The pioneering study of Mass Drug Administration with Primaquine in Iran

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Abstract

Mass drug administration (MDA) is considered one of the WHO's Global Strategies to eliminate malaria. Therefore, we aimed to evaluate the impact of this achievement on reducing malaria transmission. Primaquine was chosen as an antimalarial drug for this purpose; then, a total of 168 Pakistani cases receiving MDA were examined from September to December 2021 (for 8 weeks) in the Lirdaf district of Jask county, Hormozgan province, south of Iran. Three asymptomatic vivax malaria carriers were detected. 30 out of the 168 people treated with primaquine, were excluded from the study; Considering that, 26 of them had G6PD deficiency. Three people were eliminated from the project, one due to family problems, and the other two due to access constraints. One person, who was positive and also asymptomatic at the beginning of the study, became positive again; so, this case was disregarded from the survey. All cases were followed up routinely; and interestingly, no relapse was observed in our target population. We suggested that MDA should be implemented in the elimination phase associated with other interventions.

Introduction

Globally, a decline in incidence of malaria from 80 cases per 1000 population at risk to 57 cases per 1000 population at risk was estimated in 2000 and 2019, respectively. In addition, malaria cases dropped in the WHO Eastern Mediterranean Region by about 5 million. Approximately a quarter of these patients were with Plasmodium vivax malaria, predominantly in Afghanistan, Pakistan, and some countries which were under the elimination phase (WHO 2020). It should be noted that asymptomatic individuals effectively hinder the malaria elimination program; because they lead to the maintenance and survival of parasites and ultimately malaria transmission. (Stresman et al. 2010). Since these cases do not realize that they are infected, they do not seek treatment and could serve as a great reservoir for malaria transmission (Ganguly et al. 2013). In areas of high transmission where People are heavily/ highly exposed to Anopheles bites, immunity develops earlier and parasite density is limited according to age (Cheaveau et al. 2019). Rapid diagnostic tests (RDTs), have been approved because of their sensitivity and specificity to detect parasitemia in asymptomatic malaria infection (Douamba et al. 2012). Giemsa-stained blood smears under microscopic examination can also detect parasite densities > 10 parasites per µl of blood (Bousema et al. 2014); although, some researchers believe that the PCR technique is more reliable (Lee et al. 2020). It is noteworthy that authorities should focus on low parasitemia to eliminate malaria where other factors are under control (Coulibaly et al. 2017). Mass drug administration (MDA) is applied to remove the gametocytes of low-density P. falciparum or P. vivax infections from asymptomatic carriers; and its effectiveness has been confirmed in several areas, including some regions of Myanmar (Chaumeau et al. 2019). MDA with ivermectin has been implemented to reduce the malaria burden in areas with relatively short transmission seasons as well (Slater et al. 2020). Additionally, primaquine has been recommended for MDA use against the hypnozoite stage of P. vivax, as well as mature gametocytes of P. falciparum in asymptomatic individuals in districts under elimination (Hsiang et al. 2013). Iran has also scheduled an elimination strategy to interrupt indigenous transmission of malaria since 2010 (Azizi
et al. 2014; Khosravani et al. 2017). Currently, imported malaria acts as a significant problem because of the traveling of foreign immigrants from neighboring countries to work in the south of Iran (Mohebbi Nodez et al. 2018). This study aimed to assess the impact of MDA with primaquine in Jask county, southeast Iran. In order to achieve malaria elimination, all positive cases, especially those without symptoms and even those with few parasites, should be diagnosed and punctually treated. Removing parasites in asymptomatic individuals is vital to reduce malaria cases. Since this study is the first survey of MDA in Iran, our project can be productive along with the elimination program.

