# Effectiveness, safety, and acceptability of primaquine mass drug administration in low-endemicity areas in southern Thailand: A proof-of-concept study

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Submitted to: JMIR Public Health and Surveillance
on: August 19, 2023

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## *Abstract*

**Background:** A challenge in achieving the malaria-elimination target in the Greater Mekong Subregion, including Thailand, is the predominance of Plasmodium vivax malaria, which has shown extreme resilience to control measures.

**Objective:** This proof-of-concept study aimed to provide evidence for implementing primaquine mass drug administration (pMDA) as a strategy for P.vivax elimination in low-endemicity settings.

**Methods:** The study employed a mixed-methods trial to thoroughly evaluate the effectiveness, safety, acceptability and community-engagement of pMDA. The quantitative part was designed as a two-period cluster-crossover randomized control trial. The intervention was pMDA augmented to the national prevention and control standards with directly observed treatment (DOT) by village health volunteers. The qualitative part employed indepth interviews and brainstorming discussion. The study was conducted in seven clusters in two districts of two southern provinces in Thailand with persistently low P.vivax transmission. In the quantitative part, five cross-sectional blood surveys were conducted for both pMDA and control groups before and 3-months after pMDA. The effectiveness of pMDA was determined by comparing proportions of P.vivax per 1000 population between the two groups with a multilevel zero-inflated negative-binomial model adjusted for cluster and time as covariate and interaction. The safety data comprised adverse events after drug administration. Thematic content analysis was used to assess the acceptability and engagement of stakeholders.

**Results:** At the pre-pMDA period, the proportions of P.vivax in the pMDA (n=1536) and control (n=1577) groups were 13.0 (95%CI: 8.2-20.4) and 12.0 (95%CI: 7.5-19.1), respectively. At month-3 post-pMDA, the proportions of P.vivax of the pMDA (n=1430) and the control (n=1420) groups were 8.4 (95%CI: 4.6-15.1) and 5.6 (95%CI: 2.6-11.5), respectively. No statistically significant differences were found between the two groups. The number of malaria cases was reduced in all clusters, regardless of their being in the pMDA group or control group, and thus the impact of the pMDA was inconclusive. There were no major safety concerns. Acceptance among the study participants and public healthcare providers at local and national levels was high,

and they believed that pMDA had boosted awareness in the community.

**Conclusions:** pMDA showed high adherence, safety and tolerability, but may not significantly impact P.vivax transmission. As a proof-of-concept, we decided not to go with the scaleup with larger sizes of clusters and samples. An alternative approach is currently being implemented, a targeted primaquine treatment strategy, providing primaquine with DOT only to the targeted population in the households around each index case in the intervention clusters. However, we have a success story of effective healthcare workforces at the point-of-care, collaborations with community, and commitment from authorities at local and national levels. Our efforts boosted the acceptability of the malaria-elimination initiative. In striving to achieve elimination targets, community-engagement with any elimination measures is recommended. Clinical Trial: Thai Clinical Trials Registry. TCTR ID :TCTR20190806004 :

(JMIR Preprints 19/08/2023:51993)
DOI: https://doi.org/10.2196/preprints.51993

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**Results:** At the pre-pMDA period, the proportions of *P.vivax* in the pMDA (n=1536) and control (n=1577) groups were 13.0 (95%CI: 8.2-20.4) and 12.0 (95%CI: 7.5-19.1), respectively.. At month-3 post-pMDA, the proportions of *P.vivax* of the pMDA (n=1430) and the control (n=1420) groups were 8.4 (95%CI: 4.6-15.1) and 5.6 (95%CI: 2.6-11.5), respectively. No statisticaly significant differences were found between the two groups. The number of malaria cases was reduced in all clusters, regardless of their being in the pMDA group or control group, and thus the impact of the pMDA was inconclusive. There were no major safety concerns. Acceptance among the study participants and public healthcare providers at local and national levels was high, and they believed that pMDA had boosted awareness in the community.

**Conclusion:** pMDA showed high adherence, safety and tolerability, but may not significantly impact *P.vivax* transmission. As a proof-of-concept, we decided not to go with the scaleup with larger sizes of clusters and samples. An alternative approach is currently being implemented, a targeted primaquine treatment strategy, providing primaquine with DOT only to the targeted population in the households around each index case in the intervention clusters. However, we have a success story of effective healthcare workforces at the point-of-care, collaborations with community, and commitment from authorities at local and national levels. Our efforts boosted the acceptability of the malaria-elimination initiative. In striving to achieve elimination targets, community engagement with any elimination measures is recommended.

**Trial registration:** Thai Clinical Trials Registry. TCTR ID : TCTR20190806004 : (https://www.thaiclinicaltrials.org/show/TCTR20190806004)

**Funding:** The National Institute for Allergy and Infectious Diseases, National Institutes of Health, USA (U19 AI089672).

**Keywords:** mass drug administration, cluster-crossover randomized control trial, community-based trial, participatory epidemiology, *Plasmodium vivax*, primaquine

## Introduction

***Background***

As part of the World Health Organization (WHO) campaign for “zero malaria”, the Greater Mekong Subregion (GMS) of Southeast Asia has developed a strategic plan for regional malaria elimination by 2030, while Thailand aims to achieve this goal by 2024 [1,2]. One major challenge facing the GMS is the predominance of *Plasmodium vivax* malaria [3,4], which has shown extreme resilience to control measures [5,6]. Initiatives to eliminate malaria have an excellent impact on P. falciparum but not on *P.vivax* malaria worldwide due to various unique aspects of *P.vivax* biology. One challenge is asymptomatic infections with *P.vivax* which are undetected and untreated, potentially contributing to transmission over several weeks or months [7]. Asymptomatic infections are especially common in low-endemicity areas where control tools have reduced the malaria burden [8-10]. A study along the Thailand-Myanmar border noted that while the proportions of severe *P.vivax* malaria varied across different geographic regions and transmission settings, a significant proportion of the community had asymptomatic parasitemia, even in low-transmission areas [9].

The identification and appropriate treatment of asymptomatically infected individuals, typically missed by clinical case-based surveillance, have become critical for interrupting malaria transmission in the final elimination phase [11,12]. Several approaches have been proposed to accelerate *P.vivax* elimination, for example, novel serological test-and-treat interventions, radical cure strategies, case-centered surveillance and response systems, and mass drug administration (MDA) [13-15]. To deal with low blood parasitemia and the formation of hypnozoites associated with *P.vivax* infections that evade conventional diagnosis, presumptive preventive treatment of an endemic population by MDA using a hypnozoiticidal drug, such as primaquine (PQ), is often the chosen strategy to eliminate residual *P.vivax* transmission [15-17]. A large-scale MDA with pyrimethamine and PQ was associated with decreased *P.vivax* transmission in central and southern China [14].

