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Efficacy of Plasmoquine for the Treatment of Plasmodium Vivax and Plasmodium Falciparum

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Abstract

This study is a response to the challenge of malaria infections, which remain a major public health in South Africa. Reports of malarial outbreaks in the country have been predominant in KwaZulu-Natal, Mpumalanga, and Limpopo provinces. Currently, combination therapy referred to artemisinin-based combination treatments (ACTs) has been recommended both by the World Health Organization and the National Department of Health of South Africa. However, due to widespread reports of artemisinin resistance, other alternative treatment options were explored. The aim of the study was thus to establish the efficacy of plasmoquine as an alternative treatment option among malaria patients in Johannesburg, the economic capital of South Africa, found in the Gauteng Province. The study adopted a quantitative approach, and a purposive retrospective investigation was adopted. Patient data from 2018-2022 was analyzed to determine the incidence of malaria in the study location and the efficacy of treatment with plasmoquine. The results of this study, therefore, indicate that P. falciparum is still the main cause of malaria in the study area. A total of 322 patient files were included in the study, with P. falciparum determined to be the main cause of infection over the four-year data assessed. Furthermore, plasmoquine was determined to be effective in treating malaria among 298 of the study population, with only 24 (7.5%) experiencing the development of vomiting after the treatment course. The findings of the study offer government makes policymakers the opportunity to develop policies that enhance the re-introduction of plasmoquine to combat malaria in South Africa.

Keywords: *Artemisinin-based combination treatments; Artemisinin resistance, Malaria; Plasmoquine.*

Introduction

Malaria has been a prominent human illness for thousands of years. Only four *Plasmodium* species often infect humans: *P. falciparum, P. vivax, P. malariae,* and *P. ovale* [1]. The great majority of cases are caused by *P. falciparum* and *P. vivax*. *Plasmodium falciparum* malaria, for example, is responsible for more than 90% of malaria cases and almost all malaria fatalities globally [2].

According to the World Health Organization (WHO) study, no substantial progress was made in lowering worldwide malaria between 2015 and 2017 [3]. The eradication of malaria in at least ten countries that were malaria endemic in 2015 is one of the Global Technical Strategy (GTS) 2020 goals [4].

Malaria, in reality, is a preventable and treatable illness. Plasmoquine has long been indicated as a therapy option. Plasmoquine is a quinine derivative that also possesses anti-inflammatory and anti-pain effects [5]. In addition to malaria, it has been used to treat amoebic hepatitis and abscesses, discoid and systemic lupus erythematosus, and rheumatoid arthritis.

According to published studies, plasmoquine may be more efficient than quinine in the treatment of malaria. For example, [6] Carman

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(1935) discovered that administering plasmoquine led in the eradication of malarial parasites in all infected individuals, but quinine treatment resulted in the removal of parasites in 29% of patients.

A quinine intravenous infusion or intramuscular injection has been the usual therapy for severe malaria (WHO 2000) [7]. However, due to reports of resistance to quinine and its derivatives, the introduction of new malarial treatment was championed. Currently, the WHO recommends artemisinin-based combination treatments (ACTs) for the treatment of malaria [8].

The key benefit of combination therapy is that artemisinin rapidly and dramatically decreases the bulk of malaria parasites, while companion medicine clears the remaining small number of parasites [9].

ACTs are the most recent class of anti-malarials to be utilized globally Artemisinin-resistant hotspots have been identified in Cambodia, Thailand, and along the Thai Myanmar border [10]. Resistance to artemisinin's in falciparum would not only limit treatment choices in afflicted areas, but it might also jeopardize the management of uncomplicated malaria patients in other countries where ACT is commonly recommended [11].

Despite the introduction of ACT for malaria treatment to address parasite resistance, increasing resistance to anti-malarial medicines is one of the keys aims for moving from malaria control to eradication. As a result, assessing the effectiveness of anti-malarial medications is a critical component of malaria control and eradication. The efficacy of chloroquine to treat *P. vivax* malaria has not been evaluated in South Africa. The present single-arm study was performed to evaluate the efficacy and tolerance of chloroquine in *P. vivax*-infected, symptomatic patients in South Africa where *P. vivax* has emerged in recent years.

