Intermittent preventive treatment for forest goers by forest malaria workers: an observational study on a key intervention for malaria elimination in Cambodia

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Summary

Background Cambodia targets *P. falciparum* malaria elimination by 2023 and all human malaria species by 2025, aligning with WHO's Mekong Malaria Elimination program. The Intermittent Preventive Treatment for Forest Goers (IPTf) project aimed at forest-specific malaria elimination. The study aims to pinpoint the main factors driving malaria transmission in Cambodian forests and evaluate the initial implementation and effectiveness of IPTf in accelerating the elimination of malaria by treating and preventing infections among at-risk populations in these areas.

Methods From March 11, 2019, to January 30, 2021, a malaria intervention program took place in isolated forests in Northeast Cambodia. The first phase focused on observing forest goers (FGs) within the forests, documenting their malaria risk. In the second phase, a monthly artesunate-mefloquine IPTf was implemented by trained forest malaria workers who were former FGs conducting interviews, blood collection, and IPTf administration.

Findings Throughout the two-year period, 2198 FGs were involved in 3579 interviews, with 284 in both the observation and intervention phases. Following IPTf implementation, PCR-confirmed malaria prevalence significantly decreased from 2.9% to 0.5% for *P. falciparum* and from 21.0% to 4.7% for *P. vivax*. Among the 284 participants tracked through both phases, malaria prevalence fell from 2.5% to 0.3% for *P. falciparum* and from 22.5% to 3.7% for *P. vivax*. The intervention phase demonstrated a rapid decline in *P. falciparum* prevalence among mobile and previously inaccessible populations, while also revealing a higher *P. falciparum* infection risk associated with activities inaccurately labelled as farming, underscoring the need for customized interventions.

Interpretation The successful implementation of IPTf in Cambodia's remote forests has markedly decreased malaria prevalence among high-risk groups. Cambodia's National Malaria Program has acknowledged this strategy as essential for malaria elimination intervention, endorsing forest-specific approaches to meet the 2025 goal of eradicating all human malaria species in Cambodia.

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Keywords: Intermittent preventive treatment; Forest goer; Forest malaria worker; Malaria; Elimination; Greater mekong subregion; Cambodia; Forests

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Research in context

Evidence before this study

We conducted a comprehensive PubMed search for primary research articles published from January 2000 until October 25, 2023. We focused on interventional strategies related to malaria control, elimination, or eradication in forest remote settings. The search terms included "malaria [MeSH Terms]" AND ("2000" [Date-Publication]: "2023" [Date-Publication]) AND ("interventional strategy" OR "elimination" OR "eradication") AND ("hard-to-reach populations" OR "forest workers" OR "forest goers"). Among the 87 articles identified, 33 reported specific interventions in the high-risk areas or mixed strategies within national or subnational elimination programs. These interventions encompassed various approaches, including community-based initiatives, active or passive case detection (ACD or PCD), vector control, improved access to diagnosis and treatment (such as artemisinin-based combination therapy–ACT), chemoprophylaxis, and mass drug administration. Most interventions targeting the human reservoir predominantly relied either on Mass Screening and Treatment (MSAT) intervention alone, such as ACD or PCD using Rapid Diagnostic Tests (RDTs) or microscopy for diagnosis and treatment; or on the combination of MSAT with the distribution of malaria vector prevention (16 articles). Two articles described self-diagnosis and self-treatment by distribution of a "Malaria kit", which includes a diagnosis test and anti-malarial medicine. Additionally, six articles described mass drug administration (MDA) interventions in high-risk villages, employing anti-malarial chemoprophylaxis with Dihydroartemisinin-piperaquine (DP) or Artemether-lumefantrine (AL). These studies demonstrate the safety and effectiveness of targeted MDA in reducing the *P. falciparum* reservoir, particularly in stable populations. However, evidence supporting the relevance and efficacy of intermittent preventive treatment strategies in mobile and hard-to-reach populations remains limited.

Added value of this study

This study is a pioneering investigation into the implementation and impact of IPTf in high-transmission forest areas. It presents empirical evidence of IPTf's significant role in reducing malaria incidence and prevalence among mobile and hard-to-reach forest populations, who remain a vulnerable group affected by rapidly changing environmental conditions and lifestyles.

Implications of all the available evidence

Our findings are crucial for malaria control and elimination strategies, extending beyond Cambodia to similar epidemiological settings. They highlight the necessity for bespoke interventions catering to the unique challenges faced by transient and high-risk populations, such as forest goers. The study underscores the effectiveness of IPTf in addressing residual malaria in these populations. By aligning with the World Health Organization's goal to eliminate malaria in the Greater Mekong Subregion (GMS) by 2030, our research has influenced the Cambodian National Malaria Program to adopt IPTf as a key strategy, a decision validated by the Ministry of Health's official endorsement in January 2021. Additionally, Laos, initiated a similar strategy in July 2021, demonstrating the growing recognition of IPTf's potential in enhancing malaria control and elimination efforts.

Introduction

Malaria remains a significant public health concern in the Greater Mekong Subregion (GMS), encompassing Cambodia, China (specifically Yunnan Province), Laos People's Democratic Republic, Thailand, and Vietnam. Notably, from 2000 to 2021, the GMS witnessed a significant reduction in both malaria cases and deaths, with indigenous cases of all species dropping by 76.5%, and those of *P. falciparum*, in particular, decreasing by 94.1%.[1] However, the GMS has been identified as a hotspot for the transmission of drug-resistant malaria parasites, specifically *Plasmodium falciparum*.[2,3] Cambodia, in particular, has emerged as the epicenter of emergence of *P. falciparum* parasites resistant to all antimalarial drugs introduced since the era of chloroquine in the 1950s.[4,5] Artemisinin and its derivatives stand as the most effective treatments for uncomplicated *P. falciparum* malaria, the species responsible for a majority of malaria-related deaths. The resistance to artemisinin and its partner drugs compromises the efficacy of artemisinin-based combination therapy (ACT), which is the first-line treatment recommended by the World Health Organization (WHO) since 2006.[6] Presently, there are no alternative antimalarial medications that offer the same level of effectiveness and tolerability as ACTs. The urgency to address this issue has prompted both the GMS and the WHO to prioritize malaria elimination efforts, leading to the development of the Strategy for Malaria Elimination in the GMS for the period 2015–2030.[7]

