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Post-trial malaria surveillance following community-wide mass drug administration and delayed implementation in Ghana: a repeated cross-sectional study

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Abstract

Background

Community-wide mass drug administration (MDA) can reduce malaria transmission by clearing symptomatic and asymptomatic infections and reducing the parasite reservoir. However, evidence on persistence of these reductions after intensive MDA and malaria trends following delayed implementation in untreated communities remains limited. We assessed malaria prevalence and childhood anaemia during post-MDA surveillance following a cluster-randomised MDA trial in Ghana.

Methods

Repeated cross-sectional surveillance was conducted in 18 communities (nine intervention and nine former control communities) in November 2024, March 2025, and July 2025. The November 2024 parent-trial endline also served as the post-MDA surveillance baseline, before post-trial MDA. Subsequent MDA was implemented four months apart in both arms, with booster MDA in intervention communities and delayed MDA in former control communities. Approximately 100 randomly selected participants per community were assessed at each survey using HRP2-based rapid diagnostic tests; haemoglobin was measured among children aged ≤ 15 years.

Results

At the November 2024 post-MDA baseline, malaria prevalence was 1.5% (15/974) in intervention communities versus 26.2% (236/902) in former control communities. Prevalence remained low in intervention communities (1.8% and 0.9% in March and July 2025, respectively) and declined in former control communities (9.0% and 0.7%). By July 2025, prevalence had converged to low levels. Among children aged ≤ 15 years, anaemia prevalence was 8.9% in intervention communities and 54.5% in former control communities at baseline, declining to 8.9% and 9.0%, respectively, by July 2025.

Conclusions

Very low RDT-detectable malaria prevalence was maintained in intervention communities, while prevalence in former control communities declined during delayed implementation and became similarly low by July 2025. Together with the marked reduction in childhood anaemia, these findings indicate favourable health gains following the broader MDA intervention package and highlight the value of continued community-based surveillance as malaria prevalence approaches very low levels. This context provides an opportunity to layer complementary elimination interventions, including malaria vaccination and transmission-reducing approaches such as gametocytocidal therapy, alongside surveillance and targeted responses to residual infection. Although the non-randomised post-trial design limits causal attribution of subsequent changes specifically to delayed or booster MDA, the findings can inform integrated strategies to sustain and advance malaria elimination.

Introduction

Malaria remains a major global public health challenge despite unprecedented investments in prevention, diagnosis, and treatment. According to the World Health Organization (WHO), an estimated 263 million malaria cases and 597,000 malaria-related deaths occurred globally in 2023, with approximately 94% of cases and deaths occurring in the WHO African Region [1]. Although the scale-up of insecticide-treated nets (ITNs), indoor residual spraying (IRS), seasonal malaria chemoprevention (SMC), and artemisinin-based combination therapies (ACTs) has substantially reduced malaria burden over the past two decades, progress has plateaued in many endemic countries. Persistent transmission is increasingly driven by marked spatial heterogeneity, asymptomatic and low-density infections, residual parasite reservoirs, and the emergence of antimalarial drug resistance, all of which are inadequately captured through routine health-facility surveillance [1–4].

Ghana remains among the countries with a high malaria burden, where malaria continues to be a leading cause of outpatient attendance, hospital admission, and childhood morbidity [1, 5]. Although transmission occurs throughout the year, its intensity varies across ecological zones according to rainfall patterns, vector ecology, and local environmental conditions [6]. Longitudinal studies from the Kintampo Health and Demographic Surveillance System and other endemic settings have demonstrated that substantial reservoirs of *Plasmodium falciparum* infection persist despite widespread implementation of routine malaria control interventions [6–8]. Similarly, therapeutic efficacy and sentinel surveillance studies have documented considerable temporal and geographical variation in malaria transmission across Ghana and highlighted the importance of continuous surveillance for monitoring intervention effectiveness and informing national malaria elimination strategies [9–15]. However, routine passive surveillance primarily detects symptomatic infections among healthcare-seeking individuals and substantially underestimates the community reservoir of asymptomatic infections that sustain ongoing transmission [16–18].

To address these limitations, community-based malaria surveillance has increasingly been incorporated into malaria control and elimination programmes to directly measure parasite prevalence and characterize transmission dynamics [19–26]. Compared with routine facility-based surveillance, repeated community surveys provide greater spatial and temporal resolution for assessing intervention-associated changes, identifying persistent areas of detectable infection, and monitoring possible resurgence [15–18, 27, 28]. In Ghana, studies have demonstrated that meaningful community engagement is fundamental to the successful implementation of malaria interventions [29, 30], while broader evaluations of community-based surveillance systems have highlighted their value in strengthening disease detection and public health response[31–33]. Studies by our research team have also examined community-delivered mass testing and treatment and MDA approaches in Ghana [34–37]. Community engagement has additionally been important in implementation of emerging malaria interventions, including malaria vaccination [38].

Growing evidence from Zambia, Kenya, Senegal, Burkina Faso, The Gambia, and other endemic African settings demonstrates that repeated rounds of high-coverage MDA can rapidly reduce malaria infection prevalence [26, 39–45]. Nevertheless, resurgence or persistence of detectable infection has been reported after intensive MDA, reflecting residual parasite reservoirs, importation of infections, seasonal transmission, and incomplete population coverage [40, 44, 46]. Despite these observations, most intervention trials conclude at their primary endpoint, and relatively little is known about malaria prevalence patterns during the post-trial period. An important but underexplored consideration is what occurs when an effective intervention is subsequently extended to communities that did not receive it during the randomized phase. Ethics-approved delayed implementation can therefore provide an opportunity to describe malaria prevalence trajectories after both groups have received MDA and to assess whether the low prevalence achieved during the intensive intervention phase is maintained during post-trial follow-up.

Unlike conventional intervention trials that conclude at the primary endpoint, this surveillance framework enabled assessment of malaria prevalence after intervention delivery had transitioned from a randomized trial setting to an operational post-trial implementation context. Following completion of the five-round cluster-randomised MDA trial in the Pokrom sub-district of Ghana, the Institutional Review Board of the Noguchi Memorial Institute for Medical Research required, as a condition of ethical approval, that MDA be extended to the former control communities if the intervention was shown to be effective. Accordingly, following the November 2024 endline assessment, the former control communities received three delayed MDA rounds in November 2024, March 2025, and July 2025, while the original intervention communities received three booster rounds over the same period. This ethics-approved delayed implementation created an opportunity to describe the post-MDA prevalence trajectory in communities previously exposed to intensive MDA and to characterise the changes in RDT-detectable malaria infection prevalence following delayed implementation in the former control communities.

The four-month interval between subsequent surveillance assessments reflected the post-trial implementation schedule. The surveillance was not intended to reproduce the parent-trial evaluation or estimate the pharmacological duration of DHAP protection; rather, it was designed to describe population-level malaria and anaemia patterns during the post-MDA period.

Here, we report findings from repeated cross-sectional community surveillance conducted in November 2024, March 2025, and July 2025. We assessed temporal changes in RDT-detectable malaria prevalence, community-level heterogeneity, haemoglobin concentration and childhood anaemia during the post-MDA period. We also compared prevalence patterns between original intervention and former control communities as delayed implementation was extended to the former control arm.

Methods

Study design and setting

This post-MDA surveillance study was conducted in 18 geographically distinct communities (nine original intervention and nine former control communities) in the Pokrom sub-district of the Akwapim South District, Eastern Region of Ghana. The surveillance followed a cluster-randomised MDA trial in which the original intervention communities completed five community-wide MDA rounds between December 2023 and August 2024.

The November 2024 endline assessment, conducted approximately three months after the fifth and final MDA round, also served as the post-MDA surveillance baseline. This assessment therefore represented the population status after completion of the intensive MDA phase and before initiation of post-trial MDA. As a condition of ethical approval, the Institutional Review Board of the Noguchi Memorial Institute for Medical Research (NMIMR), University of Ghana, required that, if the intervention was shown to be effective, MDA be extended to the original control communities following completion of the trial endline assessment, thereby ensuring equitable access to a potentially beneficial intervention. Accordingly, immediately after the November 2024 assessment, the former control communities received their first delayed MDA round, while the original intervention communities received their first booster round. Two further post-trial MDA rounds were subsequently implemented in March and July 2025, at approximately four-month intervals, with delayed MDA in former control communities and booster MDA in the original intervention communities. The surveillance therefore captured population-level malaria and anaemia patterns between successive post-trial MDA rounds rather than during the intensive bimonthly intervention phase.