The WHO concluded lessons learned from MDA implementation, the so called “mass primaquine preventive treatment (MPPT)” in several temperate countries, such that MPPT combined with vector control and other preventive measures resulted in the rapid containment of *P.vivax* epidemics and may have contributed to the interruption of transmission in low transmission settings [18]. Prior to 2019, there were no data on the implementation of MPPT in tropical and subtropical areas. In 2019, when this project started in Thailand, the WHO reported two MDA studies in the GMS with differing results, with one study demonstrating only short-term reduction in *P.vivax* transmission and the other finding no effect [18]. It appears that MDA with PQ has been successful in eliminating temperate-zone *P.vivax* [11,15,19,20], but its applicability and effectiveness for eliminating *P.vivax* in tropical countries remain to be evaluated.

Therefore, as part of the International Center of Excellence for Malaria Research (ICEMR)

project, supported by the US-NIH (U19 AI089672), this study was conducted to evaluate the effectiveness, safety and acceptability of MDA with PQ in low-endemicity areas in a tropical country. Particularly, this study was considered a proof-of-concept evaluation of MDA with PQ, termed “pMDA”, using a cluster-crossover randomized trial design to provide the evidence base for designing and implementing a pMDA strategy in low malaria-endemic settings in Thailand. With the planning of the pMDA strategy by the National Malaria Control Program in Thailand, we also sought to critically assess the acceptability and engagement of stakeholders at various levels. According to the main ICEMR project, if the pMDA (Phase I) proved effective, safe and acceptable, the pMDA intervention would be scaled up to cover >100,000 villagers in 200 clusters in 8 provinces (Phase II) using a stepped-wedge design to provide a statistically robust evaluation of pMDA.

### *Objectives*

The goal of this proof-of-concept study was to thoroughly assess the effectiveness, safety, acceptability and community engagement of pMDA as a strategy for malaria elimination in Thailand. Specific aims were: (1) to compare the proportions of *P.vivax* between communities under the national standard of prevention and control (SPC) program and communities under SPC augmented with pMDA, (2) to assess the safety of PQ implemented in the communities, and (3) to assess acceptability and stakeholder engagement for the possibility to scale-up to Phase II.

## Methods

### *Trial design*

The study employed a mixed method, comprising quantitative and qualitative approaches. The quantitative part, for assessing the effectiveness and safety of pMDA intervention, adopted a cluster-crossover randomized control trial, a modified cluster randomized design, which is particularly feasible in pragmatic clinical trials in healthcare systems [21,22]. This design was selected as it is suitable for determining the effectiveness of routinely used interventions in healthcare practice in which the interventon was randomized (turned on and off) at the community level instead of the individual level [23]. In this study, clusters were randomized to a sequence of treatment conditions; a group of clusters received pMDA in the first period (Year 1) and SPC in the second period (Year 2), while the other group of clusters received these preventive activities in reverse order.

The qualitiative part, assessing the acceptability and stakeholder engagement, utilized indepth interviews (IDI) and brainstorming among stakeholders. The stakeholders were primarily sensitized before the study started and informed regularly during the study period.

***Settings and location***

The study was conducted in two districts of two southern provinces in Thailand (Yala and Narathiwat), with persistently low vivax malaria transmission. The study sites comprised seven purposively selected villages, the smallest administrative unit in Thailand, each typically having about 200-400 residents. The seven villages were selected according to their reported malaria incidences in 2018 from routine passive case detection in the malaria surveillance system of Thailand (unpublished data). Five villages (#1, 2, 4, 5, and 6) were in Yala Province, with *P.vivax* incidence rates of 4–7%; two had unexpectedly high rates (over 30%) in 2018. Two villages (#3 and 7) were in Narathiwat Province, with *P.vivax* incidence rates of 1–2%. For the study design, one group of villages served as the pMDA treatment group, while the other served as the control group. In the following year, the intervention was swapped between the two groups of villages. A map showing locations and distances among the two sets of seven clusters (Clusters 1-3 vs. Clusters 4-7) in the two provinces is shown in ***Figure 1***. The nearest distances between two sets of clusters are 3.7-4.5 kilometers. It should be noted that primary healthcare management in each village is independent of each another. On average, one village health volunteer (VHV) is responsible for providing healthcare services for 10 households in the village. Each VHV assists the local health workers in promoting health, preventing diseases and providing basic health services to local communities. In this study, VHVs were assigned to implement pMDA and collect data from the study participants in their non-overlapping households for which they were responsible.

----- *Insert Figure 1 about here* ------

*Figure 1: Clusters assigned to pMDA vs control groups in Yala and Narathiwat Provinces during the two-period cluster-crossover randomized control trial*

***Study participants***

For the quantitative study, all villagers living in the selected clusters were invited to join the study if they were aged one year or older. For PQ administration, the exclusion criteria included (1) pregnant and lactating women, (2) age < 7 years, (3) glucose-6-phosphate dehydrogenase deficient - G6PDd, (4) hemoglobin level < 8 g/dl, (5) body weight < 15 kg, (6) history of allergy to PQ, and (7) history of drug reaction, such as hemolysis or dark urine after PQ intake.

For the qualitative study, key informants included stakeholders representing four levels of engagement and participation: national-level (malaria expert/consultant, Thailand Ministry of Public Health - MOPH), regional- and provincial-level (health officers/authorities), district-level (personnel at operational units of the district hospitals), and local-level (community leaders, religion gatekeepers, VHVs). Villagers in the community were also invited, regardless of whether

they participated in pMDA activities, or not.

***Intervention***

The control group was exposed to SPC, the routine malaria prevention and control program, implemented by the MOPH. The SPC includes routine case report, case investigation, and disease/vector-control activities at the village level. Besides the routine activities, eligible subjects within the pMDA group received a dose of 0.25 mg/kg of PQ daily for 14 days. The 0.25 mg/kg dose was selected according to the WHO recommendation and evidence supported by previous studies, as it is well tolerated in G6PD-normal individuals [11,24]. Those who were G6PDd were excluded from PQ administration. Directly observed treatment (DOT) was performed to ensure compliance.

***Outcomes and study procedures***

For the quantitative study, the primary outcome was the proportion of *P.vivax* infections among the study participants within each cluster before and after two rounds of pMDA. The secondary outcome was the safety of the study particiants who took PQ, which was closely monitored during the 14-day treatment. The study procedure is shown in Figure 2. Baseline demographic information was collected by structured questionnaire at the start of the study. One-time testing for G6PD was performed for all villagers using qualitative CareStart™ G6PD RDT before pMDA to assess the eligibility of study participants to receive PQ. For each round of pMDA, an initial cross-sectional blood survey (CSS) was conducted for both pMDA and control groups before pMDA implementation and follow-up CSS was performed three months after pMDA. As additional post-intervention follow-up, a CSS was performed for both groups six months after the second round of pMDA. At each survey, finger-prick blood was collected from each participant to prepare dried filter-paper blood-spots, which were later used for *Plasmodium* detection by quantitative PCR (qPCR) to detect asymptomatic infection cases in the CSS population. At the time of each survey period, those in the CSS population who had clinical symptoms and were detected by microscopic method in the routine MOPH malaria surveillance system were also subsequently verified by qPCR and counted as confirmed *P.vivax*-infected cases. The prevalence, defined as proportion of confirmed *P.vivax* infection at the community-level in different periods, was calculated from the number of PCR-confirmed *P.vivax* cases*, both asymptomatic and symptomatic cases,* divided by the total number of those in each round of the CSS.

