by the CHVs on days 1, 2, 3, and 7 after initiation of each MDA round. Adherence indicators included completion of the full 3-day treatment course and attendance at follow-up visits. To ensure that the drugs are being taken, the CHVs asked to see the drug package. Adverse events were actively monitored during follow-up and recorded using standardised forms on days 1, 2, 3, and 7. Severe adverse events were referred to the nearest health facility for appropriate care.

Clusters allocated to the control arm did not receive MDA and continued to receive routine malaria prevention and case management (standard of care) in accordance with national guidelines, including access to malaria diagnosis using rapid diagnostic tests (RDTs), treatment with artemisinin-based combination therapy for confirmed cases, and promotion of insecticide-treated net (ITN) use.

To evaluate the impact of the intervention, cross-sectional household surveys were conducted at baseline (November 2023) and endline (November 2024), in both intervention and control clusters. In the intervention clusters, predefined follow-up timepoints, cross-sectional household surveys were also conducted before each intervention from December 2023 to August 2024. While entire populations were targeted in the intervention

clusters during household surveys, only 100 participants per cluster were randomly selected using the household registers during baseline and endline surveys. Data collected included demographic characteristics, malaria status, Hb status, and self-reported ITN use (previous night), self-reported febrile illness (not presented). Post-MDA clusters in both study arms continued to receive the standard of care through the health facilities in the study site while team surveillance.

## Data collection

Following informed consent, capillary blood samples were obtained via finger prick from all participants. Malaria infection was assessed on-site using HRP2-based RDTs in accordance with national guidelines, and individuals testing positive were managed per standard treatment protocols. In addition, approximately two drops of blood were collected onto filter paper to prepare dried blood spots (DBS) for downstream molecular analyses. The DBS were air-dried, individually packaged in sealed bags containing desiccant, and transported to the Epidemiology Department at the Noguchi Memorial Institute for Medical Research, where they were stored under appropriate conditions until processing.

Haemoglobin concentration was measured among randomly selected children aged  $\leq 15$  years using a portable automated haemoglobinometer (HemoCue®), calibrated daily according to manufacturer specifications. Anaemia was defined as haemoglobin (Hb)  $< 10$  g/dL, while severe anaemia was defined as Hb  $< 7$  g/dL. Participants identified with severe anaemia were referred to the Pokrom Health Centre for clinical evaluation and management. Structured questionnaires were administered at the household level by trained field workers to collect data on reported malaria illness (within the preceding two weeks), treatment-seeking behaviour, and malaria prevention practices, including insecticide-treated net (ITN) use. Bimonthly cross-sectional surveys were conducted over time in the intervention clusters. A comprehensive community register was used to ensure consistent participant tracking and to monitor survey coverage across all rounds.

## Outcomes

The primary outcome was cluster-level prevalence of RDT-confirmed malaria infection at endline. Secondary outcomes included temporal changes in parasite prevalence across rounds, age-stratified prevalence ( $\leq 15$  years vs  $> 15$  years), haemoglobin concentration, prevalence of anaemia, and reinfection risk (new RDT positivity at endline among those negative at baseline).

## Sample size and power calculation

Sample size and power were determined for a two-arm cluster-randomized trial evaluating the effect of the intervention on malaria prevalence. Calculations assumed a baseline prevalence of 25% in the control arm and targeted relative reductions of 50–70% in the intervention arm. The design specified nine clusters (communities) per arm, with an average cluster size ranging from 200 to 600 individuals.

Power was estimated using simulation based on a cluster-level one-sided  $t$ -test with a significance level of  $\alpha = 0.025$ , providing a conservative assessment of the ability to detect a reduction in prevalence. A range of intra-cluster correlation coefficients (ICC = 0.05–0.15) was explored to reflect plausible levels of within-cluster correlation.

Under a conservative ICC of 0.10, the study achieves  $> 90\%$  power to detect a 60% relative reduction in malaria prevalence with nine clusters per arm. At lower ICC values ( $\approx 0.05$ ), power exceeds 95% across all effect sizes considered, including a 50% reduction. As ICC increases to 0.15, power declines, particularly for smaller effect

sizes ( $\approx 50\text{--}55\%$  power for a 50% reduction), while remaining acceptable for larger reductions ( $\approx 75\%$  for 60% reduction and  $> 90\%$  for 70% reduction) (Fig. 1). These estimates indicate that the proposed design was sufficiently powered to detect moderate-to-large intervention effects ( $\geq 60\%$  reduction) under realistic assumptions, while maintaining robustness across a range of ICC values and cluster sizes.

## Statistical analysis

All analyses were conducted according to the intention-to-treat principle, whereby participants were analysed according to the clusters to which they were originally assigned, irrespective of participation in intervention rounds. Clustering at the community level was accounted for using mixed-effects regression models with random intercepts for clusters.

The primary outcome, defined as RDT-confirmed malaria infection (binary outcome), was analysed using mixed-effects Poisson regression models with robust standard errors to estimate prevalence rate ratios (PRRs) and corresponding 95% CI. PRRs were obtained by exponentiating model coefficients, with CI calculated using the Wald method on the log scale. Models were adjusted for prespecified covariates, including age, sex, and baseline insecticide-treated net (ITN) use.

Haemoglobin concentration (g/dL) was initially analysed as a continuous variable to assess the distribution pattern based on descriptive statistics and then employed to determine anaemia status as normal ( $\text{Hb} \geq 10$  g/dL), moderate ( $7 \leq \text{Hb} < 10$  g/dL), severe anaemia ( $\text{Hb} < 7$  g/dL), and any anaemia ( $\text{Hb} < 10$  g/dL). Associations between malaria infection and anaemia at the community level were assessed using Poisson regression models incorporating an offset for community population size.

Missing data were handled using a complete-case approach. For the primary outcome, individuals without RDT results were excluded from both descriptive analyses and generalised linear models. For secondary haemoglobin outcomes, analyses were restricted to participants aged 15 years or younger with available haemoglobin measurements. No imputation was performed, and missingness was assumed to be independent of the outcome conditional on observed covariates. Sensitivity analyses using mixed-effects logistic regression, including alternative missing data assumptions and intra-cluster correlation specifications, were performed to evaluate the robustness of the primary results.

Prespecified subgroup analyses were conducted by age group (entire population,  $\leq 5$  years, and 6–15 years). Adjusted models included baseline malaria infection, baseline anaemia status, and baseline ITN use. All statistical tests were two-sided, with  $p < 0.05$  considered statistically significant. Statistical analyses and data visualisation were performed using R (version 4.4.2) [42].

## Results

A total of 18 clusters were assessed and randomized equally to intervention ( $n = 9$  with a  $n$  estimated population of 6000) and control ( $n = 9$  with a population of 3000) arms, with all clusters receiving their allocated assignment and none lost to follow-up (Fig. 2). At baseline, 1,785 individuals were enrolled across clusters (intervention:  $n = 933$ ; control:  $n = 852$ ), increasing to 1,878 at endline (intervention:  $n = 976$ ; control:  $n = 902$ ), indicating stable and comparable populations over time. Five rounds of mass drug administration (MDA) were implemented in the intervention arm only. Participation increased from 4,117 individuals in intervention 1 to 4,253 in intervention 2, followed by a marked rise in intervention 3 (5,701) and intervention 4 (5,927), and remained high in intervention 5

(5,875), demonstrating rapid scale-up and sustained high coverage (Fig. 5). The control arm did not receive MDA and maintained a stable cohort throughout the study period.

Baseline demographic characteristics were well balanced between arms (Table 1). The mean number of participants sampled per cluster was approximately 99 at baseline and 104 at endline, with comparable cluster sizes between groups. Median cluster-level age was similar in intervention and control clusters (20 years in both arms;  $p = 0.825$ ), and age distributions were comparable, with similar proportions of children  $\leq 15$  years (44.3% vs. 43.7%) and adults  $> 15$  years (55.7% vs. 56.3%) in control and intervention arms, respectively ( $p = 0.86$ ) (Fig. 3). These findings confirm baseline comparability prior to intervention implementation.

**Table 1:** The description of the study population at baseline between Control arm and Intervention arms at individual and cluster level in a Mass drug Administration (MDA) trial

| Group                                                           | CLUSTER LEVEL     |                    |                         |                | INDIVIDUAL LEVEL     |                    |                         |                |
|-----------------------------------------------------------------|-------------------|--------------------|-------------------------|----------------|----------------------|--------------------|-------------------------|----------------|
|                                                                 | Characteristic    | Control<br>(n = 9) | Intervention<br>(n = 9) | p <sup>1</sup> | Overall<br>N = 1,785 | Control<br>N = 852 | Intervention<br>N = 933 | p <sup>1</sup> |
| Overall                                                         | Age, median (IQR) | 20<br>(19,23)      | 20<br>(17, 22)          | 0.825          | 18<br>(10, 40)       | 18<br>(9, 38)      | 18<br>(9, 40)           | 0.09           |
|                                                                 | Age category, (%) |                    |                         | 0.86           |                      |                    |                         | 0.8            |
|                                                                 | ≤ 15 years        | 44.3               | 43.7                    |                | 744<br>(42)          | 364<br>(44)        | 397(43)                 |                |
|                                                                 | > 15 years        | 55.7               | 56.3                    |                | 1,026<br>(58)        | 458<br>(56)        | 516 (57)                |                |
|                                                                 | Sex, (%)          |                    |                         | 0.480          |                      |                    |                         | 0.4            |
|                                                                 | female            | 57.7               | 55.8                    |                | 1,011<br>(57)        | 492<br>(58)        | 518 (56)                |                |
|                                                                 | male              | 43.3               | 44.2                    |                | 771<br>(43)          | 359<br>(42)        | 412 (44)                |                |
|                                                                 | ITN use, (%)      | 21.4               | 31.5%                   | 0.376          | 470<br>(26)          | 181<br>(21)        | 289 (31)                | < 0.001        |
|                                                                 | RDT, n (%)        | 25.8%              | 28.8%                   | 0.377          | 490<br>(27)          | 223<br>(26)        | 267 (29)                | 0.3            |
| ≤ 15 Years                                                      | Age, median (IQR) | 8.11<br>(8,9)      | 8.17<br>(8,9)           | 0.85           | 8.0<br>(3.0, 11.0)   | 8.0<br>(3.0, 11.0) | 7.0<br>(3.0, 11.0)      | 0.9            |
|                                                                 | Sex, n (%)        |                    |                         | 0.54           |                      |                    |                         | 0.4            |
|                                                                 | female            | 54.5               | 50                      |                | 392<br>(53)          | 192<br>(54)        | 200 (52)                |                |
|                                                                 | male              | 45.5               | 50                      |                | 351<br>(47)          | 163<br>(46)        | 188 (48)                |                |
|                                                                 | ITN use, n (%)    | 21.9               | 32.0                    | 0.37           | 208<br>(28)          | 79 (22)            | 129 (33)                | 0.004          |
|                                                                 | RDT, n (%)        | 32.5               | 31.8                    | 0.9            | 248<br>(33)          | 124<br>(35)        | 124 (32)                | 0.5            |
| > 15 Years                                                      | Age, median (IQR) | 35.1<br>(32,40)    | 36.7<br>(35,40)         | 0.59           | 35<br>(23, 50)       | 34<br>(23, 49)     | 35<br>(23, 50)          | 0.5            |
|                                                                 | Sex, n (%)        |                    |                         | 0.72           |                      |                    |                         | 0.6            |
| <sup>1</sup> Wilcoxon rank sum test; Pearson's Chi-squared test |                   |                    |                         |                |                      |                    |                         |                |