MDA implementation coverage

MDA implementation during the post-trial period was documented using community treatment registers, with the timing of each MDA round recorded relative to the surveillance surveys. Detailed MDA coverage results from the parent trial are reported separately [37, 47].

Three repeated cross-sectional surveillance surveys were conducted in November 2024, March 2025, and July 2025, immediately before scheduled post-trial MDA rounds. Approximately 100 individuals were randomly selected from each of the 18 communities at each survey using updated household registers, yielding a target of approximately 1,800 participants per survey. Surveillance participants were sampled independently at each time point; therefore, the surveys did not constitute a longitudinal cohort. MDA was offered to all eligible residents in each community, irrespective of surveillance participation.

Study population and participant recruitment

The study population comprised permanent residents who had lived in the selected communities for at least six months before each survey. Individuals selected through the surveillance sampling framework were invited to participate in the survey, while all eligible residents of the study communities were subsequently offered MDA according to the study protocol, irrespective of whether they had been selected for surveillance. Individuals who were severely ill, unable to provide informed consent or assent, or unable to provide a finger-prick blood sample were excluded from surveillance participation.

Before each surveillance survey, community mobilisation activities were undertaken through engagement with traditional leaders, community announcements, and household sensitisation led by trained community health volunteers (CHVs). Selected participants were visited at their households by CHVs. Written informed consent was obtained from adults aged ≥ 18 years. For participants younger than 18 years, written parental or guardian consent was obtained, together with written assent from children aged 12–17 years.

Sample size considerations

The surveillance component maintained the sampling framework used in the parent cluster-randomised MDA trial, with approximately 100 randomly selected participants from each of the 18 study communities at each surveillance survey, giving a target sample of approximately 1,800 participants per survey. This approach was intended to support comparable community- and arm-level estimates of malaria prevalence and assessment of temporal trends while accounting for community-level clustering. The surveillance was designed primarily to monitor malaria prevalence following the intensive MDA phase and during subsequent delayed and booster implementation, rather than as an independently powered intervention trial; therefore, no formal hypothesis-driven sample size calculation was performed. Precision was interpreted in light of the clustered sampling design and variation in prevalence between communities.

Data collection procedures

Data were collected during household visits by trained field workers using standardised case report forms. Structured questionnaires were administered to collect demographic characteristics, recent history of malaria symptoms, and ownership and use of insecticide-treated nets (ITNs), including ITN use on the night preceding the survey. Completed forms were reviewed daily by field supervisors for completeness and consistency before transfer to the Epidemiology Department of the Noguchi Memorial Institute for Medical Research. Data were independently double-entered into a secure electronic database, and discrepancies were resolved by comparison with the original source documents.

Treatment with DHAP

The post-trial MDA schedule is relevant to interpretation of surveillance findings. The first post-trial MDA round was implemented after completion of the November 2024 baseline/endline assessment, with booster MDA in original intervention communities and delayed MDA in former control communities. Further rounds were implemented approximately four months apart in March and July 2025. Detailed dosing and implementation procedures for the primary five-round MDA intervention are reported in the parent-trial manuscript [47]. This surveillance study focuses on outcomes measured between post-trial MDA rounds.

Malaria diagnosis

Capillary blood samples were collected by finger prick from all consenting participants. Malaria infection was assessed using a World Health Organization-prequalified histidine-rich protein 2 (HRP2)-based rapid diagnostic test (RDT), performed according to the manufacturer's instructions and Ghana National Malaria Elimination Programme guidelines. MDA was subsequently offered to all eligible residents, irrespective of RDT result, during the scheduled post-trial MDA rounds. Individuals requiring additional clinical assessment were referred to the nearest health facility. The primary malaria measure was RDT-confirmed malaria prevalence, defined as the proportion of participants with a positive RDT result among selected participants tested during each surveillance survey.

Haemoglobin measurement and anaemia assessment

Haemoglobin concentration was measured among randomly selected children aged ≤ 15 years using a portable automated haemoglobinometer (HemoCue® Hb 301, HemoCue AB, Ängelholm, Sweden), which was calibrated daily according to the manufacturer's specifications. The prespecified study definition of anaemia was a haemoglobin concentration < 10 g/dL, while severe anaemia was defined as haemoglobin < 7 g/dL. These thresholds were applied consistently across all surveillance surveys. Children identified with severe anaemia were referred to the Pokrom Health Centre for further clinical evaluation and appropriate management.

Outcome measures

The primary outcome was the prevalence of RDT-confirmed malaria infection during each surveillance survey. Secondary outcomes included: 1) malaria prevalence by study arm and community; 2) changes in malaria prevalence between post-MDA baseline, Surveillance 1, and Surveillance 2; 3) haemoglobin concentration distributions across surveillance rounds; 4) prevalence of anaemia; and 5) temporal changes in haemoglobin levels following MDA implementation.

Statistical analysis

Data were analysed using R statistical software version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarised using medians and interquartile ranges (IQRs), and categorical variables using frequencies and percentages. Differences in participant characteristics between original intervention and former control communities were assessed using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables, as appropriate.

Malaria and anaemia prevalence were calculated as the proportion of participants with the respective outcome among those assessed at each survey, with corresponding 95% confidence intervals (CIs) calculated using the exact binomial method. Temporal changes in malaria prevalence were examined descriptively at study-arm and community levels. Between-arm associations in malaria prevalence at each surveillance survey were assessed using mixed-effects Poisson regression models with robust standard errors to estimate prevalence ratios (PRs) and adjusted prevalence ratios (aPRs) with 95% CIs. Community was included as a random intercept to account for clustering arising from the original cluster-randomised design. Adjusted models included ITN use, age group, and sex. Separate analyses were conducted for the overall population and by age group (≤ 15 years and > 15 years). Because the post-trial phase was not randomised and both arms subsequently received MDA, estimates were interpreted as adjusted between-arm associations rather than causal post-trial treatment effects.

To assess changes in the between-arm malaria prevalence ratio across the surveillance period, an additional mixed-effects Poisson regression model included study arm, survey period, and the arm × survey interaction as fixed effects, with community as a random intercept and adjustment for age group, sex, and ITN use. Adjusted prevalence ratios comparing the original intervention with former control communities at each survey were estimated from model-based marginal means using the emmeans approach. The arm × survey interaction represents the change in the intervention-to-control prevalence ratio at each subsequent survey relative to the post-MDA baseline. Two-sided P values were calculated for the marginal between-arm comparisons and interaction terms.

Haemoglobin concentration (g/dL) was analysed descriptively as a continuous measure and categorically to define normal haemoglobin (Hb ≥ 10 g/dL), moderate anaemia (7 ≤ Hb < 10 g/dL), severe anaemia (Hb < 7 g/dL), and any anaemia (Hb < 10 g/dL). Haemoglobin distributions across surveillance surveys were visualised using violin plots with embedded boxplots, and differences between surveys were assessed using the Kruskal–Wallis rank-sum test. Because the surveys comprised repeated cross-sectional samples, changes were interpreted at the population level rather than as individual trajectories. Community-level malaria and anaemia patterns were additionally visualised using maps to describe spatial heterogeneity across the surveillance period. All tests were two-sided, with statistical significance defined as $p < 0.05$.

Community-level prevalence was visualised using heatmaps showing RDT-detectable malaria prevalence across all 18 communities and anaemia prevalence among children aged ≤ 15 years across the three surveillance surveys. Heatmap cells

represented the percentage of participants with the respective outcome within each community and survey period, allowing visual assessment of spatial and temporal heterogeneity.

Human Ethics and Consent to Participate declarations

Ethical approval

was obtained from Noguchi Memorial Institute for Medical Research Institutional Review Board (Noguchi-IRB), (005/23–24). The study was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments [48].