In line with these efforts, Cambodia's National Center for Parasitology, Entomology, and Malaria Control (CNM) has set an ambitious goal of eliminating all human malaria species by 2025 in Cambodia. To achieve this, they have implemented several strategies, including strengthening surveillance systems, expanding access to malaria diagnosis and treatment, and targeting high-risk populations.[8] The challenge of addressing malaria in Southeast Asia's forested areas is particularly daunting due to the outdoor and dawn/dusk biting habits of forest malaria vectors such as *An. dirus* and *An. minimus*.[9,10] While traditional vector control

tools such as long-lasting insecticidal nets (LLINs) and long-lasting insecticide-treated hammock nets (LLIHNs) have shown effectiveness in preventing malaria among forest workers and villagers in Cambodia[11] and Central Vietnam,[12] their coverage in high-risk forested regions is limited, primarily due to practical challenges associated with their use in highly mobile activities.[10,13] Nonetheless, the majority of malaria cases in Cambodia are reported among forest goers (FGs) who live and work in or near forested areas, where transmission of malaria is particularly challenging to control and interrupt, and not yet fully understood.[14,15] To address this challenge, a malaria control project was initiated among FGs in high transmission areas of Cambodia. As of late 2018, the CNM implemented an "intensification plan" funded by reprogrammed Global Fund resources from the Regional Artemisinin-resistance Initiative. This plan ensures supplies of Rapid Diagnostic Tests (RDTs) and ACTs to existing village malaria workers (VMWs), while also strengthening the VMW network by deploying 200 mobile malaria workers (MMWs) along the primary routes to and from the forest. This initiative aims to provide accessible "test and treat services" for FGs.[16,17] However, few MMWs can reach the deep forest areas associated with high malaria transmission rates.

To confront this challenge, the adoption of drug-based interventions has emerged as a practical approach. Pharmaceuticals play a crucial role in eliminating parasites in hard-to-reach areas. In particular, Intermittent Preventive Treatment for Forest Goers (IPTf) has been identified as a strategic approach. This choice is informed by the limitations of reactive strategies such as Mass Screening and Treatment (MSAT), where the low sensitivity of RDTs limits their effectiveness.[18] Moreover, a recent review[19] highlights the complex evidence regarding the effectiveness and economic value of MSAT.

By opting for IPTf, we address both the challenges of deep forest environments and the limitations of reactive strategies, ensuring a more effective and focused intervention. Our study, a quasi-experimental interventional based on the monthly administration of IPTf, aims to assess its feasibility and impact within the unique context of forest environments. Focusing on FGs, at the highest risk of malaria infection, we explore their characteristics and behaviors to identify the primary drivers of malaria transmission in Cambodian deeply forested regions. Additionally, we aim to demonstrate the effectiveness of this strategy in accelerating malaria elimination by treating and preventing infections within this population.

Methods

Study site and forest sectorization

The identification of the study forest areas began with an analysis of satellite imagery, followed by on-site field investigations to confirm their suitability. The initial selection criteria comprised verifying the documented presence of *P. falciparum* through information obtained from peripheral health centers (HCs) and ensuring isolation from other forests. Initially, 30 sectors were designated, each overseen by a Forest Malaria Worker (FMW). However, due to low FG activity in some sectors, seven sectors (1, 4, 6, 12, 13, 20, and 21) were replaced by seven new sectors (31, 32, 33, 34, 35, 36, and 37) after field investigations. The median sector size was 15.2 km^2, with an interquartile range (IQR) of 13.5 to 15.6 km^2.

Study design and participants

We conducted a two-year quasi-experimental study based on a prospective cohort of FGs in the isolated forest regions situated of Koh Nhek district (22,223 inhabitants[20]) in Mondulkiri province and Lumphat district (27,839 inhabitants[20]) in Ratanakiri province, northeastern Cambodia, known high-risk area of *P. falciparum* (Fig. 1). This study, comprised two distinct phases which carried out from March 11, 2019, to January 30, 2021, encompassed a pre-implementation observation phase and a post-implementation intervention phase. It included individuals engaged in variety of forest-related activities such as logging, gathering forest products, farming and hunting. The study area was divided into 30 sectors, each managed by a Forest Malaria Worker (FMW).

During the observation phase, (March 2019–June 2020), FG's characteristics were documented and malaria risk were meticulously monitored without implementing intervention strategies. Malaria RDTs (SD Bioline Malaria Ag P.f/P.v) and artesunate-mefloquine (AS-MQ) (Artesunate/Mefloquine 100 mg/200 mg tablets, Cipla) were only provided for unwell FGs unable to access health facilities. FGs aged 10 or older were invited to participate in the study, providing informed consent (including additional parental or guardian consent for FGs under 18), and a DBS biweekly at most.

In the intervention phase (June 29, 2020–January 30, 2021), monthly IPTf with AS-MQ (Artesunate/Mefloquine 100 mg/200 mg tablets, Cipla) was administered to all FGs in the study forest areas, regardless of their infection status. Children under 13 and women were excluded to avoid administering AS-MQ to non-recommended age groups or unknown first trimester pregnancies.[6] Informed consent, including parental or guardian consent and child assent for FGs under 18, was obtained from all eligible participants.

Three cross-sectional studies (CSS) were conducted over two days each at the end of September 2020, November 2020, and January 2021, respectively, as part of this phase to assess malaria prevalence. AS-MQ, was used as IPTf, providing ongoing protection against infection during forest-visit. All eligible FGs received a full therapeutic dose of AS-MQ (two tablets per day for three consecutive days) monthly (Table 1).

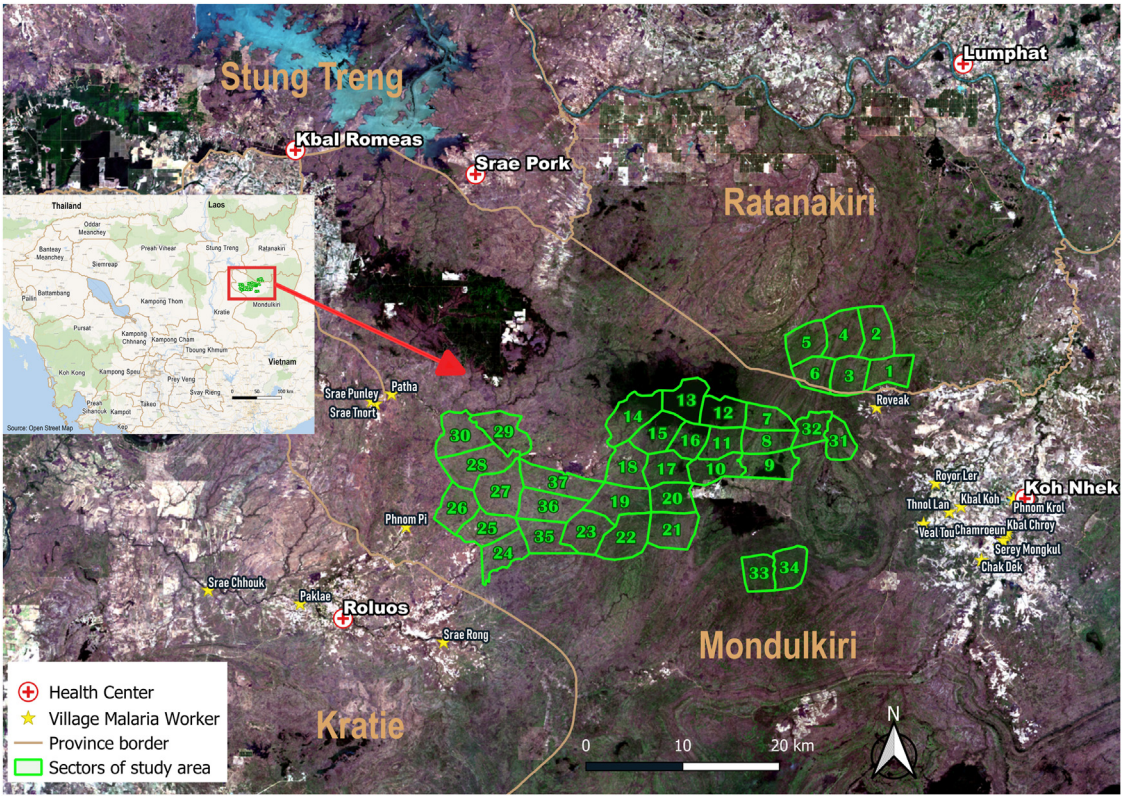

Fig. 1: Map of study areas inside forests. The main image shows Sentinel-2 image of the study areas downloaded on 11 March 2022.

