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Adapting malaria indicator surveys to investigate treatment adherence: a pilot study on Bioko Island, Equatorial Guinea

David S. Galick[1*], Olivier Tresor Donfack[1], Teresa Ayingono Ondo Mifumu[1], Cristina Ngui Otogo Onvogo[1], Teobaldo Babo Dougan[1], Monica Idelvina Aling Ayen Mikue[1], Godino Esono Nguema[1], Charity Okoro Eribo[1], Maria Mirella Buila Euka[1], Kate P. Marone Martin[2], Wonder P. Phiri[1], Carlos A. Guerra[2] and Guillermo A. García[2*]

Abstract

Background Adherence to anti-malarial treatment regimens is an important aspect of understanding and improving the impact of malaria case management. However, both adherence to artemisinin-based combination therapy (ACT) and the factors driving it vary widely. While many other evaluation activities have been conducted on Bioko Island, until now adherence to anti-malarial treatments, and in particular ACT has not been evaluated.

Methods The implementation of a malaria indicator survey (MIS) conducted on Bioko in 2023 was leveraged to evaluate adherence to ACT provided to individuals testing positive following the survey. A follow-up team visited the targeted households, physically observed treatment blisters where possible, and provided messaging to household members on the importance of adhering to the treatment guidelines to household members. The team used survey data from the targeted households to make messaging as relevant to the household's particular context as possible.

Results Overall ACT adherence on Bioko Island was low, around 50%, and this varied demographically and geographically. Some of the highest transmission areas had exceptionally low adherence, but no systematic relationship between proper adherence and *Plasmodium falciparum* prevalence was detected. Estimates of adherence from follow-up visits were much lower than survey-based estimates in the same households (52.5% versus 87.1%), suggesting that lack of proper adherence may be a much larger issue on Bioko Island than previously thought.

Conclusion Representative surveys can be easily adapted to provide empirical estimates of adherence to anti-malarial treatments, complementary to survey-based and health facility-based estimates. The large discrepancy between adherence as measured in this study and survey-based estimates on Bioko Island suggests a health facility-based study to quantify adherence among the population receiving treatment for symptomatic malaria may be necessary.

*Correspondence:
David S. Galick
dgalick@mcd.org
Guillermo A. García
ggarcia@mcd.org
[1] MCD Global Health, Malabo, Equatorial Guinea
[2] MCD Global Health, Silver Spring, MD, USA

Background

Prompt and efficacious treatment is a core pillar in the control and eventual elimination of malaria, and a significant portion of the global reductions in malaria morbidity and mortality since the year 2000 has been attributed to the deployment of artemisinin-based combination therapy (ACT) [1]. However, lack of proper adherence to treatment dosing and timing can lead to increased

treatment failure and therefore worse clinical outcomes at the individual level, as well as significantly higher transmission intensity at the community level [2, 3]. In addition, lack of proper adherence to treatment can cause patients to have sub-therapeutic doses, one of the factors implicated in the spread of anti-malarial (in particular, artemisinin) resistance [4]. First identified in Cambodia, partial artemisinin resistance has now been identified in multiple sub-Saharan African countries, where it could threaten to reverse the gains ACTs have provided [5, 6].

Anti-malarial drug resistance monitoring is a large topic, and beyond the present scope, but understanding real treatment use patterns is one key aspect in such monitoring. Unfortunately, the global evidence base on ACT adherence, and especially the factors driving adherence (or lack thereof) is limited [7]. Most of the existing evidence comes from studies following up with malaria patients identified at health facilities. These studies most often count the number of pills missing and conduct interviews to measure adherence [8–11], although in some cases use an electronic monitoring system to precisely track when pills are taken or measure drug concentrations by biological assays [12–16]. Some representative surveys have also provided adherence data, but the quality of the information available is limited by the often small number of respondents with recent use of the medication of interest in low to moderate transmission areas in addition to response and social desirability biases [17, 18].

Despite the number of studies conducted, the differing designs and adherence definitions make consolidation into a unified evidence base difficult. Systematic reviews of the relevant literature have found large variation in the estimated adherence rates, and even larger variation in the factors driving adherence, in many cases with studies providing contradicting results about even the direction of effect (e.g. older age being associated with higher adherence in some cases and lower adherence in others) [7, 19, 20]. This heterogeneity is likely driven in part by factors difficult to account for in studies, such as the quality of care and medications available in the local medical system, sociocultural context, and the interaction of these and other factors determining trust in both medical facilities and the medications they provide [17]. Such context-specificity and substantial unexplained quantitative variation makes even moderately generalizable studies on approaches to improve adherence difficult. Nevertheless, there is some evidence that adapting treatment packages and implementing targeted communication activities have some success in increasing adherence in the population, with the caveat that effectiveness varies by context [21–23]. Hence, it may often be necessary for malaria control programmes to conduct a local assessment of treatment adherence in order to provide a relevant evidence base for decision-making on treatment-related activities, including social behaviour change communication (SBCC) to improve knowledge of and adherence to treatment guidelines. The present study presents results of a pilot implementation of such an assessment on Bioko Island, linked to and supported by the 2023 malaria indicator survey (MIS).

Since the onset of intensive malaria control on Bioko Island in 2004, several evaluations of impact have been conducted, mostly focused on vector control and entomological outcomes [24, 25], or disease burden [26–28], while more recent work has primarily considered the role of off-island travel and imported infections in malaria trends on Bioko [29–32]. Nevertheless, relatively little work has been undertaken to assess the effectiveness or contribution of case management to the progress observed. This is in part because any such evaluation must consider difficult questions such as the care-seeking rate, quality of care delivered throughout the health system (in both public and private facilities, as well as informal settings) and adherence to treatment guidelines. Routine health facility supervisions are conducted, which provide some information on the quality of care in public facilities but do not reach the private or informal sector. On the other hand, the MIS provides some information about these important dimensions of malaria case management, but is limited by recall and other types of response bias. The MIS also provides an opportunity to follow up with individuals testing positive for malaria with relatively little additional resources. Thus, this study, which leverages the MIS to investigate treatment adherence, is a first step to begin bridging the evidence gap on the impact of case management and related activities on Bioko Island.