Written or thumb-printed informed consent was obtained from all adult participants. For participants younger than 18 years, written parental or guardian consent and child assent were obtained as appropriate. Participant confidentiality was maintained through the use of unique study identification numbers. Confidentiality was maintained by anonymising the data before analysis. Electronic databases were password protected and accessible only to authorised study personnel.

Results

Baseline characteristics of the surveillance population

A total of 1,876, 1,838, and 1,829 participants were enrolled during the three repeated cross-sectional surveillance surveys conducted in November 2024 (post-MDA baseline/endline), March 2025 (Surveillance 1), and July 2025 (Surveillance 2), respectively. The November 2024 assessment represented the population status after completion of the primary MDA phase and before post-trial MDA was introduced. Subsequent surveys characterised malaria and anaemia during the lower-frequency post-trial MDA period.

Participant characteristics during post-MDA surveillance

Participant characteristics were broadly similar between former control communities and the intervention communities, although differences in age distribution emerged during follow-up. At the post-MDA baseline, median age was 17 years (IQR: 8–40) and did not differ significantly between original intervention and former control communities ($p = 0.10$). Participants in the intervention arm were younger at Surveillance 1 (median 13 vs. 18 years; $p = 0.004$) and Surveillance 2 (median 13 vs. 15 years; $p = 0.001$), reflecting a higher proportion of children aged ≤ 15 years in original intervention communities (54% vs. 44% and 57% vs. 48%, respectively; both $p < 0.001$) (Table 1). The proportion of female participants remained similar between study arms across all surveys, accounting for approximately half of participants. ITN use was consistently low (26–29%) and comparable between arms, except for minor differences observed among children and adults at Surveillance 1 (Table 1).

Table 1
Participant characteristics at post-MDA surveillance baseline (November 2024)

Group	Characteristic	Overall	Control	Intervention	P-value[1]
	N	1,876	**902**	974	
Overall	Age, median (IQR), years	17 (8–40)	18 (8–39)	15 (7–38)	0.13
	Age ≤ 15 years, n (%)	401 (21.4)	182 (45.4)	219 (54.6)	0.05
	Age > 15 years, n (%)	1,475 (78.6)	720 (48.8)	755 (51.2)	0.05
	Female, n (%)	983 (52)	485 (49)	498 (51)	0.14
	ITN use, n (%)	536 (29)	249 (28)	287 (29)	0.90
	RDT positive, n (%)	251 (13.4)	236 (26.2)	15 (1.5)	< 0.001
≤ 15 years	Age, median (IQR), years	7.0 (4.0–12.0)	7.0 (4.0–12.0)	7.0 (4.0–11.0)	> 0.90
	Female, n (%)	436 (51)	204 (47)	232 (53)	0.09
	ITN use, n (%)	262 (31)	114 (30)	148 (32)	0.90
	RDT positive, n (%)	59(14.7)	52(28.5)	7(3.2)	< 0.001
> 15 years	Age, median (IQR), years	38 (25–51)	37 (25–51)	39 (25–51)	0.60
	Female, n (%)	515 (50)	251 (48)	264 (52)	0.80
	ITN use, n (%)	273 (27)	134 (26)	139 (27)	0.80
	RDT positive, n (%)	192 (13.0)	184 (25.6)	8 (1.1)	< 0.001

Table 1. Data are presented as median (IQR) or n (%). Continuous variables were compared using the Wilcoxon rank-sum test and categorical variables using Pearson's chi-squared test or Fisher's exact test, as appropriate. Malaria prevalence was determined using rapid diagnostic testing (RDT). Results are presented overall and stratified by age group (≤ 15 and > 15 years).

RDT-confirmed malaria infection prevalence was substantially lower in the original intervention communities than in former control communities at the November 2024 post-MDA baseline (1.5% vs. 26.2%; p < 0.001). During post-MDA surveillance, prevalence remained low in the original intervention communities (1.8% in March and 0.9% in July 2025), while former control communities experienced a progressive decline (9.0% and 0.7%, respectively). By July 2025, prevalence was similarly low in both groups (Table 2 and Fig. 1B).

Among children aged ≤ 15 years, the median age (7 years) and sex distribution were similar between study arms throughout follow-up. ITN use remained stable (29–30%) and was significantly higher in the original intervention arm only at Surveillance 1 (33% vs. 24%; $p = 0.001$) (Table 1). RDT-detected malaria infection was consistently lower in the original intervention arm at the first post-MDA survey (2.4% vs. 31%; $p < 0.001$) (Table 1) and Surveillance 1 (2.0% vs. 12%; $p < 0.001$) compared to the former conrol arm, but by Surveillance 2 had declined to < 1% in both groups (0.4% vs. 0.7%; $p = 0.70$) (Table 2 and Fig. 1B).

Among adults, median age range from 33–37 years and sex distribution remained comparable between study arms throughout the study. Adult ITN use declined from 28% at the first post-MDA survey to 22% at Surveillance 2 and was significantly lower in the intervention arm only at Surveillance 1 (21% vs. 27%; $p = 0.025$). As observed in children, malaria RDT positivity was markedly lower in the intervention arm at the first post-MDA survey (0.8% vs. 26%; $p < 0.001$) and Surveillance 1 (1.6% vs. 6.5%; $p < 0.001$), with no significant difference at Surveillance 2 (1.5% vs. 0.6%; $p = 0.30$) (Table 2 and Fig. 1C).

Table 2
Participant characteristics during follow-up surveillance

Group	Characteristic	Surveillance 1 (March 2025)				Surveillance 2 (July 2025)			
		Overall / N = 1,838	**Control / N = 914**	**Intervention / N = 924**	**P-value[1]**	**Overall / N = 1,829**	**Control / N = 914**	**Intervention / N = 915**	**P-value[1]**
Overall	Age, median (IQR), years	15 (7–35)	18 (8–38)	13 (7–33)	0.006	14 (7–32)	15 (7–35)	13 (6–28)	0.001
Age	≤ 15 years, n (%)	395 (21.5)	186 (47)	209 (53)	0.24	442 (24.1)	200 (45)	242 (55)	0.02
	> 15 years, n (%)	1,443 (78.5)	728 (53)	715 (47)	0.26	1,387 (75.9)	714 (52)	673 (48)	0.91
Female, n (%)		975 (52)	497 (54)	478 (52)	0.30	926 (51)	464 (51)	462 (50)	0.90
ITN use, n (%)		488 (27)	235 (26)	253 (27)	0.40	472 (26)	221 (24)	251 (27)	0.11
RDT positive, n (%)		99/1,838 (5.4)	82/914 (9.0)	17/924 (1.8)	< 0.001	14/1,829 (0.8)	6/914 (0.7)	8/915 (0.9)	0.59

[1]P-values for comparisons between control and intervention groups: Wilcoxon rank-sum test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables.

Table 2. Participant characteristics, ITN use, and malaria prevalence in the former control and original intervention arms at Surveillance 1 (March 2025) and Surveillance 2 (July 2025). Data are presented as median (IQR) or n (%). Continuous variables were compared using the Wilcoxon rank-sum test and categorical variables using Pearson's chi-squared test or Fisher's exact test, as appropriate. Malaria prevalence was determined using rapid diagnostic testing (RDT).

Malaria prevalence trends across communities during the surveillance period

At the post-MDA baseline survey (November 2024), RDT detected malaria infection prevalence remained heterogeneous between communities (Figs. 2 & 3). Original intervention communities had low prevalence, ranging from 0% to 5.9%, whereas former control communities ranged from 9.0% in Agyanoa to 45.0% in Akwakupom. These differences describe the post-MDA starting point for surveillance rather than a new pre-intervention comparison.

By Surveillance 1 (March 2025), RDT detected malaria infection prevalence had declined in both study arms but remained significantly lower in original intervention communities (1.8%; 17/924) than former control communities (9.0%; 82/914; $p < 0.001$). Intervention communities maintained prevalence below 4%, whereas residual transmission persisted in several control communities, particularly Apantem (20.4%), Mariakrom (15.3%), and Agyanoa (13.0%).

At Surveillance 2 (July 2025), RDT detected malaria infection prevalence declined further to 0.8% overall (14/1,829). Prevalence was comparable between original intervention (0.9%; 8/915) and former control communities (0.7%; 6/914), with no statistically significant difference ($p = 0.60$). Seven of nine control communities recorded no infections, while residual infections were detected only in Agyanoa (5.0%) and Obodan/Alata (0.9%), (Figs. 2 & 3).