| Group                                                           | CLUSTER LEVEL  |                    |                         |                | INDIVIDUAL LEVEL     |                    |                         |                |
|-----------------------------------------------------------------|----------------|--------------------|-------------------------|----------------|----------------------|--------------------|-------------------------|----------------|
|                                                                 | Characteristic | Control<br>(n = 9) | Intervention<br>(n = 9) | p <sup>1</sup> | Overall<br>N = 1,785 | Control<br>N = 852 | Intervention<br>N = 933 | p <sup>1</sup> |
|                                                                 | female         | 60.1               | 60.9                    |                | 613<br>(60)          | 296<br>(61)        | 317 (59)                |                |
|                                                                 | male           | 39.9               | 39.1                    |                | 411<br>(40)          | 188<br>(39)        | 223 (41)                |                |
|                                                                 | ITN use, n (%) | 21.0               | 31.2                    | 0.42           | 262<br>(26)          | 102<br>(21)        | 160 (30)                | 0.004          |
|                                                                 | RDT, n (%)     | 20.2               | 25.6                    | 0.48           | 238<br>(23)          | 96 (20)            | 142 (26)                | 0.015          |
| <sup>1</sup> Wilcoxon rank sum test; Pearson's Chi-squared test |                |                    |                         |                |                      |                    |                         |                |

## Endline Characteristics

# Endline population and primary outcome (RDT positivity)

At endline (N = 1,878 individuals) both arms were comparable in many baseline demographic characteristics (Table 2). Cluster-level median age remained similar between arms (control 16 [IQR 16–22] versus intervention 16 [IQR 14–20]; p = 0.426). However, the most striking finding at endline was a large reduction in RDT positivity in the intervention arm compared with control. At the cluster level, RDT positivity at endline was 28.3% in control arm versus 1.6% in intervention arm (Pearson's  $\chi^2$ ; p < 0.001). Correspondingly, individual-level RDT-positivity at endline was 26.2% in control arm (n = 236/902) versus 1.5% in the intervention arm (n = 15/976) (Pearson's  $\chi^2$ ; p < 0.001). This pattern held in age-stratified analyses: among children  $\leq$  15 years, endline individual RDT-positivity was 31% in control versus 2.4% in intervention (Pearson's  $\chi^2$ ; p < 0.001), and among those > 15 years, RDT-positivity was 26% in control versus 0.8% in intervention (Pearson's  $\chi^2$ ; p < 0.001). These results indicate a very large absolute and relative reduction in point-of-care RDT positivity associated with the MDA intervention at endline.

## ITN use distributions

At endline, reported ITN use was similar between arms at the cluster level (control 29.5% versus intervention 30.4%; p = 1.00) and at the individual level (control 28% versus intervention 29%; p = 0.5), suggesting convergence in reported net use over time (Table 2).

## Cluster size/sample characteristics

Cluster size and sampling intensity were similar between arms (median cluster samples  $\sim$  9 per cluster), and the sex and age composition of sampled individuals did not differ substantially between arms at endline. The trial achieved similar numbers of individuals in intervention and control arms at both time points, reducing the risk that differences in sample size drove the observed RDT differences (Figs. 3 and 4).

Table 2

Description of study population at endline between control and intervention arms at cluster and individual levels.

| Group      | Cluster Level     |                    |                         |                | Individual Level     |                    |                         |                |
|------------|-------------------|--------------------|-------------------------|----------------|----------------------|--------------------|-------------------------|----------------|
|            | Characteristic    | Control<br>(N = 9) | Intervention<br>(N = 9) | p <sup>1</sup> | Overall<br>N = 1,878 | Control<br>N = 902 | Intervention<br>N = 976 | p <sup>1</sup> |
| Overall    | Age, median (IQR) | 16<br>(16,22)      | 16<br>(14, 20)          | 0.426          | 17<br>(8, 40)        | 19<br>(8, 39)      | 15<br>(7, 38)           | 0.09           |
|            | Age category, %   |                    |                         | 0.310          |                      |                    |                         | 0.016          |
|            | ≤ 15 years        | 44.7               | 50.3                    |                | 852<br>(46)          | 383<br>(43)        | 469 (52)                |                |
|            | > 15 years        | 55.3               | 49.7                    |                | 1,011<br>(54)        | 511<br>(57)        | 500 (52)                |                |
|            | Sex, n (%)        |                    |                         | 0.185          |                      |                    |                         | 0.3            |
|            | female            | 54.3               | 50.8                    |                | 983<br>(52)          | 485<br>(54)        | 498 (51)                |                |
|            | male              | 45.7               | 49.2                    |                | 891<br>(48)          | 416<br>(46)        | 475 (49)                |                |
|            | ITN use, %        | 29.5               | 30.4                    | 1.000          | 536<br>(29)          | 249<br>(28)        | 287 (29)                | 0.5            |
|            | RDT, %            | 28.3               | 1.6                     | < 0.001        | 251<br>(14)          | 236<br>(26.2)      | 15 (1.5)                | < 0.001        |
|            |                   |                    |                         |                |                      |                    |                         |                |
| ≤ 15 Years | Age, median (IQR) | 7.78<br>(7,9.0)    | 7.56<br>(7,8.5)         | 0.58           | 7.0<br>(4.0, 11.0)   | 7.0<br>(4.0, 11.0) | 7.0<br>(4.0, 11.0)      | 0.9            |
|            | Sex, %            |                    |                         | 0.14           |                      |                    |                         | 0.2            |
|            | female            | 51.6               | 46.5                    |                | 412<br>(49)          | 195<br>(51)        | 217 (47)                |                |
|            | male              | 49.4               | 53.5                    |                | 437<br>(51)          | 188<br>(49)        | 249 (53)                |                |
|            | ITN use, n (%)    | 29.4               | 31.1                    | 0.9            | 253<br>(30)          | 110<br>(29)        | 143 (30)                | 0.6            |
|            | RDT, n (%)        | 30.7               | 3.0                     | < 0.001        | 124<br>(15)          | 113<br>(31)        | 11 (2.4)                | < 0.001        |
| > 15 Years | Age, median (IQR) | 37.8<br>(35,40)    | 38.9<br>(37,40)         | 0.63           | 37<br>(24, 50)       | 35<br>(24, 50)     | 37<br>(24, 50)          | 0.7            |
|            | Sex, n (%)        |                    |                         | 0.86           |                      |                    |                         | 0.18           |

| Group                                                           | Cluster Level  |                    |                         |                   | Individual Level     |                    |                         |                   |
|-----------------------------------------------------------------|----------------|--------------------|-------------------------|-------------------|----------------------|--------------------|-------------------------|-------------------|
|                                                                 | Characteristic | Control<br>(N = 9) | Intervention<br>(N = 9) | p <sup>1</sup>    | Overall<br>N = 1,878 | Control<br>N = 902 | Intervention<br>N = 976 | p <sup>1</sup>    |
|                                                                 | female         | 56.4               | 55.3                    |                   | 565<br>(56)          | 286<br>(56)        | 279 (56)                |                   |
|                                                                 | male           | 43.6               | 44.7                    |                   | 446<br>(44)          | 225<br>(44)        | 221 (44)                |                   |
|                                                                 | ITN use, n (%) | 28.5               | 29.7                    | <b>0.93</b>       | 276<br>(28)          | 134<br>(27)        | 142 (28)                | 0.5               |
|                                                                 | RDT, n (%)     | 26.8               | 0.6                     | <b>&lt; 0.001</b> | 124 (1)              | 120<br>(26)        | 4 (0.8)                 | <b>&lt; 0.001</b> |
| <sup>1</sup> Wilcoxon rank sum test; Pearson's Chi-squared test |                |                    |                         |                   |                      |                    |                         |                   |

Table 2 presents the demographic and behavioural characteristics of participants at endline, disaggregated by study arm at both cluster level (N = 18 clusters; 9 per arm) and individual level (N = 1,878 participants). Cluster-level summaries show median age, age-category distributions, sex composition, insecticide-treated net (ITN) use, and rapid diagnostic test (RDT) positivity. Individual-level summaries provide corresponding proportions and median ages, stratified by age category ( $\leq 15$  years and  $> 15$  years). Statistical significance was assessed using the Wilcoxon rank-sum test for continuous variables and Pearson's  $\chi^2$  test for categorical variables. Percentage values represent row percentages unless otherwise stated. Cluster-level medians represent aggregated means per cluster. ITN use reflects self-reported use two weeks before the survey. RDT positivity reflects point-of-care test results at survey time.