----- Insert Figure 2 about here ----

*Figure 2: Study procedures to assess the effect of pMDA for reducing P.vivax infection in the community in the two-period cluster-crossover randomized control trial during the period*

*2019-2022.*

For the qualitative study, the primary outcome was information about acceptability and stakeholder engagement to the pMDA implemented in their localities. Information was collected using IDIs at the study participant's homes and/or community meeting places. A brainstorming meeting at the regional health office was also arranged for collective opinions among representative authorities at national, regional and provincial levels. Data collection was performed after Round 2 at the conclusion of the study.

***Sample size***

For the quantitative study, sample size was calculated with the notation that it was a proof-of-concept study to assess the potential impact of pMDA implementation. A go/no go decision to scaleup the study with a larger sample size would be made based on the potential effectiveness and feasibility of the intervention with the interclass cluster correlation effect learned from this study. We planned for a sample size of 1500 study participants per group. With this sample size, the power to detect the difference between the two groups varied according to the baseline proportions of *P.vivax* in the study areas, with a two-tailed type I error of 5%. With a sample size of 1500 per group, when the baseline proportion of *P.vivax* in the cluster was low at 3% (30 in 1000) and the effect size (difference between the pMDA and the control groups) was 50% and 75%, a power of 79.1% and 99.5%, respectively, would be achieved. In areas with a very low baseline at 1% (10 in 1000) and the effect size of 50% and 75% differences, the study would have a power of detection of 35.5% and 74.1%, respectively.

For the qualitative study, IDIs were planned to include study participants in 24 families, at least six key informants in two villages of each province, including those who completed PQ, those who did not complete pMDA, and those who did not participate in pMDA. IDIs were planned for stakeholders in the pMDA areas, including 12 VHVs (at least six per province), 4 healthcare authorities (district- and provincial-level), and 4 local leaders/gatekeepers (village heads and religious masters). A brainstorming meeting at the conclusion of the study was planned to include 15 representatives, including MOPH consultative experts, authorities from regional and district vector-borne units, regional and district health offices, hospitals at the sub-district level, and staff who worked in the selected areas.

***Randomisation***

To plan and evaluate the intervention, we subdivided the selected study areas into villages, the smallest administrative units in Thailand. A village is considered a cluster and treated as the unit of randomization. The sizes of the purposively selected clusters by authorities in the study areas were about 150-250 with one larger size of around 600 residents. Considering the cluster

sizes and the distances between clusters, we purposively allocated 2 out of 5 villages in Yala and 1 of 2 villages in Narathiwat to receive pMDA intervention in Round 1 (year 1) and switch to be the control in Round 2 (year 2).

***Statistical methods***

The potential effectiveness of pMDA was explored in terms of reductions in the prevalences, proportions of confirmed *P.vivax* with qPCR in the CSS populations, comparing the intervention group with the control group. This was a two-period cluster-crossover study, forming two cluster periods, with a multiple CSS, before and after pMDA at each period. As suggested in the literaure, the data should be analyzed with hierarchical models with random effects in order to allow for different outcome probabilities in each period, cluster, and cluster-period [25,26]. With the cluster-level randomization design, it is thus statistically more efficient to employ the model adjusted for cluster effect [22]. As a proof-of-concept for a pragmatic trial in the community setting, the potential effectiveness of pMDA was thus determined by comparing the proportions of *P.vivax* infection between the two groups at each period of CSS and the two-periods combined representing the overall impact of the intervention. An additional comparison of *P.vivax* proportions between the two groups at six months after Round 2 was also performed to explore a longer-term effect. Since the study was conducted in low-endemic areas, it is most likely that most study participants would be non-infected cases. Therefore the analysis utilized an R package, NBZIMM, that provides functions for setting up the multilevel zero-inflated negative binomial model adjusted for random intercepts of the clusters [27,28] The model for the overall impact of the intervention of two-period crossover was adjusted for cluster effect plus time period and the interaction between the time period and the intervention. The prevalence ratio (PR) and its 95%CI from the model were reported with statistical significance set at p-value < 0.05.

The safety of pMDA was monitored in terms of adverse events that occurred after drug administration throughout the follow-up period. All events were presented descriptively. The prevalence of G6PDd was described with its 95% confidence interval.

The acceptability and stakeholder engagement to the pMDA strategy were examined using a qualitative analysis. IDIs and brainstorming were led by trained facilitators, including an experienced lead facilitator, four co-facilitators and note-takers, and two local healthcare staff. All team members, with training on ethical considerations for human research subject, had read the study protocol, and data collection methodologies; they discussed the important points to be explored. Audio recordings of the IDIs and the meeting were transcribed; the transcriptions were reviewed and classified into key themes per the study objectives and/or the themes that emerged during reviews. Thematic analyses were conducted on notes of participants' responses and the determined themes. The content was analyzed to identify themes by manually exploring,

interpreting, and categorizing the data via consensus among facilitators. The priority themes set according to the study objectives included: perceptions, expectations, engagemen, factors influencing the decision to participate or not to participate, factors influencing non-completion of the 14-day regimen, perceived achievements, blockage and solutions in pMDA, and challenges in pMDA implementation.

### *Ethical Considerations*

This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (Approval Number: MUTM 2019-033-01). All participants consented to participate in this study before enrollment. Participants under 18 years of age were consented/assented along with consent from their parents. Community leaders and authorities in national and local health facilities were informed, provided consent and involved as part of the community sensitization prior to the study's initiation. All staff responsible for research activities were trained in human subject research protection. The identifiable information of the study participants was treated as confidential information; the participants' identification numbers were coded. To treat pMDA as an additional part to the routine malaria prevention activities by the healthcare personnel and VHVs in natural settings, no compensation was given to the consented study participants. Generative AI was not used in any portion of manuscript preparation.

## Results

### *Study participant characteristics and intervention implementation and coverage*

A total of 2550 individuals resided in seven clusters. In Round 1, 1624 consented to CSS, 925 in Clusters 1-3 and 699 in Clusters 4-7 were allocated to pMDA and control groups. Among the three villages allocated to pMDA, 70.8% (655/925) were eligible according to the inclusion-exclusion criteria, and 87.8% (575/655) received pMDA. The follow-up CSS at month-3 after PQ administration was performed among 1423 study participants, 92.0% (851/925) in the pMDA clusters versus 81.8% (572/699) in the control clusters.

