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Assessing strategies to improve adherence to vivax malaria treatment in the Amazon region using educational materials and a mobile health strategy (AdheVivax Project): An exploratory mixed-method study

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Abstract

Background

Adherence to the complete chloroquine–primaquine regimen is important for achieving a radical cure of *Plasmodium vivax* malaria. However, the 7- or 14-day treatment course and its associated challenges may hinder consistent medication use in endemic areas. This study aimed to assess a combined educational and mHealth intervention to support adherence to *P. vivax* treatment in the Brazilian Amazon.

Methods

We conducted a sequential exploratory mixed-methods study in two municipalities of the Brazilian Amazon. In Phase 1, semi-structured interviews were conducted with patients and healthcare providers (HCPs) to explore perceptions, barriers, and facilitators related to P. vivax treatment adherence. These findings informed the co-design of a culturally adapted adherence support intervention, consisting of a printed educational envelope and SMS and/or WhatsApp messages delivered throughout treatment. In Phase 2, a cluster-randomized trial was conducted in 10 health units in Manaus, comparing the intervention (educational envelope plus messages) with standard care. Adherence was assessed between days 7 and 12 using the Morisky Medication Adherence Scale. A qualitative sub-study was conducted to assess the acceptability and appropriateness of the intervention.

Results

In Phase 1, qualitative findings identified key determinants of adherence, including the role of directly observed therapy, barriers related to pill burden and side effects, and the potential of digital reminders. These findings informed the development of a combined adherence support intervention, consisting of a printed educational envelope (validated by 16 HCPs) and a set of SMS and/or WhatsApp messages. In Phase 2, 227 participants were enrolled across 10 health units, with 117 in the intervention group and 110 in the control group. Overall adherence was 79%, with no substantial difference observed between the intervention and control groups (81% vs 77%). The qualitative sub-study indicated high acceptability of the intervention. The educational envelope supported medication organization, while cell phone message reminders helped reduce forgetfulness.

Conclusions

Although no significant improvement in adherence was observed, the intervention was feasible, well accepted, and contextually appropriate. Low-cost, culturally adapted tools may complement directly observed therapy in urban Amazonian settings and be adapted for remote areas with limited connectivity to support malaria elimination in Brazil.

Introduction

Globally, poor adherence to the standard chloroquine–primaquine (CQ-PQ) regimen for *P. vivax* sustains malaria transmission by reducing the likelihood of achieving a radical cure. Evidence from diverse endemic regions demonstrates that incomplete compliance with PQ is consistently associated with a higher risk of recurrence [1]. Additional barriers include social and economic constraints, health system limitations, and treatment-related factors such as the bitter taste of CQ, the high pill burden, adverse side effects, and difficulty swallowing large tablets, all of which further undermine adherence [2,3]. Given that non-adherent patients are more than twice as likely to experience recurrence, poor adherence represents a major obstacle to malaria elimination efforts [4].

In Brazil, non-adherence to the 7-day *P. vivax* treatment regimen has been reported to range from 13% to 33%, driven primarily by forgetfulness, misinterpretation of dosing instructions, early symptom relief, and alcohol consumption during therapy [5–7]. This challenge is particularly relevant in Brazil, which remains the country with the highest number of malaria cases in the Americas, accounting for 24.4% of all reported cases in the region in 2024 [8]. Malaria transmission in the country is almost entirely concentrated in the Amazon region, where 99% of cases occur, with *P. vivax* responsible for 82.5% of infections [9]. Recognizing the importance of improving treatment outcomes, Brazil's National Plan for Malaria Elimination aims to achieve zero autochthonous malaria cases by 2035, a goal that will require not only effective case management but also strategies to improve adherence to treatment, particularly for *P. vivax* with its longer therapeutic regimen [3,5,6].

Educational strategies have shown promise in improving adherence to antimalarial treatment, especially in resource-limited and endemic areas. Community-based educational interventions foster awareness, encourage early treatment-seeking, and strengthen adherence [10]. In Myanmar, such interventions increased adherence to the 14-day PQ regimen for *P. vivax* malaria [11]. Supportive tools, including pictorial instructions, simplified packaging, and SMS reminders, have further reduced missed doses and improved treatment completion [12,13].

Building on these advances, mobile health (mHealth) interventions have consistently improved treatment adherence for infectious diseases, particularly in resource-limited settings. Randomized trials demonstrate that simple text message reminders can significantly enhance adherence to antimalarial therapies, while meta-analyses indicate similar benefits for antiretroviral treatment, especially with interactive messages [12,14]. mHealth tools have also improved access to appropriate treatment for childhood illnesses and enhanced community health worker performance [15]. With mobile and satellite internet coverage gradually expanding in the Amazon, digital solutions offer a feasible and scalable strategy to support malaria elimination goals. Despite the growing use of educational and digital health strategies, there remains limited evidence on the effectiveness of combined, culturally adapted interventions to support adherence to P. vivax treatment in real-world settings in the Amazon region.

This study aimed to identify key barriers and facilitators to treatment adherence and to design and evaluate a culturally adapted educational and mHealth intervention to support treatment completion in the Brazilian Amazon.

Methods

Study site

This sequential exploratory mixed-methods study was conducted in two malaria-endemic municipalities in the state of Amazonas, Brazil: Manaus and Ipixuna. These sites were selected to reflect contrasting *P. vivax* transmission settings, health system capacities, and socioeconomic context (Figure 1). Manaus, the state capital and largest city, is an urban center with extensive healthcare infrastructure, high population mobility, and expanding peri-urban settlements. In contrast, Ipixuna is a remote municipality near the Peruvian border, characterized by geographic isolation, limited health services, and a predominantly rural and Indigenous population.

According to the Sustainable Cities Development Index (IDSC-BR), which scores municipalities on a scale from 0 to 100, Ipixuna received just 28.52 points, ranking last among all 5,570 Brazilian municipalities and classified as having a very low sustainable development. Manaus, in comparison, scored 44.73 points, corresponding to the "low" development category[16].

Malaria transmission intensity also diverged markedly between sites. In 2023, the Annual Parasite Index (API) was 27.7 cases per 1,000 inhabitants in Ipixuna, indicating high transmission, while in Manaus the API was 1.8, consistent with low endemicity [17]. Including Ipixuna ensured representation of highly vulnerable and hard-to-reach areas of the Amazon. In these settings, geographic, infrastructural, and socioeconomic barriers compound the challenges of malaria control and treatment adherence. However, due to the absence of mobile network and internet connectivity, Ipixuna only participated in the phase 1 and was excluded from the subsequent mHealth-based trial.

Study Design

The study was structured into two interdependent phases. In the first phase, we conducted qualitative interviews with patients and healthcare providers (HCPs) in both urban and remote settings to identify key barriers and facilitators to adherence to *P. vivax* treatment. These findings guided the design, leading us to develop culturally adapted educational materials and an mHealth intervention. The second phase consisted of a cluster-randomized trial to assess the intervention's effectiveness on adherence outcomes, conducted in primary health units in Manaus, where mobile communication infrastructure was available. This trial was prospectively registered in the Brazilian Clinical Trials Registry (ReBEC; RBR-3p8pxy5) and was reported in accordance with the CONSORT guideline (Additional file 1).

Phase 1 – Exploratory qualitative study and co-design of adherence support intervention

This phase integrated an exploratory qualitative study with the co-design of a culturally adapted adherence support intervention. It aimed to identify barriers and facilitators to *P. vivax* malaria treatment adherence and to translate these findings into intervention components. This phase was conducted across both study sites.

Qualitative data were collected between August 2023 and December 2024 through semi-structured interviews with two key groups: (a) patients diagnosed and treated for uncomplicated *P. vivax* malaria, and (b) HCPs involved in malaria case management, including physicians, nurses, and community health workers.