### Temporal trends in malaria prevalence following repeated MDA

Malaria point prevalence at baseline was highest among children aged  $\leq 15$  years and was comparable between intervention and control communities across all age groups, indicating similar transmission intensity before implementation of MDA (Fig. 5). Baseline prevalence was 28.6% in intervention communities and 26.2% in control communities.

Graphical trend analysis demonstrated a rapid decline in malaria prevalence immediately following implementation of MDA. Prevalence in intervention communities decreased from 28.6% at baseline to 3.1% after the second MDA round. Following the third, fourth, and fifth rounds, prevalence remained below 1% (0.65%, 0.96%, and 0.68%, respectively) (Table 3), indicating sustained suppression of malaria parasitaemia throughout the intervention period. Although a slight increase was observed at endline, prevalence remained substantially lower in intervention compared with control communities during the entire follow-up period. By endline, malaria prevalence in intervention communities had declined to 1.5% (15/976), whereas prevalence in control communities remained high at 28.0% (236/852), representing a relative reduction of more than 94%. In contrast, no meaningful reduction in malaria prevalence was observed in control communities over the study period.

## Effect of MDA on malaria prevalence at endline

At endline, malaria prevalence was substantially lower in intervention compared with control communities (PR = 0.06, 95% CI 0.02–0.11;  $p < 0.001$ ). This association remained robust after adjustment for baseline malaria prevalence, insecticide-treated net (ITN) use, age, and sex (adjusted PR [aPR] = 0.07, 95% CI 0.02–0.10;  $p < 0.001$ ) (Table 3).

Participants who were malaria-negative at baseline remained substantially less likely to become infected at endline in intervention communities (1.54%) compared with control communities (28.1%). Among individuals who were RDT-positive at baseline, no infections were detected at endline in either study arm; however, the risk of reinfection was markedly lower in intervention communities (PR = 0.052, 95% CI 0.046–0.061;  $p < 0.001$ ).

Although baseline ITN coverage was higher in intervention communities, adjusted analyses showed no evidence that the observed intervention effect was confounded by ITN use. Among ITN users, the unadjusted analysis suggested a protective association (PR = 0.22, 95% CI 0.15–0.32;  $p < 0.001$ ); however, this association was attenuated after adjustment (aPR = 1.14, 95% CI 1.04–1.26;  $p = 0.62$ ).

At endline, malaria prevalence differed only marginally by sex in control communities (27.8% in males vs 23.5% in females). In intervention communities, prevalence remained low in both males (1.1%) and females (1.7%), with no significant sex-related difference observed after adjustment (aPR for females = 1.05;  $p = 0.70$ ). Collectively, these findings indicate a sustained population-level reduction in malaria prevalence associated with repeated MDA.

### **Age-stratified effects of MDA**

Age-stratified analyses demonstrated substantial reductions in RDT positivity among both children aged  $\leq 15$  years and adults aged  $> 15$  years in intervention compared with control communities. Among children aged  $\leq 15$  years, malaria prevalence at endline was 2.4% in intervention communities compared with 31.0% in control communities ( $p < 0.001$ ). Prevalence among adults aged  $> 15$  years was 0.8% in intervention communities compared with 26.0% in control communities ( $p < 0.001$ ).

Among children aged  $\leq 15$  years, malaria prevalence declined from 29.8% at baseline to 2.3% at endline in intervention communities, with a strong protective effect observed after adjustment (aPR = 0.48, 95% CI 0.41–0.56;  $p < 0.001$ ). Similarly, among adults aged  $> 15$  years, prevalence declined from 23.1% at baseline to 0.9% at endline, with comparable effect estimates (aPR = 0.48;  $p < 0.001$ ). These findings indicate that repeated MDA achieved consistent reductions in malaria prevalence across all age groups, with the greatest absolute reduction observed among children aged  $\leq 15$  years.

Table 3  
Unadjusted and adjusted prevalent ratio (PR) of malaria cases in both control and intervention arm.

| Overall, at<br>endline                    |        | Control<br>arm                | Intervention<br>arm           | PR (95%<br>CI)                    | <i>p</i> value    | aPR (95%<br>CI)                   | <i>p</i> value    |
|-------------------------------------------|--------|-------------------------------|-------------------------------|-----------------------------------|-------------------|-----------------------------------|-------------------|
|                                           |        | <b>28</b><br><b>(236/852)</b> | <b>1.5</b><br><b>(15/976)</b> | <b>0.06</b><br><b>(0.02–0.11)</b> | <b>&lt; 0.001</b> | <b>0.07</b><br><b>(0.02–0.10)</b> | <b>&lt; 0.001</b> |
| Baseline<br>malaria<br>detected<br>(%, n) | No     | 28.1<br>(236/841)             | 1.54<br>(15/976)              | Reference                         |                   | Reference                         |                   |
|                                           | Yes    | 0                             | 0                             | 0.052<br>(0.046–0.061)            | < 0.001           | 0.051<br>(0.045–0.059)            | < 0.001           |
| Baseline ITN<br>use<br>(%, n)             | No     | 28.8<br>(203/706)             | 1.4<br>(21/1483)              | Reference                         |                   | Reference                         |                   |
|                                           | Yes    | 13.2<br>(31/139)              | 2.6<br>(6/228)                | 0.22<br>(0.15–0.32)               | < 0.001           | 1.14<br>(1.04–1.26)               | 0.62              |
| Age<br>category<br>(years)                | ≤ 15   | 29.8<br>(108/362)             | 2.3<br>(20/884)               | Reference                         |                   | Reference                         |                   |
|                                           | > 15   | 23.1<br>(142/615)             | 0.9<br>(12/1395)              | 1.29<br>(0.96–1.74)               | 0.104             | 1.16<br>(0.89–1.52)               | 0.35              |
| Gender                                    | Male   | 27.8<br>(132/475)             | 1.1<br>(11/1024)              | Reference                         |                   | Reference                         |                   |
|                                           | Female | 23.5<br>(118/502)             | 1.7<br>(21/1255)              | 1.05<br>(0.82–1.33)               | 0.73              | 1.05<br>(0.85–1.31)               | 0.70              |
| ≤ 15 years<br>old                         |        | 29.8<br>(108/362)             | 2.3<br>(20/884)               | 0.24<br>(0.20–0.29)               | < 0.001           | 0.48<br>(0.41–0.56)               | < 0.001           |
| Baseline<br>malaria<br>detected<br>(%, n) | No     | 26.9<br>(21/78)               | 1.02<br>(71/98)               | Reference                         | Reference         | Reference                         | Reference         |
|                                           | Yes    | 0                             | 0                             | 0.07                              | < 0.001           | 0.07                              | < 0.001           |

<sup>1</sup>Wilcoxon rank sum test; Pearson's Chi-squared test

| Overall, at<br>endline                                          |     | Control<br>arm     | Intervention<br>arm | PR (95%<br>CI)            | p value   | aPR (95%<br>CI)         | p value   |
|-----------------------------------------------------------------|-----|--------------------|---------------------|---------------------------|-----------|-------------------------|-----------|
|                                                                 |     | 28<br>(236/852)    | 1.5<br>(15/976)     | 0.06<br>(0.02–<br>0.11)   | < 0.001   | 0.07<br>(0.02–<br>0.10) | < 0.001   |
|                                                                 |     |                    |                     | (0.06–<br>0.08)           |           | (0.07–<br>0.08)         |           |
| Baseline ITN<br>use<br>(%, n)                                   | No  | 26.9<br>(21/78)    | 1.02<br>(71/98)     | Reference                 | Reference | Reference               | Reference |
|                                                                 | Yes | 0                  | 0                   | 0.24<br>(0.16–<br>0.37)   | < 0.001   | 1.15<br>(1.03–<br>1.29) | 0.34      |
| Gender                                                          | M   | 29.7<br>(11/37)    | 0                   | Reference                 | Reference | Reference               | Reference |
|                                                                 | F   | 25<br>(10/40)      | 2.17<br>(1/46)      | 0.88<br>(0.68–<br>1.13)   | 0.33      | 0.96<br>(0.86–<br>1.07) | 0.49      |
| > 15 years<br>old                                               |     | 23.1<br>(142/615)  | 0.9<br>(12/1395)    | 0.20<br>(0.17–<br>0.23)   | < 0.001   | 0.48<br>(0.41–<br>0.56) | < 0.001   |
| Baseline malaria<br>detected<br>(%, n)                          | No  | 27.98<br>(101/361) | 0.77<br>(3/392)     | Reference                 | Reference | Reference               | Reference |
|                                                                 | Yes | 0                  | 0                   | 0.05<br>(0.047–<br>0.055) | < 0.001   | 0.07<br>(0.07–<br>0.08) | < 0.001   |
| Baseline ITN<br>use (%, n)                                      | No  | 27.98<br>(101/361) | 0.77<br>(3/392)     | Reference                 | Reference | Reference               | Reference |
|                                                                 | Yes | 0                  | 0                   | 0.28<br>(0.21–<br>0.37)   | < 0.001   | 1.15<br>(1.03–<br>1.29) | 0.33      |
| Gender                                                          | M   | 30.30<br>(50/165)  | 1.10<br>(2/181)     | Reference                 | Reference | Reference               | Reference |
|                                                                 | F   | 26.02<br>(51/196)  | 0.48<br>(1/210)     | 0.91                      | 0.18      | 0.96                    | 0.49      |
| <sup>1</sup> Wilcoxon rank sum test; Pearson's Chi-squared test |     |                    |                     |                           |           |                         |           |

| Overall, at<br>endline                                          | Control<br>arm  | Intervention<br>arm | PR (95%<br>CI)          | p value | aPR (95%<br>CI)         | p value |
|-----------------------------------------------------------------|-----------------|---------------------|-------------------------|---------|-------------------------|---------|
|                                                                 | 28<br>(236/852) | 1.5<br>(15/976)     | 0.06<br>(0.02–<br>0.11) | < 0.001 | 0.07<br>(0.02–<br>0.10) | < 0.001 |
|                                                                 |                 |                     | (0.79–<br>1.04)         |         | (0.86–<br>1.07)         |         |
| <sup>1</sup> Wilcoxon rank sum test; Pearson's Chi-squared test |                 |                     |                         |         |                         |         |

Table 3 presents unadjusted and adjusted prevalence ratios (PR, aPR) with 95% confidence intervals comparing malaria infection prevalence at endline between the intervention and control arms. Subgroup analyses were stratified by baseline malaria status, ITN use, age category, and gender. Adjusted models controlled for baseline malaria positivity, ITN use, age, and gender where appropriate. A PR < 1 indicates lower malaria prevalence in the intervention arm relative to control. P-values are two-sided. Wilcoxon rank-sum and Pearson  $\chi^2$  tests were used where applicable.