In Round 2, the clusters were crossed over,1489 consented to CSS, 878 in Clusters 1-3 and 611 in Clusters 4-7 switched to control and pMDA groups. For the four villages switched to pMDA, 66.8% (408/611) were eligible according to the inclusion-exclusion criteria and 91.9% (375/408) received pMDA. The follow-up CSS at month-3 after pMDA in Round 2 was conducted among 1427 study participants, 94.8% (579/611) in the pMDA clusters and 96.6% (848/878) in the control clusters. The additional post-intervention CSS at month-6 after the second PQ administration was performed among 1401 study participants, 92.9% (568/611) in the pMDA group and 94.9% (833/878) in the control group. Figure 3 presents a CONSORT diagram showing the flow of participants throughout the trial [29,30].

The demographic attributes and G6PDd statuses of the study participants in the seven clusters are shown in Table 1. Based on the census data, there were slightly fewer males than females with an age range of 1-96 years in both rounds of pMDA. Testing for G6PDd revealed an overall prevalence of 5.4% (95%CI: 4.3-6.6%) in the seven clusters. G6PDd individuals were excluded from PQ administration.

------ Insert Figure 3 about here -----

*Figure 3: CONSORT diagram showing the flow of participants throughout the two-period cluster-crossover trial*

**Table 1: Baseline characteristics of the participation populations for the two Rounds of pMDA intervention and control clusters during two-period cluster-crossover sequence**

| | pMDA clusters | | | | Control clusters | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Cluster 1** | **Cluster 2** | **Cluster 3** | **1-3 Total** | **Cluster 4** | **Cluster 5** | **Cluster 6** | **Cluster 7** | **4-7 Total** | |
| Pre-MDA CSS, N | 219 | 175 | 531 | **925** | 148 | 173 | 167 | 211 | **699** | **1624** |
| Male, n (%) | 82 (37.4) | 81 (46.3) | 242 (45.6) | **405 (43.8)** | 68 (45.9) | 85 (49.1) | 80 (47.9) | 95 (45.0) | **328 (46.9)** | **733 (45.1)** |
| Age, years Mdn (range) | 32 (1-74) | 29 (2-80) | 40 (1-91) | **37(1-91)** | 29 (1-96) | 31 (1-88) | 26 (1-77) | 46 (2-92) | **34 (1-96)** | **35 (1-96)** |
| G6PD deficient, n (%) | 12 (5,5) | 7 (4.0) | 34 (6.4) | **53 (5.7)** | - | - | - | - | - | - |
| **Round 2 pMDA** | **Control clusters** | | | | **pMDA clusters** | | | | | **Total** |
| | **Cluster 1** | **Cluster 2** | **Cluster 3** | **1-3 Total** | **Cluster 4** | **Cluster 5** | **Cluster 6** | **Cluster 7** | **4-7 Total** | |
| Pre-MDA CSS, N | 226 | 189 | 463 | **878** | 124 | 151 | 159 | 177 | **611** | **1489** |
| Male, n(%) | 88 (38.9) | 88 (46.6 ) | 204 (44.1) | **380 (43.3)** | 57 (46.0) | 68 (45.0) | 76 (47.8) | 75 (42.4) | **276 (45.2)** | **656 (44.1)** |
| Age, years Mdn (range) | 32 (3-75) | 28 (1-81) | 42 (2-92) | **36 (1-92)** | 36 (2-79) | 31 (1-89) | 27 (2-78) | 48 (3-93) | **36 (1-93)** | **36 (1-93)** |
| G6PD deficient, n (%) | - | - | - | - | 8 (6.5) | 4 (2.6) | 9 (5.7) | 13 (7.4) | **34 (5.6)** | - |

***Potential effectiveness of pMDA***

To explore the potential effectiveness of pMDA, we compared the prevalences of *P.vivax* between the two groups in each CSS period and the combined two-period crossover. With the very low number of cases found for each CSS period, the prevalences were reported as the proportions of confirmed *P.vivax* infection per 1000 population. Among the CSS population in the pre-pMDA period of Round 1 (July 2019), the proportions of *P.vivax* infection in the two groups were similar, at around 14-15 per 1000 population. Among the CSS population in the month-3 post-pMDA period (November 2019), the proportions in the pMDA and control clusters reduced to 12.9 and 8.7 per 1000 population, respectively. Comparisons of the *P.vivax* proportions per 1000 population between the two groups, pMDA vs. control, at each time period of Round 1, showed no statistically significant difference (Table 2).

Among the CSS population in the pre-pMDA for Round 2 (July 2020), the proportions of *P.vivax* infections in the cross-overed pMDA (Clusters 4-7) and the control (Clusters 1-3) were slightly different, at 11.5 and 9.1 per 1000 population, respectively. Among the CSS population in the month-3 post-pMDA period (November 2020) in the pMDA and control clusters, the proportions of *P.vivax* infection reduced to approximately 1.7 and 3.5 per 1000 population, respectively. Similarly, no statistically significant differences were found between the two groups in the Round 2 study (Table 2).

During the post-intervention follow-up period, at six months after Round 2 (March 2021), the proportions of *P.vivax* infection among the PMDA group (Clusters1-3) vs. the control (Clusters 4-7), were 2.4 and 1.8 per 1000 population. Comparison between the two groups also showed no significant difference (Table 2).

The inclusive effectiveness of pMDA for the two-period crossover is shown in Table 3. In the pre-pMDA period, the inclusive numbers of participants across seven clusters (Clusters 1-7) who underwent pMDA intervention and control were 1536 (925+611) and 1577 (878+699), respectively. The proportions of *P.vivax* infections per 1000 population between the two groups before pMDA were slightly different, at 13.0 vs. 12.0 per 1000 population, with no statistically significant difference. In the month-3 post-pMDA period, the inclusive numbers of participants across the seven clusters who underwent the pMDA intervention and the control were 1430 (851+579) and 1420 (848+572), respectively. The proportions of *P.vivax* infections per 1000 population between the two groups at three months after pMDA were 8.4 vs. 5.6, yielding no statistically significant difference.