Methods

Study site

Bioko Island is the largest island of Equatorial Guinea, containing the capital city, Malabo, and accounting for around 30% of the national population [33]. In 2004, the Bioko Island Malaria Control Project (since renamed to the Bioko Island Malaria Elimination project, or BIMEP) was founded by a public–private partnership to scale up malaria control activities on the island. Since 2004, the BIMEP has conducted intensive vector control campaigns, including annual rounds of indoor residual spraying (IRS), periodic distributions of long-lasting insecticide-treated bed nets (LLIN), and more recently, larval source management (LSM) primarily via BTI larviciding. To complement vector control, the BIMEP provides malaria case management and diagnostics training and supervision, and distributes anti-malarial treatments

and rapid diagnostic tests free of charge to public health facilities on the island. To monitor the impact of these activities, an annual MIS is conducted, along with continuous routine epidemiological and entomological surveillance.

MIS methodology

Details on the standard MIS methodology applied on Bioko have been published elsewhere [28]. In brief, the MIS questionnaire was adapted from the RBM MIS toolkit [34], and a stratified cluster sampling design was used with a total of 109 clusters (equivalently called primary sampling units, or PSUs). The target sample size was 25% of inhabited households per PSU in the rural/high transmission stratum, and 5% in the urban/low transmission stratum, for a total target sample size of around 5000 households. Malaria testing was performed on all consenting household members using rapid diagnostic tests (STANDARD Q Malaria Pf/Pan RDT, SD BIOSENSOR). As in all years since 2018, treatment distributors visited households with individuals testing positive by RDT during the survey to provide artemether/lumefantrine (AL) in accordance with national guidelines [35]. Children under age 15 were weighed prior to treatment administration to ensure distribution of the proper treatment dose: a blister pack of 6 (AL6) for children < 15 kg, pack of 12 (AL12) for children from 15–24 kg, pack of 18 (AL18) for children from 25–34 kg, and pack of 24 (AL24) for children ≥ 35 kg and adults. In 2023, distributors also digitized this data in the field on tablets using the same system as is used for MIS and other field intervention data, linking to the MIS data by the previously defined unique household identifier [36, 37]. As part of the data collection process, tablets automatically recorded the date and time of treatment distribution, and distributors registered information about both the responsible household member who received the treatment on behalf of all household members testing positive, as well as basic demographic information (e.g. age and gender) of the RDT-positive household members.

Adherence follow-up

Data collected by treatment distributors enabled daily preparation of a list of households with individuals who tested positive and received a treatment for follow-up on the final (third) day of their treatment. The follow-up visit had two main goals: (1) to physically observe treatments where possible and register the type and number of tablets missing, to assess adherence to treatment guidelines; and (2) to leverage the visit for SBCC, to foster knowledge of and adherence to malaria treatment protocols. Where RDT-positive members (or for children, their caretakers) were not present at the time of visit, the study team made at least 2 re-visit attempts. For households visited, all available treatment blisters for RDT-positive members were examined, and these examinations were the basis for adherence estimates. Initially, the team attempted to visit all households with an RDT-positive member. The first week of fieldwork showed the workload to be excessive given the size and logistical resources available to the follow-up team. Thus, a decision was made to adjust the protocol to reduce the number of households to visit, prioritizing those houses where multiple members tested positive, or a child under age 10 or pregnant woman tested positive, given their higher apparent risk. This selection was maintained for the remainder of the activity.

Training

Given that one important aim of follow-ups was to encourage proper adherence behaviours, five members of the existing BIMEP SBCC team were selected to carry out the activity, along with one member of the monitoring and evaluation team. None of the six team members were involved in MIS implementation. After identifying the follow-up team, a series of training sessions were organized for familiarization with the protocol, data collection instruments and, most importantly, to practice tailored, data-driven SBCC. Because individuals receiving follow-up had been surveyed in the last 3 days, a variety of information about their demographics, health and living situation was available prior to follow-up. One of the principal aims of the follow-up activity was to leverage this information to provide targeted messaging. For example, households which had a febrile member testing positive could be reminded of the free malaria diagnosis and treatment available in the nearest public health facility, while households with members testing positive who had bed nets but did not use them could also receive messaging on the preventative benefit of sleeping under a net. This method of communication is substantially different than the one-size-fits-all approach of messaging which had historically been used by the SBCC team.

To provide ample practice honing messaging and communication skills, a series of practice exercises was performed. Real survey data was used to provide realistic situations that the team could encounter in the field, and members role-played follow-up visits to households. Through these sessions, team members improved their ability to use information gathered in the MIS to adjust the communication style and messaging to be most relevant to the household encountered, and have a higher chance of achieving a change of behaviour, where desired. Throughout the follow-up activity, the team performed follow-up visits only three days per week, using other

days for other activities, and importantly to practice and plan approaches for follow-up.

Adherence definition

For the purposes of this study, proper adherence was defined as follows:

- If the treatment was distributed before 11AM, two doses were taken on the day of distribution, otherwise only one dose
- If the follow-up visit was after 11AM, one dose was already taken on that day, otherwise none, unless the follow-up visit occurred after treatment should have been finished (i.e. after the third day)
- For any days between the day of distribution and of verification visit, two doses were taken per day

While other adherence definitions were considered, this definition was chosen because it does not require that follow-up visits be performed after the full course should have been taken, or after both doses on a particular day should have been taken.