#### Haemoglobin Distribution at Baseline and Endline – (Median-Based Non-Parametric Analysis)

The haemoglobin level –a biomarker for anaemia–distribution in the baseline and endline were assessed (Fig. 6). At baseline, the distribution of haemoglobin was comparable between intervention and control arms with no significant difference. Both intervention and control arms displayed median Hb values around 10–11 g/dL, with wide dispersion and numerous observations falling below the WHO anaemia thresholds. The result further demonstrates a comparable distributional spread, indicating no evidence of systematic baseline imbalance in haemoglobin status between study arms. By endline, intervention communities exhibited a clear upward shift in the median haemoglobin concentration with the median rising to approximately 11–12 g/dL and a marked reduction in observations below 10 g/dL. In contrast, Hb values in control communities remained broadly similar to baseline, persistently skew towards lower Hb levels.

A Wilcoxon rank-sum test confirmed a significant distributional difference at endline between arms ( $p < 0.0001$ ). These median-based improvements aligned with a substantial reduction in anaemia prevalence, which declined from 50.9% in control communities to 9.23% in the intervention arm (aPR = 0.72, 95% CI: 0.64–0.80) (Fig. 7). Reductions in anaemia were consistent across age groups among individual exposed to MDA interventions  $\leq 5$  years (aPR = 0.67, 95% CI: 0.56–0.79),  $6 \leq 15$  years (aPR = 0.58, 95% CI: 0.47–0.73) (Table 4).

Table 4

Unadjusted and adjusted prevalence ratios for anaemia at endline by study arm and baseline characteristics

| Overall                           |     | Control arm       | Intervention arm  | PR (95% CI)          | p value | aPR (95% CI)        | p value |
|-----------------------------------|-----|-------------------|-------------------|----------------------|---------|---------------------|---------|
| Overall                           |     | 50.9<br>(161/316) | 9.23<br>(35/379)  | 0.62<br>(0.55–0.69)  | < 0.001 | 0.72<br>(0.64–0.80) | < 0.001 |
| Baseline anaemic (% , n)          | No  | 50.9<br>(161/316) | 9.23<br>(35/379)  | Reference            |         | Reference           |         |
|                                   | Yes | 0<br>(0/316)      | 0<br>(0/379)      | 0.25<br>(0.23–0.26)  | < 0.001 | 0.22<br>(0.20–0.23) | < 0.001 |
| Baseline malaria detected (% , n) | No  | 50.9<br>(161/316) | 9.23<br>(35/379)  | Reference            |         | Reference           |         |
|                                   | Yes | 0<br>(0/316)      | 0<br>(0/379)      | 0.71<br>(0.59–0.85)  | 0.004   | 1.55<br>(1.42–1.70) | 0.0006  |
| Baseline ITN use (% , n)          | No  | 50.9<br>(161/316) | 9.23<br>(35/379)  | Reference            |         | Reference           |         |
|                                   | Yes | 0<br>(0/316)      | 0<br>(0/379)      | 0.84<br>(0.68–1.04)  | 0.207   | 1.56<br>(1.40–1.75) | 0.003   |
| Gender                            | M   | 46.2<br>(145/314) | 46.2<br>(174/376) | Reference            |         | Reference           |         |
|                                   | F   | 53.8<br>(169/314) | 53.8<br>(202/376) | 0.884<br>(0.79–0.98) | 0.06    | 0.94<br>(0.85–1.04) | 0.354   |
| ≤5 years old                      |     | 54.9<br>(62/113)  | 9.56<br>(13/136)  | 0.56<br>(0.47–0.677) | < 0.001 | 0.67<br>(0.56–0.79) | 0.0010  |
| Baseline anaemic (% , n)          | No  | 54.9<br>(62/113)  | 9.56<br>(13/136)  | Reference            |         | Reference           |         |
|                                   | Yes | 0<br>(0/113)      | 0<br>(0/136)      | 0.26<br>(0.23–0.28)  | < 0.001 | 0.23<br>(0.21–0.26) | < 0.001 |

<sup>1</sup>Wilcoxon rank sum test; Pearson's Chi-squared test

| Overall                           |     | Control arm      | Intervention arm | PR (95% CI)         | p value | aPR (95% CI)        | p value |
|-----------------------------------|-----|------------------|------------------|---------------------|---------|---------------------|---------|
| Baseline malaria detected (% , n) | No  | 54.9<br>(62/113) | 9.56<br>(13/136) | Reference           |         | Reference           |         |
|                                   | Yes | 0<br>(0/113)     | 0<br>(0/136)     | 0.66<br>(0.48–0.90) | < 0.001 | 1.56<br>(1.32–1.84) | 0.06    |
| Baseline ITN use (% , n)          | No  | 54.9<br>(62/113) | 9.56<br>(13/136) | Reference           |         | Reference           |         |
|                                   | Yes | 0<br>(0/113)     | 0<br>(0/136)     | 0.68<br>(0.52–0.89) | 0.041   | 1.43<br>(1.24–1.65) | 0.08    |
| Gender                            | M   | 46.9<br>(53/113) | 55.6<br>(75/135) | Reference           |         | Reference           |         |
|                                   | F   | 53.1<br>(60/113) | 44.4<br>(60/135) | 0.84<br>(0.71–0.99) | 0.081   | 0.90<br>(0.77–1.1)  | 0.31    |
| 6 ≤ 15 years old                  |     | 48.8<br>(99/203) | 9.05<br>(22/243) | 0.65<br>(0.56–0.75) | < 0.001 | 0.58<br>(0.47–0.73) | 0.0203  |
| Baseline anaemic (% , n)          | No  | 48.8<br>(99/203) | 9.05<br>(22/243) | Reference           |         | Reference           |         |
|                                   | Yes | 0<br>(0/203)     | 0<br>(0/243)     | 0.24<br>(0.22–0.26) | < 0.001 | 0.21<br>(0.19–0.23) | < 0.001 |
| Baseline malaria detected (% , n) | No  | 48.8<br>(99/203) | 9.05<br>(22/243) | Reference           |         | Reference           |         |
|                                   | Yes | 0<br>(0/203)     | 0<br>(0/243)     | 0.73<br>(0.58–0.90) | 0.025   | 1.54<br>(1.37–1.72) | 0.0052  |
| Baseline ITN use (% , n)          | No  | 48.8<br>(99/203) | 9.05<br>(22/243) | Reference           |         | Reference           |         |
|                                   | Yes | 0<br>(0/203)     | 0<br>(0/243)     | 1.04<br>(0.74–1.46) | 0.85    | 1.70<br>(1.42–2.05) | 0.0106  |

<sup>1</sup>Wilcoxon rank sum test; Pearson's Chi-squared test

| Overall                                                         |   | Control arm       | Intervention arm  | PR (95% CI)         | p value | aPR (95% CI)        | p value |
|-----------------------------------------------------------------|---|-------------------|-------------------|---------------------|---------|---------------------|---------|
| Gender                                                          | M | 45.8<br>(92/201)  | 52.8<br>(127/241) | Reference           |         | Reference           |         |
|                                                                 | F | 54.2<br>(109/201) | 47.3<br>(114/241) | 0.92<br>(0.79–1.06) | 0.32    | 0.97<br>(0.85–1.09) | 0.685   |
| <sup>1</sup> Wilcoxon rank sum test; Pearson's Chi-squared test |   |                   |                   |                     |         |                     |         |

Table 4 depicts the unadjusted prevalence ratios (PR) and adjusted prevalence ratios (aPR) with 95% confidence intervals compare endline anaemia prevalence between the intervention and control arms overall and within key subgroups. Adjusted models control for baseline anaemia status, malaria infection, insecticide-treated net (ITN) use, age, and gender as appropriate for each stratum. PR < 1 indicates lower anaemia prevalence in the intervention arm relative to control. All p-values are two-sided.

No participants classified as anaemic at baseline remained anaemic at endline in the intervention arm, a pattern not observed in the control arm. Similarly, children residing in the intervention arm with malaria infections at baseline showed greater Hb gains and lower anaemia prevalence, suggesting an indirect effect of repeated parasite clearance on Hb recovery. Overall, there was a consistent downward shift in anaemia prevalence accompanied by increased haemoglobin across age groups over time.

## Change in Anaemia Severity Between Baseline and Endline

At baseline the distribution of anaemia severity in the control arm showed that 70.0% of participants were non-anaemic, 26.0% had moderate anaemia, and 4.0% had severe anaemia. Endline measurements reveal modest changes were observed. The proportion of individuals with normal haemoglobin decreased to 56.5%, whereas moderate anaemia increased slightly to 32.3%. Severe anaemia also rose from 4.0% at baseline to 11.3% at endline. These shifts indicate a worsening of anaemia status in the absence of intervention activities (Fig. 7).

In contrast, Intervention communities exposed to repeated MDA demonstrated substantial improvements in anaemia status between baseline and endline (Fig. 7). At baseline, 53.5% of participants were non-anaemic, 32.4% had moderate anaemia, and 14.1% had severe anaemia. Endline measurements revealed a marked improvement following MDA interventions. The proportion of individuals classified as non-anaemic increased sharply to 91.3%, while moderate anaemia declined to 8.7%. Notably, no cases of severe anaemia (0%) were detected at endline. This represents a substantial reduction across all levels of anaemia severity, with the most dramatic improvement observed in the elimination of severe anaemia and the large net gain in normal haemoglobin status. Together, the findings demonstrate divergent anaemia trends between the intervention and control arms. While anaemia prevalence and severity did not improve in the control arm, substantial improvements were evident in the intervention group reinforcing the potential of repeated MDA strategies to improve population-level haematological indices, likely through interrupting malaria transmission, reducing asymptomatic infections, and preventing recurrent parasitaemia. The near elimination of severe anaemia in the intervention arm is particularly noteworthy, underscoring the capacity of community-wide chemoprevention to mitigate high-risk haematological.