Recruitment of forest malaria workers

FMWs were selected from a group of former FGs who had an in-depth understanding of the study forests. Being former members of this group, they were well placed to establish relationship based on mutual trust for the study. Each FMW was assigned to a specific forest sector, where they spent five days per week, with the objective of enrolling any FGs from that sector in the study. These FMWs were trained to execute study procedures and collect data within their assigned sectors. Whenever a FG settled in or traveled through a FMW's area, the FMW administered a questionnaire using the Kobo application and collected a dried blood spot (DBS) for PCR detection of *Plasmodium* malaria parasites, conducted by the malaria unit of the Institut Pasteur du Cambodge.

Data collection

During the observation phase, FMWs used the Kobo application on smartphones to interview eligible FGs. The questionnaire covered socio-demographics, residence, forest location, malaria history, temperature measurements, knowledge of malaria prevention strategies, healthcare-seeking behaviour, duration of time spent in the forest, forest travel information, and forest activities. Concurrently, DBS samples were routinely

	Observation year (Y1)	Intervention year (Y2)
Objectives	Observing the characteristics of forest goers and the malaria risk inside the selected forests to understand better the malaria epidemiology in the forests	Implementing intervention to eliminate malaria in the selected forests, and assess the effectiveness of the intervention implemented
Time period	March 2019–June 2020	June 29, 2020–January 30, 2021
Activity	Questionnaire only	IPTf every month
Sampling	DBS (continuous) for PCR	DBS for PCR every 2 months (three cross-sectional studies)
Number of sectors	30 sectors (1 FMW per sector)	30 sectors (1 FMW per sector)

FMW, Forest Malaria Worker; IPTf, Intermittent Preventive Treatment for forest goers; DBS, Dried Blood Spot.

Table 1: **Overview of the study inside the forests in both phases.**

collected for PCR detection of *Plasmodium* malaria parasites when FGs were encountered by FMWs.

During the intervention phase, all FGs eligible for the study and entering the forests were administered IPTf after their consent was obtained. To enhance the acceptability among FGs for potential repeated interviews and thereby improve the coverage of IPTf within the study forests, FMWs used a concise questionnaire via the Kobo application, focusing exclusively on demographic information. All FGs were invited to participate in bi-monthly cross-sectional studies (CSS) at predetermined locations and dates, as detailed in distributed leaflets. Throughout this phase, three CSS sessions were conducted, during which FGs provided Dried Blood Spot (DBS) samples and completed short questionnaires. Additionally, FMWs offered IPTf to those FGs who had not received it or any other anti-malarial treatment in the preceding 28 days.

Biological diagnosis

DBS samples were analysed using real-time PCR for malaria detection. Parasite DNA extraction employed Instagene matrix resin, and the cytochrome b gene was targeted to identify *Plasmodium* species, following the method described by Canier et al.[21] and estimate parasites density based on cycle threshold (Ct) values.

Statistical analysis

All statistical analyses were conducted using STATA® version 18.0 (StataCorp, College Station, Texas, USA). Descriptive analyses encompassed the characteristics of individual FGs during the observation phase, including sociodemographic, forest-related activities, and malaria history, as well as during the intervention phase, where only sociodemographic characteristics were considered, presented as medians with interquartile ranges and percentages. Malaria prevalence rates were calculated by dividing the number of malaria-positive cases by the total number of DBS samples collected for both the observation and intervention phases. Comparisons were made using the Fisher's exact test. Poisson regression analysis was employed to investigate the factors, acting as independent variables that are associated with malaria infection, which served as the dependent variable during the observation phase. This approach effectively addressed the potential intra-individual correlation of repeated measurements over time in the analysis of *P. falciparum* malaria infection relative to observed risk factors by assessing the clustering of observations within groups in the dataset. Variables that achieved a significance level of $p < 0.20$ in the univariate analysis were included in the multivariate analysis. Individuals present in both the observation and intervention periods were identified, and their malaria infection status was compared between the two phases. Prevalence Rate Ratios (PRR) with their corresponding 95% confidence intervals (95% CI) are reported from Poisson regression analysis.

Ethics statements

The study received approval from the National Ethics Committee for Health Research (NECHR) of Cambodia. The observation phase protocol was approved on October 19, 2018 (Study number 281), and renewed on December 6, 2019 (study number 306). The intervention phase protocol was approved on April 24, 2020 (study number 100).

Role of the funding source

The funder had no role in the study's design, data collection, analysis, interpretation, or report writing.

Results

Study participation

Between March 11, 2019 and January 30, 2021, 2198 FGs participated in 3579 interviews, with 2409 (67.3%) interviews in the observation phase and 1170 (32.7%) interviews in the intervention phase (Table 2). A total of 1381 (38.6%) participants were interviewed multiple times, averaging 1.3 interviews [min:1; max:10] in the observation phase and 1.75 times [min:1; max:13] in the intervention phase (Table 2). Of these, 1530 (69.6%) FGs participated only in the observation period, 384 (17.5%) in the intervention period only, and 284 (12.9%) in both. Throughout the entire period, a total of 2768 DBS samples were collected and tested, leading to the detection of 580 malaria-positive cases, with 551 cases identified during the observation phase and 29 cases during the intervention phase.

Observation phase FGs characteristics

During the observation period (Table 3), the 1814 participating FGs were predominantly male (90%) with a median age of 28 years (IQR: 21–37.5). Fever (≥37.5 °C) was experienced by 1.5% of FGs with two positive malaria cases detected and treated. Most participants hailed from Kratie (61.8%) and Mondulkiri (32.5%), with approximately half (47%) residing locally for over a year. Only 6% of interviewees came from other provinces. Reported activities included gathering food products (46.9%), logging (42.1%), fishing (23.8%), farming (10.9%), and hunting (8.3%). Frequency-wise, 15.8% visited the forest daily, 39.1% weekly, 21.2% monthly, and 23.9% less than monthly. Nearly half (49.9%) stayed over two nights, averaging 3.2 days per visit with a planned duration of 5.7 days.

