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An Innovative Evaluation of Mass Drug Administration with Primaquine in Iran

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Abstract

Background: A key strategy in the global fight against malaria, endorsed by the World Health Organization (WHO), is mass drug administration (MDA). Evaluating the impact of this initiative on malaria transmission reduction is crucial.
Objectives: This study aimed to assess the effectiveness of MDA combined with primaquine (PQ) in the southern Iranian region of Jask, specifically in Lirdaf.
Methods: Primaquine was chosen as the antimalarial drug for this intervention. A total of 168 Pakistani individuals receiving MDA were evaluated over an eight-week period from September to December 2021.
Results: Three cases of vivax malaria were identified. Among the 168 patients receiving PQ, 26 were found to have a deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD), leading to the exclusion of thirty participants from the trial. Additionally, three individuals were withdrawn from the project due to restricted access (two cases) and family-related issues (one case). One participant, initially asymptomatic and positive, later tested positive again, and this case was excluded from the analysis. Regular follow-up assessments were conducted on all participants, revealing no cases of relapse throughout the project duration.
Conclusions: Our findings suggest that employing MDA in combination with supplementary interventions during the elimination phase holds promise for malaria control efforts.

Keywords: Mass Drug Administration, Malaria Vivax, Primaquine, Asymptomatic, Iran

1. Background

Globally, a decline in malaria incidence from 80 cases to 57 cases per 1 000 population at risk was estimated in 2000 and 2019, respectively. Additionally, malaria cases decreased in the World Health Organization (WHO) Eastern Mediterranean Region by about five million. Approximately a quarter of these cases were attributed to *Plasmodium vivax* malaria, primarily in Afghanistan, Pakistan, and some countries in the elimination phase (1). It is important to note that asymptomatic individuals pose a significant challenge to malaria elimination programs as they contribute to the persistence and survival of parasites, thus sustaining malaria transmission (2). Since these individuals are unaware of their infection, they do not seek treatment and can serve as a reservoir for malaria transmission (3). Immunity develops earlier, and parasite density varies with age in high-transmission areas where *Anopheles* mosquitoes frequently bite humans (4). Rapid

diagnostic tests (RDTs) have been validated for their sensitivity and specificity in detecting parasitemia in asymptomatic malaria infections (5). Giemsa-stained blood smears under microscopic examination can also detect parasite densities exceeding 10 parasites per μL of blood (6), although some researchers argue that the polymerase chain reaction (PCR) method is more accurate (7). It is crucial for authorities to target low parasitemia to achieve malaria elimination when other factors are under control (8). Mass drug administration (MDA) is employed to clear gametocytes from asymptomatic carriers with low-density *Plasmodium falciparum* or *P. vivax* infections. Its effectiveness has been demonstrated in various settings, including certain regions of Myanmar (9). In areas where the malaria transmission season is brief, MDA combined with ivermectin has been utilized to reduce the malaria burden (10). Furthermore, the administration of primaquine (PQ) for MDA against *P. vivax* at its hypnozoite phase and *P. falciparum* gametocytes has been recommended for asymptomatic patients in regions undergoing elimination (11). Since 2010, Iran has been implementing an elimination strategy to interrupt indigenous malaria transmission (12, 13). Currently, imported malaria poses a significant challenge due to the influx of foreign immigrants from neighboring countries who come to work in southern Iran (14).

2. Objectives

This study aimed to evaluate the effects of MDA with PQ in the Jask Region, south of Iran. To achieve malaria elimination, all positive cases, especially asymptomatic ones, even those with low parasite counts, should be promptly diagnosed and treated. Clearing parasites in asymptomatic individuals is crucial for reducing malaria cases. As the first survey of MDA in Iran, our project can contribute significantly to the elimination program.