Anaemia prevalence among children aged < 15 years showed markedly divergent temporal trends between intervention and control communities from baseline (November 2023) to endline (November 2024) (Fig. 7). At baseline, prevalence was similarly high in both arms (approximately 45–50%). Following initiation of the intervention(A) in December 2023, the intervention arm exhibited a steady and progressive decline across successive MDA rounds. Modest reductions were observed after rounds 1 (December 2023) and 2 (February 2024), followed by a more pronounced decrease by round 3 (April 2024), when prevalence declined to ~ 30%. Further substantial reductions occurred through rounds 4 (June 2024) and 5 (August 2024), with prevalence falling to below 15%, indicating a cumulative effect of repeated MDA. By endline (November 2024), anaemia prevalence in the intervention arm reached just above 10%, corresponding to an absolute reduction of approximately 30–35 percentage points from baseline.

outcomes among vulnerable populations.

In contrast, the control arm (B) showed no sustained improvement over the same period (Fig. 7B and C). Anaemia prevalence increased gradually from approximately 45% at baseline to > 50% at endline, with minor fluctuations at intermediate time points (December 2023, February 2024, April 2024, June 2024, and August 2024), consistent with seasonal variation rather than a systematic decline.

Overall, the intervention arm demonstrated a rapid and sustained reduction in anaemia prevalence across all five MDA rounds, whereas the control arm showed a slight upward trend. By endline, the between-arm difference was substantial (approximately 35–40 percentage points), indicating a strong intervention effect. This pattern was consistent within the < 15-year subgroup and aligned with trends observed in the overall study population, supporting a robust impact of the intervention on malaria-associated anaemia.

## Adverse Events

Though many participants reported adverse event such as dizziness, headache, nausea, vomiting, stomach upset, rashes etc these were mostly transient and no severe case requiring hospitalisation was recorded in the study communities. The number of reported adverse events decreased over time.

## Discussion

### Principal findings

This cluster-randomised controlled trial demonstrated that repeated community-wide mass drug administration (MDA) with DHAP was associated with a 94% reduction in malaria parasite prevalence and substantial improvements in haemoglobin levels and anaemia compared with routine malaria control. The intervention achieved consistently significant reductions across both children and adults, indicating that repeated MDA effectively reduced the burden of asymptomatic malaria infections in the communities. These findings reinforce evidence that asymptomatic and low-density infections constitute an important reservoir sustaining malaria transmission in endemic settings and that strategies targeting the entire population can substantially reduce parasite prevalence when high intervention coverage is achieved [7–9, 24, 29–31, 43].

The cluster-randomised design strengthens causal inference by minimising contamination between study arms while evaluating the intervention under routine community conditions. The marked divergence in malaria prevalence between intervention and control communities throughout follow-up, together with the persistence of

low parasite prevalence after successive MDA rounds, suggests that repeated community-wide treatment can achieve sustained suppression of malaria infection beyond that attainable through routine malaria control alone. Although the present study was not designed to measure transmission directly, the observed reduction in asymptomatic infections is consistent with a substantial reduction in the community parasite reservoir, which is widely recognised as a major driver of continued malaria transmission in high-burden settings [7–9, 43, 44].

## **Interpretation in relation to previous studies**

Our findings are consistent with growing evidence that repeated MDA can substantially reduce malaria prevalence when implemented with high population coverage alongside existing malaria control interventions. Similar reductions have been reported from trials conducted in Zambia, The Gambia, Mozambique, Senegal and other parts of sub-Saharan Africa, although the magnitude and duration of effect have varied according to transmission intensity, intervention coverage, population movement, and local epidemiological conditions [24, 27–30, 45]. Collectively, these studies suggest that repeated MDA is likely to be most effective in geographically defined communities with stable populations where high treatment coverage can be maintained.

The findings also support the strategic direction of the World Health Organization Global Technical Strategy for Malaria, which emphasises integrated approaches targeting both symptomatic and asymptomatic malaria infections to accelerate progress towards malaria elimination [1, 46]. Rather than replacing existing interventions, repeated MDA should be considered as a complementary strategy that addresses residual parasite carriage while conventional measures, including insecticide-treated nets, prompt diagnosis and treatment, and vector control, continue to reduce human-vector contact and clinical disease. Furthermore, including a gametocidal drug such as primaquine during MDA or one round of vaccination of a suitable vaccine post-MDA could improve sustainability.

The substantial improvements in haemoglobin concentration and the marked reduction in anaemia are biologically plausible and consistent with previous studies demonstrating that effective malaria control reduces malaria-associated anaemia through sustained parasite clearance, decreased haemolysis, reduced inflammatory responses, and improves haemoglobin recovery [24, 25, 36, 47, 48]. The concurrent decline in malaria prevalence and improvement in haematological outcomes observed in this study provide additional evidence that reducing chronic and recurrent malaria infections can generate important population-level health benefits beyond reductions in parasite prevalence alone.

## **Baseline comparability and attribution of effect**

The comparable demographic characteristics and malaria prevalence observed between study arms at baseline strengthen the internal validity of the trial and increase confidence that the observed differences at endline were attributable to the intervention rather than pre-existing imbalances [49–51]. Although baseline insecticide-treated net (ITN) use was modestly higher in intervention communities, adjustment for ITN use had little influence on the estimated intervention effect, indicating that the substantial reduction in malaria prevalence was independent of differences in baseline vector control coverage. This finding is consistent with previous studies showing that while ITNs remain highly effective for preventing mosquito bites and reducing clinical malaria, they have limited impact on established asymptomatic infections [13]. Community-wide MDA therefore offers a complementary mechanism by directly clearing existing infections that would otherwise remain untreated and continue to sustain transmission [3, 7, 32, 52].

## **Impact on parasite prevalence and transmission**

The decline in parasite prevalence (RDT positivity) from approximately 28% to below 1% following repeated MDA rounds indicates near-suppression of detectable infection and substantial contraction of the parasite reservoir [27, 28]. Because MDA clears both symptomatic and asymptomatic infections, this likely reflects disruption of transmission through depletion of subclinical reservoirs [24, 53]. Achieving such low prevalence represents an important epidemiological threshold. At this level, transmission may be further reduced through integration with complementary interventions such as gametocytocidal therapy (e.g., primaquine) or vaccination [54, 55], beyond which continued surveillance is critical [21, 56].

## Population-wide impact across age groups

The observed divergence between intervention and control communities strengthens causal inference. Malaria prevalence remained stable in control clusters, consistent with broader evidence that, in the absence of intensified intervention, transmission remains relatively stable in endemic settings [3, 22]. Similar patterns of divergence between intervention and control arms have been reported in MDA trials in Africa and Asia [28, 29]. The lack of interaction between MDA and ITN use is consistent with their distinct mechanisms of action. ITNs reduce vector-human contact and clinical disease but have limited impact on established asymptomatic infections [3, 13, 17]. In contrast, MDA directly clears blood-stage parasites, including sub-microscopic infections [33, 57]. These findings support integrated malaria control strategies that combine vector control and chemotherapeutic interventions to achieve maximal impact [58–61].

## Reinfection and transmission dynamics

Reinfection risk was substantially lower in intervention clusters ( $PR \approx 0.05$ ), indicating reduced exposure to infectious vectors following depletion of the parasite reservoir. This is consistent with transmission models showing that reducing parasite prevalence at the population level decreases the probability of onward transmission [24, 62–64]. Similar reductions in reinfection following MDA have been reported in multiple settings [7, 28, 29, 65]. The significant reduction prevalence observed suggests that repeated MDA may reduce the effective reproductive number below unity, a key condition for interrupting transmission [63]. However, sustainability of this effect will likely depend on rigorous surveillance, community engagement and intervention coverage [36, 63].

Repeated administration of DHAP raises important considerations regarding antimalarial resistance. While drug pressure may select for resistant strains [66, 67], reductions in parasite population size may concurrently limit opportunities for resistance emergence and spread [52]. Continued molecular and therapeutic efficacy surveillance is therefore essential to monitor resistance dynamics in the context of repeated MDA. The absence of meaningful decline in control clusters, which remained at approximately 25–30% prevalence, further strengthens causal attribution and reduces the likelihood that these findings are explained by seasonal or secular trends [59, 67–69].

## Haemoglobin and anaemia outcomes

The temporal patterns in anaemia observed over time are consistent with the cross-sectional analyses, which demonstrated a substantial reduction in anaemia prevalence in the intervention arm, alongside a rightward shift in haemoglobin distribution and marked improvements in anaemia severity, including suppression of severe anaemia. The divergence between study arms closely parallels the decline in malaria parasitaemia observed

across successive MDA rounds, supporting the interpretation that sustained parasite clearance contributed to improved haematological outcomes.

Improvements in haemoglobin concentration and reductions in anaemia closely paralleled declines in parasite prevalence. Clearance of chronic low-density infections is known to facilitate haematological recovery and reduce anaemia burden [27, 36, 48]. Rapid improvements in anaemia after early MDA rounds are consistent with clearance of low-density infections and associated inflammatory processes [27, 70]. Seasonal increases in anaemia during the third round likely reflect rainy-season transmission dynamics typical of West Africa [48, 71–74]. Despite this fluctuation, overall anaemia prevalence declined to below 10% at endline, with improved haemoglobin concentration and reduced moderate-to-severe anaemia [75]. These findings suggest meaningful population-level health benefits. Given established links between malaria-associated anaemia and impaired cognitive development and productivity [37], these findings have important public health implications.

## Operational implications

Operationally, the sustained reductions in both parasitaemia and anaemia observed in this study indicate that high-coverage MDA is feasible when supported by effective community engagement and delivery systems [76, 77]. Achieving and maintaining high coverage is a critical determinant of MDA effectiveness, as demonstrated in both empirical and modelling studies [24, 31]. These findings support the use of MDA as a complementary strategy in settings where conventional interventions have plateaued.