The interview guide (Additional file 2) explores participants' understanding of the treatment regimen, perceived barriers to completing the full course of medication, and their perspectives on communication strategies, such as SMS/WhatsApp reminders and health educational materials. The design of the interview guide was informed by previous research exploring malaria-related knowledge, illness perceptions, and therapeutic itineraries in the Amazon region, particularly among vulnerable and mobile populations [19,20].

Participants were selected through purposive sampling, and interviews were conducted by trained qualitative researchers (HSSG and APSO), with experience in community-based health research. To ensure confidentiality and participant comfort, interviews were conducted face-to-face in private rooms within health units and in participants' homes, with only the researchers present. The IDIs were scheduled according to participant availability, with an average duration of 40 minutes. They were audio-recorded and transcribed without personal identifiers for subsequent analysis. No prior relationship existed between researchers and participants. Data collection and analysis occurred iteratively, with interviews conducted until theoretical saturation was reached. This was defined by the point at which no new ideas emerged, and additional interviews failed to provide further depth or nuance to existing themes [21].

Thematic analysis was performed using MAXQDA (version 2020), employing a mixed coding strategy that integrated deductive categories derived from the literature with inductive codes emerging from the data. Analytic

rigor was ensured through coding by two independent researchers (HSSG and APSO), peer debriefing, and triangulation with field observations. Thematic categories were grouped into broader domains representing individual, interpersonal, and system-level barriers and facilitators to treatment adherence. Emerging themes were discussed with the broader research team and cross-checked against the original transcripts. Field observations were recorded in structured field logs and used to contextualize interview data and support thematic triangulation. Disagreements were resolved by consensus, and coding reliability was assessed through double coding of a subsample of transcripts.

Development of educational materials and mHealth messages

The findings from the qualitative exploratory part guided the co-design of a two-component adherence support intervention: (i) a printed educational envelope for medication organization, and (ii) a series of SMS/WhatsApp messages delivered throughout the treatment course.

Phase 2 - Evaluation of the mHealth-enhanced adherence intervention

This phase evaluated the effectiveness of a combined intervention strategy comprising printed educational materials and automated mHealth reminders for adherence to *P. vivax* treatment, compared with standard care.

Given its reliable mobile network coverage and communication infrastructure, this phase was conducted exclusively in Manaus. Ten primary health units (PHUs) with the highest number of *P. vivax* cases reported in 2023 were selected in collaboration with municipal health authorities. Due to logistical constraints and the operational complexity of individual-level randomization, a cluster randomization design was employed at the PHU level. This approach reduced the risk of contamination between groups and facilitated the practical implementation of the intervention under routine service delivery conditions.

This pragmatic selection strategy ensured the feasibility of study implementation, maximized the number of eligible participants during the study period, and enabled evaluation of the intervention in settings with sustained malaria transmission and routine malaria case management. Focusing on high-burden PHUs enabled the assessment of the intervention under real-world conditions where adherence challenges are most relevant and programmatic impact is likely to be greatest.

HCPs participating in the study were exclusively assigned to the primary health units (PHUs) included in the trial and did not rotate across other units during the study period. In addition, patient care within the Brazilian Unified Health System (SUS) is organized according to territorial assignment (*adscrição territorial*), whereby individuals are linked to a defined PHU that serves as their reference point for primary health care. As a result, patients rarely seek malaria diagnosis or treatment outside their reference unit, reducing the likelihood of contamination between study arms.

All patients allocated to the intervention group received the educational envelope at the start of treatment. However, although the mHealth component was delivered systematically, the platform only recorded whether messages were sent and did not allow confirmation of message delivery, opening, or reading. This limitation is common in SMS-based interventions, where exposure to messages is difficult to quantify and process measures often rely on records of sent messages rather than confirmation of message reading [22]. Therefore, exposure to the digital component of the intervention could not be directly quantified, and the analysis reflects an intention-to-treat approach rather than confirmed intervention uptake.

The 10 participating PHUs were randomized in a 1:1 ratio to intervention or control after cluster eligibility had been confirmed and before participant recruitment began. The allocation sequence was generated by an independent statistician in R version 4.3.3 using block randomization (block size = 2), stratified by malaria case volume. To preserve allocation concealment, PHUs were coded numerically during sequence generation, and the allocation list was released to the field coordination team only after assignment had been finalized. Because of the nature of the intervention, blinding of PHU staff and participants was not feasible; however, follow-up telephone assessments were conducted using a standardized script, and all primary analyses accounted for clustering at the PHU level.

The trial arms were defined as follows:

- Intervention group (5 PHUs): Participants received standard antimalarial treatment (CQ + PQ) along with the educational envelope and daily SMS/WhatsApp reminders.

- Control group (5 PHUs): Participants received standard treatment only, with no additional materials or digital messaging.

Study participants

Eligible participants were aged 16 years or older, had a laboratory-confirmed diagnosis of uncomplicated *P. vivax* malaria, were prescribed a 7-day regimen of CQ and PQ following national guidelines (Table 1) [23], possessed a mobile phone capable of receiving SMS or WhatsApp messages, and provided written informed consent before enrollment.

Table 1. Eligibility criteria for patient enrollment in Phase 2 (intervention study)

Domain	Eligibility Criteria
Age	≥16 years old at the time of enrollment
Diagnosis	Laboratory-confirmed *P. vivax* infection, eligible for standard treatment
Treatment	Prescribed a daily regimen of chloroquine and primaquine following national guidelines
Communication	Access to a personal mobile phone capable of receiving SMS or WhatsApp messages
Consent	Provided written informed consent before study participation

Sample size

The sample size was informed by the best available evidence in the absence of reliable local estimates of the expected effect of the intervention on treatment adherence measured by the MMAS-4. To anchor the sample size planning to a clinically meaningful outcome closely linked to the intervention mechanism, we used data from a previous study evaluating supervised antimalarial treatment, which demonstrated a substantial reduction in P. *vivax* recurrences among patients receiving supervised therapy compared with those receiving unsupervised treatment (17.9% vs 36.1%) [24]. Using these parameters, the original sample size calculation assumed a two-sided significance level of 0.05 and 90% statistical power to detect a difference of this magnitude in recurrence proportions.

In the present study, the number of primary health units was determined by operational feasibility within the public health system, resulting in a final sample of 227 participants (117 in the intervention group and 110 in the control

group). With this sample size, the study retains adequate power to detect clinically plausible absolute differences in treatment adherence (approximately 12–15 percentage points, depending on baseline adherence levels). All inferential analyses were planned to account for the cluster-randomized design at the primary health unit level.

The primary outcome of the study was the proportion of patients classified as adherent to *P. vivax* treatment. Adherence was measured using the 4-item Morisky Medication Adherence Scale (MMAS-4), a validated instrument for assessing self-reported medication-taking behavior [25,26]. MMAS-4 was administered via telephone between days 7 and 12 after treatment initiation. Each item required a binary (yes/no) response, generating a total score ranging from 0 to 4. Patients were classified as adherent only when they had a total MMAS-4 score of 0 (no positive responses); any score ≥ 1 was considered non-adherence [27]. The primary endpoint was the difference in adherence rates between the intervention and control groups. The analysis focused on complete adherence because full completion of the chloroquine–primaquine regimen is clinically essential to achieve radical cure of *P. vivax* malaria and prevent relapse.

A secondary outcome was the time to first recurrence of *P. vivax* malaria within 90 days following treatment initiation, defined as a new laboratory-confirmed episode of infection. This follow-up period was selected to capture short-term recurrences, which are most likely associated with relapses due to hypnozoite activation, as described in previous clinical trials [28,29]. Recurrence data were obtained from the Brazilian Malaria Epidemiological Surveillance Information System (SIVEP-malaria).