Participants frequently reported using multiple sleeping arrangements, with 82.9% utilizing tents or tarpaulins and 77.8% hammocks, showcasing the adaptability in their sleeping preferences.

Approximately 35.8% of participants reported experiencing fever in the last month, of which 15.4% were

	Total	Observation N (%)	Intervention N (%)
Number of interviews with consent	3579	2409 (67.3%)	1170 (32.7%)
Number of individuals	2198[a]	1814 (73.1%)	668 (26.9%)
Mean interviews by individuals [min; max]	1.6 [1; 13]	1.3 [1; 10]	1.8 [1; 6]
Number of DBS samples collected	2768	2211 (79.9%)	557 (20.1%)
Interviews eligible for IPTf given	1014	–	1014 (100%)
Interviews during 3 Cross-sectional studies	593	–	593 (100%)
Malaria prevalence[b] [95% CI] (n_1/n_2)			
P. falciparum	2.4% [1.8–3.0] (66/2768)	2.9% [2.2–3.6] (63/2211)	0.5% [0.1–1.6] (3/557)
P. vivax	17.7% [16.2–19.3] (490/2768)	21.0% [19.1–22.9] (464/2211)	4.7% [3.0–6.8] (26/557)
Mixed (*P. falciparum* + *P. vivax*)	0.9% [0.6–1.3] (24/2768)	1.1% [0.7–1.6] (24/2211)	0% [0.0–0.7] (0/557)
P. falciparum prevalence [95% CI] during:			
1st Cross-sectional study	–	–	0% [0.0–1.9] (0/190)
2nd Cross-sectional study	–	–	0.6% [0.01–3.1] (1/179)
3rd Cross-sectional study	–	–	1.1% [0.1–3.8] (2/188)
P. vivax prevalence [95% CI] during:			
1st Cross-sectional study	–	–	6.8% [3.6–11.7] (13/190)
2nd Cross-sectional study	–	–	3.9% [1.6–8.1] (7/179)
3rd Cross-sectional study	–	–	3.2% [1.2–6.9] (6/188)

Abbreviations: DBS, Dried Blood Spot; IPTf, Intermittent Preventive Treatment for forest goers; CI, Confidence Interval. [a]Among 2198 forest goers, 284 individuals were enrolled in both the observation and intervention phases. [b]Malaria species prevalence in each phase was calculated from malaria species positive cases confirmed by PCR (n_1) among the DBS samples collected (n_2). The 95% confidence intervals (95% CI) for prevalence were calculated using the formula: Poisson mean ± 1.96*sqrt (Poisson mean/n).

Table 2: **Consent interviews, participant inclusion, and malaria prevalence during the two study periods.**

treated for malaria less than a month ago, distinct from the 22.3% who received treatment for malaria at some point earlier in the last year, with no overlap between the groups. Notably, 27% had never heard about malaria. Excluding these individuals, 88.1% used insecticide-treated nets (ITNs), 79.5% reported using LLIHN, 75.8% wore long clothes, 25.9% used repellents and 26.3% used smoke from bonfires as mosquito repellent.

When unwell, 73.1% sought assistance at HCs, 19.6% approached VMWs, 5.6% visited private clinics, 1.1% sought care at referral hospitals, and 0.6% sought MMWs. Healthcare choice was influenced by distance (51.9%), cost (35.7%), availability of tests and medicines (33.4%), quality of care (33.3%), waiting time (12.5%), and provider friendliness (4.7%).

Travel time to healthcare facilities varied, with 19.3% reaching in less than 15 min, 19% in 15–30 min, 13.1% in 30 min to 1 h, 32.6% in 1–2 h, and 16% over 2 h.

During the intervention period (Table 3), a total of 668 FGs actively participated. It's noteworthy that 284 FGs, involved in both phases, were previously described in the observation phase, indicating an overlap between the two phases. Consequently, this collective participation represented 384 individuals, a demographic distribution of 90% of male and 10% of female. Their median age was 30 years with IQR ranged from 21.5 to 38.0 years. The majority of FGs resided in Kratie, accounting for approximately 61%, followed by Mondulkiri with 37%, only 0.8% in Ratanakiri, and 1.3% in others provinces. Additionally, a mere 0.8% of FGs were reported experiencing fever.

PCR malaria prevalence and risk factors during observation phase

Overall, DBS collection was achieved in 91.8% (2211/2409) of the visits during the observation phase. Prevalence rates were 2.9% (95% CI: 2.2–3.6) for *P. falciparum*, 21.0% (95% CI: 19.1–22.9) for *P. vivax*, and 1.1% (95% CI: 0.7–1.6) for mixed infections (Table 2).

Few risk factors were associated with *P. falciparum* and mixed infections in the univariate analysis (Table 4). Key factors increasing the risk included gender, forest activities, recent fever, and frequency of forest visits. Specifically, engaging in two or more forest-related activities and daily forest travels were associated with increases of 4.13-fold (95% CI: 1.27–13.41) and 2.41-fold (95% CI: 1.22–4.76) in risk, respectively, while recent fever showed a 1.80-fold (95% CI: 1.17–2.77) increase. Conversely, female participants had a lower risk, with a risk reduction factor of 0.23 (95% CI: 0.06–0.94). Other factors like age, type of forest activity, and malaria prevention methods, such as ITN use, did not show significant associations.

In multivariate analysis, only farming activity was significantly associated with a higher risk of *P. falciparum* infection, increasing the risk by 4.25 times (95% CI: 1.11–16.26).

	Observation (N = 1814)	Intervention (N = 668[a])
Age in year, median [IQR]	28 [21–37.5]	30 [21.5–38.0]
Gender		
Female	184 (10.1%)	38 (9.9%)
Male	1630 (89.9%)	346 (90.1%)
Residence (N)		
Kratie province	1121 (61.8%)	234 (60.9%)
Mondulkiri province	590 (32.5%)	142 (37.0%)
Ratanakiri province	85 (4.7%)	3 (0.8%)
Other provinces	18 (1.0%)	5 (1.3%)
Fever today	27 (1.5%)	3 (0.8%)
Fever last month	650 (35.8%)	–
Living in this area		
<6 months ("mobile")	757 (41.7%)	–
6 months-1 year ("migrant")	204 (11.3%)	–
>1 year ("local")	853 (47.0%)	–
Gathering forest products	851 (46.9%)	–
Fishing	431 (23.8%)	–
Logging	763 (42.1%)	–
Hunting	151 (8.3%)	–
Farming	198 (10.9%)	–
Travel frequency in the forest		
<1 time/month	434 (23.9%)	–
Every month	384 (21.2%)	–
Every week	709 (39.1%)	–
Every day	287 (15.8%)	–
Length of forest stays		
No overnight stay	389 (21.4%)	–
1 overnight stay	199 (11.0%)	–
2 nights to 1 week	905 (49.9%)	–
1 week to 2 weeks	237 (13.1%)	–
2 weeks to 1 month	84 (4.6%)	–
Days planned in the forest, mean [min; max]	5.7 [1; 30]	–
Days already spent in the forest, mean [min; max]	3.2 [1; 30]	–
Type of housing[b]		
Thatched grass	93 (5.1%)	–
Sago palm leaves	11 (0.6%)	–
Bamboo	19 (1.1%)	–
Iron sheet	31 (1.7%)	–
Wood	87 (4.8%)	–
Tent or tarpaulins	1505 (82.9%)	–
Hammock	1411 (77.8%)	–
No house	23 (1.3%)	–
Others	25 (1.4%)	–
Open shelter[c]		–
Yes	1770 (97.6%)	–
No	44 (2.4%)	–
Treated for malaria before		
Never	248 (13.7%)	–
<1 month ago	280 (15.4%)	–
<1 year ago	405 (22.3%)	–
>1 year ago	392 (21.6%)	–
Never heard about malaria	489 (27.0%)	–
Use insecticide-treated nets (ITNs)	1598 (88.1%)	–
Use insecticide-treated hammocks (LLIHNs)	1442 (79.5%)	–