Regionally, the impact of MDA has been heterogeneous, largely reflecting differences in transmission intensity, coverage achieved, and integration with complementary control strategies. Seasonal malaria chemoprevention effectively reduces clinical malaria in children but does not address the broader asymptomatic reservoir [15, 16]. Previous MDA programmes in West Africa have shown transient reductions in parasitaemia, with rebound occurring when coverage or repetition is insufficient [23, 25, 30]. In contrast, the sustained reductions observed in this study underscore the importance of repeated rounds and high operational fidelity. Unlike child-targeted strategies such as SMC, population-wide treatment likely reduced both symptomatic and asymptomatic infections, thereby disrupting onward transmission networks.

## Strengths and limitations

This study has several strengths, including its cluster-randomised design, strong baseline comparability, and consistent effects across age groups. The repeated cross-sectional design strengthens inference regarding community-level transmission dynamics. However, limitations should be considered. Reliance on RDTs may underestimate sub-microscopic infections [34, 35, 78], effects of ecological zones and seasonal variation may influence cross-sectional prevalence estimates [70, 71]. Longer-term follow-up is required to assess durability of impact, particularly in higher-transmission settings. Molecular analyses to assess resistance markers and subpatent infections are ongoing, and results will be reported separately. As with all cluster-randomised trials, residual within-cluster correlation and potential heterogeneity between clusters may influence effect estimates. Although analyses accounted for clustering, variation in baseline transmission intensity across communities cannot be fully excluded.

## Conclusion

Repeated, high-coverage mass drug administration with dihydroartemisinin–piperaquine was associated with a 94% reduction in malaria prevalence and sustained interruption of detectable malaria infection across all age groups compared with routine. These findings demonstrate that population-wide chemotherapeutic interventions can substantially reduce the parasite reservoir and interrupt transmission in endemic settings.

Beyond parasitological outcomes, MDA was associated with significant improvements in haemoglobin concentration and reductions in anaemia, highlighting important population-level health benefits. When implemented with high coverage and operational fidelity, MDA represents a powerful complementary strategy for accelerating malaria control and advancing toward elimination. Future efforts should prioritise integration of MDA with vector control, surveillance, and resistance monitoring, alongside evaluation of long-term sustainability and cost-effectiveness in national malaria control programmes.

## **Declarations**

## **Consent for publication**

Not applicable

## **Competing interest**

All authors declare no competing interest.

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## **Author Contribution**

N.I.C. led the experimental design, field work, data analysis, and wrote the first draft of the manuscript. C.E.C., N.M., O.O, C.S.A. and A.A.-N. contributed to experimental design, field work, and writing. C.A.B., G.A.A., D.O., D.T.N., M.D., K.K., E.A., N.Y.P., and K. M. contributed to field work implementation. M.D., N.H.N., B.N.A.-N., and N.M., contributed data analysis and writing. All authors reviewed the manuscript.

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# Data Availability

The dataset used and analysed during the study is available from the corresponding authors on reasonable request.

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Figures

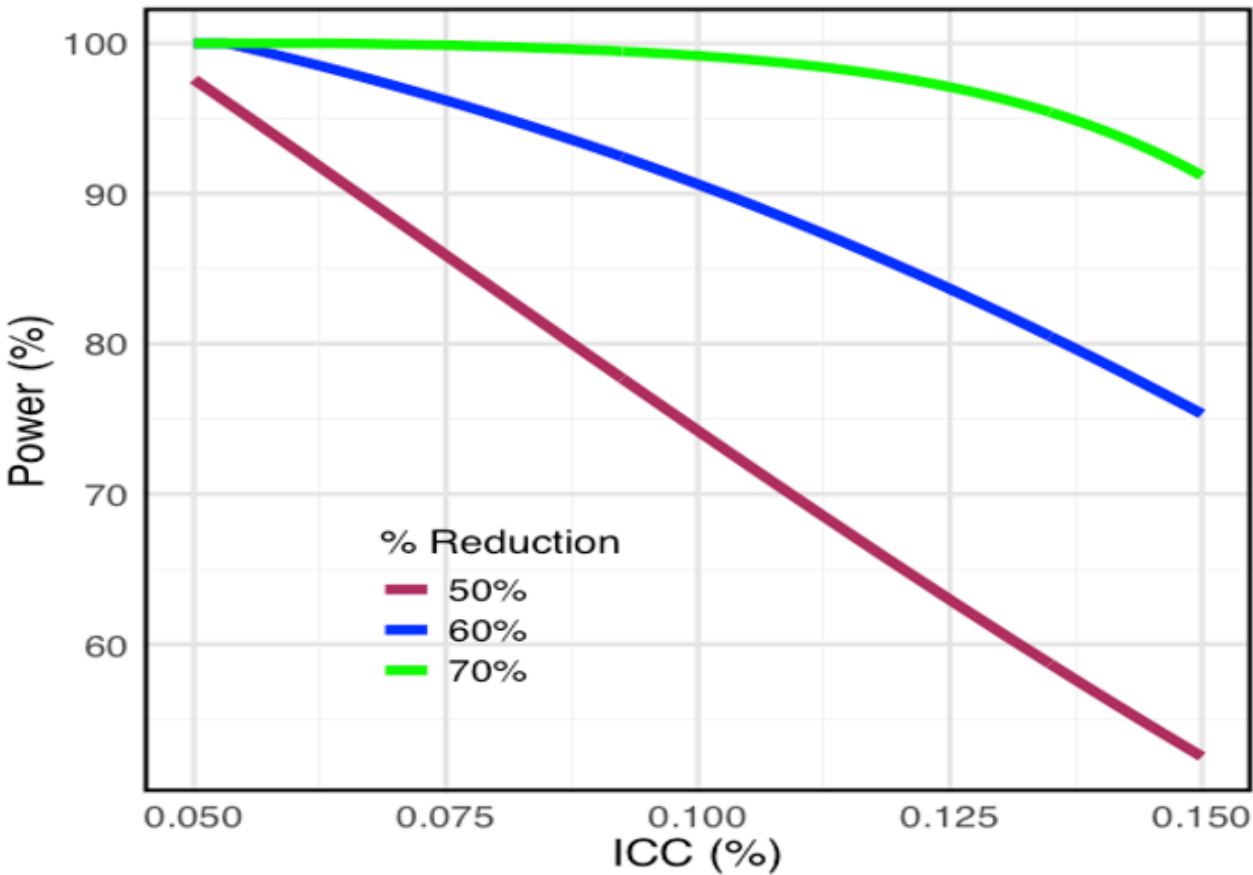


Figure 1

Power by ICC to detect a 50%-70% reduction in malaria prevalence (nine communities per arm, 25% prevalence in the control).

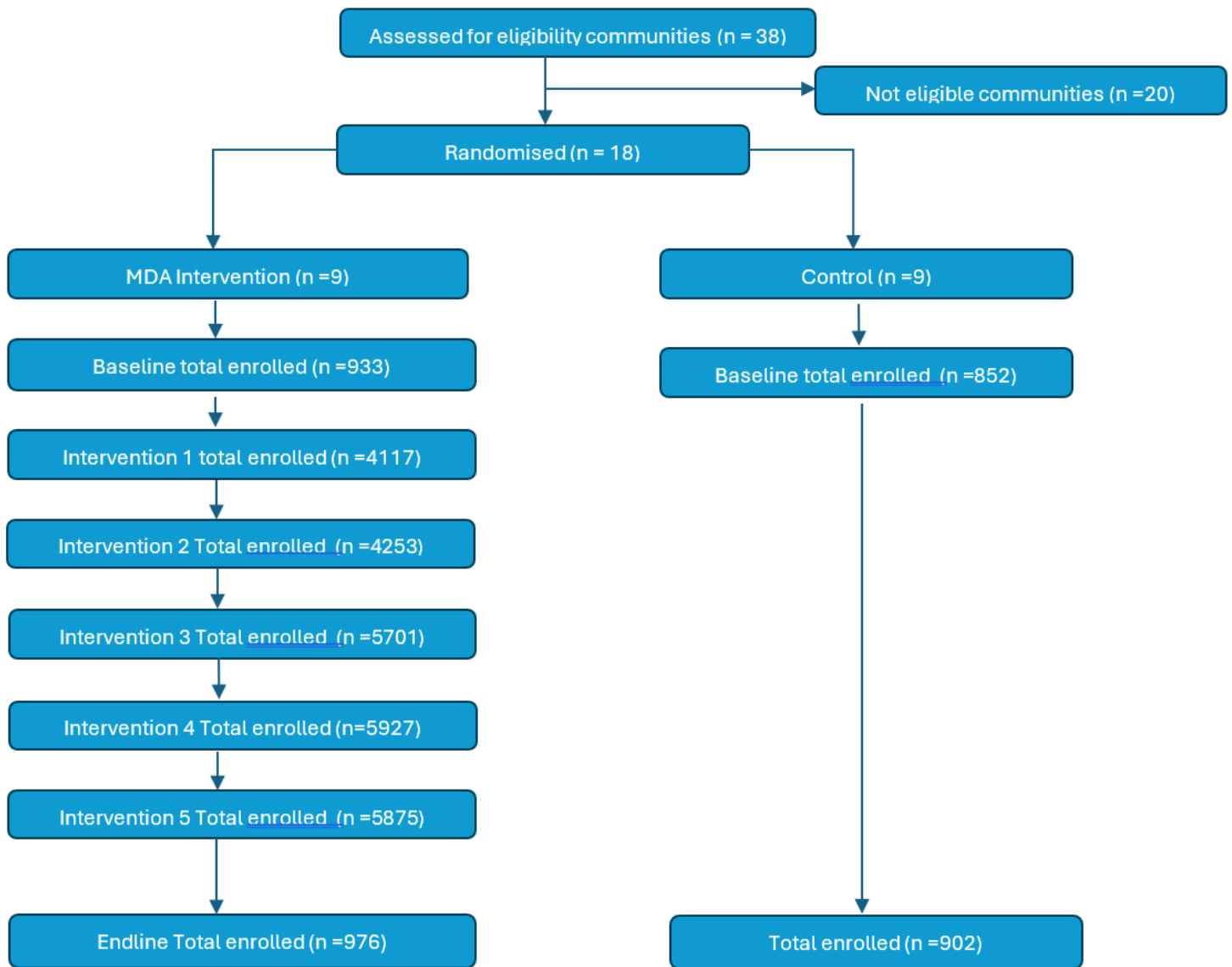


**Figure 2**

Participant flow chart and number of individuals enrolled across five rounds of MDA intervention.