All analyses were followed with participants analyzed according to the arm assigned to their primary health unit (COD_UNIN). The primary outcome (binary adherence) was compared between groups using a modified Poisson regression to estimate risk ratios (RR), with robust (sandwich) standard errors clustered at the unit level (cluster = COD_UNIN). Given the small number of clusters and highly unbalanced cluster sizes, CR2 small-sample corrections (Satterthwaite degrees of freedom) were applied for inference (95% CIs and p values). As secondary outcomes, recurrence by day 90 (binary) was analyzed using the same framework (modified Poisson with unit-clustered robust variance). Time to first recurrence within 90 days was summarized with Kaplan–Meier curves; confidence intervals were obtained using arm-stratified cluster bootstrap resampling at the unit level to preserve intracluster correlation. Group differences in time to recurrence were estimated using Cox proportional hazards models with robust sandwich variance clustered by unit; the proportional hazards assumption was assessed via graphical checks and Schoenfeld residual tests (cox.zph), interpreted cautiously due to the limited number of clusters. All statistical analyses were performed using R version 4.3.3.

Acceptability and perceived appropriateness of the intervention

Furthermore, to better understand the mechanisms underlying the intervention's effects and to explore participants' experiences with its implementation, a qualitative subcomponent was incorporated into the study. This component was conducted exclusively with patients from the intervention group, using a random purposive sampling strategy. This multistage approach consists of first defining a purposive subgroup, followed by the application of random selection within that group [30]. In this study, all eligible participants were from the intervention group and included both adherent and non-adherent individuals. Participants were randomly selected through a simple lottery procedure[40]. Semi-structured interviews were then conducted by HSSG and analyzed to assess key implementation outcomes, including acceptability and appropriateness, using an interview guide (Additional file 3).

Subsequently, the interviews were transcribed, and the analysis employed was deductive coding guided by theoretical domains defined by Proctor *et al [31]*. For systematic organization, a structured Excel spreadsheet was

created to align with the following domains: acceptability and appropriateness. This framework enabled an understanding of implementation impacts and the challenges. The spreadsheet featured one column listing the domains, while subsequent columns categorized coded data by participant group.

To ensure reliability, two researchers (HSGM and APCS) independently performed line-by-line coding. Subsequently, two additional researchers (FLGM and RND) reviewed the coded data, resolving discrepancies through consensus to finalize domain assignments and codes.

Research team and reflexivity

The qualitative component of the study was conducted by a multidisciplinary team of five PhD-level researchers (APCS, VAM, WMM, SRR, and FLGM) with formal training and experience in qualitative research on neglected tropical diseases in the Amazon region [32–34]. All team members had previously conducted qualitative studies with malaria patients and healthcare providers in similar contexts, contributing to their familiarity with local health systems and sociocultural dynamics. The larger study team included ten women and eleven men, ensuring gender balance.

To minimize potential researcher influence, interviewers received standardized training and adopted a neutral, non-judgmental approach during data collection. No prior personal or professional relationship existed between the researchers and the participants, and interviews were conducted in private settings to ensure participants' comfort.

Reflexivity was ensured through regular debriefing sessions involving interviewers and the broader research team. These sessions enabled critical reflection on interview experiences, emerging interpretations, and potential sources of bias, informing iterative analytic refinement.

The study adhered to the COREQ guidelines (Consolidated Criteria for Reporting Qualitative Research) to ensure high-quality reporting of the research process and findings. See (Additional file 4) for COREQ items from Domain 1 to 3 [35].

Results

Phase 1 - Contextual realities shaping adherence to *P. vivax* treatment in urban and remote Amazonian settings

Between February 2024 and January 2025, a total of 40 interviews were conducted (18 patients and 22 HCPs) (Table 2). Participants ranged in age from 18 to 65 years old, and the sample was balanced in terms of gender and municipality of residence.

Table 2. Distribution of qualitative interviews by participant characteristics and study site (Phase 1)

Participant type	Manaus (Metropolitan)	Ipixuna (Remote City)	Total	Female n (%)	Male n (%)	Age, years (median, IQR)
Patients	8	10	18	12 (67%)	6 (33%)	35 (28–46)
Healthcare providers (HCPs)	10	12	22	9 (41%)	13 (59%)	38 (31–49)
Total interviews	18	22	40	21 (53%)	19 (47%)	36 (29–48)

Thematic analysis revealed three key themes influencing adherence to *P. vivax* treatment in Manaus and Ipixuna: (1) the benefits and challenges of directly observed therapy (DOT); (2) barriers related to medication characteristics and side effects; (3) the role of educational materials and reminder messages in supporting adherence. Each theme is illustrated with excerpts from patients and HCPs.

Supervision constraints and need for supportive alternatives

DOT was described as an effective strategy to ensure adherence, particularly in remote settings. However, its implementation was challenged by limited workforce capacity, geographic barriers, and patients' mobility due to subsistence activities. These constraints often resulted in missed doses or incomplete treatment, highlighting the need for complementary adherence strategies that do not rely solely on daily supervision.

"I go to the patient's house every day, even on weekends. I stay until I see they've taken the medicine (HCP 14, female, 46 years, Ipixuna).

"I only took the pills when they arrived. I didn't trust myself to remember alone." (Patient 07, female, 35 years, Ipixuna).

Medication-related barriers to adherence

Participants consistently reported challenges related to pill burden, especially on the first day of treatment, as well as side effects such as nausea and abdominal discomfort. These factors contributed to treatment discontinuation, particularly when symptoms improved early. Both patients and HCPs emphasized that the intensity of the regimen and its adverse effects reduced motivation to complete treatment.

Communication gaps and opportunities for intervention

Although patients reported receiving instructions on how to take medication, inconsistencies in communication and difficulties understanding dosing schedules were common. Participants highlighted the importance of clear, structured, and visual guidance to support day-by-day treatment adherence.

In addition, both patients and HCPs recognized the potential of mobile-based reminders (SMS/WhatsApp) to address forgetfulness, support patients during periods of mobility, and reinforce adherence messages throughout treatment.

Development of educational tools and mHealth messages

These findings directly guided the development of educational tools and mHealth message content implemented in subsequent phase (Table 3). The common use of improvised packaging by HCPs inspired the design of the printed envelope, highlighting the value of simple, low-cost, and locally adapted communication strategies to improve *P. vivax* malaria treatment adherence.

Table 3. Qualitative findings informing the design of the adherence intervention

Concern Identified	Participant Quote	Analytical Interpretation	Incorporation into educational material
Confusion regarding dosing instructions despite receiving standard guidance	*"They always give the medicine and say, 'You take one dose each day, always at the same time. But this can still be confusing."* (Patient 02, female, 35 years, Ipixuna).	Verbal instructions may be insufficient or misunderstood, leading to confusion about dosing schedules.	Creation of individual daily envelopes, with color differentiation for days in which the number and type of pills differ.
High pill burden, particularly on the first day of treatment	*"The medicine is strong. The first day was the worst, too many pills, I almost couldn't take them."* (Patient 12, female, 42 years, Manaus).	The high number of pills, especially on the first day, may negatively affect tolerability and discourage adherence.	Reinforcement messages delivered via SMS/WhatsApp on Day 0 and Day 2, emphasizing treatment continuation despite symptom improvement.
Early treatment discontinuation due to symptom relief and side effects	*"They feel better and stop. They don't see why they should keep taking something that makes them nauseous."* (HCP 13, female, 45 years, Manaus).	Symptom improvement on the third day of treatment decreases the perceived need to continue the treatment.	Inclusion of a cartoon illustration on the outer envelope showing malaria recurrence if treatment is interrupted.
Perceived adequacy of instructions by HCPs versus patient-reported confusion	*"We always explain everything. We never just hand it over. We say, 'this is the first day, this is the second.' I think they're all well oriented."* (HCP 06, female, 45 years, Manaus).	HCPs perceive communication as sufficient, but variability in patient understanding suggests gaps in comprehension of treatment.	Inclusion of structured, day-by-day instructions within the educational envelope, supported by visual cues.