3. Methods

This clinical trial study was conducted during the malaria transmission seasons from September 25, 2021, to December 2, 2021, in the southern Iranian province of Hormozgan, specifically in the Lirdaf district of Jask County. Mass drug administration with PQ (45 mg once a week for eight weeks) was studied in asymptomatic and low parasitemia cases involving 168 Pakistani individuals who had illegally migrated from malaria-endemic areas in Pakistan to this region. Additionally, a control group was randomly selected from the Pakistani population in the area. This population primarily resided in rural areas near gardens and farms, with distances ranging from 50 meters to 7 kilometers between the residences of Pakistani cases and indigenous people. They were distributed across five villages named Askani Kach, Sohroki, Kormi, Ranaz, and Taratekan, with ages ranging from 17 to 50 years. Malaria transmission typically peaked between April and June and again in the fall. Before commencing MDA, active case detection was conducted every three days in spring and fall, and the results were documented. The research was initiated based on the criterion of achieving a prevalence of more than 2%, as determined by the outcome of intensified case detection according to the national program. Microscopy and malaria RDTs were utilized to detect active cases. Glucose-6-phosphate dehydrogenase (G6PD) levels were measured in all 168 cases, and screening was conducted for severe anemia, active rheumatoid arthritis, systemic lupus erythematosus (SLE), favism, and patients treated with quinacrine in the previous three months.

The test results were archived for at least 18 months. Due to PQ contraindications, pregnant and lactating mothers, as well as children under four years old, were not permitted to participate in the study. Individuals with moderate and severe G6PD deficiency, severe anemia, active rheumatoid arthritis, lupus, favism, and those treated with quinacrine in the past three months were also excluded. Regular check-ups were conducted every two weeks to monitor and prevent medication side effects, such as pallor, dizziness, hypotension, dark urine, abdominal cramps, epigastric pain, mild hemolytic anemia, methemoglobinemia (MetHb), cyanosis, leukocytosis, and leukopenia. Symptoms indicating red blood cell hemolysis, such as a change in urine color after taking the drug, were also monitored; if observed, drug use was discontinued. Participants were advised to seek medical attention at the Lirdaf health center in case of bruised fingers, cyanosis of the lips and skin, difficulty breathing, or vertigo. To minimize potential digestive disorders, the drug was administered with food or an antacid. Side effects were closely monitored, and the findings were documented. Participants were referred to the available health center physician after discontinuing PQ use. Importantly, the treatment process was conducted under the direct supervision of healthcare providers. Interventions, including indoor residual spraying (IRS), the distribution of 332 insecticide-treated nets (ITNs), larvicides (3 000 m^3) with Bacillus thuringiensis (Bt), and thermal fogging around the patients' residences, were carried out every three days before sunrise and sunset to prevent local transmission in the area

following the identification of positive malaria cases. All participants provided voluntary consent for treatment, and informed consent was obtained from each participant before implementation.

4. Results

Active case detection was conducted in three stages, resulting in the diagnosis of nine individuals as positive cases. Among these, five positive cases were detected in the first stage, three in the second stage, and one in the third stage. Furthermore, six out of the nine positive cases had vivax malaria, two had falciparum malaria, and one was identified as a mixed infection (*P. vivax* + *P. falciparum*). Only three out of the five positive cases were identified in the first stage, and two of the three patients identified in the second stage were asymptomatic. One case of asymptomatic vivax malaria was also discovered in the third stage. Thirty out of the 168 patients who received PQ treatment were excluded from the study; among these, 26 patients lacked G6PD deficiency. Three individuals were removed from the project: Two due to accessibility issues, and one due to family matters. One case, initially asymptomatic and positive, was omitted from the survey. Two cases of vivax malaria were identified in the control group. Importantly, there were no reports of adverse drug reactions by participants in the present study. All subjects were routinely followed up, and no relapses or deaths were observed in the target population in our project.

5. Discussion

This survey was conducted on Pakistani immigrants who had moved to Iran from malaria-endemic areas in Pakistan without completing their treatment. During the treatment period in our study, three asymptomatic cases were identified. Asymptomatic individuals do not meet the standard diagnostic criteria because they do not exhibit clinical manifestations or fever, despite harboring parasites (15). These carriers contribute to the high prevalence of malaria in endemic countries in Asia, while control measures typically target symptomatic individuals (16). As mentioned earlier, our cases were Pakistanis from bordering areas of Iran, the majority of whom had migrated from the Baluchistan province in Pakistan to work in rural and suburban parts of southern Iran. It is noteworthy that *P. vivax* and *P. falciparum* are more prevalent among children and adults in Baluchistan, Pakistan (17). The period from June to September is a peak time for the blood-feeding activity of *Anopheles* mosquitoes in Pakistan. Additionally, 60% of Pakistani civilians reside in malaria-endemic areas, leading to significant mortality due to falciparum malaria in these regions (18). Some of the immigrants had received incomplete doses of antimalarial drugs before moving to Iran.