Materials and Methods

Description of the Site

The study adopted a retrospective investigation that was conducted in a clinic in Johannesburg, Gauteng Province, South Africa. The city is the biggest metropolitan with an estimated population of 4.9 million residents in 2022. The clinic is privately owned and situated approximately 10 kilometres from Johannesburg's central business district (CBD).

Description of Experiments Done

A total of 322 patient files were purposively sampled for the study. The following were the enrolment criteria:

1. No prior enrolment in the study.
2. Age 6-59 months.
3. Absence of severe malnutrition.
4. Fever, defined as an axillary temperature of 37.5°C or a history of fever in the preceding 24 hours.
5. No history of serious adverse effects or hypersensitivity reactions to plasmoquine.
6. No use of medications that could interact with plasmoquine
7. No evidence or danger signs of severe malaria.
8. No evidence of concomitant febrile illness.
9. No recurring vomiting after the first dosage of study medicine; and
10. Malaria Rapid Diagnostic Tests (RDTs) were used to confirm infections. As a retrospective study, malaria patients with data fitting this criterion from 2018-2022 were included in the study.

Description of Statistical Methods Used

In this study, data was analysed using Stata 14.2 (Stata) and R Studio 1.0.143. Continuous variables were compared using the independent-sample t-test and the Wilcoxon rank sum test, while categorical variables were compared using the Fisher exact test. P values were calculated without regard for multiple

testing, and statistical significance was considered as a P value of 0.05.

Results

Demographics of Malaria Patients

Table 1 below presents the demographic profiles of the patients whose data was used for the study.

A total of 322 patients in total were selected for this study. The distribution of the patients by year ranged from a low of 34 patients (in 2022) to 92 patients (2020) (See Table 1). The majority of the patients selected for this study were males (318), with only 4 identified as females. Furthermore, the categorization of these participants based on age indicates a disproportionate distribution, with the majority of the participants within the age group of 19-45 (210 participants). The categorization of the participants by marital status indicates that the majority of patients (74) reported to have never been married. Only 40 patients indicated that they were married. The data corresponds to the fact majority of these participants are within the age of 19-45. Furthermore, most of the participants reported to have received some level of education, with only 52 being illiterates. The data revealed that patients who attended primary education were (133) and secondary level education (115) was the highest (See Table 1). The employment status of the participants also varied, with the majority (282) being unemployed, this could also be related the age of the participants and their level of education as mentioned earlier.

Table 1. Demographic of Malaria Patients

Measure	Item	Count	Percentage
Gender	Male	318	98.8
	Female	4	1.2
Age	<12	0	0
	12-18	76	23.6
	19-45	210	65.2
	>50	36	11.2
Marital Status	Never Married	274	85.1
	Married	40	12.4
	Divorce	8	2.5
Education	illiterate	52	16.1
	Primary	133	41.3
	Secondary	115	35.7
	University	22	6.9
Occupation	Non-Employment	282	87.6
	Self-employment	22	6.8
	Employed	18	5.6

Dominant Species of Plasmodium Parasites in the Study Population

The study focused on *P. vivax* and *P. falciparum* because these were the common malarial parasites recorded. Over the five (5) year period of the study, the proportion of infections caused by these two parasites varied. For instance, in 2018, out of the 84 cases of malaria recorded, 62 were caused by *P. falciparum*, and 20 of the patients in that year had infections from both *P. vivax* and *P. falciparum* (Figure 1). Consistently, throughout the study *P. falciparum* was observed as the main contributor to malaria in the study population irrespective of the year, with the exception of 2019, where infections caused by

both *P. vivax* and *P. falciparum* (mixed infections) was the most common (a total of 47 out of 57 infections).