The envelope format was informed by qualitative findings showing the routine use of improvised packaging by HCPs for dispensing antimalarial medication. An earlier version of the envelope, previously validated in a study conducted in Manaus, served as the basis for adaptation [36]. This model was subsequently refined to reflect specific practices and communication needs identified in the current study. A multidisciplinary team composed of malaria researchers, implementation scientists, public health professionals, and a graphic designer collaboratively refined the content and layout. The final version incorporated simplified daily dosing instructions, visual adherence reminders, and culturally relevant illustrations designed to support understanding among patients with limited literacy (Additional file 5). All elements were adapted to reflect the workflow of local health services and to address key barriers identified in qualitative data.

Envelope validation involved 16 HCPs providing malaria care in Manaus through individual interviews and one focus group. Participants reviewed printed excerpts of the prototype and used a color-coded feedback technique, in which green indicated clarity and red suggested confusion. This approach was adapted from the method proposed by Dowse and Ehlers [37]. Audio recordings from the validation activities were analyzed using rapid qualitative techniques, following the procedures outlined by Vindrola-Padros et al [38]. Feedback was incorporated into two successive revisions, resulting in the final version implemented in the study (Figure 3).

Development and Implementation of mHealth Messages

The SMS and WhatsApp message content was developed in parallel with the printed educational material, aiming to address behavioral barriers to treatment adherence identified in the qualitative data. These included perceptions regarding partial cure, early treatment discontinuation due to symptom relief, and forgetfulness. Additionally, the development of the intervention was primarily informed by the qualitative findings generated in this study and further supported by evidence from prior research. These included a qualitative study conducted in the Brazilian Amazon that demonstrated the acceptability and clarity of SMS reminders for P. vivax malaria treatment [33], and an implementation study in Manaus showing the feasibility of using SMS messages as part of a multicomponent strategy to support adherence and pharmacovigilance in routine malaria care [36].

Four concise and supportive messages were designed for delivery on treatment days 0, 2, 4, and 6, following the patient journey and the treatment timeline (Table 4). Each message had a specific purpose, aimed at addressing the adherence barriers identified in the qualitative data. The first message (Day 0) welcomed patients to the system and reinforced the importance of completing treatment, creating an initial bond of trust and support. The second message (Day 2) targeted the common tendency to interrupt treatment after symptom relief, reminding patients that feeling better does not mean being cured. The third message (Day 4) provided a safety orientation, encouraging patients to seek care in case of adverse effects, thus addressing concerns about side effects that often undermine adherence. The final message (Day 6) congratulated patients for completing treatment, offering positive reinforcement to close the cycle and reinforcing self-efficacy. Together, these messages functioned not only as reminders but also as motivational and educational tools, helping patients overcome forgetfulness, misperceptions of cure, and fear of side effects, while strengthening their commitment to completing the whole treatment.

Table 4. Text messages sent during *P. vivax* malaria treatment

Day	Message content
D0	Hello! Welcome to our free message system to support your malaria treatment. Remember: take one dose every day at the same time. We are with you to ensure malaria does not return.
D2	Treatment reminder: You may already feel better, but it is essential to complete all days of treatment to prevent malaria from returning. Do not stop taking the pills, even if the malaria symptoms have gone away. Some people feel nausea or stomach pain with malaria pills. Do not stop. If symptoms are too strong, seek the health unit.
D4	Safety: If you experience any symptoms described in the treatment envelope, please visit the nearest health unit.
D6	End of treatment: Congratulations! Today you complete your treatment. Your effort protects you and prevents malaria from coming back.

To ensure scalability and consistency, a web-based platform was created to automate message delivery, synchronized with each patient's treatment start date. The system allowed HCPs to register patient information, including name, phone number, address, treatment schedule, and medication type. Messages were sent automatically according to the programmed treatment schedule. The platform was developed using PHP and the CodeIgniter framework, and message logs were stored to document the timing of message dispatch for monitoring and evaluation purposes.

Phase 2 - Outcomes of an educational and mHealth intervention

In Phase 2, 274 participants were recruited across 10 PHUs in Manaus, including 140 in the intervention group and 134 in the control group. For the primary outcome, 23 participants in the intervention group and 24 in the control group did not complete the MMAS-4 assessment, leaving 117 and 110 participants, respectively, with evaluable adherence data.

Among participants with completed MMAS-4 assessments, overall treatment adherence was 79.3% (180/227), corresponding to 81.2% (95/117) in the intervention group and 77.3% (85/110) in the control group. The sex distribution was similar across groups, with a predominance of male participants (57% in the intervention group and 61% in the control group) and no severe malaria cases were reported. Likewise, the distribution of self-reported race/ethnicity followed a comparable pattern across groups, with most participants identifying as Brown (93% in the intervention group and 90% in the control group). Regarding educational attainment, participants were predominantly concentrated in intermediate education levels, particularly those who had completed elementary school or high school (Table 5), which together accounted for more than 60% of the total sample.

Table 5. Sociodemographic characteristics of participants by study group

	Group		Total
Characteristics	**Intervention Group**	**Control Group**	
	n = 117	n = 110	n = 227
Lost to follow-up (status)	23 (20%)	24 (22%)	47 (21%)
Sex			
Female	50 (43%)	43 (39%)	93 (41%)
Male	67 (57%)	67 (61%)	134 (59%)
Self-reported race/ethnicity[1]			
White	3 (2.6%)	5 (4.5%)	8 (3.5%)
Black	1 (0.9%)	5 (4.5%)	6 (2.6%)
Indigenous	4 (3.4%)	1 (0.9%)	5 (2.2%)
Brown (Mixed race)	109 (93%)	99 (90%)	208 (92%)
Education			
Illiterate	2 (1.7%)	2 (1.8%)	4 (1.8%)
Incomplete 1st to 5th grade of Elementary School	9 (7.7%)	6 (5.5%)	15 (6.6%)
Completed 5th grade of Elementary School	14 (12%)	7 (6.4%)	21 (9.3%)
Incomplete 6th to 9th grade of Elementary School	21 (18%)	20 (18%)	41 (18%)
Completed Elementary School	34 (29%)	12 (11%)	46 (20%)
Incomplete High School	12 (10%)	27 (25%)	39 (17%)
Completed High School	21 (18%)	34 (31%)	55 (24%)
Incomplete Higher Education (Undergraduate level)	1 (0.9%)	0 (0%)	1 (0.4%)

Table 6 summarizes the primary and secondary outcomes. For the primary outcome of adherence, the estimated risk ratio was 1.04 (95% CI 0.99–1.11; p = 0.07), indicating similar adherence levels between groups. For recurrence by day 90, the risk ratio was 0.90 (95% CI 0.49–1.66; p = 0.74), suggesting a non-significant 10% relative reduction in recurrence in the intervention group. The hazard ratio for time to first recurrence within 90 days was 0.87 (95% CI 0.15–4.99; p = 0.90), indicating a non-significant reduction in the hazard of recurrence over time. Overall, effect estimates were close to the null value, and confidence intervals were wide for recurrence-related outcomes.

Table 6. Summary of primary and secondary outcomes and statistical analyses

Outcome	Effect estimate (95% CI)	P-value
Adherence (primary)	RR 1.04 (0.99–1.11)	0.07
Recurrence by day 90	RR 0.90 (0.49–1.66)	0.74
Time to first recurrence (≤90 days)	HR 0.87 (0.15–4.99)	0.90

Note: RR, risk ratio; HR, hazard ratio; CI, confidence interval; PHU, primary health unit. All estimates obtained using models accounting for cluster randomization at the PHU level.

Time to malaria recurrence was assessed in all 227 participants during the 90-day follow-up period (Figure 4). The recurrence-free probability curves were comparable between the intervention and control groups throughout follow-up. Although recurrences occurred slightly later in the intervention group, the 95% confidence intervals overlapped across time points. The number of participants at risk decreased progressively in both groups, with follow-up completed by day 90.