Overall, malaria prevalence remained low in the original intervention communities throughout post-MDA surveillance, whereas former control communities experienced a substantial decline after delayed MDA was introduced. The initial between-arm difference progressively narrowed, and by July 2025 both groups had similarly low RDT-detectable prevalence.

Figure 3. Spatial distribution of RDT-detectable malaria prevalence across the study communities during the surveillance period. Bubble size represents community-level malaria prevalence. This map was designed for this study by Ndong Henry Ndang and Brandon Nji Amambua-Ngwa using R version 4.4.1 and Canva.

Malaria prevalence Impact Analysis during post-trial surveillance

A mixed-effects Poisson regression model with a random intercept for community was fitted to estimate the effect of the intervention over time. The model included study arm (control vs intervention), survey period (Post-MDA baseline, Surveillance 1, Surveillance 2), the arm × survey interaction, age, sex and ITN use. Immediately after MDA (post-MDA baseline, November 2024), malaria prevalence was much lower in original intervention communities (1.5%, 15/974) than in former control communities (26.2%, 236/902). The adjusted prevalence ratio (aPR) comparing intervention with control was 0.053 (95% CI: 0.030–0.094), corresponding to about a 95% lower prevalence in the intervention arm (Fig. 3).

In control communities, malaria prevalence declined substantially over time, being roughly 70% lower at Surveillance 1 (aPR for time vs baseline = 0.304, 95% CI: 0.235–0.392) and near zero by Surveillance 2 (aPR = 0.022, 95% CI: 0.010–0.050). Despite this decline, the intervention arm still showed lower prevalence at Surveillance 1: the adjusted PR comparing intervention with control was 0.21 (95% CI: 0.15–0.28), indicating that prevalence in original intervention communities remained about 80% lower than in former control communities. The arm × survey interaction aPR at Surveillance 1 was 3.86 (95% CI: 1.85–8.09), demonstrating attenuation of the intervention effect compared with the immediate post-MDA period.

Table 3
Mixed-effects Poisson regression of malaria prevalence with arm × survey interaction.

Survey period	Control arm n/N (%)	Intervention arm n/N (%)	Adjusted PR (95% CI)	Adjusted PR, Intervention vs Control† (95% CI; emmeans score)	Intervention vs Control (P value)*	Interaction aPR‡ (95% CI)	Interaction (P Value)&
Post-MDA baseline (Nov 2024)	236/902 (26.2)	15/974 (1.5)	0.053 (0.031–0.093)	0.053 (0.030–0.094; ≈1/18.729)	P < 0.0001	Reference	Reference
Surveillance 1 (Mar 2025)	82/914 (9.0)	17/924 (1.8)	0.304 (0.235–0.392)	0.21 (0.15–0.28; ≈1/4.85)	P < 0.0001	3.86 (1.85–8.09)	P < 0.05
Surveillance 2 (Jul 2025)	6/914 (0.7)	8/915 (0.9)	0.022 (0.010–0.050)	1.30 (1.22–1.56)	P = 0.6328	24.34 (7.49–79.07)	P < 0.05

†Adjusted prevalence ratio comparing intervention with control communities at each survey, derived from model-based marginal means (emmeans). ‡Interaction term: ratio of the intervention effect at that survey relative to the effect at Post-MDA baseline. *P value from emmeans analysis comparing intervention with control communities at each survey &P value from analysis of the intervention effect at survey time-points relative to post-MDA baseline malaria prevalence. Model adjusted for age, sex, ITN use and clustering by community (random intercept).

Surveillance 1 and Surveillance 2

At Surveillance 1 (March 2025), malaria prevalence remained substantially lower in the original intervention communities than in former control communities (1.8%, 17/924 vs. 9.0%, 82/914; Table 2). Although the difference observed at the November 2024 post-MDA baseline had narrowed, prevalence remained lower in the original intervention communities. The adjusted between-arm estimates are presented in Table 3. Age-stratified analyses showed a similar pattern, with lower RDT-detectable malaria prevalence in the original intervention communities among both children aged ≤ 15 years and participants aged > 15 years (Table 4). These comparisons describe population-level differences during the non-randomised post-trial period.

Table 4
Prevalence ratios (PRs) for RDT-confirmed malaria during Surveillance 1 (March 2025).

Group	Control Arm (N = 914)	Intervention Arm (N = 924)	Unadjusted PR (95% CI)	Adjusted PR[1] (95% CI)	ICC*
Overall n (%)	82/914 (9.0)	17/924 (1.8%)	0.214 (0.099–0.463)	0.205 (0.099–0.460)	0.116
≤ 15 years, n (%)	24/186 (12.9)	4/209 (1.9%)	0.142 (0.039–0.520)	0.160 (0.041–0.619)	0.204
> 15 years, n (%)	58/728 (8.0)	13/715 (1.8%)	0.242 (0.106–0.555)	0.236 (0.102–0.545)	0.104

[1]Mixed-effect Poisson Regression Model

At Surveillance 2 (July 2025), malaria prevalence was very low in both study arms: 0.7% (6/914) in former control communities and 0.9% (8/915) in original intervention communities. The separate mixed-effects model estimated an adjusted PR of 2.32 (95% CI: 0.33–12.43; Table 5). The wide confidence interval reflects the small number of malaria-positive observations and substantial statistical uncertainty; the estimate should therefore be interpreted cautiously. Age-specific prevalence was also below 2% in both groups, with no clear evidence of a meaningful between-arm difference. Overall, the convergence of prevalence by July 2025 represents a temporal pattern during a period when both arms had received post-trial MDA, rather than a causal estimate of delayed or booster MDA effectiveness.

Table 5
Prevalence ratios (PRs) for RDT-confirmed malaria during Surveillance 2 (July 2025).

Group	Control Arm (N = 914)	Intervention Arm (N = 915)	Unadjusted PR (95% CI)	Adjusted PR (95% CI)	ICC*
Overall	6/914 (0.7)	8/915 (0.9)	1.33 (0.331–12.38)	2.32 (0.33–12.43)	0.224
≤ 15 years	3/200 (1.5)	1/242 (0.4)	0.29 (0.02–4.08)	0.23 (0.01–6.73)	0.243
> 15 years	3/714 (0.4)	7/673 (1.0)	2.49 (0.64–9.69)	4.763 (0.40–56.17)	0.311

[1]Mixed-effect Poisson Regression Model

Haemoglobin Distribution Across Surveillance Surveys

In the former control arm, haemoglobin distributions differed significantly across the surveillance period (Kruskal–Wallis, $p < 0.0001$) (Fig. 4). Median haemoglobin concentration increased progressively from the post-MDA baseline to Surveillance 2, with a marked reduction in children with haemoglobin concentrations < 10 g/dL and a corresponding increase in those with concentrations ≥ 11 g/dL, indicating improved haematological status.

In the former control arm, haemoglobin distributions differed significantly across the surveillance period (Kruskal–Wallis, $p < 0.0001$) (Fig. 4). Median haemoglobin concentration increased progressively from the post-MDA baseline to Surveillance 2, with fewer children having haemoglobin concentrations < 10 g/dL and more having concentrations ≥ 11 g/dL. In contrast, haemoglobin distributions in the original intervention arm remained stable across surveys (Kruskal–Wallis, $p = 0.44$), with median concentrations ranging from 10.5 to 11.0 g/dL. By Surveillance 2, haemoglobin distributions in the two arms were similar, with values predominantly clustering between 10 and 12 g/dL (Fig. 4).

Community-level variation in anaemia prevalence

Anaemia prevalence varied substantially between communities during the surveillance period (Fig. 5). In the original intervention communities, prevalence ranged from 0.0% to 23.0% at the November 2024 post-MDA baseline, with most communities below 10%. By March 2025, prevalence had increased in several communities, reaching 43.1% in

Obengkrom/Adukro, 29.4% in Nkumkrom, and 25.8% in Yaw Duodu/Kwesikrom. By July 2025, prevalence had declined to 1.3–15.4%, with only Nkumkrom (15.4%) and Dunpong (11.6%) exceeding 10%.