The 8-aminoquinoline is an antimalarial drug currently recommended for treating liver-stage parasites in vivax malaria, with PQ acting as a medication for eliminating hypnozoites (dormant liver stages). To prevent malaria relapses in asymptomatic individuals entering malaria-free areas, the use of this drug in MDA programs is crucial (19). Primaquine, when combined with chloroquine, is effective against drug-resistant *P. vivax* due to its blood schizonticidal activity (20). In our study, we used a weekly dose of 45 mg, as recommended by the WHO. primaquine and tafenoquine, at doses ranging from 1.5 to 5 mg base/kg, exhibit good radical cure or hypnozoitocidal effects in certain malaria regions. An effective outcome was demonstrated with a total dose of 3.5 mg base/kg, equivalent to 0.25 mg/kg per day for 14 days or 0.5 mg/kg daily for 7 days (21). It is plausible that the treatment dosage affects the timing of latent hypnozoite activation, consequently influencing the intervals between relapses. Therefore, different geographical regions have resulted in varied histories for different parasite strains (22). Primaquine is believed to be converted into oxidative chemicals, such as H_2O_2, linked to cytochrome P450 2D6 (CYP2D6) and NADPH cytochrome P450 oxidoreductase (CPR), to inhibit hypnozoites. Hypnozoites might develop resistance to PQ due to drug interactions, the dosage of PQ, or the development of an anti-oxidative mechanism by hypnozoites; however, there is no confirmed report of increased resistance in *P. vivax* so far (23). According to the results, a total of 26 subjects had G6PD deficiency and thus did not receive PQ. Although PQ had a long history of use as an antimalarial drug, by 1 952, it caused a blood disorder and acute hemolysis in G6PD-deficient individuals. Importantly, pregnant and lactating women are also vulnerable to PQ, constituting a significant population at risk for *P. vivax* (19). The adverse effect of PQ on patients with G6PD deficiency has been reported in some countries, such as Afghanistan, Tajikistan, and Korea. However, this medication at a low dose remains reliable and could either prevent relapse in vivax and ovale malaria or act as a gametocytocide in falciparum malaria (24). Some studies have reported drug resistance associated with different PQ usage strategies (25). Interestingly, the standard dosage and shorter regimens could be crucial in the efficacy of PQ (26). This drug resistance is

expected to occur in symptomatic cases with severe levels of parasitemia, which is not the priority of MDA (4). Further research is needed to detect the dynamics of drug resistance and specify it concerning MDA.

5.1. Conclusions

More specific techniques need to be developed to identify individuals with asymptomatic parasitemia before transmission. Additionally, surveillance should be more agile to detect cases more promptly. We suggest equipping checkpoints along the border with laboratory facilities and qualified experts to detect asymptomatic subjects with unknown malaria histories. These individuals illegally migrate to Iran and pass through many cities on their way to settling close to ethnic groups with a common culture or language. Typically, it is challenging to track these travelers. Alternatively, conducting entomological surveys and epidemiological studies periodically can meticulously monitor this issue. There is a higher likelihood that incomplete drug uptake by malaria cases in migrants will lead to significant resistance to PQ in the future. However, this trend requires more extensive studies with larger sample sizes. We propose implementing MDA in conjunction with other therapies throughout the elimination phase.

Footnotes

Authors' Contribution: The project design and literature search: S.F.J; data collection, drafting the manuscript, and finalizing the version: F.S., M.KH., H.T., and A.GH; the procurement of necessary drugs and equipment in the field: A.R.; data collection and follow-up : Z.G., B.H., A.CH., and H.A. All authors have read and approved the final manuscript.

Clinical Trial Registration Code: 970134

Conflict of Interests: The authors declare that there is no conflict of interest.

Data Availability: The data presented in this study have been uploaded during submission as a supplementary file and are openly available for readers upon request.

Ethical Approval: This study was approved under the ethical approval code IR.HUMS.REC.1397.230 .

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Informed Consent: Informed consent was obtained from all participants.

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