Acceptability and appropriateness of the educational envelope and mHealth strategies

Qualitative data from phase 2 indicated **high acceptability and contextual appropriateness** of both components of the intervention. A total of 35 semi-structured interviews were conducted with patients from the intervention group in Manaus who received both components of the intervention. Participants described the educational envelope as a practical and intuitive tool that supported daily medication management, while reminder messages reinforced engagement through treatment.

"[The envelope] is very informative, it really helps with [organizing the medication] by day, because they come [separated by dose] [...] and also in different colors." (Participant 19, female, 23 years, Manaus).

Participants highlighted that each component fulfilled a distinct role in supporting adherence. The educational envelope was primarily associated with organization, dose sequencing, and visual guidance, whereas the reminder messages were perceived as motivational prompts that sustained attention to treatment over time.

"*I was surprised [by the material], it was so well prepared. Both together [envelope and messages] are great, but I believe the envelope alone would already be enough."* (Participant 21, female, 50 years, Manaus).

"*I didn't even expect any follow-up [during treatment], because usually when we get a message like that, there's no follow-up, right? And we actually got follow-up (via SMS and WhatsApp). So for me, it was great. A ten out of ten for you*." (Participant 21, female, 50 years Manaus).

The intervention was also considered appropriate to the participants' daily routines and communication practices. The use of WhatsApp, the most widely used messaging platform in Brazil, facilitated engagement, while the color-coded envelopes supported memorization of daily doses, particularly among participants with visual limitations.

"*Both [the envelope and text messages] are good. For example, the envelope says you have to take [the medication] every day, and the messages are also helpful, because I like WhatsApp, I always check it*." (Participant 36, male, 70 years, Manaus).

"*[The different colors on the envelope] help a lot, even for people with [vision problems], to check if it's the first, second, or third day of treatment [...] so it's a very useful [tool], very useful, because if you are in a situation like that, you take the medication [...]*" (Participant 24, male, 71 years, Manaus).

"*Like, the first one is yellow, the next two are red, and the rest to finish the treatment are white. That [color scheme] helped me a lot [...] it really helped, because I memorized the colors, you know...*" (Participant 28, male, 27 years, Manaus).

Participants further reported that the materials facilitated safe storage and independent management of medications. The separation of doses into smaller, color-differentiated envelopes reduced confusion regarding treatment duration and daily intake, while the combined use of envelopes and messages supported completion of the full treatment course.

"*[I understood] even the tiny [pills], that's really cool. [Also, I didn't lose] a single one [of the medications], they're all stored, all seven.*" (Participant 28, male, 27 years, Manaus).

"*For me, it was really good, because it's another little piece of information we have access to. [So it helps] us not get lost, because we also check the date [on the envelope]. If I lose track [of the doses], the date on the envelope tells me which one I already took*." (Participant 20, female, 41 years, Manaus).

Below (Table 7) is a summary of the findings by domain, with representative quotes presented.

Table 7. Selected quotes by implementation outcomes framework

Domain	Main idea	Participant Quote
Acceptability	Helpful but not always consulted	*"I didn't read everything inside. I just took the pills each day"* (Participant 25, male, 52 years, Manaus).
	Perceived support	*"Just knowing someone cares about our health is very important"* (Participant 20, female, 41 years, Manaus).
Appropriateness	Visual format praised	*"Even someone who doesn't read well can understand it"* (Participant 38, male, 60 years, Manaus).
	Text comprehension barriers	*"I only looked at the pills. I didn't understand the papers inside"* (Participant 31, female, 33 years, Manaus).

Discussion

The overall adherence rate to *P. vivax* treatment observed in this study was 79% across both groups, reinforcing that malaria elimination efforts in Brazil must extend beyond timely diagnosis and appropriate treatment to include strategies specifically designed to support adherence throughout the complete therapeutic course. Although no statistically significant difference was observed between the intervention and control groups, adherence was slightly higher among participants receiving the combined educational and mHealth intervention (81% versus 77%). Consistent with this, the estimated risk ratio for adherence was 1.04 (95% CI 0.99–1.11; p = 0.07), indicating no statistically significant difference between groups. Qualitative findings help contextualize this trend, indicating that

the intervention was well accepted, integrated into participants' daily routines, and perceived as helpful for organizing medication intake and reinforcing dose reminders.

One possible explanation for the absence of a between-group difference is that some degree of behaviour change may have occurred in both arms as a result of study participation itself. In the Brazilian Amazon, Pereira, Ishikawa and Fontes reported high adherence to chloroquine plus primaquine (86.4%) in a study in which adherence was assessed through home follow-up on day 7, suggesting that adherence estimates may be influenced by the context and procedures used for assessment [39](. More broadly, evidence on research participation effects indicates that enrolment, consent procedures, and subsequent outcome assessment may influence participants' behaviour even in the absence of an active intervention [40] (. In our trial, participants in the control group were not exposed to the educational envelope or reminder messages, but they were informed about the study at enrolment and later contacted for the MMAS-4 assessment. Although this contact was limited, it may still have contributed to treatment completion in both groups and thereby reduced the contrast between intervention and control.

The qualitative findings nevertheless indicate that treatment completion remains vulnerable to structural and contextual barriers, especially in Amazonian settings. Previous studies in the Brazilian Amazon have shown that difficulties understanding treatment instructions, forgetting doses, early symptom improvement, and barriers in access to care may interfere with completion of chloroquine plus primaquine regimens [39]. In our qualitative data, similar challenges emerged in both study settings and were particularly visible in remote areas such as Ipixuna, where geographic isolation, unstable access to care, work-related mobility, low literacy, and treatment complexity were described by patients and healthcare professionals as barriers that may hinder treatment completion. Taken together, these findings support the continued relevance of adherence-support strategies, even though the specific intervention tested here did not produce a statistically significant effect in Manaus.

Despite the central role of adherence in achieving radical cure of *P. vivax*, Brazil's National Malaria Elimination Program does not currently define explicit targets or indicators for adherence monitoring. Evidence suggests that adherence rates above 50% to PQ-based regimens can reduce *P. vivax* transmission by more than 70% [41]. In this study, self-reported adherence exceeded 75%, a notable finding given the challenges imposed by the 7-day PQ regimen. However, achieving malaria elimination will likely require adherence levels above 90%, particularly under the 7-day course of PQ at 0.5 mg/kg/day currently recommended in Brazil [29]. This dosing scheme, corresponding to a total dose of 3.5 mg/kg, is associated with lower hypnozoiticidal efficacy (72.3%) compared with higher-dose regimens or tafenoquine [41–43]. Thus, even modest shortfalls in adherence may substantially compromise the impact of treatment on transmission. The absence of defined adherence benchmarks represents a critical gap in national malaria policy, especially given the heightened risk of treatment discontinuation inherent to *P. vivax* management.

Barriers to adherence identified in this study included adverse drug effects, high pill burden, early symptom resolution leading to premature treatment discontinuation, and challenges related to mobility and subsistence work. In contrast, engaged healthcare professionals, treatment supervision, and clear instructions emerged as key facilitators. Similar patterns have been reported in endemic settings in Asia, where adherence to PQ regimens is shaped by social, economic, and cultural factors, as well as by limited access to health services among mobile and vulnerable populations [44,45]. Findings from Phase 1, conducted in both urban and rural Amazonian settings, mirrored these dynamics. Participants frequently reported interrupting treatment due to travel for fishing or forest-based activities, in addition to experiencing adverse effects such as nausea and abdominal pain. Low literacy and limited use of visual communication tools further contributed to incorrect or incomplete medication use. These

findings suggest that, despite geographic differences, recurring patterns of vulnerability demand context-sensitive and sustainable adherence-support strategies.

Adherence to *P. vivax* treatment is an essential component of elimination strategies, as incomplete PQ regimens compromise radical cure, increase the risk of relapse, and sustain hypnozoite reservoirs that perpetuate transmission [1]. This challenge is particularly relevant in the Brazilian Amazon, where population mobility, geographic isolation, and social vulnerability hinder continuous follow-up. In Ipixuna, included in Phase 1, these difficulties were especially pronounced due to a limited healthcare workforce, infrastructural constraints, limited digital connectivity, and long distances between communities and health facilities.