Former control communities had higher anaemia prevalence at baseline, ranging from 26.7% to 64.8%, with the highest values in Apantem (64.8%), Mariakrom (63.9%), Aburi Amanfrom (57.9%), Oboadaka (56.2%), and Peperwani (54.3%). Although prevalence generally declined during follow-up, substantial community-level variation persisted in March 2025, when Oboadaka reached 81.8%. By July 2025, prevalence had declined to 3.5–12.0% across all former control communities.

Anaemia among children aged ≤ 15 years

Figure 5 and Table 6 summarise anaemia prevalence among children aged ≤ 15 years across the three post-MDA surveillance surveys. At the November 2024 baseline/endline assessment, anaemia prevalence was 8.9% (95% CI: 6.5–12.2) in the original intervention communities and 54.5% (95% CI: 49.2–59.7) in former control communities. All anaemia cases in the intervention communities were moderate, whereas severe anaemia affected 22.5% of children in former control communities.

By March 2025, anaemia prevalence was 25.2% (95% CI: 21.2–29.6) in the intervention communities and 46.6% (95% CI: 41.6–51.6) in former control communities. Severe anaemia remained uncommon in the intervention communities (0.9%) but declined from 22.5% to 7.8% in former controls. By July 2025, anaemia prevalence was similar in the two groups: 8.9% (95% CI: 6.6–12.0) in the intervention communities and 9.0% (95% CI: 6.5–12.2) in former controls; severe anaemia was < 1% in both groups.

Table 6
Prevalence of anaemia among children aged ≤ 15 years by survey round and study arm.

	Intervention			**Former Control Arm**		
	Nov-2024	**Mar-2025**	**Jul-2025**	**Nov-2024**	**Mar-2025**	**Jul-2025**
n/N (%; 95% CI)						
Normal	347/381 (91.1%; 87.8–93.6)	321/429 (74.8%; 70.4–78.8)	389/427 (91.1%; 88.1–93.4)	158/347 (45.5%; 40.3–50.8)	206/386 (53.4%; 48.4–58.4)	364/400 (91.0%; 87.8–93.4)
Moderate anemia	34/381 (8.9%; 6.5–12.2)	104/429 (24.2%; 20.4–28.5)	37/427 (8.7%; 6.4–11.7)	111/347 (32.0%; 27.3–37.1)	150/386 (38.9%; 34.1–43.9)	33/400 (8.2%; 5.9–11.4)
Severe anemia	0	4/429 (0.9%; 0.4–2.4)	1/427 (0.2%; 0.0–1.3)	78/347 (22.5%; 18.4–27.2)	30/386 (7.8%; 5.5–11.0)	3/400 (0.8%; 0.3–2.2)
Total anemia	34/381 (8.9%; 6.5–12.2)	108/429 (25.2%; 21.2–29.6)	38/427 (8.9%; 6.6–12.0)	189/347 (54.5%; 49.2–59.7)	180/386 (46.6%; 41.6–51.6)	36/400 (9.0%; 6.6–12.2)

Table 6 depicts prevalence of normal haemoglobin, moderate anaemia, severe anaemia, and total anaemia among children aged ≤ 15 years by study arm across the three post-MDA surveillance surveys. Data are presented as n/N (%; 95% CI). Anaemia was classified according to study-defined haemoglobin thresholds. CI, confidence interval; MDA, mass drug administration.

Discussion

The November 2024 assessment provides the key starting point for interpreting the post-MDA period. It was conducted after completion of the intensive five-round intervention and before the subsequent post-trial MDA phase. The March and July 2025 surveys then captured population-level malaria prevalence approximately four months apart during the lower-frequency post-trial implementation period. This design allowed assessment of whether the low prevalence observed after the intensive

MDA phase was maintained and how prevalence changed in former control communities following delayed implementation [47].

The four-month surveillance interval was also relevant to interpretation of the pharmacological contribution of DHAP. Piperaquine has a relatively long elimination half-life and provides longer post-treatment prophylactic protection than some other antimalarial combinations, with protection against new infections reported to extend for several weeks and, in some studies, up to approximately 63 days [49, 50]. Thus, the persistence of very low RDT-detectable malaria prevalence several months after completion of the intensive five-round MDA phase is unlikely to be explained solely by residual drug activity. Rather, the findings are consistent with continued population-level suppression of detectable infection following the intensive intervention. Importantly, however, the original intervention communities received booster MDA during the surveillance period; the findings therefore should not be interpreted as evidence of sustained suppression after complete cessation of MDA.

RDT-detectable malaria prevalence remained very low in the original intervention communities throughout surveillance, while former control communities, which had substantially higher prevalence at the November 2024 post-MDA baseline, experienced a marked decline during follow-up. Previous studies have shown that substantial reductions following MDA can persist for several months, although the magnitude and duration of these effects vary according to transmission intensity and local epidemiological conditions [26, 39–45]. Modelling studies have similarly shown that sustained high population coverage over multiple MDA rounds can markedly reduce the malaria parasite reservoir and support progress towards elimination[40, 44]. Conversely, resurgence following MDA has also been documented, including in Kenya, where malaria prevalence rebounded following community-wide artemisinin–piperaquine MDA, highlighting the potential importance of residual local transmission and parasite importation [51]. These observations underscore the importance of continued surveillance after intensive MDA [40, 44, 46, 51].

In the present study, the decline in former control communities occurred during a period in which delayed MDA was introduced under the ethics-approved study plan. Although this temporal pattern is consistent with a substantial decline during delayed implementation, the post-trial phase was not randomised: former control communities received delayed MDA while the original intervention communities received booster rounds, and no contemporaneous untreated comparison remained. Seasonal variation, routine malaria-control activities, community-level differences and other factors could therefore have contributed to the observed changes. The findings should consequently be interpreted as post-trial temporal associations rather than causal estimates of delayed or booster MDA effectiveness [47].

The community-level results further demonstrate the value of repeated surveillance. Marked heterogeneity in RDT-detectable malaria prevalence was evident at the November 2024 baseline, particularly among former control communities, but progressively fewer communities recorded positive participants during follow-up. By July 2025, seven of nine former control communities had no detected infections, with residual positivity confined to two communities. Such heterogeneity is relevant to malaria elimination programmes because declining prevalence may become increasingly focal and difficult to characterise through routine facility-based surveillance alone [15, 20, 27, 52, 53]. At very low prevalence, however, isolated positive observations should not automatically be interpreted as persistent transmission hotspots, particularly given the small number of positive observations in the final survey [54]. Molecular surveillance would be required to characterise low-density and submicroscopic infections not detected by the HRP2-based RDT [17, 50].

The temporal patterns in haemoglobin and anaemia provide an additional population-level perspective on the post-MDA period. Children in the original intervention communities entered surveillance with substantially lower anaemia prevalence than children in former control communities. Former control communities subsequently experienced marked reductions in anaemia, and by July 2025 anaemia prevalence was similar in the two groups. This pattern is biologically plausible given the established relationship between malaria and childhood anaemia and is consistent with previous Ghanaian studies linking reductions in malaria infection with improvements in haemoglobin and anaemia outcomes [20, 30, 36, 37]. However, the repeated cross-sectional design does not permit attribution of individual changes in haemoglobin or anaemia to malaria or MDA exposure. The observed convergence should therefore be interpreted as a population-level temporal pattern rather than evidence of an individual treatment effect.

An important strength of this study is the use of repeated community-based cross-sectional surveys across the post-MDA period. Sampling approximately 100 participants per community at each survey allowed assessment of both arm-level trends and community-level heterogeneity while avoiding assumptions that the same individuals were followed over time. The surveillance also captured the transition from intensive bimonthly MDA to lower-frequency post-trial implementation, providing information on malaria patterns during a period that is often not assessed after completion of an intervention trial [20, 27, 52].