Analysis

Using the above definition, the proportion of treatments observed which were being taken properly was calculated overall and by various demographic breakdowns. Data from visits to households in the first week which did not meet the prioritization criteria later imposed (a pregnant woman, children under age 10, or multiple members testing positive) were excluded from the analysis. Because the data was collected as a non-random sub-sample of a complicated survey design, confidence intervals were not calculated, and no formal tests of statistical significance were performed. However, to examine a possible relationship between malaria prevalence and adherence, a smoother was fit to the relationship between the *Plasmodium falciparum* prevalence rate (*Pf*PR) estimated from the 2023 MIS RDT results and proportion of observed treatments following guidelines, by primary sampling unit (PSU), weighted by the number of treatments observed in the PSU. To examine the importance of possible outliers, this analysis was performed twice, once excluding a single PSU with particularly high *Pf*PR (and thus also many follow-up visits) and low adherence, located on the northwest coast of Bioko Island. PSUs with small numbers of observations were not excluded from any analysis, since the model structure of the smoother encoded the reduced information available in these data points via weighting. All data was processed and analysed using R version 4.2.2, and smoothers were fit with generalized additive models using a logit link, as implemented in the mgcv package [38, 39].

In addition to the data collected during follow-up visits, household-level information collected during the distribution of anti-malarial medication to individuals testing positive was leveraged for this study, including the age, gender, education level and relation of the responsible household member who received treatment on behalf of all RDT-positive household members. MIS data from the household was also linked, in order to stratify adherence among households where at least one member testing positive had a history of malaria symptoms. History of symptoms was defined as either an objective fever (temperature $\geq$ 38 °C measured on the day of the interview) or self-reported history of fever within the two weeks preceding the survey. Finally, households were assigned a wealth quintile based on a wealth index constructed by principal components analysis on household possessions, using the full MIS dataset.

For the purposes of comparison, estimates of *Pf*PR and (self-reported) anti-malarial drug adherence from the 2023 MIS are reported here. As noted above, *Pf*PR was based on results from a malaria RDT. Self-reported adherence was calculated from the responses to two questions posed to household members: first, whether they had taken any anti-malarial medication in the last 8 weeks, and second (for those reporting having taken an anti-malarial) whether they finished all pills in the most recent anti-malarial treatment. These questions were introduced in the questionnaire to provide a coarse measurement of the overall use of anti-malarials in the population, so were unrelated to reported history of fever, and use a longer recall period than standard (2 weeks) to reduce error by increasing the number of respondents with non-missing data, despite the risk of increased recall bias. Estimation for these indicators used the full MIS dataset (4998 households with 19,669 household members) and fully accounted for the complex design, including clustering at PSU and household levels and differing sampling probabilities by strata and PSU [40]. Unweighted estimates (i.e. crude estimates, which do not account for clustering or sampling probability) of self-reported adherence in only the households followed-up in this study are also presented for comparison.

Results

Treatment adherence

In total, the follow-up team visited 241 households across Bioko Island and physically observed 549 treatments. This accounted for 4.8% of the households surveyed (N = 4998), and 18% of the households with a positive RDT (N = 1332). The average number of treatments observed per household was 2.3 (range 1–10). Acceptance of the follow-up visits was very high, likely because all houses had previously agreed to the full MIS, but the

data collection form was only used for accepting households so no acceptance data was collected. Among treatments observed, the vast majority (85.4%, 469 of 549) received follow-up on the third (i.e. final) day of treatment, while small numbers of follow-ups were performed on the 2nd or 4th days of treatment (3.3% and 11.3%, 18 and 62 treatments observed, respectively). Observation and sensitization was performed in most inhabited areas of Bioko Island, with the exception of low-transmission areas outside of the main urban area, Malabo (Fig. 1).

Overall, adherence to treatment was low, around 50%. Contrary to expectations, adherence was slightly worse for AL6 (i.e. for young children) than other treatment types, and the presence of symptomatic infections in the household at the time of survey was not associated with adherence (Table 1). The factors with which adherence varied most were the age of the person who received treatments (higher among ages 25–54, 50–65%, than younger or older groups), their education level (highest among those with post-secondary education, 72.6%), and the socioeconomic status of the household (a clear gradient of adherence increasing with household wealth). Importantly, these trends concern to the household member who received treatment on behalf of other household members, and not necessarily for treatments intended for individuals among these groups. Due to the non-random nature of sampling, reliable confidence intervals could not be calculated, so while trends in adherence could be observed, no formal statistical tests were performed. Nearly all treatments observed had already been started (515 of 549, 93.8%), so adherence among individuals who had begun their treatment was highly consistent with adherence overall (Table 1).

Evaluation of the patterns and causes of non-adherence in this study were limited by the data available. However, a basic analysis showed that failure to start treatment formed a small portion of non-adherence (13% overall), while in most cases non-adherence was related to the number of pills taken (Table 2). Follow-up visits performed later had a lower proportion of treatments which had not been started (4.9% on day 4 compared to 14.3% on day 3), indicating that late initiation of treatment could be one driver in the non-adherence observed here. However, the low numbers of treatments observed on day 4 weaken the strength of this interpretation. It is important to note that since the criteria to define adherence were based on total pills taken since treatment distribution, late initiation of treatment would be classified as non-adherent according to the definition used here. In contrast to adherence, patterns of non-adherence were remarkably consistent across demographic breakdowns.

Estimates of adherence based on the MIS interview (i.e. self-reported adherence) were much higher than the estimates based on treatment inspection during follow-up visits (> 80% compared to around 50%, Table 3). Many factors could contribute to this large discrepancy, including recall and social desirability bias elevating survey-based estimates, the differing definitions of adherence in the MIS interview and follow-up visits, and the survey-based estimates implicit selection of patients seeking treatment.