In this setting, DOT was highly valued by both healthcare professionals and patients, functioning as an important mechanism to support adherence. However, challenges to its implementation were evident, particularly in areas with extensive geographic coverage, limited staff, and logistical barriers to access. These findings are especially relevant in the context of Brazil's goal to eliminate malaria by 2035. As incidence declines, there is a risk of reduced investment in intensive strategies such as DOT, potentially undermining adherence support at a critical stage of elimination. At the same time, sustaining DOT becomes increasingly complex in low-incidence settings, where maintaining trained and motivated teams is resource-intensive.

Evidence from the Brazilian Amazon indicates that supervised anti-malarial treatment substantially reduces recurrence rates compared to routine unsupervised care, with recurrence rates of 36.1% in the unsupervised group versus 17.9% in the supervised group [24]. This reinforces the point that adherence to the full primaquine regimen remains a critical bottleneck to achieving radical cure and, consequently, to vivax malaria elimination efforts. Against this backdrop, the mHealth intervention evaluated in this study emerges as a possible ally to DOT, particularly in urban and peri-urban settings where daily supervision is operationally challenging. The mHealth reminders, in turn, were perceived as helpful prompts that helped prevent forgetfulness and abandonment. The educational envelope was perceived as a useful tool for organizing medications, even though its written educational component was not always consulted. Together, these components offered low-cost, contextually adapted support that aligned with patients' daily routines and communication practices.

Regarding recurrence, we found no clear reduction by day 90 and no difference in time to first recurrence between groups. This finding should be interpreted cautiously and in light of previous studies that evaluated recurrence under substantially different conditions. In the Brazilian Amazon, supervised chloroquine plus primaquine was associated with a lower risk of recurrence over 180 days than routine unsupervised treatment, suggesting that more intensive treatment support can affect recurrence when follow-up is longer and recurrence is the main outcome [24]. In a multicentre randomized trial, both supervised 7-day and supervised 14-day primaquine regimens were associated with much lower recurrent *P. vivax* parasitaemia over 12 months than placebo, highlighting the importance of radical-cure intensity and regimen design for recurrence prevention [46]. At the same time, Brazilian data have shown that recurrence may still occur even after supervised treatment, particularly when primaquine dosing is subtherapeutic, indicating that recurrence reflects not only treatment completion but also dose adequacy and other biological factors[47]. Our study differed from these earlier investigations because it evaluated an adherence-support strategy based on educational materials and digital reminders, rather than supervised treatment or alternative primaquine regimens. In addition, recurrence was not the main outcome used to structure the trial, follow-up was limited to 90 days, the number of participants and clusters was small, and few recurrence events were observed. Under these conditions, the study had limited ability to detect modest differences in recurrence between groups.

This study has important limitations that should be considered when interpreting its results. First, the intervention was implemented exclusively in Manaus due to the requirement for mobile phone coverage and internet connectivity, which limits the generalizability of the findings to rural and remote Amazonian settings such as Ipixuna, where structural and logistical barriers to adherence may be more pronounced. Second, the primary outcome was based on self-reported adherence measured with the MMAS-4, which is operationally feasible but may overestimate adherence because of recall and social desirability bias. Third, recurrence was ascertained through routine surveillance records, which may not capture all episodes equally and does not allow perfect distinction between relapse, reinfection, or other sources of recurrent parasitaemia. Future studies should explore adaptations suitable for low-connectivity contexts, including offline educational tools, enhanced visual materials, or community-based communication strategies.

Second, the pragmatic, cluster-based design involved a limited number of primary health units, which may have reduced statistical power to detect small differences in adherence outcomes and constrained the ability to fully account for between-cluster heterogeneity. In addition, baseline adherence levels were relatively high in both study arms, particularly in high-burden units with established malaria care routines, potentially resulting in a ceiling effect that limited the detection of incremental benefits associated with the intervention.

Finally, although all participants allocated to the intervention group received the educational envelope, exposure to the mHealth component could not be directly monitored. Variability in engagement with text messages may have diluted the observed effect of the intervention at the group level. Despite these limitations, the study provides relevant insights into the feasibility and performance of low-cost adherence-support strategies implemented under routine conditions within the Brazilian Unified Health System.

Conclusions

This study demonstrated that although a combined intervention using educational medication envelopes and mHealth reminders did not result in a statistically significant improvement in adherence compared with standard care, it was feasible, well accepted, and contextually appropriate in the Amazonian setting. By addressing key adherence barriers, such as side effects, pill burden, early symptom relief, and patient mobility, the intervention provided practical support that complemented routine malaria care.

As Brazil advances toward its malaria elimination goal by 2035, strengthening adherence to *P. vivax* treatment will be essential to ensure effective radical cure and prevent relapses. Low-cost, culturally adapted tools, such as those evaluated here, may serve as valuable complements to directly observed therapy, particularly in urban settings where daily supervision is difficult to sustain and, if appropriately adapted, in remote areas with limited connectivity. Integrating adherence-focused strategies into routine malaria control programs may help sustain gains as transmission declines and health system priorities shift.

Abbreviations

mHealth – Mobile health

HCPs – Healthcare providers

SMS – Short Message Service

PHUs – Primary health units

SUS – Brazilian Unified Health System (Sistema Único de Saúde)

CQ – Chloroquine

PQ – Primaquine

API – Annual Parasite Index

IBGE – Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística)

ReBEC – Brazilian Clinical Trials Registry (Registro Brasileiro de Ensaios Clínicos)

MMAS-4 – 4-item Morisky Medication Adherence Scale

DOT – Directly observed therapy

SIVEP-malaria – Brazilian Malaria Epidemiological Surveillance Information System

Declarations

Ethical considerations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Universidade do Estado do Amazonas (CAAE: 17408719.2.0000.5016). All participants received detailed information about the study objectives and procedures and provided written informed consent prior to participation. The study was conducted in accordance with relevant ethical guidelines and regulations.

Consent for publication

Written informed consent for publication of anonymized information was obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files. Data from SIVEP-malaria are publicly available through the Brazilian Ministry of Health, subject to access regulations. Qualitative data are available from the corresponding author on reasonable request due to ethical restrictions.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HSSG, SRR and FLGM conceived and designed the study. FLGM, SRR, APCS, MVGL and WMM coordinated the study and provided overall supervision. HSSG, PCSB, AASB, APSO, APCS, EARTS, RND, HAAJ, YEARS, GCM and ESC carried out field activities, data collection and logistical coordination. VSS, MBM, EAGF, EFSJ and SRR contributed to laboratory procedures, data acquisition and technical support. VAM and YEARS participated in data interpretation and the critical discussion of the findings. DBC, HSSG, GCM, and FLGM performed data analysis and interpretation. HSSG and FLGM drafted the first version of the manuscript. All authors contributed to the critical revision of the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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Figures