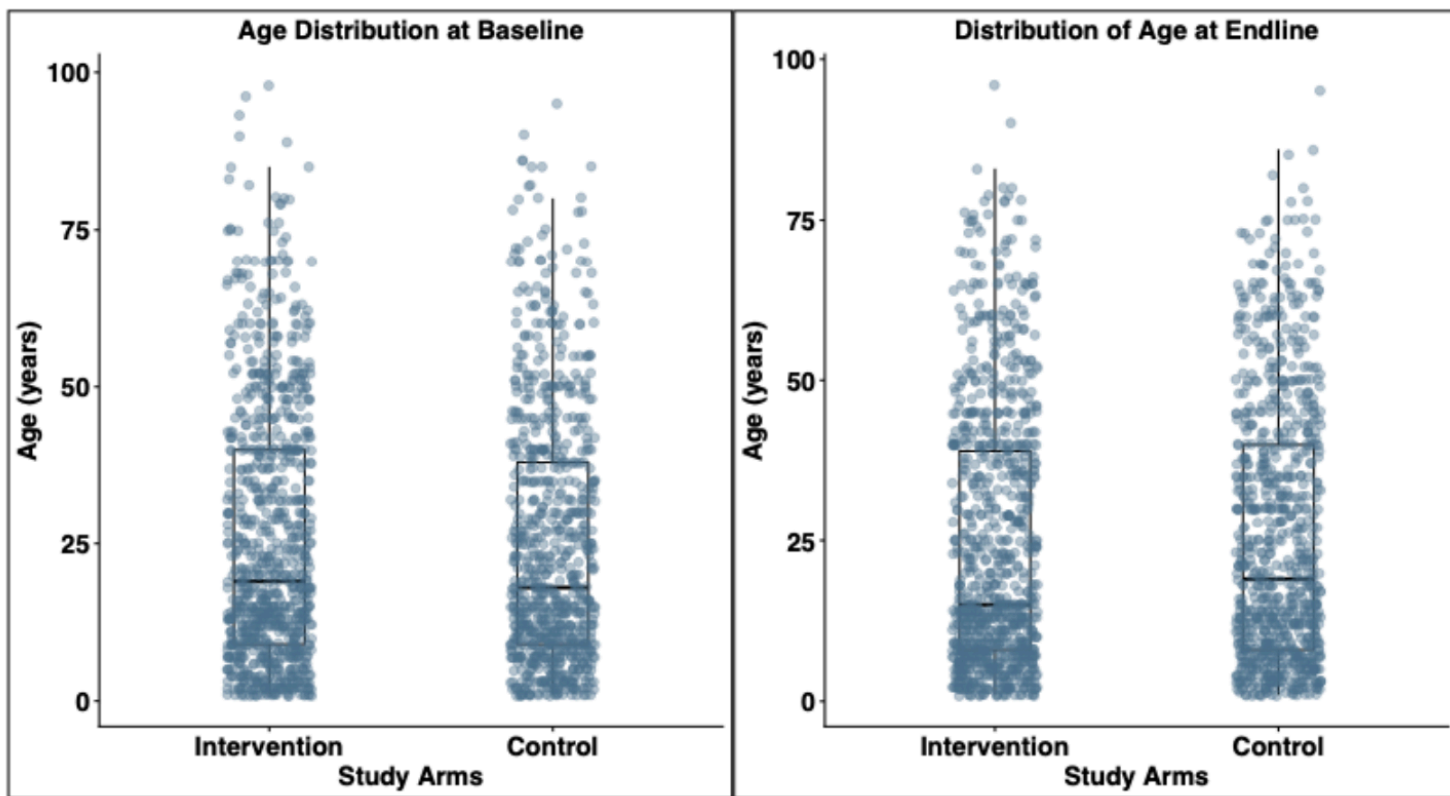


Figure 3

Distribution of age across community-type (intervention and control) arm both at baseline and endline

The figure presents the age distribution of participants in the intervention and control communities at two time points: baseline (left panel) and endline (right panel). Each panel depicts a combination of scatter points and boxplots, allowing visualization of both individual variability and central tendencies.

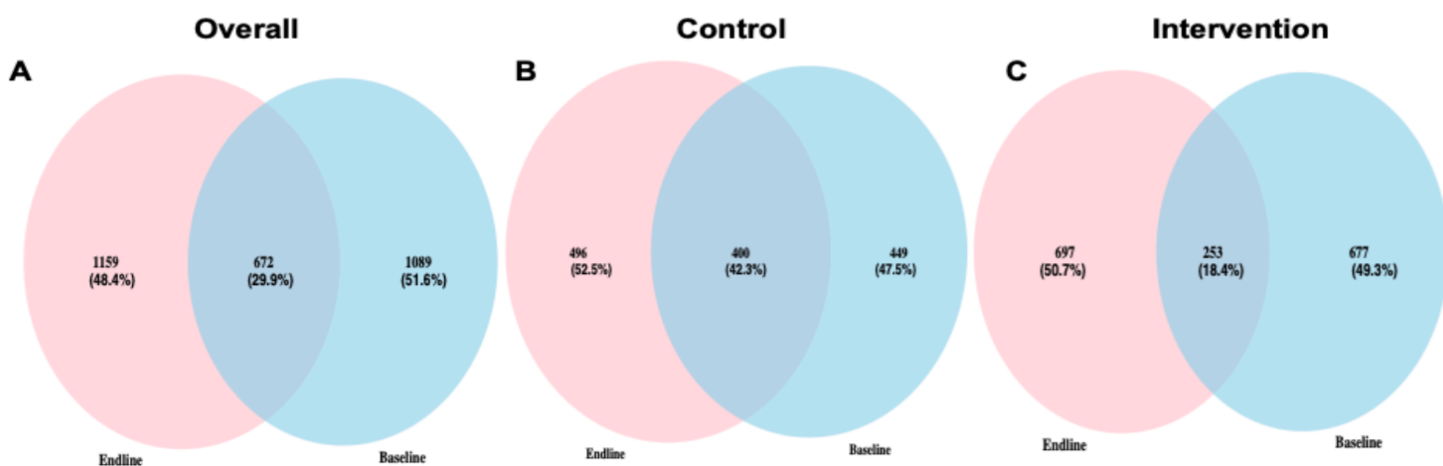


Figure 4

**Number of individuals sampled in both endline and baseline.** A) The overall individuals sampled at endline while already sampled at baseline in both control and intervention arms of the study. B) The individuals sampled at

endline while already sampled at baseline in only control arm of the study. C) The individuals sampled at endline while already sampled at baseline in the only intervention arms of the study.

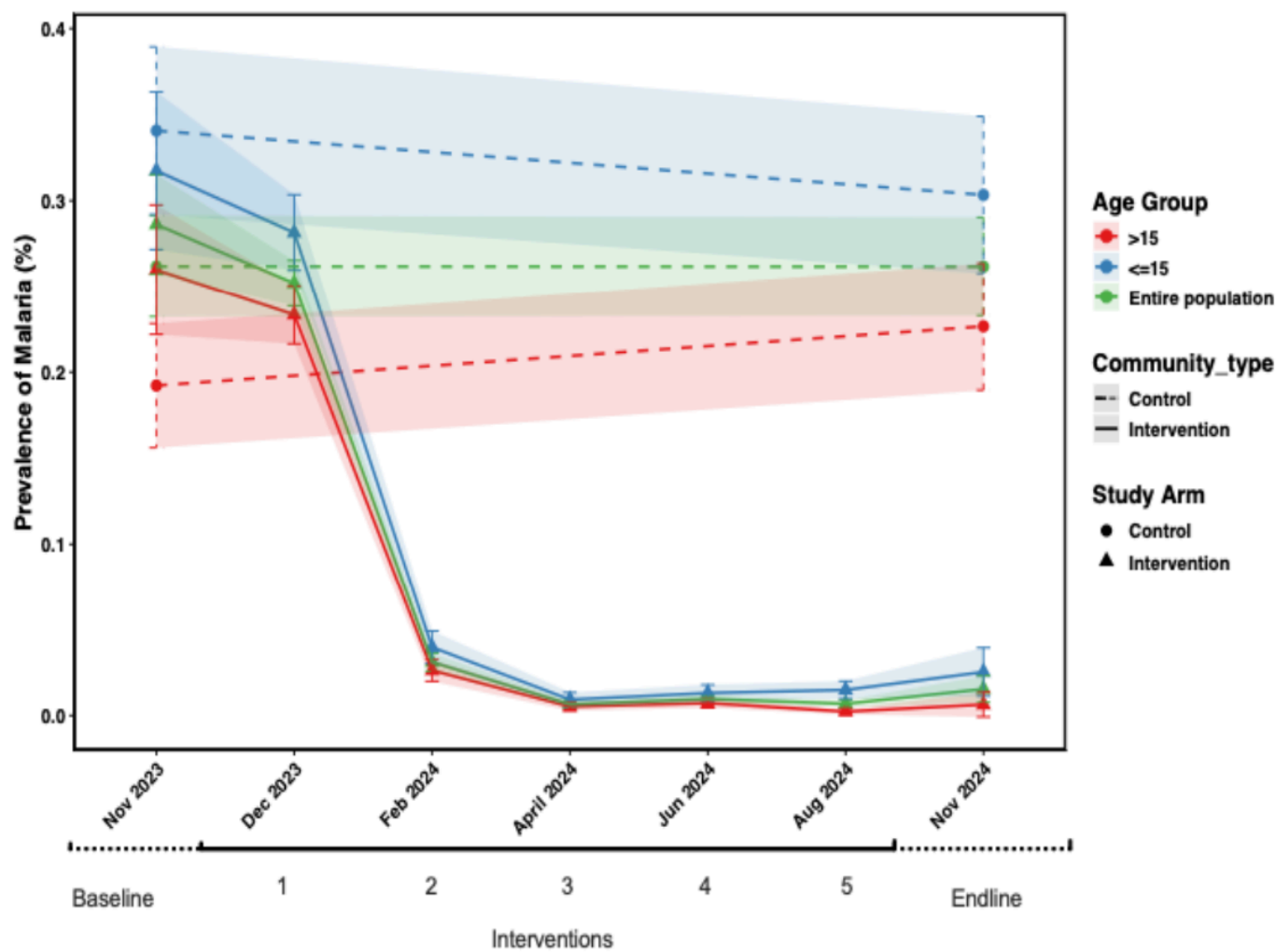


Figure 5

**Trends in malaria prevalence across sequential intervention rounds in control and intervention communities, stratified by age group.** Malaria point prevalence (%) is plotted for participants ≤15 years, >15 years, and the entire population spanning baseline, through intervention rounds, to endline. Solid lines represent intervention communities and dashed lines represent control communities. Across all strata, malaria prevalence declined sharply following the first round of mass drug administration (MDA) and remained near zero throughout subsequent survey rounds in intervention areas, while control communities showed only modest reductions and persistent higher prevalence, particularly among participants ≤15 years.