An important implementation feature of the preceding MDA intervention was the household-collaborative delivery model. Community health volunteers (CHVs) directly observed the first dose of the three-day DHAP regimen, while subsequent doses were supervised by a responsible household member, typically a parent, guardian or older sibling. CHVs conducted follow-up visits on days 1, 2, 3, and 7 after treatment initiation to inspect blister packs, verify completion of the three-day treatment course, monitor adherence and identify adverse events. Missed doses, vomiting and other adverse events were documented, with severe adverse events referred for clinical management [47]. This approach combined community-based supervision with household responsibility for treatment completion, extending delivery capacity while reducing the operational burden on CHVs. The model was implemented alongside community mobilisation, household enumeration and follow-up and was associated with progressively high MDA coverage during the intensive intervention phase [47]. Community perspectives from the study setting also support the acceptability and feasibility of household participation in MDA delivery [37]. For the present surveillance study, this implementation approach provides important context for interpreting the subsequent epidemiological trajectory. However, because the surveillance study was not designed to isolate the independent contribution of the household-collaborative model from other components of MDA implementation, its role should be considered an implementation feature rather than a separately estimated intervention effect.

The findings have important implications for surveillance and programme adaptation in settings where malaria prevalence has been reduced to very low levels. Continued community-based surveillance can help determine whether low RDT-detectable prevalence is maintained, identify communities in which residual infection persists, and provide information to guide the intensity and targeting of subsequent malaria-control activities [20, 52, 53]. As prevalence declines, infections may become increasingly focal and more difficult to detect through routine facility-based surveillance alone, making sensitive molecular diagnostics and targeted surveillance or treatment approaches potentially more relevant [55–57]. In addition, the reduction of malaria to very low levels may create opportunities to introduce or strengthen complementary interventions aimed at preventing reinfection and interrupting residual transmission. Single low-dose primaquine has been proposed as a transmission-reducing adjunct to antimalarial treatment programmes [58, 59], while malaria vaccines can provide additional protection against infection and clinical disease and may be particularly valuable for maintaining gains as transmission declines [60–63]. Mathematical modelling has similarly suggested that combining complementary interventions may achieve greater reductions in transmission than relying on a single intervention as malaria approaches elimination thresholds [40, 64]. In the present study, malaria prevalence had fallen to below 1% in both study arms by Surveillance 2, indicating a setting in which the emphasis of malaria programmes may increasingly shift from broad suppression towards surveillance, identification of residual infection, and targeted strategies to prevent resurgence and sustain progress towards elimination [2, 65, 66]. The very low prevalence observed at Surveillance 2 may therefore provide a favourable epidemiological context for considering complementary interventions such as malaria vaccination [67], although the present study did not evaluate vaccination or other transmission-blocking strategies and cannot determine their incremental benefit.

This study has several strengths. First, repeated community-based cross-sectional surveillance was conducted across all 18 study communities, allowing malaria prevalence and childhood anaemia to be assessed at both study-arm and community levels over the post-MDA period. Second, the sampling framework used in the parent cluster-randomised trial was retained, with approximately 100 randomly selected participants per community at each surveillance survey, supporting comparability of population-level estimates across surveillance periods while maintaining coverage of all study communities. Third, the study captures the transition from an intensive five-round community-wide MDA phase to a lower-frequency post-trial implementation period, including delayed MDA in former control communities and booster MDA in original intervention communities. Fourth, the inclusion of all communities enabled assessment of community-level heterogeneity as malaria

prevalence declined to very low levels, providing greater epidemiological resolution than arm-level estimates alone. Fifth, **t**he study includes both malaria and haemoglobin/anaemia outcomes, allowing the post-MDA period to be characterised beyond infection prevalence alone. Sixth, the surveillance was conducted within communities in which MDA had been delivered through a documented household-collaborative model, in which CHVs observed the first dose, household members supervised subsequent doses, and CHVs conducted follow-up visits on days 1, 2, 3 and 7 to verify treatment completion and monitor adherence and adverse events [37]. This provides an important implementation context for interpreting the observed post-MDA trajectory and strengthens the practical relevance of the findings for community-based delivery of repeated MDA.

Several limitations should nevertheless be considered. First, malaria was assessed using an HRP2-based RDT, which has lower sensitivity than molecular methods for detecting low-density and submicroscopic infections; consequently, the reported prevalence represents RDT-detectable infection rather than total parasite carriage. Second, the November 2024 assessment occurred after completion of the intensive five-round MDA phase and therefore cannot be used to establish pre-intervention comparability between the original intervention and former control communities. Third, the post-trial phase was not randomised and both study arms subsequently received MDA, limiting causal inference regarding the effects of delayed versus booster MDA. Fourth, the repeated cross-sectional design means that changes across surveys describe population-level patterns rather than individual trajectories. Fifth, the surveys were conducted at different calendar times, so seasonal variation and other changes in malaria-control activities may have contributed to the observed temporal patterns. Finally, although the very low number of RDT-positive observations at Surveillance 2 (14/1,829) represents an important programme-level achievement, the small number of events limits the precision of comparative statistical estimates, as reflected in the wide confidence intervals of some adjusted prevalence ratios.

Conclusions

Overall, this study describes malaria and childhood anaemia during an eight-month post-MDA surveillance period following completion of an intensive community-wide MDA phase. Very low RDT-detectable malaria prevalence was maintained in the original intervention communities, while prevalence in former control communities declined substantially during the period of delayed implementation and became similarly low by July 2025. Together with the marked reduction in childhood anaemia, these findings illustrate substantial favourable population-level health patterns following the broader MDA intervention package and demonstrate the value of continued community-based surveillance as malaria prevalence approaches very low levels. The resulting epidemiological context may provide an important opportunity to strengthen and layer complementary elimination interventions, including malaria vaccination and transmission-reducing approaches such as gametocytocidal therapy, alongside sensitive surveillance and targeted responses to residual infection. Although the non-randomised post-trial design does not permit causal attribution of the subsequent temporal changes specifically to delayed or booster MDA, the findings provide important evidence to inform the design of integrated strategies for sustaining and advancing malaria elimination. alone.

Abbreviations

aPR, adjusted prevalence ratio; CI, confidence interval; DHAP, dihydroartemisinin–piperaquine; Hb, haemoglobin; ITN, insecticide-treated net; IQR, interquartile range; MDA, mass drug administration; PR, prevalence ratio; RDT, rapid diagnostic test.

Declarations

The trial was registered retrospectively due to an administrative oversight following ethics approval (**Noguchi-IRB 005/23–24),** with registration subsequently completed on ClinicalTrials.gov on 15 January 2026 (NCT07389057).

Human Ethics and consent to participate

Ethical approval was obtained from the Noguchi Memorial Institute for Medical Research Institutional Review Board (Noguchi-IRB 005/23–24). Written informed consent or parental/guardian consent and child assent were obtained for children 12-17 years.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

All authors declare no competing interests. Fosun Pharma supplied DHAP for the study but had no role in the study design, implementation, data collection, analysis, interpretation of findings, or preparation of the manuscript.

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Authors' contributions

I.C.N. 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., K.M and E.C. contributed to field work implementation. V.N-N., M.D., N.H.N., B.N.A.-N., and N.M. contributed to data analysis and writing. All authors reviewed the manuscript.

Use of artificial intelligence

An artificial intelligence language model (ChatGPT, OpenAI) was used to assist with language editing and manuscript organisation. All scientific content, analyses, interpretations and final text were reviewed and approved by the authors, who remain responsible for the accuracy and integrity of the manuscript.