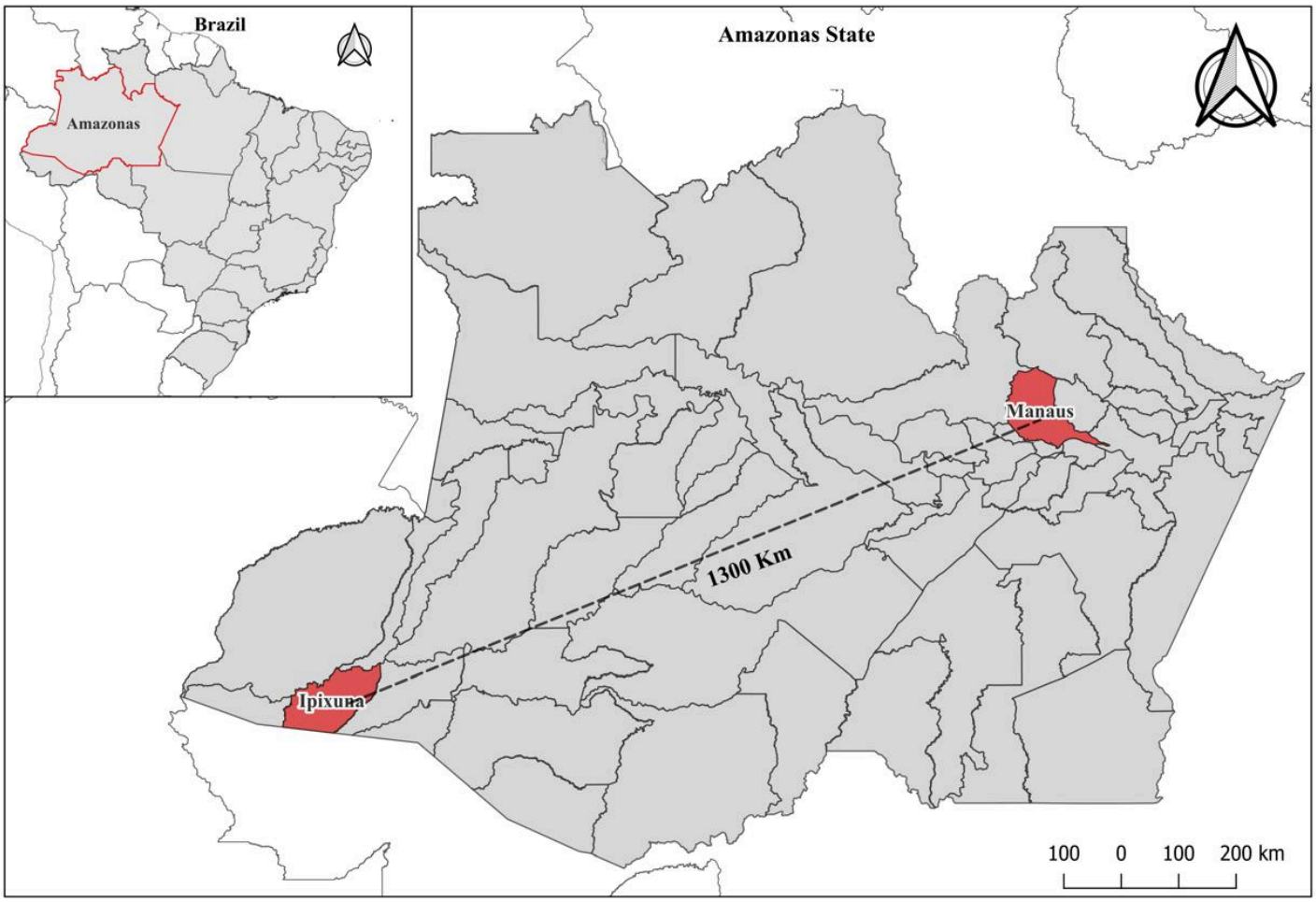


Figure 1

Phase 1 study sites: Ipixuna and Manaus, Amazonas, Brazil. Selected for their contrasting malaria transmission contexts, these sites illustrate regional variability in transmission patterns and health system infrastructure. The base used to create the map is from the IBGE (Brazilian Institute of Geography and Statistics), which is freely accessible for creative uses in shapefile format, in accordance with the Brazilian Access to Information Law (12,527/2011) [18].

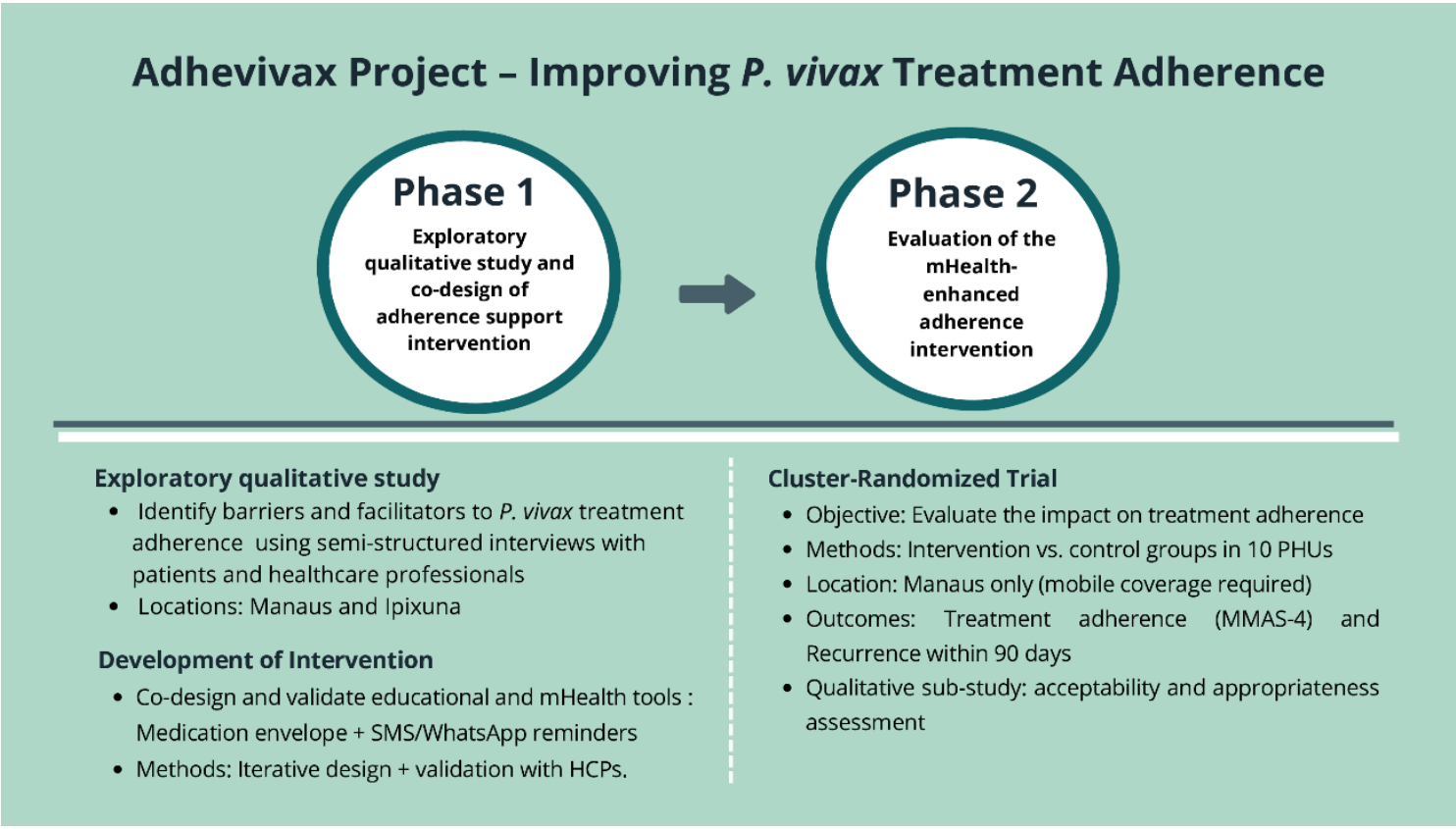


Figure 2

Overview of the AdheVivax project phases.