**Materials And Methods**

This clinical trial study was conducted during the malaria transmission seasons from September 25, 2021 to December 2, 2021 (for 8 weeks) in the Lirdaf area of Jask county, Hormozgan province, south of Iran. MDA with primaquine (15 mg base once a week) was studied, in asymptomatic and low parasitemia cases, on 168 Pakistani cases who had illegally moved from malaria-endemic spots in Pakistan to the given region. This target population mostly lived in countryside near gardens and farms. The distance of the Pakistani cases' residence to the indigenous peoples was varied from 50 meters to 7 kilometers. They were distributed into five villages named Askani Kach, Sohroki, Kormi, Ranaz, and Taratekan in the age range of 17–50 years. The two peaks of malaria transmission were from April to June and the fall season, respectively. Before initiating the MDA, active case detection was accomplished every three days in the spring and fall seasons, and their results were recorded. The criteria for carrying out our research was to reach a prevalence of more than 2% based on the outcome of the intensified case detection in accordance with the national program. For this purpose, Microscopy and malaria rapid diagnostic tests (RDTs) were used to detect active cases. Glucose-6-phosphate dehydrogenase (G6PD) was measured in all 168 cases; in addition, severe anemia, active rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), favism, and patients treated with quinacrine during the previous 3 months were assessed. It should be noted that the test results were archived for at least 18 months. Due to the primaquine contraindication, pregnant, lactating mothers, and children under 4 years were excluded from the study. Individuals with moderate and severe G6PD deficiency; some patients with severe anemia, active rheumatoid arthritis, lupus, favism, and also cases treated with quinacrine in the past three months, were excluded. Regular check-ups were done every two weeks to prevent side effects caused by medications such as pallor, dizziness, hypotension, dark urine, abdominal cramps, epigastric pain, mild hemolytic anemia, methemoglobinemia (MetHb), cyanosis, leukocytosis, and leukopenia. Symptoms such as a change in urine color, which is a sign of hemolysis of red blood cells after taking the drug, were also observed; in that case, the drug use was stopped. People were advised to refer to the physicians in the Lirdaf health center in case of bruised fingers, cyanosis of lips and skin, difficulty in breathing, and vertigo. To minimize any possible digestive disorders, the drug was taken with food or an antacid medicine. Side effects were followed up and the results were reported. Patients were referred to the physician, in the available health center, after stopping the use of primaquine. Notably, the treatment process was carried out under the direct supervision of the health providers. Interventions such as the distribution of 332 ITNs (insecticide-treated nets), indoor residual spraying (IRS) of 345,360 m², larvicide
in the amount of 3000 m$^3$ with Bacillus thuringiensis (Bt), and thermal fogging around the dwellings of the patients were carried out once every three days before sunrise and sunset to prevent local transmission in the zone after identifying positive malaria cases. This work was approved by the research ethics committee of Hormozgan University of Medical Sciences (HUMS).

Results

The active case detection was done in three stages, and a total of nine individuals were diagnosed as positive cases. Of these, five positive cases were detected in the first step, three in the second step, and one case in the third time. Besides, out of nine positive cases, six people were suffering from vivax malaria, two cases were with falciparum, and one case recognized as a mixed infection ($P. vivax + P. falciparum$). Only three patients out of five positive cases identified in the first phase, and also two of the three patients recognized in the second case-finding were asymptomatic. one case of asymptomatic vivax malaria was also found in the third period. Thirty, out of 168 people treated with primaquine were excluded from the study, 26 of whom had G6PD deficiency. Three people, one due to family problems and the other two due to access constraints, were removed from the project. One re-positive case, who was positive and asymptomatic at the beginning of the study, was disregarded from the survey. It should be noted that there were no drug complaints of the participating individuals in the present study. All subjects were followed up routinely, and no relapses or deaths were seen in the target population in our project.