Relationship between adherence and prevalence

A possible relationship between the spatial variation in adherence and the corresponding variation in the *Pf*PR was investigated, since people living in higher malaria

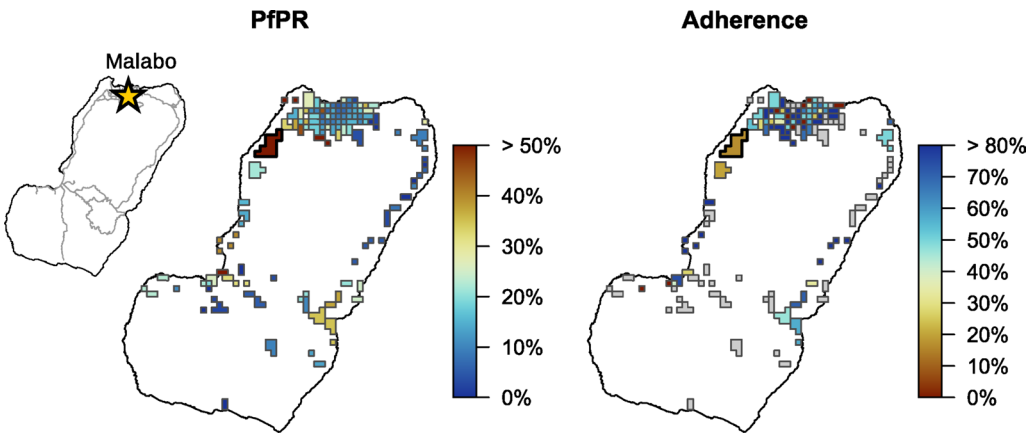

Fig. 1 *Pf* PR and proportion of individuals adhering to treatment up to time of follow-up visit by primary sampling unit (PSU). PSUs where no follow-up visits were conducted are shown in gray. Note that several PSUs with observed adherence of 0 or 1 have only a single observation. The PSU identified as a possible outlier is outlined in thicker black line. The inset at far left shows the location of the capital and only major city, Malabo (yellow star), and road network on Bioko Island for context

Table 1 Adherence among all individuals and among those who started the treatment as observed during follow-up visit by type of treatment distributed, time of follow-up (day in the treatment course, where day 3 corresponds to the final day of treatment), the relation to household head, gender, age and education level of the person that received the treatment (in many cases on behalf of the patient), survey stratum, whether any of the individuals testing positive reported symptoms during the survey, and the socioeconomic status of the household

	Overall		**Individuals who started treatment**	
	Adherence	**N observed**	**Adherence**	**N observed**
Treatment type				
AL6	44.80%	58	43.30%	60
AL12	58%	143	55.30%	150
AL18	53.30%	90	53.30%	90
AL24	58.50%	224	52.60%	249
Follow-uptime				
Day2	88.20%	17	83.30%	18
Day3	58%	438	53.70%	469
Day4	35.00%	60	33.90%	62
Gender of receiver				
Male	55.00%	120	50.00%	132
Female	56%	395	53.20%	417
Age of receiver				
< 25	38.50%	78	35.30%	85
25–34	61%	194	58.30%	204
35–44	56.80%	148	53.20%	158
45–54	68.30%	63	65.20%	66
55 +	37.50%	32	33.30%	36
Education level of receiver				
Atmost primary	50.00%	144	45.90%	157
Secondary	55%	308	51.10%	329
Post-secondary	76.20%	63	76.20%	63
Relation of receiver to household head				
Head	50.30%	197	46.70%	212
Spouse	58%	185	55.10%	196
Other	60.90%	133	57.40%	141
Stratum				
Rural/high transmission	54.40%	294	51.30%	312
Urban/low transmission	58%	221	54.00%	237
Symptoms in household				
Household with symptomatic infection	54.90%	164	50.60%	178
Household with no symptomatic infections	56%	351	53.40%	371
Wealth quintile				
Lowest	26.10%	88	23.20%	99
Second	58%	118	54.40%	125
Middle	56.80%	132	55.10%	136
Fourth	70.60%	102	64.90%	111
Highest	66.70%	75	64.10%	78
Overall	**56%**	**515**	**52.50%**	**549**

prevalence could be less likely to adhere to treatment if their malaria infections are more often asymptomatic or they are more used to living with symptoms. Geographically, there was notable variation in adherence to treatment. Disaggregation by primary sampling unit (PSU) showed that adherence was lower in some parts of the island, in particular the northwest coast and to a lesser extent the southeast coast (Fig. 1). By

Table 2 Characteristics among all non-adherent individuals, including the percentage of non-adherers who failed to start the treatment, and percentage of pills required for adherence taken by non-adherers as observed during follow-up visit by type of treatment distributed, time of follow-up (day in the treatment course, where day 3 corresponds to the final day of treatment), the relation to household head, gender, age and education level of the person that received the treatment (in many cases on behalf of the patient), survey stratum, whether any of the individuals testing positive reported symptoms during the survey, and the socioeconomic status of the household

	N observed	% Not started	N started	% Pills taken in treatments started
Treatment type				
AL6	34	5.9%	32	53%
AL12	67	10.4%	60	58%
AL18	42	0.0%	42	63%
AL24	118	21.2%	93	52%
Follow-up time				
Day2	3	33.3%	2	50%
Day3	217	14.3%	186	54%
Day4	41	4.9%	39	66%
Gender of receiver				
Male	66	18.2%	54	57%
Female	195	11.3%	173	55%
Age of receiver				
< 25	55	12.7%	48	54%
25–34	85	11.8%	75	56%
35–44	74	13.5%	64	55%
45–54	23	13.0%	20	58%
55 +	24	16.7%	20	61%
Education level of receiver				
Atmost primary	85	15.3%	72	52%
Secondary	161	13.0%	140	56%
Post-secondary	15	0.0%	15	65%
Relation of receiver to household head				
Head	113	13.3%	98	54%
Spouse	88	12.5%	77	58%
Other	60	13.3%	52	55%
Stratum				
Rural/high transmission	152	11.8%	134	55%
Urban/low transmission	109	14.7%	93	57%
Symptoms in household				
Household with symptomatic infection	88	15.9%	74	59%
Household with no symptomatic infections	173	11.6%	153	54%
Wealth quintile				
Lowest	76	14.5%	65	49%
Second	57	12.3%	50	59%
Middle	61	6.6%	57	54%
Fourth	39	23.1%	30	62%
Highest	28	10.7%	25	63%
Overall	**261**	**13.0%**	**227**	**56%**