**Table 2: Comparisons of proportions of *P.vivax* during two rounds between pMDA intervention clusters and control clusters at each time period of the two-period cluster-crossover sequence**

| **Round 1 pMDA** | **pMDA clusters** | | | | **Control clusters** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Cluster 1** | **Cluster 2** | **Cluster 3** | **1-3 Total** | **Cluster 4** | **Cluster 5** | **Cluster 6** | **Cluster 7** | **4-7 Total** | ***PR (95%CI)**** | ***P-value*** |
| Pre-pMDA CSS, N | 219 | 175 | 531 | **925** | 148 | 173 | 167 | 211 | **699** | | |
| Pre-pMDA, n (Infection/1000) (95%CI) | 2 (9.1) | 8 (45.7) | 3 (5.7) | **13 (14.1) (7.8-24.6)** | 0 (0.0) | 8 (46.2) | 3 (18.0) | 0 (0.0) | **11 (15.7) (8.3-28.9)** | **2.0 (0.1, 34.3)** | ***.549*** |
| 3-months Post-pMDA CSS, N | 206 | 163 | 482 | **851** | 108 | 148 | 155 | 161 | **572** | | |
| 3-months Post-pMDA, n (Infection/1000) (95%CI) | 1 (4.9) | 7 (42.9) | 3 (6.2) | **11 (12.9) (6.8-23.7)** | 1 (9.3) | 4 (27.0) | 0 (0.0) | 0 (0.0) | **5 (8.7) (3.2-21.5)** | **2.3 (0.2, 29.2)** | ***.438*** |
| **Round 2 pMDA** | **Control clusters** | | | | **pMDA clusters** | | | | | | |
| | **Cluster 1** | **Cluster 2** | **Cluster 3** | **1-3 Total** | **Cluster 4** | **Cluster 5** | **Cluster 6** | **Cluster 7** | **4-7 Total** | | |
| Pre-pMDA CSS, N | 226 | 189 | 463 | **878** | 124 | 151 | 159 | 177 | **611** | | |
| Pre-pMDA, n (Infection/1000) (95%CI) | 1 (4.4) | 3 (15.9) | 4 (8.6) | **8 (9.1) (4.2-18.6)** | 0 (0.0) | 7 (46.4) | 0 (0.0) | 0 (0.0) | **7 (11.5) (5.0-24.5)** | **0.3 (0.0, 8.1)** | ***.380*** |
| 3-months Post-pMDA CSS, N | 226 | 188 | 434 | **848** | 108 | 148 | 163 | 160 | **579** | | |
| 3-months Post-pMDA, n (Infection/1000) (95%CI) | 0 (0.0) | 1 (5.3) | 2 (4.6) | **3 (3.5) (0.9-11.2)** | 1 (9.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | **1 (1.7) (0.1-11.1)** | **0.5 (0.1, 3.9)** | ***.419*** |
| 6-months Post-pMDA CSS, N | 219 | 191 | 423 | **833** | 112 | 130 | 166 | 160 | **568** | | |
| 6-months Post-pMDA | 0 (0.0) | 0 (0.0) | 2 (4.7) | **2 (2.4)** | 0 (0.0) | 1 (7.7) | 0 (0.0) | 0 (0.0) | **1 (1.8) (0.1-** | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| n (Infection/1000) (95%CI) | | | | **(0.4-9.6)** | | | | | **11.4)** | **1 (0.0, 54.2)** | ***.995*** |

** PR, prevalence ratio of pMDA vs. Control groups, based on zero-inflated negative binomial mixed model (adjusted for cluster, without time period and interaction)*

**Table 3: Comparisons of proportions of *P.vivax* before and after pMDA between intervention group vs. control group combined over the two-period cluster-crossover**

| | Intervention group (Clusters 1-7) | Control group (Clusters 1-7) | PR (95%CI)* | P-value |
|---|---|---|---|---|
| Pre-pMDA CSS, N | 1536 | 1577 | | |
| Pre-pMDA, n (Infection/1000) (95%CI) | 20 (13.0) (8.2-20.4) | 19 (12.0) (7.5-19.1) | **2.8 (0.3, 28.4)** | ***.373*** |
| 3-months Post-pMDA CSS, N | 1430 | 1420 | | |
| 3-months Post-pMDA, n (Infection/1000) (95%CI) | 12 (8.4) (4.6-15.1) | 8 (5.6) (2.6-11.5) | **2.1 (0.3,13.7)** | ***.456*** |

*

*PR, prevalence ratio of pMDA vs. Control groups, based on zero-inflated negative binomial mixed model (adjusted for cluster, with time period as covariate and interaction with pMDA intervention)*

***Safety and adverse drug reactions for PQ during pMDA***

Adverse events potentially due to PQ intake were recorded in approximately 5% in each round (Table 4). Although study participants with G6PDd were excluded, about 1% of the participants who received PQ showed symptoms suggesting acute hemolysis. Six participants had hemoglobin levels dropped to < 8 g/dl while. another four participants had dark urine Major chief complaints after taking PQ varied including: headache, weakness, muscle aches and pain, and dry throat. All study participants with safety concerns were stopped from further PQ intake.

*Table 4: Safety and adverse drug reactions during the two-period cluster-crossover sequence*

| Study Populations | Round 1 | Round 2 |
|---|---|---|
| Total population with at least 1-day drug administration | 575 | 375 |
| Total population with adverse effect | 30 (5.2%) | 20 (5.3%) |
| • Blood concentration < 8 g/dl | 2 (0.3%) | 4 (1.1%) |
| • Dark urine | 2 (0.3%) | 2 (0.5%) |
| • Other adverse events (chief complaints) | | |
| Headache | 8 (1.4%) | 5 (1.3%) |
| Weakness | 7 (1.2%) | 1 (0.3%) |
| Dry throat | 5 (0.9%) | 0 (0.0%) |
| Muscle ache and pain | 1 (0.1%) | 4 (1.1%) |
| Tachycardia | 2 (0.3%) | 0 (0.0%) |
| Chest tightness | 1 (0.1%) | 2 (0.5%) |
| Constipation | 2 (0.3%) | 0 (0.0%) |
| Diarrhea | 0 (0.0%) | 1 (0.3%) |
| Vomiting | 1 (0.1%) | 1 (0.3% |
| Itching | 0 (0.0%) | 2 (0.5%) |

***Acceptability of the pMDA***

Information was collected from community representatives, 12 from two villages in Yala Province and 12 from two villages in Narathiwat Province. Key informants also included 11 VHVs in the selected villages, (7 from Yala and 4 from Narathiwat), 18 representatives of healthcare personnel staff who worked in the study areas and MOPH consultative experts. Among the 53 key informants, 34 were male and 19 female, aged 18-86 years. Some of the study participants were community and religious leaders. Most VHVs and their family members participated in the pMDA activities. In assessing the acceptance of the pMDA and stakeholder engagement, five themes were explored:

***Perceptions, expectations, and engagement***: Study participants informed us that they were willing to participate in pMDA because they recognized malaria was a major problem

around their residential areas. Many of them, particularly the older generation, had experienced malaria. All villagers who agreed to CSS, but could not participate in pMDA due to the exclusion criteria, perceived the program's benefits. On the other hand, all those who rejected pMDA stated that they or their families had never been infected with malaria, that they would seek treatment should they be infected, and that therefore prevention was not necessary. VHVs, the key players in pMDA implementation, perceived the program's benefits. Almost all of them indicated that it would not be a burden as they have to do the home visits and other activities in the villages as part of their routine jobs anyway. All local healthcare officers at the district and sub-district levels noted that they expected the program would help reduce malaria cases in their area. They said they had no worries about program implementation, as they could easily collaborate with community leaders and VHVs.