(Table 3 continues on next page)

	Observation (N = 1814)	Intervention (N = 668[a])
(Continued from previous page)		
Use long clothes	1375 (75.8%)	–
Use repellent	471 (25.9%)	–
Use bonfires for smoke[d] (N = 1158)	304 (26.3%)	–
Use others measures	25 (1.4%)	–
Duration to Health Center		
<15 min	351 (19.3%)	–
15–30 min	345 (19.0%)	–
30–60 min	237 (13.1%)	–
1–2 h	591 (32.6%)	–
>2 h	290 (16.0%)	–
Preferred type of health facility in case of illness[d] (N = 1158)		
Health Center	846 (73.1%)	–
VMW	227 (19.6%)	–
MMW	7 (0.6%)	–
Private Clinic	65 (5.6%)	–
Referral Hospital	13 (1.1%)	–
Reason for choosing healthcare[b,d] (N = 1158)		
Distance (closer)	601 (51.9%)	–
Cost (cheaper)	413 (35.7%)	–
Quality of care (better care)	385 (33.3%)	–
Friendliness of health staff	54 (4.7%)	–
Availability of tests and medicines in stock	387 (33.4%)	–
Less waiting time	145 (12.5%)	–

[a]A total of 668 participants were in the intervention phase, but 284 individuals who participated in both phases had already been described in the observation phase. [b]The type of housing and the reason for choosing healthcare are presented as a multiple-choice selection question. [c]Open shelter denotes a type of shelter designed as an open space, offering less enclosure, specifically within a forest setting. [d]Regarding the use of bonfires for smoke, the type of health facility, and the reason for choosing healthcare, they were introduced after four months of implementation to investigate a specific issue important requested by local health authorities, which had not been anticipated at the start of the study. This explains why some individuals did not provide an answer.

Table 3: **Description of the forest goers' population inside the study forests in the observation and intervention phase.**

PCR malaria prevalence after implementation of IPTf

In the intervention period, out of 1170 interviews, 1014 interviews (86.7%) resulted in eligible FGs receiving IPTf, while 156 interviews (13.3%) did not, primarily due to recent anti-malarial treatment or participant age and gender. Throughout this period, 94% of 593 interviews conducted in three CSS studies successfully collected DBS, with PCR tests performed on 557 individuals, as detailed in Table 2.

We observed a significant decrease in *P. falciparum* infection rates, from 2.9% [63/2,211, 95% CI: 2.2–3.6] in the observation phase to 0.5% [3/557, 95% CI: 0.1–1.6] in the intervention phase ($p < 0.001$). Similarly, *P. vivax* prevalence dropped from 21.0% [464/2211, 95% CI: 19.1–22.9] to 4.7% [26/557, 95% CI: 3.0–6.8] ($p < 0.001$), with no mixed infections detected (Table 2). The trends of *P. falciparum* and *P. vivax* prevalence from March 2019 to January 2021 are depicted in Fig. 2. Following the interruption of continuous DBS collection in June 2020, three CSS were conducted showing a gradual decline in *P. vivax* prevalence (Table 2).

Among the 284 individuals interviewed in both periods, a total of 1226 interviews were conducted, yielding 893 DBS samples (570 from the observation period and 323 from the intervention period). In the intervention period, of the 619 conducted interviews, 539 individuals (87.1%) met IPTf eligibility, while 12.9% did not.

In the cohort of 284 participants present in both study phases, we observed a significant reduction in malaria infection rates. Specifically, the prevalence of *P. falciparum* decreased from 2.5% (14/570, 95% CI: 1.3–4.1) in the observation phase to 0.3% (1/323, 95% CI: 0.007–1.7) in the intervention phase. Concurrently, *P. vivax* prevalence also showed a significant decline from 22.5% (128/570, 95% CI: 18.7–26.7) to 3.7% (12/323, 95% CI: 1.9–6.5). The Fisher's exact test confirmed the statistical significance of these reductions, with p-values of 0.014 for *P. falciparum* and <0.001 for *P. vivax*, respectively. This effectiveness is highlighted by the minimal number of PCR-positive samples observed during the intervention phase, as detailed in Fig. 3.

Discussion

This study, leveraging a robust community network of trained peer Forest Goers (FGs), has significantly increased our understanding of malaria epidemiology in