Table 3 Percentage and number of respondents who reported receiving an anti-malarial treatment in the 8 weeks preceding the survey date, and percentage of those who received a treatment that reported finishing it according to 2023 MIS data

	Households followed-up (unweighted)	Representative estimate (weighted)
Received drug in last 8 weeks (%)	8.7%	7.2% (6.7–7.7)
Received drug in last 8 weeks (N)	157	1397
Finished most recent treatment (%)	87.1%	83.3% (80.7–85.6)

Estimates reflect self-reported use of and adherence to anti-malarial treatment for all respondents in the time period, regardless of history of fever

comparison, adherence in urban Malabo, in the north of the island, was relatively high. These differences at least somewhat follow the distribution of prevalence, with the very low adherence areas in many cases having elevated prevalence. However, this relationship did not appear to be systematic. While smoothers fit to the full data identified a trend of decreasing adherence with rising prevalence, the apparent relationship was driven by data from a single PSU on the northwest coast with particularly high *Pf*PR and particularly low adherence. On excluding this PSU, the fit to the data did not indicate a decrease in adherence with *Pf*PR (Fig. 2). Correspondingly, despite substantial differences in prevalence between strata, adherence was similar across strata.

Discussion

In this study, modest operational adjustments to the MIS were sufficient to collect information on ACT adherence based on physical inspection of treatment blisters during follow-up visits, in addition to self-reported survey data. However, it is worth mentioning that the approach used here should be regarded as complementary rather than a substitute for survey-based estimates. It is not uncommon for surveys to collect (self-reported) data on adherence, but the quality of this information is limited by social desirability and recall bias, and in some cases, particularly in low to moderate transmission areas, by the low number of respondents with recent use of the medication of interest [17, 18, 41]. On the other hand, the follow-up based approach employed here considers adherence among all RDT-positive respondents (regardless of symtomaticity or treatment-seeking), so results may not be representative of patterns for the principal population using ACT (patients seeking treatment for fever). In this study, estimates based on follow-up visits were dramatically lower than the survey-based estimates (Table 3). Despite methodological differences, and non-representative sampling of follow-ups, the magnitude of the difference in estimates suggests that adherence to treatment given in public health facilities may be substantially lower than indicated by self-reported estimates. Adherence in the households followed up in this study based on self-report was highly similar to the representative island-wide estimate, so the discrepancy observed is likely related to the method of data collection, and not a household selection bias. Moreover, since

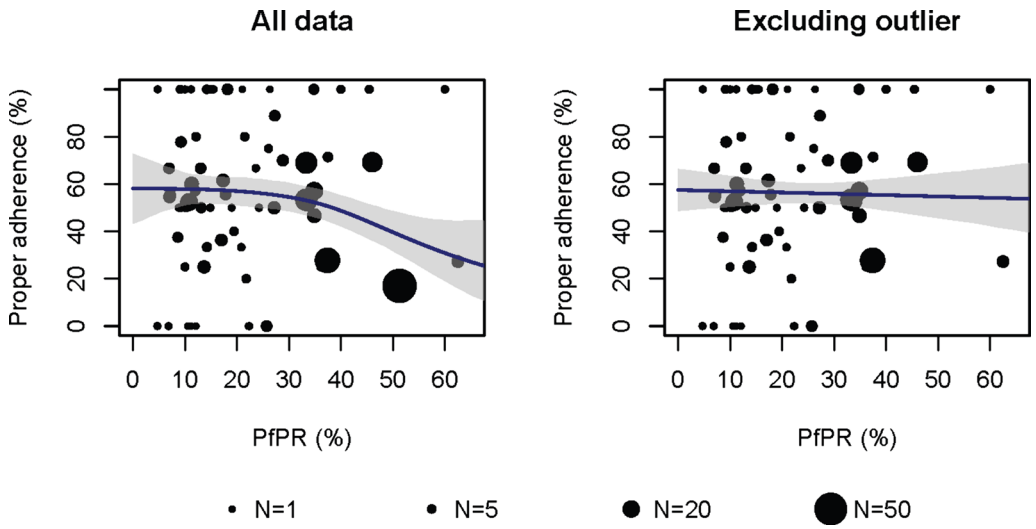

Fig. 2 Relationship between estimated *Plasmodium falciparum* prevalence (*Pf* PR) in 2023 and proper adherence to treatment protocols by PSU. Size of points indicates the number of treatments observed for adherence, and line shows a smoother fitted to this relationship with 95% confidence interval. On left, the relationship and smoother fitted using all data; on right, the same, excluding a single PSU with high *Pf* PR and low adherence

nearly all treatments observed had already been initiated, this difference was not a result of excluding treatments, which were received but never started. One factor causing the large discrepancy may be the long period of period of recall for the self-report survey questions (8 weeks). Reducing the recall period, for example to two weeks, could improve consistency between self-report and follow-up estimates, but would also likely decrease the number of individuals reporting use of anti-malarials, increasing uncertainty. These results also point to the challenges mass treatment campaigns are likely to meet on Bioko. Indeed, mass drug administration could suffer lower adherence than observed here given the lack of testing to confirm infection prior to distributing treatment.

Adherence varied notably by several characteristics of the household and the household member who received treatments on behalf of the household. Household wealth appeared to be the most important factor, with adherence increasing from only 23.2% in the lowest wealth quintile to nearly 65% in the two wealthiest quintiles. It is not clear whether this relationship is causal, or merely an association, but points to a need for targeted communication activities to reach the most marginalized communities. In addition, the increased adherence to treatments when distributed to members age 25–54 provides a lesson for drug distribution in future surveys or mass treatment campaigns, in terms of which household members should be prioritized for receiving treatments on behalf of the household where possible.