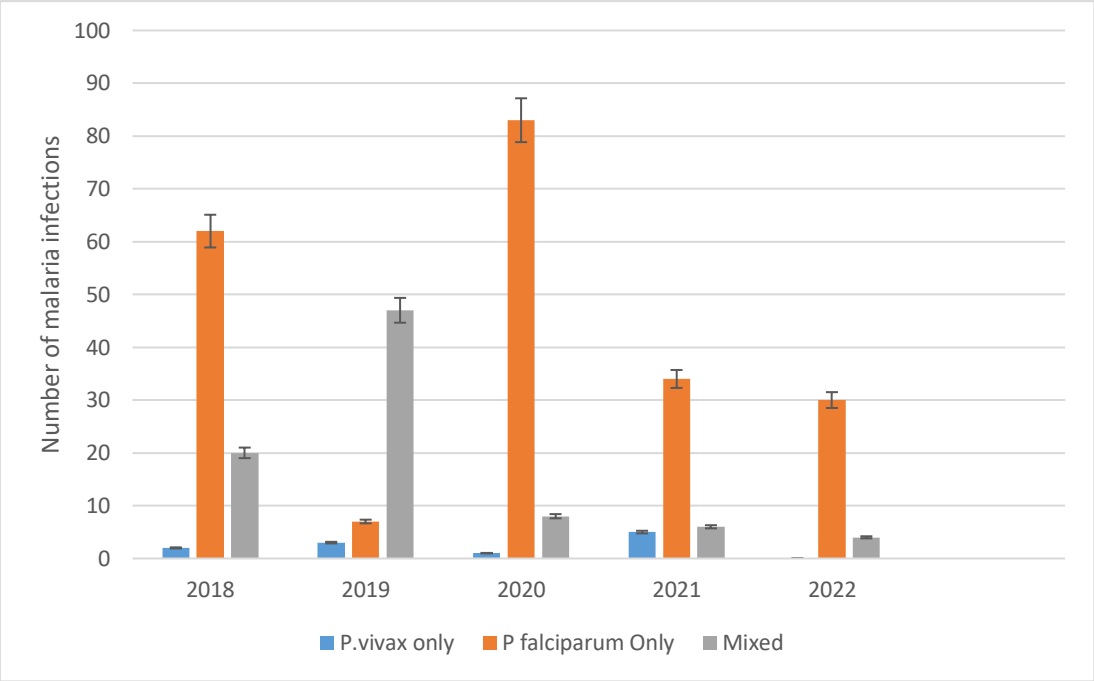

Figure 1. Distribution of Malarial Parasites Responsible for Infections Reported Each Year during the Study

Efficacy of Plasmoquine for Malaria Treatment

Plasmoquine was determined to be effective for the treatment of malaria, irrespective of the parasite responsible for the infection. Out of the total 322 cases of malaria assessed, only 24 (7.5%) reported treatment failure (See Table 2), with the remaining 298 (92.5%) reporting adequate clinical responses, which is the elimination of parasites in blood samples and recovery from all malarial symptoms within three days of treatment. The other 24 patients developed vomiting, affecting the absorption time into the bloodstream, and they were referred to a hospital.

Table 2. Efficacy of Plasmoquine to Treat Both P. Vivax and P. Falciparum

Total number of enrolled patients	322
Treatment failure	24
Adequate Clinical response	298

Discussion

Despite the fact that malaria is only found in three provinces in South Africa – Limpopo, Mpumalanga, and KwaZulu-Natal (KZN), the disease continues to pose serious public health threats throughout the country. Since 2010, South Africa has made significant progress in combating malaria within its borders. However, South Africa has experienced at least two major malaria outbreaks in the last two decades, resulting in hundreds of hospital admissions and deaths [12]. The first outbreak, which was primarily concentrated in the province of KwaZulu-Natal, occurred in early 2000, with over 60,000 cases recorded [12]. The most recent malaria outbreak was reported in South Africa in 2017, with over 28,000 cases recorded, with Limpopo province accounting for the majority of new malaria transmissions [13]. These sporadic malaria outbreaks remain a major public health concern. Cross-border

migration from neighbouring countries contributes significantly to malaria transmission in South Africa, where case importation has fuelled local malaria transmission. For example, most malaria cases in Mpumalanga and KZN provinces in the last five years have been imported from neighbouring countries. Malaria importation accounted for 82% and 72% of total cases, respectively, in Mpumalanga and KZN [12, 13].

While discussing the variability of malaria incidence in South Africa, [14] suggested that non-climatic factors such as drug/insecticide resistance, HIV prevalence, and indoor residual spraying coverage, among others, could influence malaria incidence trends. They discovered that non-climatic factors have a significant impact on the trend and variability of malaria transmission over longer time scales (several years to decades). They came to the conclusion that the transmission rate could be influenced by the effectiveness of control measures. However, despite having a good control measures in South Africa, [15] there was an increase in the number of malaria cases between 2012 and 2014.