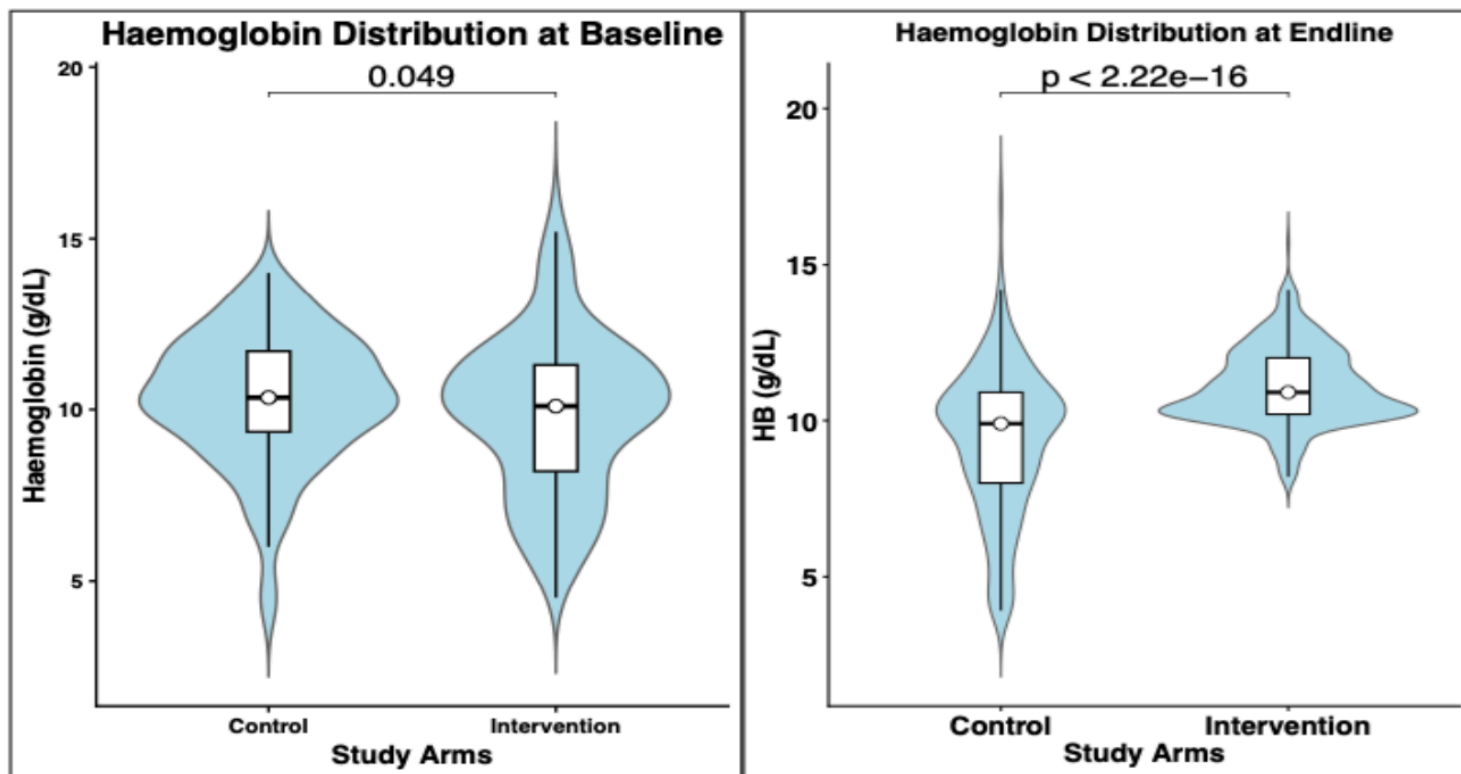


Figure 6

Haemoglobin distribution at baseline and endline in intervention and control communities. *This figure presents the distribution of individual haemoglobin (Hb) concentrations at baseline (left panel) and endline (right panel) stratified by study arm (intervention vs control). Median Hb concentrations were 10.1 g/dL in intervention communities and 10.3 g/dL in control communities at baseline, and 9.76 g/dL and 10.4 g/dL, respectively, at endline. Boxplots indicate the median and interquartile range (IQR), with whiskers representing 1.5× IQR; individual points represent participant-level Hb values. Wilcoxon rank sum test was applied to determine the significance of median haemoglobin between control and intervention arms in the baseline compared to endline. At baseline, haemoglobin distributions were broadly similar between arms, with comparable medians and variability. By endline, the intervention arm shows a modest rightward shift in central tendency and reduced spread, consistent with a relative improvement in population haemoglobin status. haemoglobin and covariates.*

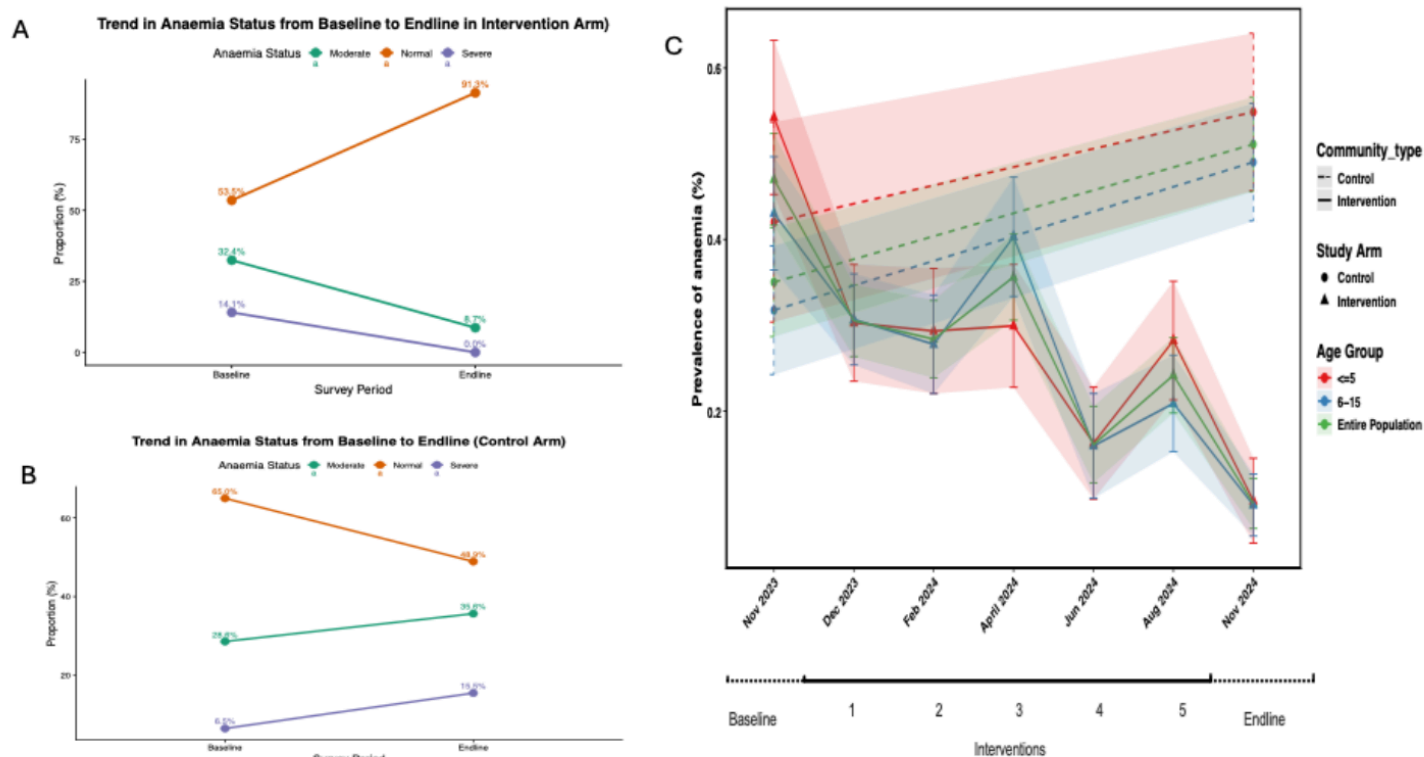


**Figure 7**

Trends in anaemia severity between baseline and endline in intervention (A) and control (B) communities and over time across age (C). *Panel A shows the distribution of anaemia severity (normal, moderate, and severe) at baseline and endline in the control arm, demonstrating a decline in the proportion of participants with normal haemoglobin and an increase in moderate and severe anaemia over time. Panel B presents the corresponding distribution in the intervention arm, illustrating substantial improvements following mass drug administration (MDA), with a marked increase in normal haemoglobin levels and the elimination of severe anaemia at endline. Panel C depicts trends in anaemia prevalence among children <15 years following 5 rounds of MDA.*

## Supplementary Files

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- [CONSORT2025editablechecklistforsubmission2.docx](#)