The low adherence in some of the highest transmission areas on the island observed in this study is especially concerning, and warranting of intervention where these patterns hold true (the northwest and west coast, and to some extent in Riaba on the southeast coast). Due to the structure of the data, treatments could not be matched to individual-level MIS data, but at least at the household level the presence of symptomatic infections did not meaningfully impact adherence to treatment, suggesting that these differences are likely driven by local behaviour and not symptomaticity of infections. Additional analysis of the relationship between 2023 prevalence and observed treatment adherence further supported this interpretation (Fig. 2). One possible explanation for the lack of importance of symptoms at diagnosis is that completing the treatment regimen may be affected most by the severity of symptoms mid-way through the course [22]. If this is true, then patients who recover from symptoms after the first few doses may be no more likely to finish the regimen than those who did not present symptoms at any time.

This pilot study highlighted the need to adapt an SBCC strategy according to the specific issues identified in the field. While evidence on the impact of messaging for improving adherence to anti-malarial medication has been mostly limited to the role of SMS reminders [13, 42, 43], various communication approaches have been shown to increase uptake or adherence to other types of medication [44, 45]. One important finding in other disease contexts has been that in many cases interventions focusing on providing education alone, and not targeting specific behaviours, had little if any impact on adherence [46]. On Bioko Island, malaria-related communication activities have generally taken this approach, focusing primarily on improving awareness of the availability and importance of malaria prevention (by ITN, IRS and eliminating larval habitats) and of free malaria diagnosis, treatment, and prophylaxis during pregnancy in public health facilities. The results of this analysis suggest that (in line with the literature) the effectiveness of this blanket SBCC strategy for treatment adherence has been limited, either because of a failure to reach important populations or to achieve behaviour change for those reached. At the same time, the context-driven communication approach taken during this pilot provides an example of how other approaches could be adopted on Bioko. During adherence follow-up visits the study team's messaging was much more dependent on context than in previous campaigns and focused primarily on the adherence behaviours desired, supported by education on their importance. As such, workers were able to tailor the way they addressed the household and how the message was delivered by leveraging specific information about individuals and households available from the survey responses.

Anecdotally, the change in approach towards more context-aware and data-driven interpersonal messaging appeared to facilitate greater uptake of desired behaviours (in this case, treatment adherence) as compared to previous campaigns. In general, this is in line with global recommendations to perform SBCC in an iterative planning, implementation and evaluation cycle [47], but takes the idea one step further by using extremely recent data from the households targeted to identify unique and relevant characteristics of the audience and adapt messaging accordingly. While it can be quite effective to segment audiences into homogeneous subgroups and develop custom messages for each segment, the approach of tailoring messages to a household, or even to an individual within the household has significant potential. Such tailoring could promote a better nexus between the communicator and the recipient, provide messages more relevant to their context, and ultimately increase uptake of the desired behaviours. Early studies of tailored messaging clearly showed that using materials adapted to individual

characteristics were more effective than more generic materials, and ongoing research has explored various applications and a wide breadth of contexts for tailoring health-related messages [48, 49]. For this study, further work will be necessary in several areas to better understand and more rigorously evaluate the role of such targeted and personalized SBCC interventions for malaria prevention and control on Bioko, including message design, consideration of other variables such as individual's perception of risk, tailoring messages using digital channels, and application of persuasion theories, above and beyond the standard behaviour change theories.

Although the results presented here provide important programmatic lessons, there are significant limitations to the data. Due to the conservative definition of proper adherence, and the fact that most follow-up visits were performed on the final day of treatment, and not after the full treatment should have been finished, these are likely over-estimates of adherence. The observed decreases in adherence (from 83.3% on the second day to 53.7% on the third day down to 33.9% on day four) support this assumption (Table 1) and give an idea of how low proper adherence to the full treatment regimen could actually be. Beyond this follow-up time bias, the non-random nature of selecting households for follow-up makes generalizing results to the wider population difficult, while the lack of formal statistical significance testing weakens any subgroup analysis. Additionally, many of the individuals receiving treatment likely would not have sought care at health facilities and received a treatment had they not been surveyed, so adherence among patients receiving anti-malarial treatments in health facilities may differ substantially. Thus, inferences from these data, especially for health facility-based activities, should be made with a high degree of caution. Nevertheless, results do provide a new base of evidence for programmatic decision-making on Bioko Island and more broadly in Equatorial Guinea.

In cases where the primary goal is to glean information about adherence to treatments for patients seeking treatment, the approach presented here is limited but could be adapted to better suit the goals. In future implementations, data should be structured such that treatments observed could be directly linked to individual-level survey data. This would allow analysis of adherence for example among symptomatic patients, providing a better approximation for the population of individuals receiving treatments during care-seeking behaviour. Model-based methods could also be used to quantify the likelihood that an individual would seek care if febrile using survey data, and leverage this to estimate the likely adherence among care-seeking individuals. Prioritization of households and/or individuals for follow-up will also be an important consideration, given the large volume of RDT-positive individuals identified by many surveys, including in this study.

The large inconsistency observed between survey-based estimates using self-reported data and physical observation on follow-up means that an important next step for Bioko Island is to conduct even a small follow-up adherence study among individuals receiving anti-malarial treatments in public health facilities. Similar studies have been conducted in many other contexts [15, 50–52], and could also be designed to investigate the impact on Bioko of low-cost adjustments which have been shown to increase adherence, such as adding stickers with short key messages to packaging or sending short SMS reminders to encourage patients to finish their anti-malarial treatments [22, 42, 43]. Qualitative research on the factors driving lack of adherence on Bioko would also be an important consideration for planning activities to improve adherence. Without these types of future research, it may not be possible to accurately understand the magnitude of the non-adherence problem on Bioko, and more importantly what can be done to make progress.

Conclusion

This study has shown that in addition to self-reported adherence data, representative surveys can be easily adapted to collect observations of treatment use behaviours in follow-up visits. This information may differ substantially from estimates based on self-reported data, due to recall bias, the effect of treatment seeking, and other factors. On Bioko Island, post-survey adherence to treatment was low, but not uniformly so, and was particularly low in some of the highest transmission areas of the island. These findings are of high importance for improving SBCC activities, and for critically assessing the feasibility of related programmatic activities, particularly mass drug administration.