	Value	N samples (%)	N Pf+ (%)	Crude PRR[a]	p-value	Adjusted PRR[a]	p-value
Age	18–49	1782 (80.6%)	67 (77.0%)	Ref	Ref	–	–
	<18	264 (11.9%)	13 (14.9%)	1.31 (0.70, 2.46)	0.40	–	–
	50+	165 (7.5%)	7 (8.1%)	1.13 (0.52, 2.43)	0.76	–	–
Gender	Male	2007 (90.8%)	85 (97.7%)	Ref	Ref	Ref	Ref
	Female	204 (9.2%)	2 (2.3%)	**0.23 (0.06, 0.94)**	**0.04**	0.26 (0.07, 1.07)	0.06
Activities in the forest	No	190 (8.6%)	3 (3.5%)	Ref	Ref	Ref	Ref
	Logging	541 (24.5%)	24 (27.6%)	2.81 (0.88, 8.93)	0.08	2.15 (0.65, 7.09)	0.21
	Gathering forest products	573 (25.9%)	15 (17.2%)	1.66 (0.52, 5.31)	0.39	1.59 (0.49, 5.20)	0.44
	Fishing	229 (10.3%)	5 (5.7%)	1.38 (0.33, 5.74)	0.66	1.22 (0.30, 5.01)	0.78
	Farming	110 (5.0%)	6 (6.9%)	3.45 (0.88, 13.7)	0.08	**4.25 (1.11, 16.26)**	**0.03**
	Hunting	77 (3.5%)	2 (2.3%)	1.65 (0.28, 9.68)	0.58	1.46 (0.24, 8.78)	0.68
	≥2 activities	491 (22.2%)	32 (36.8%)	**4.13 (1.27, 13.41)**	**0.02**	2.98 (0.87, 10.16)	0.08
Fever last month	No	1387 (62.7%)	42 (48.3%)	Ref	Ref	Ref	Ref
	Yes	824 (37.3%)	45 (51.7%)	**1.80 (1.17, 2.77)**	**0.007**	1.47 (0.93, 2.30)	0.10
Type of population	Mobile (<6 months)	805 (36.4%)	32 (36.8%)	1.15 (0.73, 1.79)	0.55	1.33 (0.85, 2.08)	0.21
	Migrant (6 months–1 year)	253 (11.4%)	15 (17.2%)	1.71 (0.96, 3.04)	0.07	1.36 (0.76, 2.45)	0.30
	Local (>1 year)	1153 (52.2%)	40 (46.0%)	Ref	Ref	Ref	Ref
Treated for malaria before	Never treated	282 (12.8%)	12 (13.8%)	Ref	Ref	–	–
	<1 month ago	354 (16.0%)	14 (16.1%)	0.93 (0.44, 1.97)	0.85	–	–
	<1 year ago	545 (24.7%)	25 (28.7%)	1.08 (0.56, 2.07)	0.82	–	–
	>1 year ago	494 (22.3%)	15 (17.2%)	0.71 (0.36, 1.42)	0.34	–	–
	Never heard of malaria	536 (24.2%)	21 (24.2%)	0.92 (0.46, 1.86)	0.82	–	–
Travel frequency in the forest	<1 time/month	496 (22.4%)	12 (13.8%)	Ref	Ref	Ref	Ref
	Every month	476 (21.5%)	16 (18.4%)	1.39 (0.68, 2.83)	0.36	1.43 (0.71, 2.90)	0.31
	Every week	862 (39.0%)	37 (42.5%)	1.77 (0.94, 3.34)	0.08	1.41 (0.73, 2.71)	0.31
	Everyday	377 (17.1%)	22 (25.3%)	**2.41 (1.22, 4.76)**	**0.01**	1.94 (0.95, 3.97)	0.07
Length of forest stays	No overnight	503 (22.8%)	19 (21.8%)	Ref	Ref	–	–
	1 overnight	230 (10.4%)	10 (11.5%)	1.15 (0.54, 2.44)	0.71	–	–
	2 nights to 1 week	1124 (50.8%)	39 (44.8%)	0.92 (0.55, 1.54)	0.75	–	–
	1 week to 2 weeks	223 (10.1%)	12 (13.8%)	1.42 (0.73, 2.77)	0.30	–	–
	2 weeks to 1 month	131 (5.9%)	7 (8.1%)	1.41 (0.61, 3.30)	0.42	–	–
Usually stay overnight	No	503 (22.8%)	19 (21.8%)	Ref	Ref	–	–
	Yes	1708 (77.2%)	68 (78.2%)	1.05 (0.65, 1.70)	0.83	–	–
Open shelter	No	66 (3.0%)	3 (3.5%)	Ref	Ref	–	–
	Yes	2145 (97.0%)	84 (96.6%)	0.86 (0.27, 2.70)	0.80	–	–
Sleeping in tent	No	400 (18.1%)	17 (19.5%)	Ref	Ref	–	–
	Yes	1811 (81.9%)	70 (80.5%)	0.91 (0.54, 1.53)	0.72	–	–
Sleeping in hammock	No	540 (24.4%)	19 (21.8%)	Ref	Ref	–	–
	Yes	1671 (75.6%)	68 (78.2%)	1.16 (0.69, 1.94)	0.58	–	–
Use insecticide-treated nets	No	254 (11.5%)	4 (4.6%)	Ref	Ref	Ref	Ref
	Yes	1957 (88.5%)	83 (95.4%)	2.69 (0.99, 7.31)	0.05	2.38 (0.83, 6.81)	0.11
Use insecticide-treated hammocks	No	438 (19.8%)	16 (18.4%)	Ref	Ref	–	–
	Yes	1773 (80.2%)	71 (81.6%)	1.10 (0.64, 1.89)	0.74	–	–
Use long clothes	No	495 (22.4%)	16 (18.4%)	Ref	Ref	–	–
	Yes	1716 (77.6%)	71 (81.6%)	1.28 (0.77, 2.12)	0.34	–	–
Use repellent	No	1602 (72.5%)	60 (69.0%)	Ref	Ref	–	–
	Yes	609 (27.5%)	27 (31.0%)	1.18 (0.74, 1.89)	0.48	–	–

[a]PRR (Prevalence Rate Ratio) was estimated using common Stata's poisson command, quantifying the risk of malaria infection associated with exposure to specific factors. Both the crude PRR and the adjusted PRR are presented in the table. However, the adjusted PRRs are only displayed for variables included in the multivariate Poisson regression analysis with a p-value of less than 0.20. Numbers in bold represent statistically significant associations with a p-value <0.05.

Table 4: **Malaria risk factors of association with *Plasmodium falciparum* (including mixed cases) during the observation phase by using Poisson model that accounted for the potential intra-individual correlation of repeated measurements (N = 2211 samples, 1664 individuals).**