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Figures

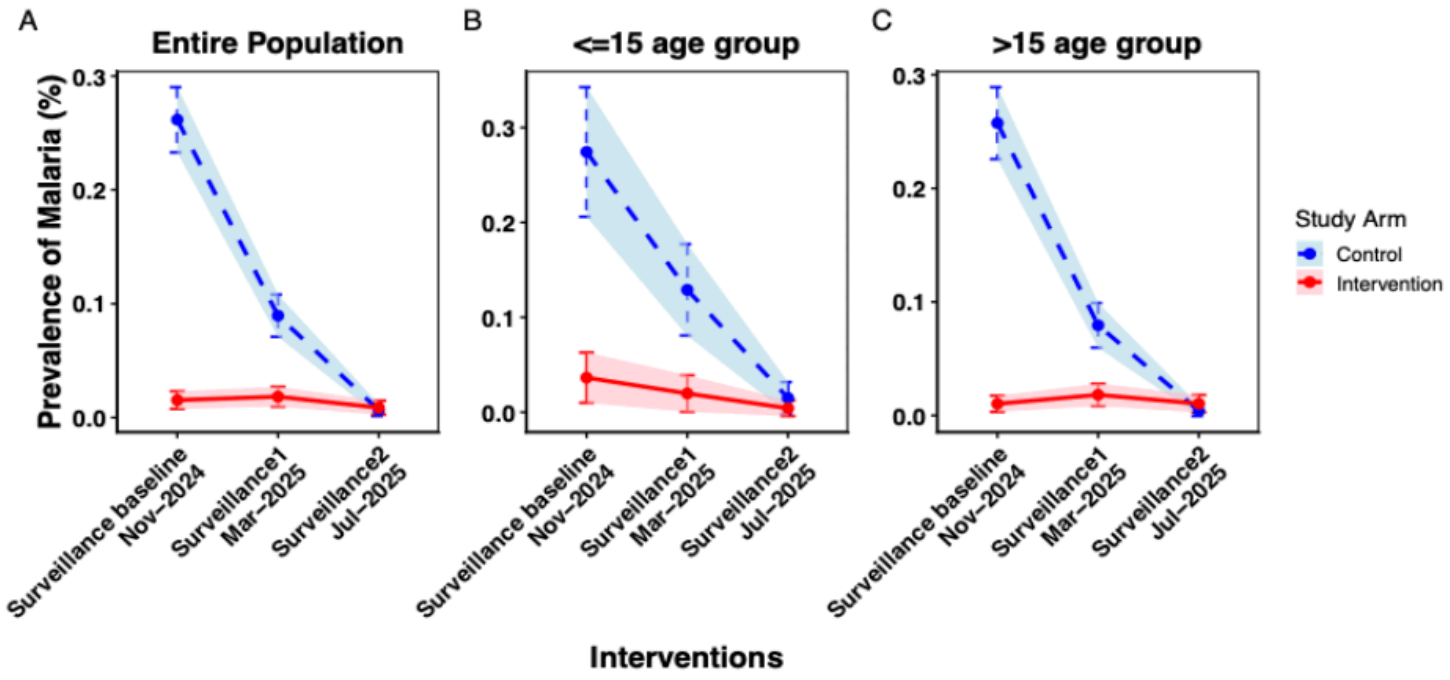


Figure 1

Temporal changes in RDT-confirmed malaria prevalence across the surveillance period for the overall population (A), children aged ≤15 years (B), and participants aged >15 years (C). Prevalence remained low in the original intervention communities and declined substantially in former control communities during follow-up.

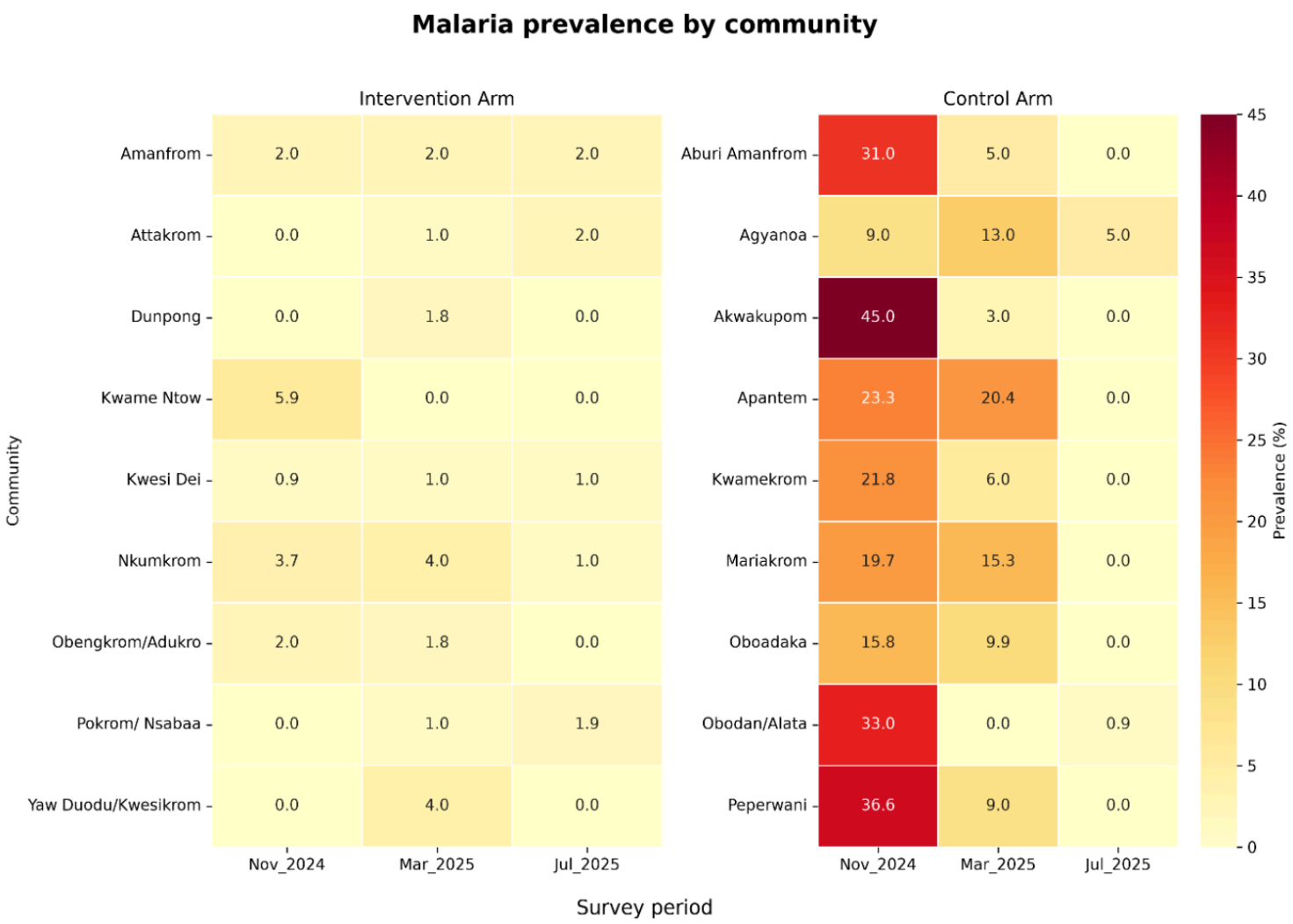


Figure 2

Community-level prevalence of RDT-detectable malaria across the 18 study communities during the three surveillance surveys.