> *"There were many malaria cases in our province – in the top ranking in Thailand. After the pMDA project, the malaria cases were reduced to none in our village… Some VHVs from other villages asked us why the project only came to our village." VHV*

***Factors influencing the decision to participate or not participate:*** Many said they decided after going to one of several community engagement meetings arranged by the research team, community and regional leaders, and the VHVs. Being well-informed about drug safety and the G6PDd survey, most participants felt safe participating in the CSS and pMDA.

> *"Both of us took the drug for 14 days without any side effects. We decided to participate after attending the community meeting. We had no worries about taking the drug and the blood draw because we both used to get malaria. If we have to take the drug once a year, we still want to do so. We will ask our children to do so next time."*
>
> *pMDA-compliant husband and wife*

In contrast, all VHVs and local healthcare staff indicated most teenagers and small children did not participate in the program. With the drug problem (including illegal herbs, amphetamine, cocaine and other drugs), particularly among the teens, they feared that CSS would reveal their drug status. Some mentioned that taking medication for 14 days was too long, and they might participate with a shorter regimen. Cultural beliefs also affected the idea of taking medication; one community leader stated that some local people believed that eating durian (a local fruit) with malaria drugs might affect people's health.

> *"Two of us in the family did not participate even though we used to get malaria – this is because we had to go work in the forest and had no time for DOT. … My son aged 18 years old did not participate in the project because he had to go and study out of town…."*
>
> *pMDA non-participant.*

***Factors influencing non-completion of 14-day regimen:*** All pMDA participants who did not complete the 14-day regimen indicated that they had to stop taking PQ because they had adverse drug reactions. A few had to withdraw via the VHVs, due to safety issues (e.g.,

dark urine, Hb < 8 g/dl).

> *"There are 5 of us in the family – only 3 participated in drug administration, the other 2 did not because of their pregnancies. I took the drug for only 4 days and stopped because I had a headache – if not, I would take it for the whole 14-days.."*
>
> *pMDA non-compliant person*

***Perceived achievements, blockages and solutions in pMDA:*** The brainstorming meeting reached a consensus that pMDA had an important impact in identifying asymptomatic infections, because no routine qPCR was performed at local sites. The screening test for G6PDd also contributed to significant implications, as there was little knowledge about G6PDd prevalence in this region. Knowing G6PDd status installed confidence in the local staff in PQ delivery during pMDA.

When asked about pMDA activities that required improvement, the government officers, confirmed by villagers and VHVs, recognized that community engagement still did not reach all target groups. All stakeholders suggested that there should be greater coverage and more frequent community sensitizations and engagement, which should be specific to the target groups, the non-participant populations. Though willing to perform home visits, some VHVs noted that there should be some ways to handle intensive 14-day DOT. The brainstorming session also indicated a lack of resources, both workforce and financial support, that could obstruct the success of prevention and control measures.

> *"At the beginning, we felt worried about our skills and the heavy workload of performing 14-day follow-ups. We also worried about getting villagers to understand the project, about taking the drug and the blood draw… The situation was better when we worked together with community leaders."*
>
> *Local healthcare officer*

***Challenges in pMDA implementation:*** As noted during the brainstorming session, human resources would be a major challenge moving forward and upscaling the pMDA. A few health authorities mentioned that in order to have a successful program, it must be a top-down approach, which means the policy must be initiated by authoritative bodies at higher levels and delegated to local operational entities. On the other hand, another MOPH authority noted that the local level should initiate the idea and propose it to the upper level. The concerns were not only about the human workforce, but also budget allocation.

> *"Taking a 14-day regimen requires a G6PDd screening test. This test is rather expensive – but if you do not do it, the villagers may not want to take the drug. This is important and we need to communicate well with villagers to have them take the drug. Importantly, we also need the full endorsement of higher-level authorities, i.e., MOPH. If the MOPH had such a policy, the local offices would do it."*
>
> *MOPH authority at local level*

## Discussion

The main goals of this study were to evaluate the effectiveness, safety, acceptability and stakeholder engagement of pMDA to accelerate *P.vivax* elimination in Thailand and to provide the

information needed by the Thai MOPH for evidence-based decision-making. The study employed a mixed-methods approach. The quantitative part of the study employed a two-period cluster-crossover randomized trial design assessing the pMDA in addition to standard prevention and control measures. The qualitiative part was performed by IDIs and brainstorming discussion.

As a proof-of-concept, the potential effectiveness of the pMDA intervention was assessed by comparing the proportions of *P.vivax* between clusters under pMDA and clusters under SPC in each period and after the two-period crossover. The study results conceded no statistically significant differences between the two groups, both before and after pMDA implementation. However, there were reducing trends in *P.vivax prevalence* after pMDA implementation in both treatment and control groups. In a systematic review in the Cochrane database, it was found that studies on MDA in Cambodia, Laos, Myanmar and Vietnam in very low- to low-endemicity settings have shown varying degrees of reductions in *P.vivax* prevalence immediately following the intervention but the effects were not sustained [31]. Similarly, WHO guidelines for malaria 2023 noted that MDA for *P.vivax* conducted in eight countries showed rapidly reductions in transmission with immediate to short-term benefits 1–3 months after the last round of MDA, but long-term benefits at 12–24 months were not apparent [32]. In this study, the comparable reduction trends in pMDA and control groups may reflect that the pMDA was not as effective as anticipated. This might be due to the Hawthorne effect (the alteration of behavior by the study subjects due to their awareness of being observed), since both study participants and healthcare workers in the study areas were aware of the additional pMDA activities in their vicinity. It is also important to note that since the study started in 2019, drastically decreasing incidences have been observed across the entire country, not only in the study clusters. Moreover, people's mobility was limited and malaria risk behaviors were less frequent during the COVID-19 pandemic, which coincidently started in 2019. Thus, it is difficult to reach definitive conclusions about the effectiveness of the pMDA intervention.

Like other studies [15,20,33] pMDA was safe and well-tolerated. Testing for G6PDd at the point-of-care before PQ administration is a precondition for safe administration [19]. Several previous studies noted that the tolerability of PQ has been good, with a low frequency of adverse events reported even with heterogeneous levels of G6PDd [15,18]. This study, however, excluded individuals with inborn G6PDd. As a safety monitoring measure, VHVs performed the intensive 14-day DOT of PQ takers residing in the households for which they were responsible. Other studies also reported that pMDA under supervision with good monitoring mechanisms for adverse events among the population would result in less severe adverse events related to PQ [15,18,19]. The adverse events reported in this study as well as other pMDA studies with dihydroartemisinin-piperaquine, and with PQ, showed similar common adverse events, including gastrointestinal disturbances (diarrhea, vomiting, abdominal pain, and nausea), dizziness, headache, and general body weakness [18,20,34]. Severe adverse events suggesting acute hemolysis, occurred among 1.1% of PQ intakers, resulting in the cessation of treatment.