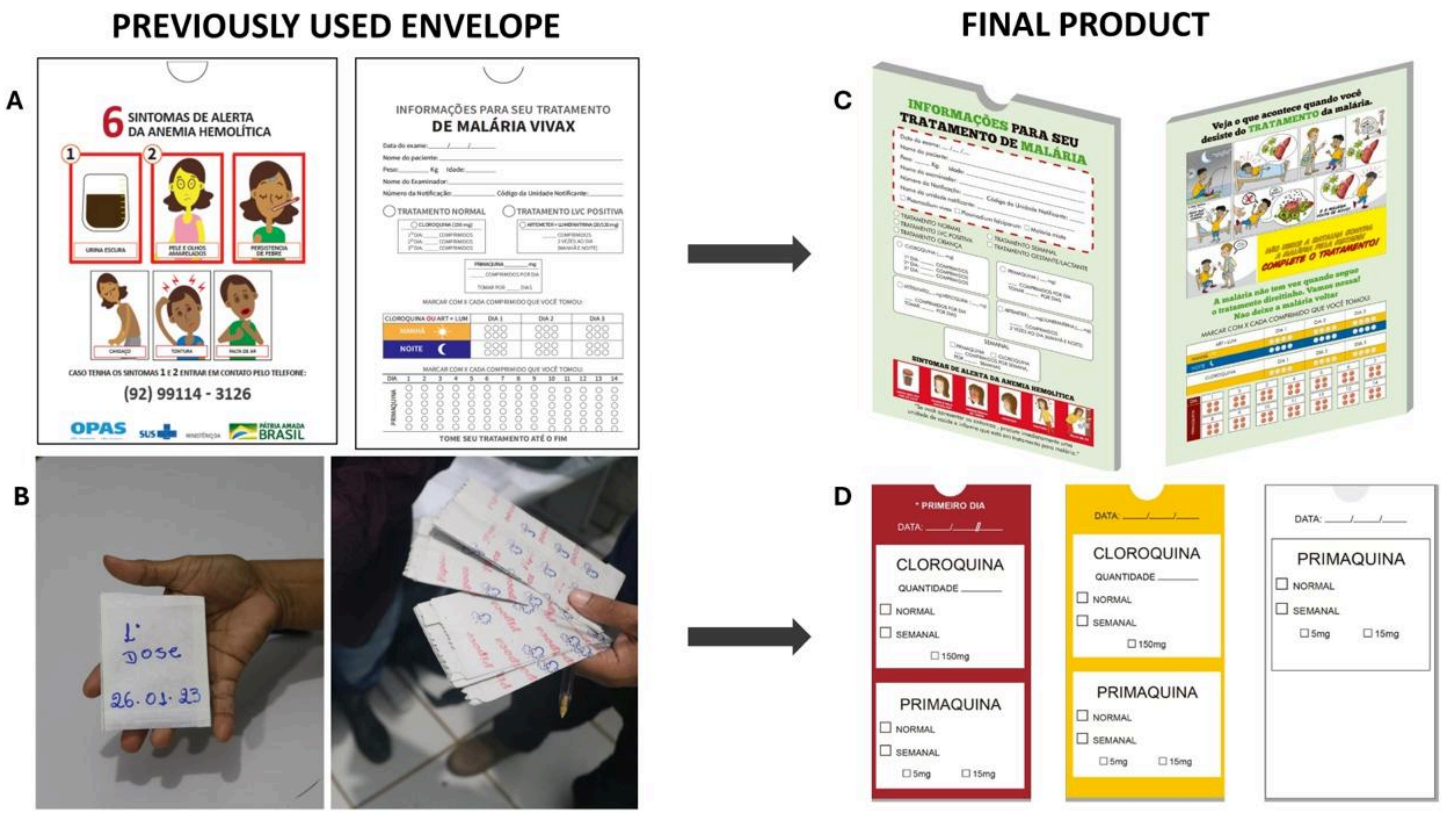
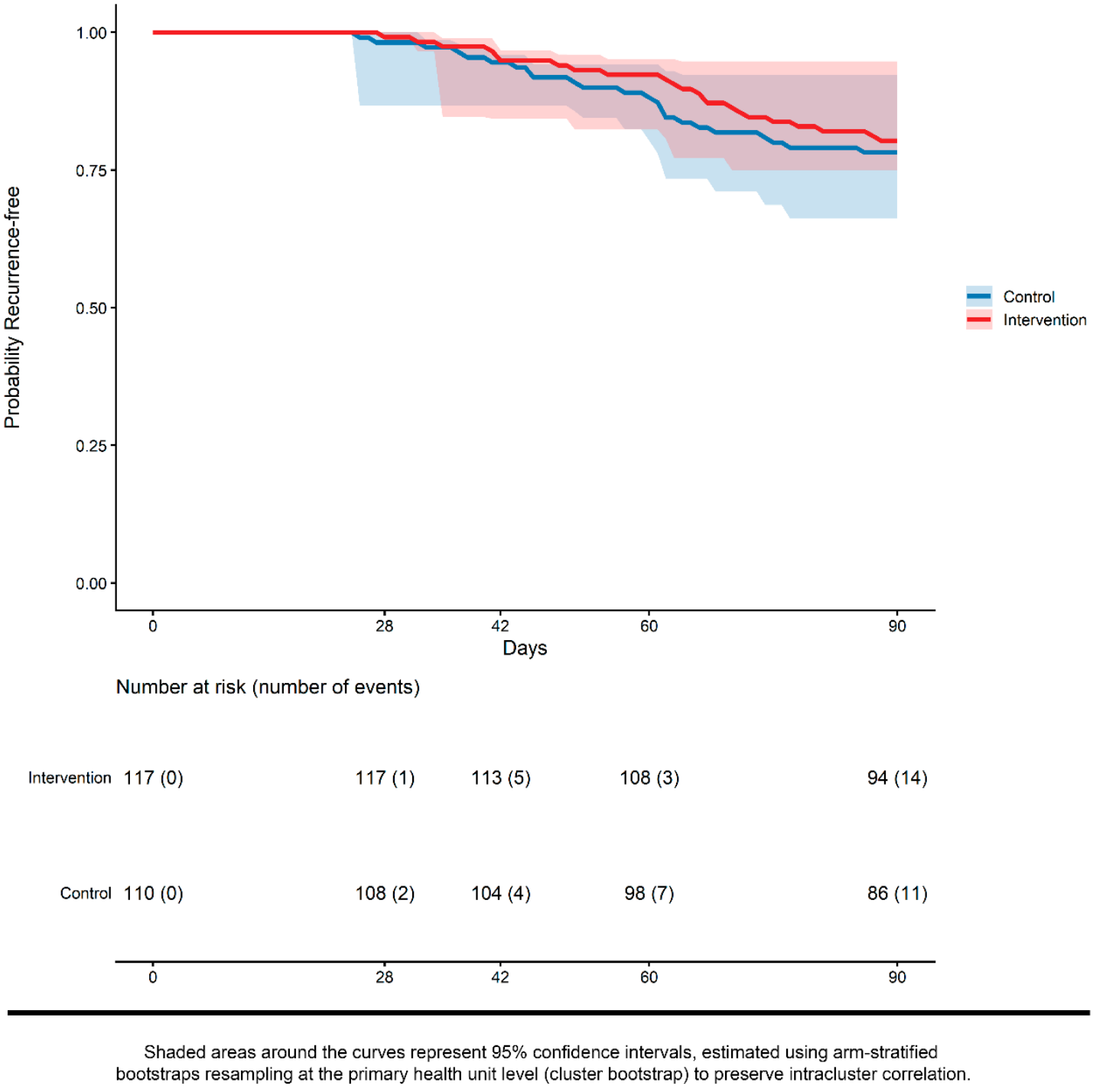


Figure 3

Evolution of the educational envelope used in the adherence support intervention. (A) Previously used envelope for dispensing antimalarial treatment in Manaus. (B) Examples of improvised packaging used by healthcare providers to organize malaria medication before the intervention. (C) Final version of the educational envelope developed in this study, incorporating culturally appropriate illustrations and simplified dosing instructions. (D) Color-coded dose envelopes are used to separate daily doses of chloroquine and primaquine, facilitating treatment organization and adherence.



Shaded areas around the curves represent 95% confidence intervals, estimated using arm-stratified bootstraps resampling at the primary health unit level (cluster bootstrap) to preserve intracluster correlation.

Figure 4

Kaplan-Meier estimates of time to *P. vivax*recurrence over 90 days by study group, Manaus, Brazil.

Supplementary Files

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