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Author contributions

DSG, OTD and GAG designed the study; TAOM, CNOO, TBD, MIAAM, GEN, COE, and MMBE conducted fieldwork; DSG and OTD oversaw fieldwork; DSG cleaned and analysed data, and prepared the first draft of the manuscript; CAG and GAG provided critical input and supervision; all authors reviewed and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was provided by the ethics committee of the Ministry of Health and Social Welfare of Equatorial Guinea to implement the Malaria Indicator Survey. All respondents provided further verbal informed consent to be interviewed during follow-up visits.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. Nature. 2015;526:207–11.
2. Challenger JD, Bruxvoort K, Ghani AC, Okell LC. Assessing the impact of imperfect adherence to artemether-lumefantrine on malaria treatment outcomes using within-host modelling. Nat Commun. 2017;8:1373.
3. Challenger JD, Gonçalves BP, Bradley J, Bruxvoort K, Tiono AB, Drakeley C, et al. How delayed and non-adherent treatment contribute to onward transmission of malaria: a modelling study. BMJ Glob Health. 2019;4: e001856.
4. Barnes KI, Watkins WM, White NJ. Antimalarial dosing regimens and drug resistance. Trends Parasitol. 2008;24:127–34.
5. Balikagala B, Fukuda N, Ikeda M, Katuro OT, Tachibana SI, Yamauchi M, et al. Evidence of artemisinin-resistant malaria in Africa. N Engl J Med. 2021;385:1163–71.
6. Uwimana A, Umulisa N, Venkatesan M, Svigel SS, Zhou Z, Munyaneza T, et al. Association of *Plasmodium falciparum* kelch13 R561H genotypes with delayed parasite clearance in Rwanda: an open-label, single-arm, multicentre, therapeutic efficacy study. Lancet Infect Dis. 2021;21:1120–8.
7. Banek K, Lalani M, Staedke SG, Chandramohan D. Adherence to artemisinin-based combination therapy for the treatment of malaria: a systematic review of the evidence. Malar J. 2014;13:7.
8. Santos HFP, Guaraldo L, Pedro RS, Damasceno LS, Daniel-Ribeiro CT, Brasil P. Methods to assess adult and adolescent patients' adherence to antimalarial treatment: a systematic review. Front Pharmacol. 2022;13: 796027.
9. Oduro AR, Chatio S, Beeri P, Anyorigiya T, Baiden R, Adongo P, et al. Adherence to dihydroartemisinin-piperaquine treatment among patients with uncomplicated malaria in Northern Ghana. J Trop Med. 2019;2019:5198010.
10. Takahashi E, Nonaka D, Iwagami M, Phoutnalong V, Chanthakoumane K, Kobayashi J, et al. Patients' adherence to artemisinin-based combination therapy and healthcare workers' perception and practice in Savannakhet province Lao PDR. Trop Med Health. 2018;46:44.
11. Lemma H, Löfgren C, San SM. Adherence to a six-dose regimen of artemether-lumefantrine among uncomplicated *Plasmodium falciparum* patients in the Tigray Region, Ethiopia. Malar J. 2011;10:349.
12. Bruxvoort K, Festo C, Cairns M, Kalolella A, Mayaya F, Kachur SP, et al. Measuring patient adherence to malaria treatment: a comparison of results from self-report and a customised electronic monitoring device. PLoS ONE. 2015;10: e0134275.
13. Steury EE. Mobile phone short message service to improve malaria pharmacoadherence in Zambia. J Nurs Scholar. 2016;48:354–61.
14. Fogg C, Bajunirwe F, Piola P, Biraro S, Checchi F, Kiguli J, et al. Adherence to a six-dose regimen of artemether-lumefantrine for treatment of uncomplicated *Plasmodium falciparum* malaria in Uganda. Am J Trop Med Hyg. 2004;71:525–30.
15. Simba DO, Kakoko D, Tomson G, Premji Z, Petzold M, Mahindi M, et al. Adherence to artemether/lumefantrine treatment in children under real-life situations in rural Tanzania. Trans R Soc Trop Med Hyg. 2012;106:3–9.
16. Minzi O, Maige S, Sasi P, Ngasala B. Adherence to artemether-lumefantrine drug combination: a rural community experience six years after change of malaria treatment policy in Tanzania. Malar J. 2014;13:267.
17. Banek K, DiLiberto DD, Webb EL, Smith SJ, Chandramohan D, Staedke SG. Exploring barriers and facilitators of adherence to artemisinin-based combination therapies for the treatment of uncomplicated malaria in children in Freetown Sierra Leone. Healthcare. 2021;9:1233.
18. Galactionova K, Tediosi F, de Savigny D, Smith T, Tanner M. Effective coverage and systems effectiveness for malaria case management in sub-Saharan African countries. PLoS ONE. 2015;10: e0127818.
19. Yakasai AM, Hamza M, Dalhat MM, Bello M, Gadanya MA, Yaqub ZM, et al. Adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria: a systematic review and meta-analysis. J Trop Med. 2015;2015: e189232.
20. Bruxvoort K, Goodman C, Kachur SP, Schellenberg D. How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs. PLoS ONE. 2014;9: e84555.
21. Fuangchan A, Dhippayom T, Kongkaew C. Intervention to promote patients' adherence to antimalarial medication: a systematic review. Am J Trop Med Hyg. 2014;90:11–9.
22. Cohen J, Saran I. The impact of packaging and messaging on adherence to malaria treatment: evidence from a randomized controlled trial in Uganda. J Develop Econom. 2018;134:68–95.
23. Swain TR, Raulo A, Mohapatra N, Singha MR. Information education and communication can improve adherence to artemether-lumefantrine combination in patients of uncomplicated falciparum malaria. J Clin Diagn Res. 2015;9:FC01-3.
24. Sharp BL, Ridl FC, Govender D, Kuklinski J, Kleinschmidt I. Malaria vector control by indoor residual insecticide spraying on the tropical island of Bioko, Equatorial Guinea. Malar J. 2007;6:52.
25. Overgaard HJ, Reddy VP, Abaga S, Matias A, Reddy MR, Kulkarni V, et al. Malaria transmission after five years of vector control on Bioko Island, Equatorial Guinea. Parasit Vectors. 2012;5:253.
26. Kleinschmidt I, Sharp B, Benavente L, Schwabe C, Torrez M, Kuklinski J, et al. Reduction in infection with *Plasmodium falciparum* one year after the introduction of malaria control interventions on Bioko Island, Equatorial Guinea. Am J Trop Med Hyg. 2006;74:972–8.
27. Kleinschmidt I, Schwabe C, Benavente L, Torrez M, Ridl FC, Segura JL, et al. Marked increase in child survival after four years of intensive malaria control. Am J Trop Med Hyg. 2009;80:882–8.
28. Cook J, Hergott D, Phiri W, Rivas MR, Bradley J, Segura L, et al. Trends in parasite prevalence following 13 years of malaria interventions on Bioko island, Equatorial Guinea: 2004–2016. Malar J. 2018;17:62.
29. Bradley J, Monti F, Rehman AM, Schwabe C, Vargas D, Garcia G, et al. Infection importation: a key challenge to malaria elimination on Bioko Island, Equatorial Guinea. Malar J. 2015;14:46.
30. Guerra CA, Citron DT, García GA, Smith DL. Characterising malaria connectivity using malaria indicator survey data. Malar J. 2019;18:440.
31. Citron DT, Guerra CA, García GA, Wu SL, Battle KE, Gibson HS, et al. Quantifying malaria acquired during travel and its role in malaria elimination on Bioko Island. Malar J. 2021;20:359.
32. García GA, Janko M, Hergott DEB, Donfack OT, Smith JM, Mba Eyono JN, et al. Identifying individual, household and environmental risk factors for malaria infection on Bioko Island to inform interventions. Malar J. 2023;22:72.
33. Instituto Nacional de Estadística de Guinea Ecuatorial. Guinea Ecuatorial en Cifras 2018. 2019. http://www.inege.gq/wp-content/uploads/2019/01/GE_Cifras_2018.pdf.
34. Roll Back Malaria. Malaria indicator survey toolkit. https://www.malariasurveys.org/toolkit.cfm.
35. Programa Nacional de Lucha contra el Paludismo. Guía terapéutica nacional del paludismo en Guinea Ecuatorial. Equatorial Guinea: Republica de Guinea Ecuatorial, Minesterio de Sanidad y Bienestar Social; 2019.
36. García GA, Atkinson B, Donfack OT, Hilton ER, Smith JM, Eyono JNM, et al. Real-time, spatial decision support to optimize malaria vector control: the