In the WHO manual for antimalarial MDA implementation, high coverage and adherence

of the target population (i.e. > 80%) must be ensured, preferably implementing centralized distribution at a fixed site and performing DOT. In this study, only about 60% consented to the initial CSS but over 90% of them were retained in the 3-year study. Among those, only 70% were eligible for MDA, with 90% taking PQ, and 90% completed the 14-day regimen under DOT. A qualitative part of this study suggested that acceptance of pMDA among study participants was predominantly due to their trust in healthcare representatives (VHVs) who actively performed home visits to provide healthcare support. This study confirms that DOT, although labor-intensive, could maintain full adherence and reassure study participants about the purposes and safety of the MDA activities. The pMDA and DOT heightened the morale and relationships between villagers and healthcare personnel in the study areas. Similarly, another study on reactive drug administration for *P.vivax* elimination in Thailand suggested that good acceptance of the program was related to education and sensitization campaigns on the purpose and rationale of the intervention [35]. Also noted in the WHO guidelines 2023, a systematic review of 18 studies reported that the most common barrier to the acceptability of MDA for *P.vivax* was fear of adverse events while some studies noted that sensitization on the benefits of the MDA helped reduce concerns about adverse effects. [32]

Community engagement is critical to the success of MDA for *P.vivax* as it affects participation rates and full treatment compliance while lack of engagement with local healthcare providers limits treatment adherence [32]. A systematic review of published, unpublished, and gray literature documenting past MDA experiences identified the importance of operational implementation and community engagement such that drug distribution and DOT were mainly performed by community volunteers and local health workers [36].The review of previous studies noted in WHO guideline 2023 also reflects the impact of MDA on *P.vivax*, whether positive or negative, was likely related to the level of acceptance of the intervention among the malaria program staff, and there have been no surveys of this key stakeholder regarding this issue [32]. As suggested in the literature, all aspects of community engagement in MDA must be tailored to local (social, cultural and political) circumstances [37,38]; this study involved community members as part of the intervention team with respect for their customs and opinions. Study participants and public healthcare providers at local and national levels, willingly accepted and believed that the preventive and control activities in this study (regardless of being in the pMDA or control groups) had boosted awareness in the community and led to personal changes in malaria-preventive behaviors. The qualitative part of this study confirms the key determinants of pMDA such that the feasibility of maintaining and/or upscaling the MDA intervention were related to the existence of active and continuous activities for community engagement, community sensitization and maintaining collaboration with those from the point-of-care level up to authorities at local and national levels.

***Limitations of the study***

This study has several limitations. The number and size of clusters were small and we may not have observed the heterogeneities among different groups. Limited mobiity due to the

COVID-19 pandemic coinciding with pMDA activities during the study follow-up period might have caused malaria prevalence in all study clusters to decline drastically. Such circumstances complicate and hinder the interpretation of the results. Moreover, there were significant heterogeneities among the different clusters, making comparison between the pMDA and control groups difficult. Regarding the study design, this study employed the cluster-crossover randomized trial which is particularly feasible for pragmatic clinical trial in healthcare systems [21,22].The design is highly efficient and should be considered as it breaks up the total trial duration into a series of repeated measures. Thus, the required number of clusters could be substantially reduced, while potentially providing generalizable, robust and internally valid evidence evaluation of effects across settings or clusters [21,39,40]. Eventhough, the cluster-crossover design is robust when the number of clusters is small [26], this study involved only seven clusters and the crossover sample size was around 1500 per group. Given the predictably large variations in malaria prevalence within each cluster one would expect that a larger sample size would have been needed. Thus, the results of this study may not have external validity and be generalizable to other settings with different natures of target populations and degrees of transmission.

## Conclusions

pMDA under DOT showed high adherence, safety and tolerability, but may not significantly impact on *P.vivax* transmission, particularly in low-transmission areas. Even though the impact of the pMDA was inconclusive, the results were consistent. The malaria cases were reduced in all clusters, regardless of whether they were in the pMDA group or not. The Hawthorne effect may reflect the trigger or accelerator of elimination by having the significant political, logistical, and financial commitment of coordinating bodies and collaborative efforts among various levels of stakeholders. We have a success story of effective healthcare workforces at point-of-care, collaborations in the community, and commitment from authorities at local and national levels. Such community engagement efforts boosted the acceptability of the malaria-elimination initiative.

Despite the safety and exemplary acceptance of the intervention, we cannot proclaim the effectiveness of pMDA. As we planned this study as a proof-of-concept study, the results were considered as a basis for a go/no go decision-making. A conditional recommendation in WHO guideline 2023 suggested the use of MDA for *P.vivax* when there is evidence of the acceptability, feasibility, impact (incidence or prevalence of malaria infection at the community level) and potential harms of MDA (including testing for G6PDd) [32]. Since we did not observe the impact of pMDA on *P.vivax* transmission during the study period and the malaria incidences in Thailand reemerged in 2023 after the study period, we decided not to scaleup the study with larger sizes of clusters and samples, Instead of implementing pMDA in the population within the intervention clusters, we are working on an on-going project with an alternative approach, a targeted PQ treatment strategy, providing PQ via DOT only to the targeted population in the households

around each index case living in the intervention clusters. The effectiveness of such an alternative approach remains to be determined.

## Contributors

JK, SLN, JP, WP and WN designed the study; WP, WN, ST, PS and PP implemented the intervention in the communities, WP, WN, AK, RP, PY, PS and MK collected the data, accessed and verified the data , and performed initial data analyses. JK, CN and SLN designed the statistical analysis. JK and MK led the qualitative data analysis. JK and WP wrote the first draft of the manuscript. JP, DP and LC provided important comments on the draft manuscript. All authors read and approved the manuscript. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Declaration of interests

All authors declare no competing interests.

## Acknowledgments

We sincerely appreciate the study participants, VHVs, and the local healthcare personnel in the communities for their kind contributions to testing the study concept. We gratefully acknowledge all staff from the Thai Ministry of Public Health for their active roles in pMDA implementation and all staff who worked under the International Centers of Excellence for Malaria Research (ICEMR) project for their assigned activities and assisting in data collection. We would like to thank Paul Adams for English editing and proofreading. This work was supported by the National Institute for Allergy and Infectious Diseases, National Institutes of Health (NIH) (U19 AI089672).

## Data availability

All data and code used in this analysis are as presented in the manuscript.