Discussion

This survey was performed on Pakistani immigrants, with uncompleted treatment for malaria, who had moved to Iran from endemic areas in Pakistan. Three asymptomatic cases were found during the treatment period in our study. Asymptomatic individuals are not diagnosed based on the standard criteria because they have no clinical manifestations or even fever, although they harbor parasites. (Laishram et al. 2012). These carriers are responsible for the high circulation of malaria in endemic countries in Asia; while control measures are focused on symptomatic subjects (Starzengruber et al. 2014). As we mentioned, our cases were Pakistani from areas bordering Iran of whom a majority had traveled from 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 in children and adults in Baluchistan, Pakistan (Yasinzai and Kakarsulemankhel 2013). June-September season is a certain time for the feeding activity of blood-sucking in Anopheles in Pakistan. Moreover, 60% of Pakistani civilians are habiting in malaria foci, leading to remarkable mortality from falciparum malaria in these regions (Farooq et al. 2020). Some of them had received a dose of antimalarial drugs, incomplete treatment, before moving to Iran. The 8-aminoquinolines are the antimalarial drug that is currently recommended for the treatment of liver stage parasites in Vivax malaria; while primaquine acts as a medicine for killing hypnozoites. (dormant liver stages). To prevent the relapse of malaria in asymptomatic people entering malaria-free areas, the use of this drug for the MDA program is very important. (Baird et al. 2018). Primaquine in combination with chloroquine is effective against drug-resistant $P. vivax$ because it also has blood schizonticide activity.
In our teamwork, 15 mg base (a week) was used for radical care. It seems that there is a controversy over the therapeutic hypnozoitocidal dose of primaquine. For example, primaquine and tafenoquine at doses of 1.5 to 5 mg base/kg have good radical care or hypnozoitocidal effects but in some malaria locations. Overall, a total dose of 3.5 mg base/kg (i.e. 0.25 mg/kg/day for 14 days or 0.5 mg/kg/day for 7 days) demonstrated an acceptable impact (White 2021). Perhaps the amount of the drug dose affects the timing of activation of latent hypnozoites and subsequently intervals between relapses, which indicates the parasite strains have shown distinct histories depending on various geographical regions (White 2011). It's supposed that primaquine is metabolized to oxidative substances such as H$_2$O$_2$ associated with NADPH cytochrome P450 oxidoreductase (CPR) and cytochrome P450 2D6 (CYP2D6) to suppress hypnozoite. Hypnozoites might become resistant to primaquine due to drug interactions, a dose of primaquine, or the development of an anti-oxidative mechanism by hypnozoites; nevertheless, there is no confirmed report of increased resistance in *P. vivax* so far (Popovici et al. 2021). According to the results, a total of 26 subjects had G6PD deficiency, thus they did not receive primaquine. Although primaquine had a long history of use as an antimalarial drug by 1952, it causes a blood disorder and acute hemolysis in G6PD-deficient people. Importantly, pregnant, and lactating women are also vulnerable to primaquine. All together consists of a bulk population at risk for *P. vivax* (Baird et al. 2018).

The adverse effect of primaquine on patients with G6PD deficiency has been reported in some countries such as Afghanistan, Tajikistan, and Korea. However, this medicine at a low dose remains reliable and could either halt relapse in vivax and ovale malaria, or act as a gametocytocide in falciparum malaria (Ashley et al. 2014). More specific techniques should be developed to identify people with asymptomatic parasitaemia before transmission. Also, surveillance should be more agile so that cases can be detected more briskly. We suggest that checkpoints along the border should be equipped with laboratory facilities and eligible experts to find asymptomatic subjects with unknown histories of malaria. They illegally move to Iran and pass through many cities on their way to inhabit some place close to ethnic groups with a common culture or language. Normally, it is so difficult to follow up these travelers. Alternatively, an entomological survey as well as an epidemiological study should be performed periodically to meticulously monitor this issue. It is more likely that uncompleted drug uptake by malaria cases in migrants will dramatically develop resistance to primaquine in the future over time. However, this trend needs more extensive studies with more samples. We suggested that MDA should be implemented in the elimination phase associated with other interventions.

**Declarations**

**Conflict of Interest** None declared.

**References**