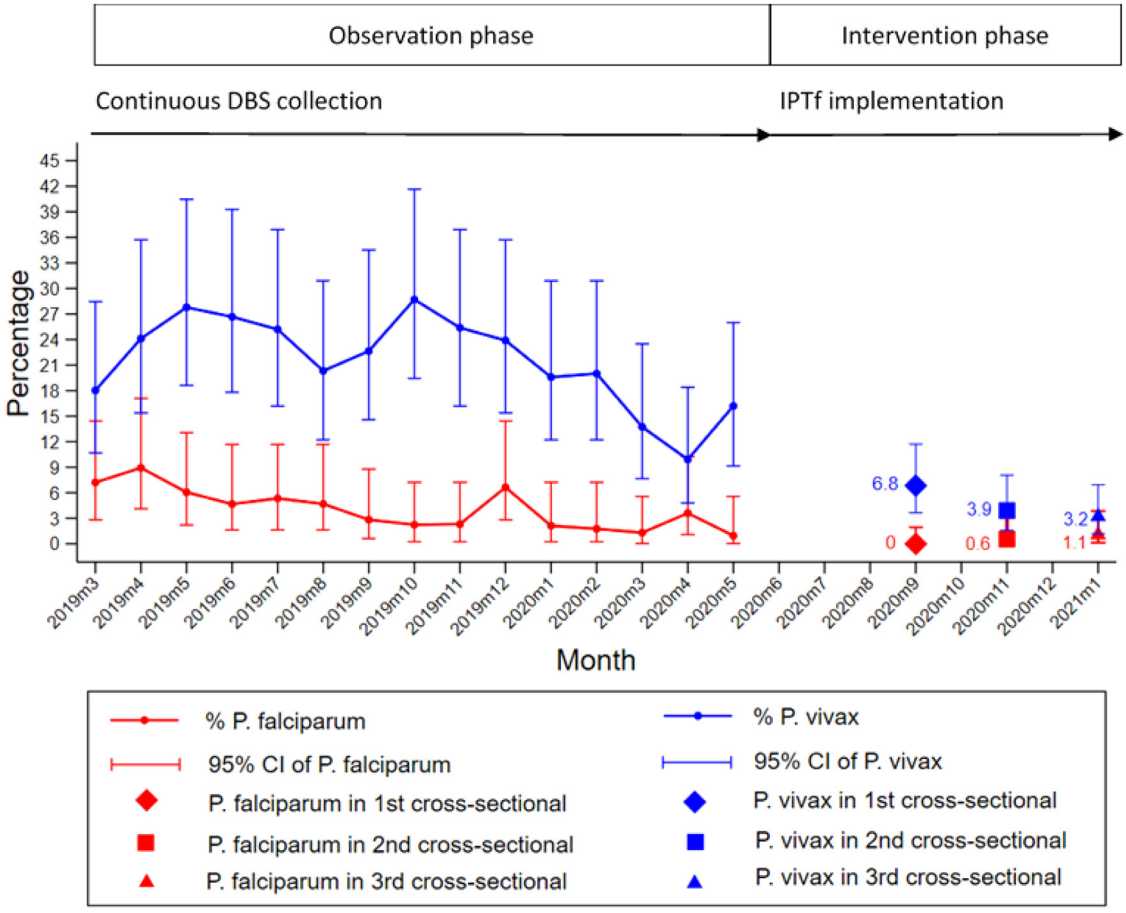

Fig. 2: Trend of malaria prevalence inside the study forests in the observation and intervention phase. Mixed cases were added in each *P. falciparum* and *P.vivax* prevalence during the observation phase.

Cambodian forests. Primarily, we demonstrated that the implementation of IPTf led to a marked decrease in malaria prevalence, with overall rates dropping from 2.9% to 0.5% for *P. falciparum* and from 21.0% to 4.7% for *P. vivax*. This consistent trend among the 284 FGs participating in both study phases, reinforces the intervention's effectiveness and underscores the reliability of our findings.

In light of the main findings, the discussion on the limited efficacy of topical repellents[22] and the challenges of conventional vector control strategies[23] gains new significance. While our study highlights the effectiveness of IPTf in drastically reducing malaria prevalence among FGs, it also suggests that in areas where conventional methods like ITNs are less effective due to the unique challenges of forest-based malaria transmission, innovative approaches are necessary. The strategy of deploying additional MMWs to remote areas has markedly reduced *P. falciparum* and mixed infections, thus complementing the existing routine malaria control efforts in Cambodia.[24]

In the context of accelerating malaria elimination, the strategy of mass drug administration (MDA), implemented in high-risk or hotspot villages along the Thailand–Myanmar border,[25] Myanmar,[26,27] Laos PDR,[28] and Cambodia[29] has informed the discussion on the need for more intensive approaches. It emphasizes the safety and efficacy of MDA in significantly reducing malaria incidence at the village level. Our findings underscore the importance of IPTf as a complementary strategy for malaria elimination, particularly in targeting parasite reservoir within hard-to-reach areas like forests. Our previous study exposed the insufficient sensitivity of RDTs for mass screening and treatment (MSAT),[18] casting doubt on the practicality of MSAT in elimination efforts. Consequently, support for MSATs has waned in elimination contexts, with a growing inclination towards adopting IPTf as a more effective strategy for intensifying malaria control and achieving elimination. This change in policy recommendations, as indicated in the WHO's Malaria Guidelines as of 2022,[30] highlights IPTf's potential in malaria elimination.

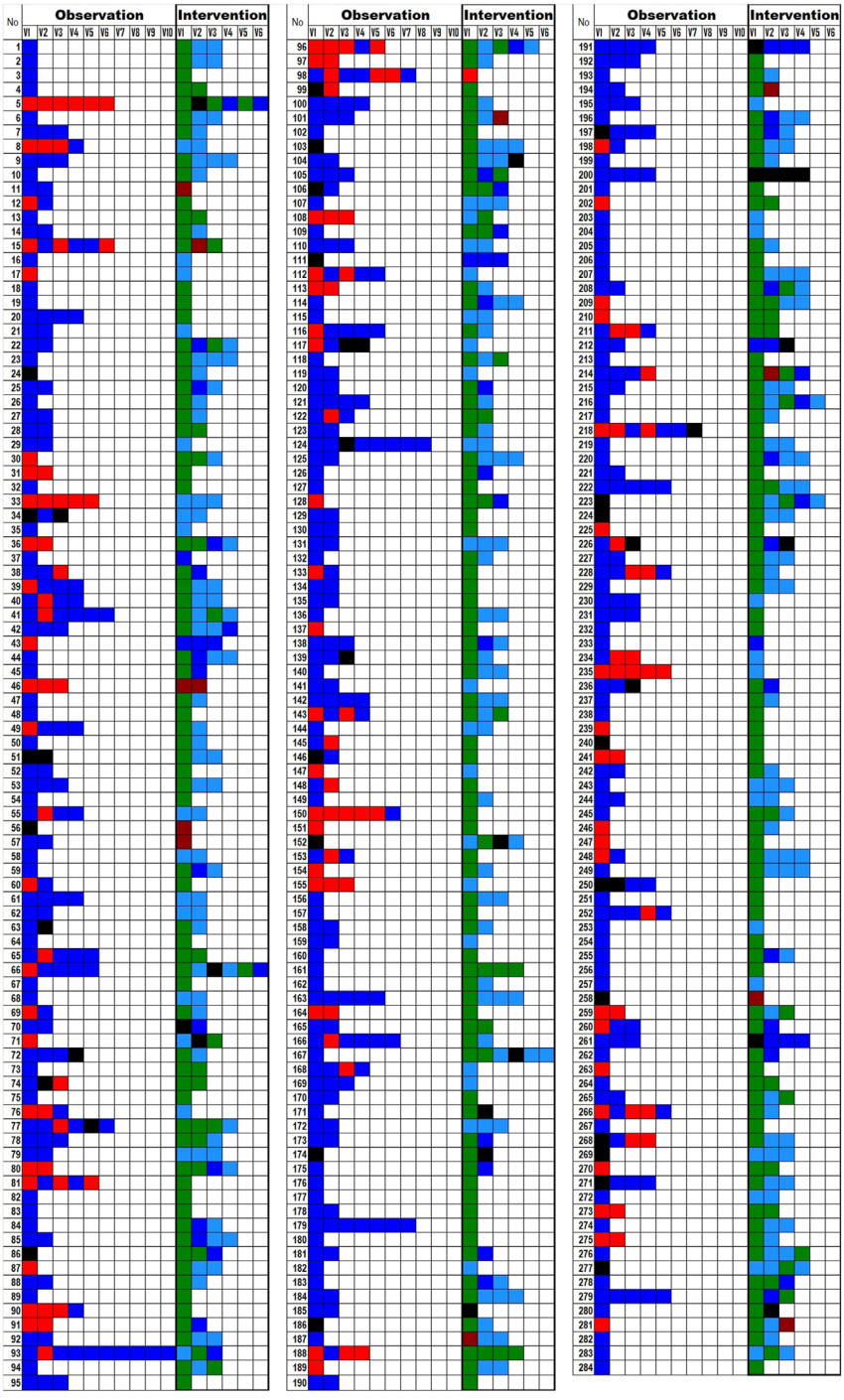

Fig. 3: Results of individuals who enrolled in both observation and intervention phases for each visit. The boxes' color legend is as follows: red (malaria positive), blue (malaria negative), green (IPTf), dark red (malaria positive + IPTf if individual never received IPTf or ever received IPTf >28 days ago), light blue (malaria negative + IPTf if individual never received IPTf or ever received IPTf >28 days ago), and black (IPTf <28 days ago/Female FG).