case of indoor residual spraying on Bioko Island Equatorial Guinea. PLoS Digit Health. 2022;1: e0000025.
37. García GA, Hergott DEB, Phiri WP, Perry M, Smith J, Osa Nfumu JO, et al. Mapping and enumerating houses and households to support malaria control interventions on Bioko Island. Malar J. 2019;18:283.
38. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2022. https://www.R-project.org/.
39. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J R Stat Soc. 2011;73:3–36.
40. Lumley T. Complex surveys: a guide to analysis using R. New Jersey: Wiley; 2010.
41. Onyango EO, Ayodo G, Watsierah CA, Were T, Okumu W, Anyona SB, et al. Factors associated with non-adherence to Artemisinin-based combination therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya. BMC Infect Dis. 2012;12:143.
42. Modrek S, Schatzkin E, De La Cruz A, Isiguzo C, Nwokolo E, Anyanti J, et al. SMS messages increase adherence to rapid diagnostic test results among malaria patients: results from a pilot study in Nigeria. Malar J. 2014;13:69.
43. Raifman JRG, Lanthorn HE, Rokicki S, Fink G. The impact of text message reminders on adherence to antimalarial treatment in Northern Ghana: a randomized trial. PLoS ONE. 2014;9: e109032.
44. Conn VS, Ruppar TM, Enriquez M, Cooper P. Medication adherence interventions that target subjects with adherence problems: systematic review and meta-analysis. Res Soc Admin Pharm. 2016;12:218–46.
45. Karki P, Prabandari YS, Probandari A, Banjara MR. Feasibility of school-based health education intervention to improve the compliance to mass drug administration for lymphatic Filariasis in Lalitpur district, Nepal: a mixed methods among students, teachers and health program manager. PLoS ONE. 2018;13: e0203547.
46. Costa E, Giardini A, Savin M, Menditto E, Lehane E, Laosa O, et al. Interventional tools to improve medication adherence: review of literature. Patient Prefer Adher. 2015;9:1303–14.
47. The Strategic Framework for Malaria Social and Behaviour Change Communication 2018–2030. The RBM Partnership to End Malaria; 2018.
48. Noar SM, Harrington NG, Aldrich RS. The role of message tailoring in the development of persuasive health communication messages. Ann Int Commun Assoc. 2009;33:73–133.
49. Pope JP, Pelletier L, Guertin C. Starting off on the best foot: a review of message framing and message tailoring, and recommendations for the comprehensive messaging strategy for sustained behavior change. Health Commun. 2018;33:1068–77.
50. Gerstl S, Namagana A, Palacios L, Mweshi F, Aprile S, Lima A. High adherence to malaria treatment: promising results of an adherence study in South Kivu, Democratic Republic of the Congo. Malar J. 2015;14:414.
51. Camara A, Moriarty LF, Guilavogui T, Diakité PS, Zoumanigui JS, Sidibé S, et al. Prescriber practices and patient adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria in Guinea, 2016. Malar J. 2019;18:23.
52. Bawate C, Callender-Carter ST, Guyah B, Ouma C. Factors influencing patients' adherence to malaria artemisinin-based combination therapy in Kamuli District, Uganda. Malar J. 2024;23:1.

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