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# Supplementary Files

Untitled.
URL: http://asset.jmir.pub/assets/4666ee17681c6a09cc464eca14fa1907.docx

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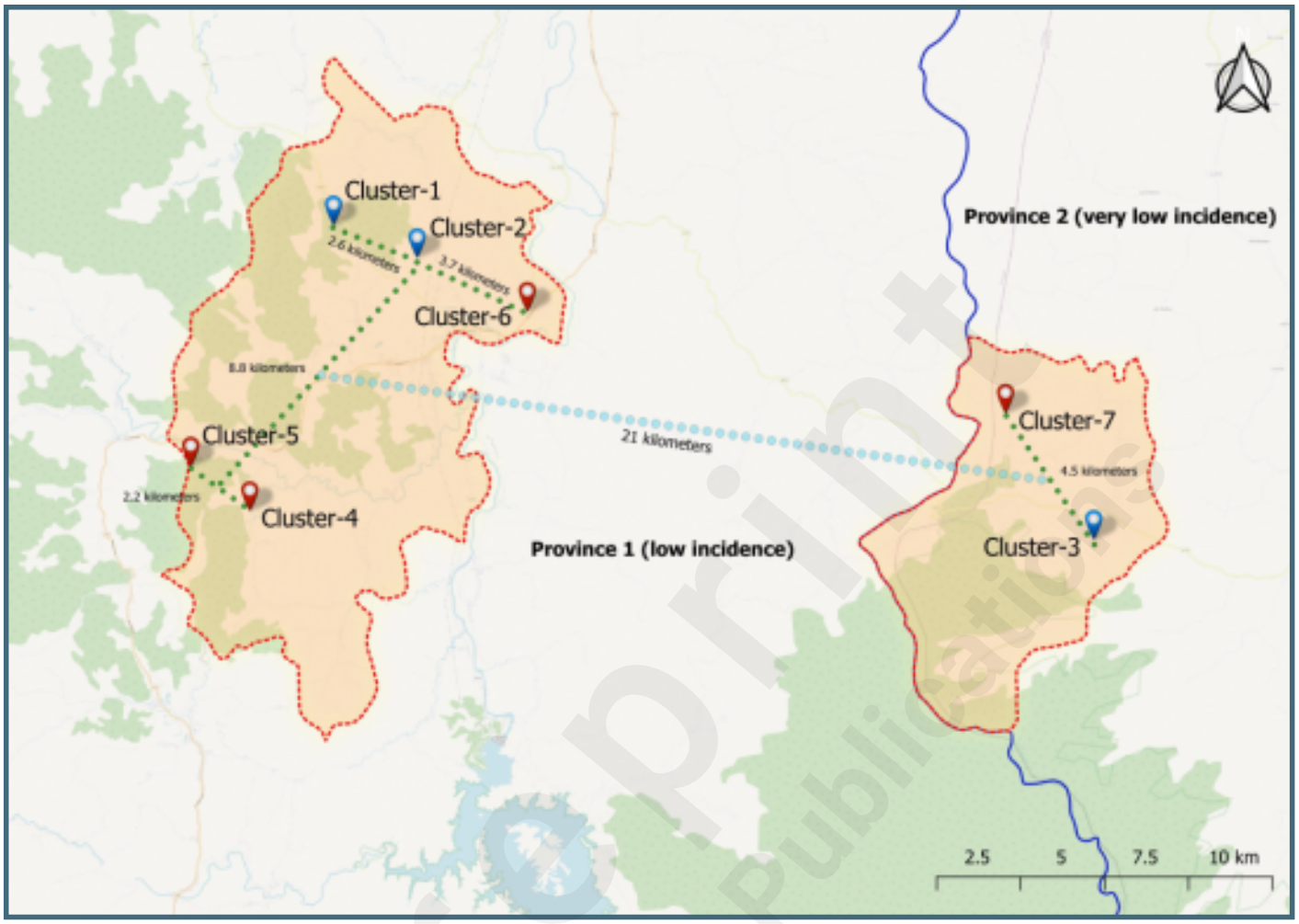
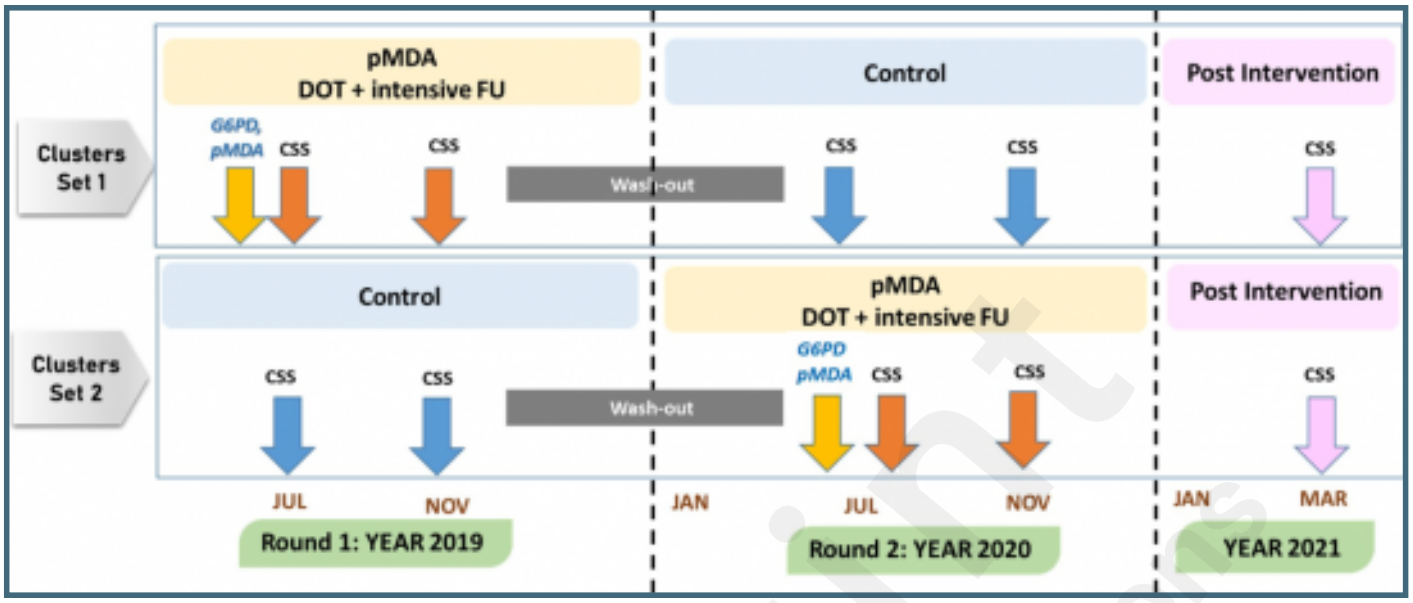
# Figures

Clusters assigned to pMDA vs control groups.



Study procedures in the cluster-crossover randomized control trial.



CONSORT diagram showing the flow of participants throughout the trial.