The project shed light on the epidemiological patterns of malaria by engaging FGs who were selected based on their understanding of the area and educational benchmarks such as literacy or previous work with environmental civil service organizations. This engagement with marginalized groups provided unique insights into their risk of malaria infection, thereby broadening the impact and scope of our research. The training of 30 FGs in malaria diagnosis using RDTs, along with prevention and treatment tactics, not only bolstered their skill set but also elevated their status within the community, improving access to healthcare.

The project was transformative for the FMWs, changing their societal role from illegal loggers to healthcare providers and opening the door to new life possibilities after the project's conclusion. The prospects of urban migration or community health roles marked a significant transition in their careers.

The FGs valued the presence of trained peers who could deliver testing or treatment services, which was particularly crucial in remote and challenging environments. The integration of IPTf marked a significant change in their behavior, with FGs feeling safeguarded from malaria during their forest ventures after initial reservations about potential side effects.

Our study has markedly advanced our understanding of malaria's epidemiology among populations in Cambodia's forests, a critical step toward addressing this public health challenge in the region. The significant mobility of FGs, with over half traveling and spending multiple nights in the forest weekly, underscores the vital need for ongoing and targeted intervention strategies. These strategies are essential not only to support newly settled groups but also to mitigate the risk in areas with high mosquito vector exposure, exacerbated by open-shelter living conditions. Alarmingly, our study found that nearly 30% of FGs lacked awareness of malaria, spotlighting the urgent requirement for enhanced educational efforts to prevent and control malaria effectively among these high-risk groups.

Our multivariate model has highlighted an increased risk of *P. falciparum* infection associated with specific activities, particularly those inaccurately described as "farming". This misrepresentation, often a euphemism for logging due to its illegality, could mask the actual risks involved. This finding calls for a nuanced understanding of the local context and the development of interventions that are both culturally sensitive and effective. Furthermore, our experience while performing study activities showed no evidence of farming in these forests. Of notice, previous research[31] has indicated that individuals engaged in farm-related work in the Greater Mekong Subregion are at risk of malaria, with pursuits such as logging heightening their vulnerability. Mislabelling these activities might unintentionally conceal the actual dangers they pose.

While IPTf with an ACT has shown significant impacts on *P. falciparum*, its effectiveness for *P. vivax* is limited due to the presence of hypnozoites. However, it is worth noting that repeated administration of ACT may affect *P. vivax* outcomes by offering temporary protection against relapses. Complete eradication of *P. vivax* requires the use of additional anti-malarial drugs such as primaquine, which targets the liver stages of the parasites. However, the administration of primaquine requires testing patients for *glucose-6-phosphate dehydrogenase* (G6PD) deficiency prior to its use, complicating its large-scale application. In endemic countries like in Cambodia where malaria transmission is restricted to pockets of endemicity with well-defined at-risk individuals (ie. adult males or forest goers), an alternative could be to specifically test for G6PD deficiency in at risk population and provide a primaquine course in addition to an ACT only to G6PD normal individuals. This would however come with significant over-administration to individuals not carrying hypnozoites of a drug with potential serious safety issues if misdiagnosis of G6PD occur. An alternative option that has been proposed in the last years would be to narrow down G6PD testing and primaquine administration to individuals displaying serological markers of recent exposure to *P. vivax*.[32] These serological markers have been shown to identify with 80% sensitivity and 80% specificity individuals infected by blood-stage *P. vivax* parasites within the past 6–9 months.[33] Such *P. vivax* serological test-and-treat approach (PvSeroTAT) would then allow to offer primaquine treatment only to individuals likely carrying hypnozoites and reduce the number of over-treated individuals.

Our study, while providing significant insights, is subject to certain limitations related to its design and study population. Firstly, achieving complete coverage of the FG population was a considerable challenge, and it is impossible to determine precisely how many were missed. The lack of systematic recording and the potential for active avoidance of contact with the FMWs further compounds this uncertainty. Moreover, it is likely that the reported numbers of people in the forest are underestimates, as FMWs occasionally observed FGs fleeing upon their approach. This evasion behavior, possibly linked to engagement in illegal logging activities, might have led to wariness towards FMWs or study staff. Nevertheless, this issue was partially mitigated by recruiting FMWs from within the forest-going community itself, thereby building a foundation of trust over time.

A significant limitation was the absence of maintained control zones during the intervention period, which hindered our ability to precisely differentiate the impact of the intervention from the general decrease in malaria cases already underway. Additionally, it is plausible that the FGs who were not interviewed could represent a distinct profile in terms of infection risk,

though the direction and extent of this potential bias are difficult to ascertain. Despite these constraints, our analysis of the changes in positive sample incidences among individuals observed in both the observation and intervention periods offers crucial insights. We noted a marked contrast in the frequency of positive samples between these periods, with a higher occurrence during the observation phase. This contrast indicates that, despite the noted limitations, the intervention likely played a significant role in reducing the risk of malaria transmission.

Conclusion

This study investigates malaria transmission risk among forest goers in Cambodia, revealing the effectiveness of Intermittent Preventive Treatment for malaria (IPTf) in forested regions. Despite challenges in statistical assessment, the data shows a significant reduction in both *P. vivax* and *P.falciparum* cases within studied forests compared to nationwide trends. Following the study's findings, IPTf has been endorsed by the Cambodia Ministry of Health as a key strategy for malaria elimination, with successful piloting in Laos. This research represents a crucial step in eliminating malaria from Cambodia's forests and Southeast Asia, highlighting the potential of IPTf as a proactive measure for at-risk populations.

Contributors

PP, BW, and CN conceived the study. PP, SI, PK, TS, and AV designed and implemented data acquisition tools. JP, SS, CK, TL, and SC performed laboratory analyses. SI, PK, CF, and PP analysed the data. SI, PP, CF, BW, JP, AB, and CCJ interpreted the data and results. SI and PK verified the data. SI, PK, CF, and PP accessed to raw data. SI and CF drafted the manuscript. All authors reviewed, edited, and approved. All authors read and approved the final manuscript. CF had final responsibility for the decision to submit for publication.

Data sharing statement

Datasets and analysis code are available from the authors upon request.

Editor note

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Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101093.

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