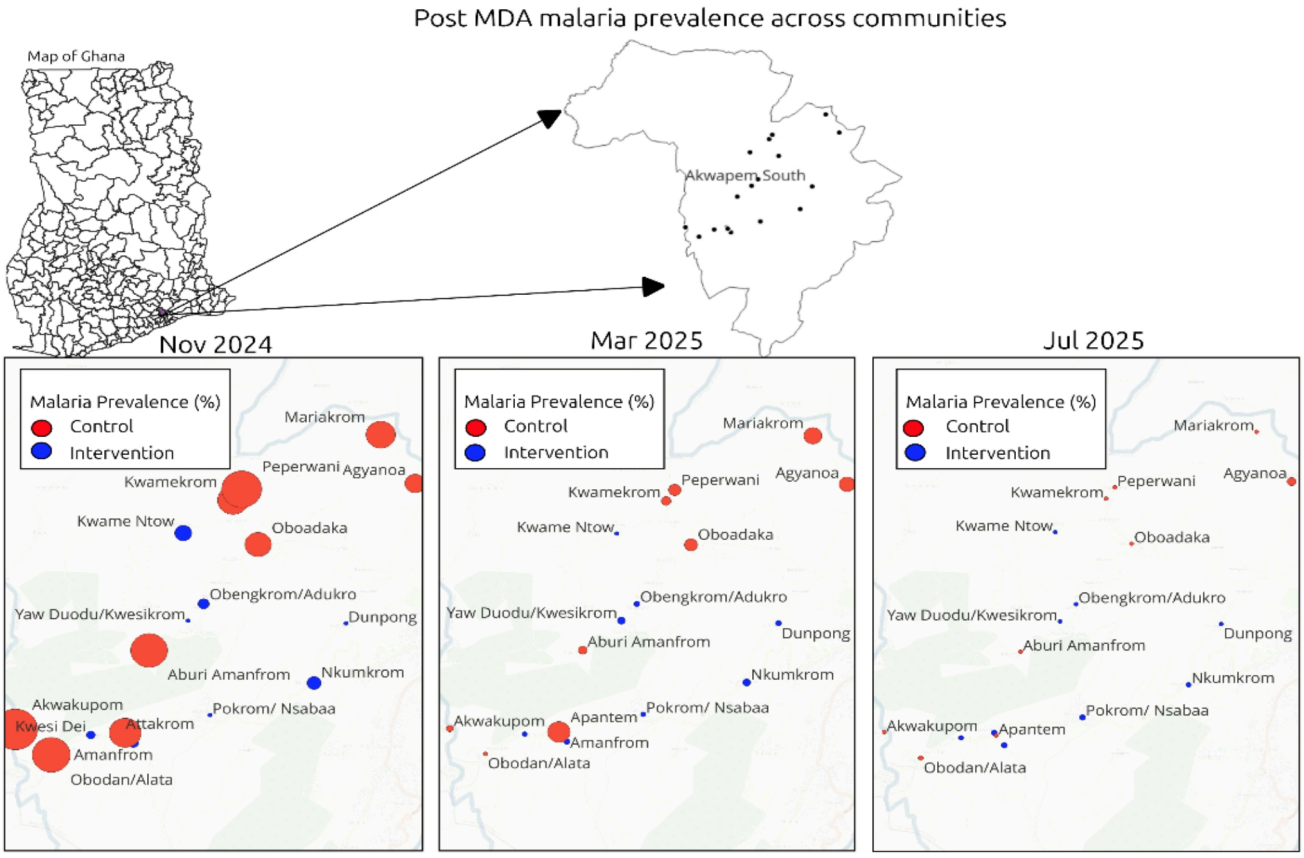


Figure 3

Spatial distribution of RDT-detectable malaria prevalence across the study communities during the surveillance period. Bubble size represents community-level malaria prevalence. This map was designed for this study by Ndong Henry Ndang and Brandon Nji Amambua-Ngwa using R version 4.4.1 and Canva.

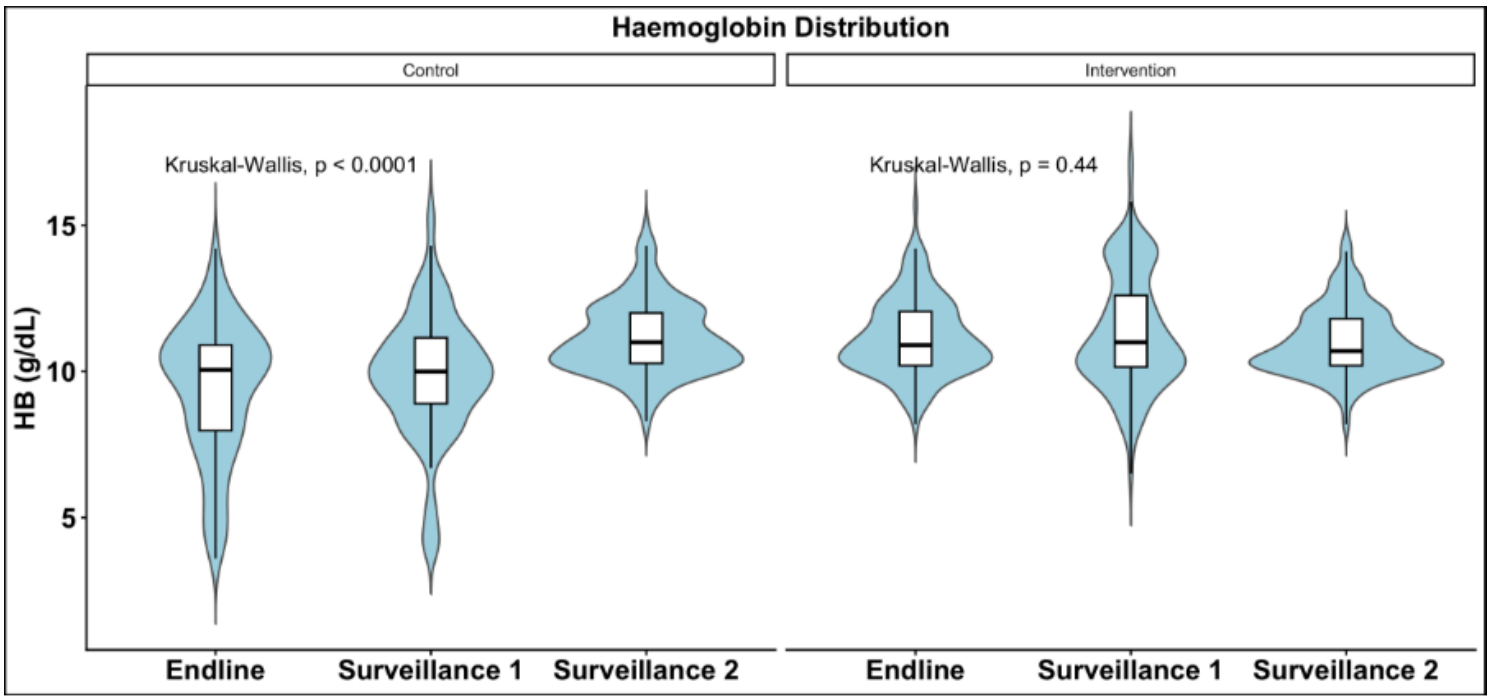


Figure 4

The distribution of haemoglobin (Hb) concentrations among children across the three surveillance surveys, stratified by study arm. Violin plots illustrate the density distribution of Hb values, while the embedded boxplots show the median and interquartile range (IQR).

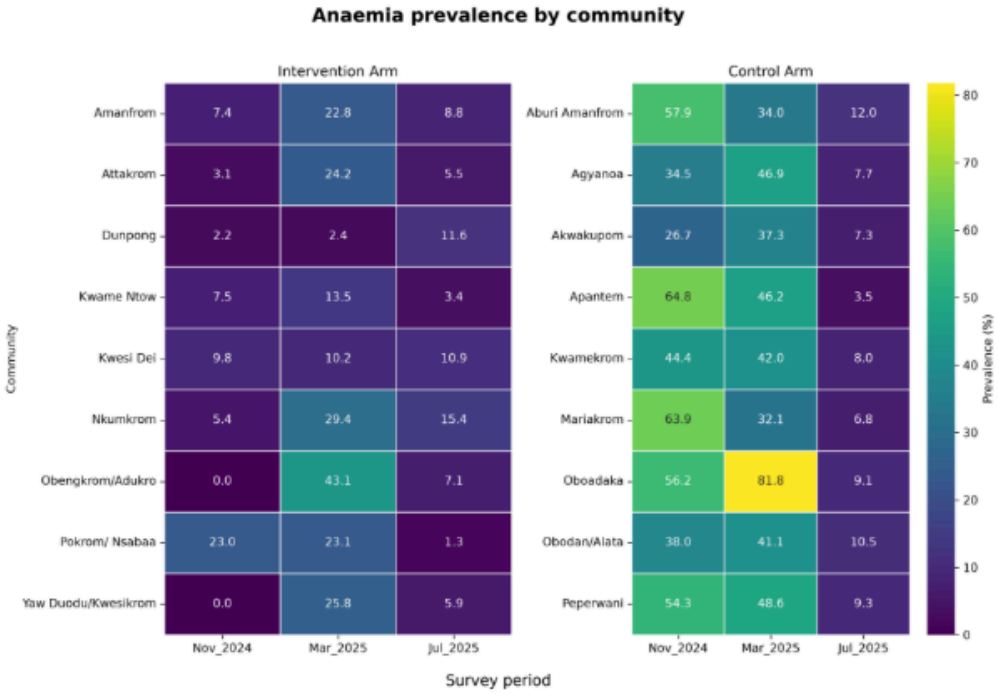


Figure 5

Heatmap showing anaemia prevalence among children aged ≤15 years across the 18 study communities during the three surveillance surveys (November 2024, March 2025, and July 2025).