The results obtained in the current study depict a lower prevalence of malaria compared to the studies mentioned above. This could be due to the difference in the study area. For instance, as mentioned above, malaria in South Africa is reportedly endemic Limpopo, KwaZulu-Natal, and Mpumalanga due transmissions from the border areas between South Africa and Mozambique, Zimbabwe and Botswana. These three countries still have high malaria cases. Therefore, the low malaria cases could be due to the fact that this study was carried out in the Gauteng province (Johannesburg). The South African Department of Health reports that plasmodium falciparum is the most common cause of malaria in the country. Furthermore, the WHO reports that *P. falciparum* is the deadliest malaria parasite and the most prevalent on the African continent. Additionally, the same body (WHO) reports that *P. vivax* is the dominant malaria parasite in most countries outside of sub-Saharan Africa. Therefore, the distribution of the two main types of malarial parasites among the study population is therefore in agreement with expected outcomes. In the current study, *P. falciparum* was the most common type of parasite. The occurrence of *P. vivax* in the study population could perhaps be due to the infections from travellers. Due to the central nature of Johannesburg as the economic capital of South Africa, it receives a high number of visitors from outside Sub-Saharan Africa.

Treatment failure in respect of malaria has been reported extensively. Over the last decade, anti-malarial drug resistance has emerged as a threat to global malaria control efforts in the Greater Mekong sub-region [16]. WHO is also concerned about more recent reports of drug-resistant malaria in Africa. However, the results from the current study indicate that effective treatment with plasmoquine can potentially address the challenge. The use of plasmoquine for treatment in the current study is in variance with the recommended treatment options for malaria treatment by the South African National Department of Health. Plasmoquine as an 8-aminoquinoline drug, is recommended in situations to prevent recurrent malaria attacks.

The results obtained in the current study indicate that the use of plasmoquine is effective in treating malaria (see Table 2). Despite the observed efficacy of plasmoquine, the most significant recent therapeutic advances in malaria have been the replacement of monotherapies such as plasmoquine, which is used for the treatment of uncomplicated falciparum malaria by artemisinin-based combinations [17]. However, artemisinin-resistant Plasmodium falciparum parasites have spread in Southeast Asia's Greater Mekong Sub-region over the last decade [18]. Because Africa accounts for 90% of malaria cases and deaths, the emergence of artemisinin resistance poses a serious threat to malaria control worldwide. As there are currently no

alternatives to artemisinin derivatives, the spread of artemisinin-resistant parasites in Africa is a concern. As a result of the findings in this study, plasmoquine may once again be an effective malaria treatment.

Conclusion and Recommendations

Malaria transmission in South Africa is seasonal, occurring during the rainy summer period from September to May. The peak malaria season in South Africa takes place during the months of January to April. Currently, only 10% of the population in South Africa live in malaria-transmission areas in malaria-endemic districts located in three provinces of Kwa-Zulu-Natal (KZN), Limpopo and Mpumalanga [19]. Transmission is regarded as low transmission due to the low burden of malaria in the country with the prevalence of less than 10% or an incidence of 100-250 cases per 1 000 population [20]. The study highlights the occurrence of malaria in Johannesburg, based on the data obtained, it can be concluded that *P. falciparum* is still the most significant contributor of malaria infections in South Africa. It is therefore in agreement with several other studies that have reported similar results. Furthermore, this study indicates that malaria infections in the Gauteng Province is lower compared to data from KwaZulu-Natal, Mpumalanga and Limpopo provinces. This is due to the common border of these provinces with neighbouring countries where malaria is still endemic. Despite the recommendation by the WHO and the South African National Department of Health to use ACT for malaria treatment, the emergence of resistance to these drug combinations calls for alternative treatment options. Therefore, the use of plasmoquine in this study and the results obtained show the potential re-introduction of this drug as an effective treatment. The study provides the needed evidence to support this re-introduction.

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Conflict-of-Interest Statement

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. This statement is signed by all the authors to indicate agreement that the above information is true and correct.

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