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Therapeutic Efficacy of Chloroquine for the Treatment of Uncomplicated Plasmodium Vivax Infection in Shewa Robit Health Center, North East Ethiopia

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THERAPEUTIC EFFICACY OF CHLOROQUINE FOR THE TREATMENT OF UNCOMPLICATED *PLASMODIUM VIVAX* INFECTION IN SHEWA ROBIT HEALTH CENTER, NORTH EAST ETHIOPIA

BY

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JULY 2021

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A THESIS SUBMITTED TO THE DEPARTMENT OF MEDICAL LABORATORY SCIENCE, SCHOOL OF HEALTH SCIENCES, COLLEGE OF MEDICINE AND HEALTH SCIENCES, BAHIR DAR UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN MEDICAL PARASITOLOGY AND VECTOR CONTROL

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Advisors' approval of thesis for defense

I hereby certify that I have supervised, read, and evaluated this thesis titled "Therapeutic efficacy of chloroquine for the treatment of uncomplicated *Plasmodium vivax* infection in Shewa Robit Health Center, Northeast Ethiopia" by Habtamu Belay ID No: BDU-1207066PR prepared under my guidance. I recommend the thesis be submitted for oral defense (mock-viva and viva voce).

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Examiners' Approval of Thesis for Defense Result

We hereby certify that we have examined this thesis entitled "Therapeutic efficacy of chloroquine for the treatment of uncomplicated *Plasmodium vivax* infection in Shewa Robit Health Center, Northeast Ethiopia" by Habtamu Belay.

We recommend that the thesis is approved for the degree of MSc with "Medical Parasitology and Vector Control"

Board of Examiners

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Internal examiner's name	Signature	Date
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Chair person's name	Signature	Date

DECLARATION

I hereby declare that this thesis is my original work and has not been presented for a degree in any other university and all sources of material used for this thesis have been properly acknowledged.

Name: Habtamu Belay

Signature_____ Date_____

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS AND ACRONYMS

AE	Adverse Events
ACPR	Adequate Clinical and Parasitological Response
CQ	Chloroquine
CQR	Chloroquine Resistance
DCQ	Desethylchloroquine
ETF	Early Treatment Failure
FMoH	Federal Ministry of Health
Hgb	Hemoglobin
LCF	Late Clinical Failure
LPF	Late Parasitological Failure
OPD	Outpatient Department
PRR	Parasite Reduction Ratio
RBCs	Red Blood Cells
WHO	World Health Organization

ABSTRACT

Background: Malaria remains the most prevalent and fatal vector-borne disease in the world. In Ethiopia, two-thirds of the population lives in areas at risk of malaria infection. The development of drug resistance to available antimalarial drugs is the main challenge in the prevention and control of malaria in all endemic areas. Chloroquine is the first-line treatment for uncomplicated *P.vivax* in Ethiopia. The emergence of *P.vivax* resistance to chloroquine in the country threatens the efficacy of *P.vivax* treatment.

Objective: This study aimed to assess the therapeutic efficacy of chloroquine among uncomplicated *P.vivax* infections at Shewa Robit Health centre, northeast Ethiopia.

Methods: Health facility-based one-arm *in vivo* prospective chloroquine efficacy study was conducted in Shewa Robit Health Centre from November 2020 to March 2021. Participants were selected and treated with a 25 mg/kg standard dose of chloroquine over three days. Thick and thin blood smears were prepared and examined to determine parasite clearance, and clinical examination was performed over 28 follow up periods. Haemoglobin level was measured by HemoCue HB 301 Sweden spectrophotometer on days 0, 14 and 28. WHO double-entry Excel sheet was used for Kaplan-Meier survival analysis and SPSS version-20 software was used to analyse the data. All comparisons were performed at 95% CI and a significance level of 0.05, P-value of <0.05 was considered statistically significant.

Result: Out of the 90 enrolled participants, about 86 completed their 28 days follow-up period. The overall cure rate of the drug was 98.8 % (95% CI: 95.3%-100%). All asexual stages and gametocytes were cleared within 48 hrs with rapid clearance of parasitemia and fever. Haemoglobin concentration had significantly recovered between days 0 and 14, 0 and 28, and 14 and 28 (*P=0.032, P<0.001, and P=0.005*), respectively. Fast resolution of clinical signs and symptoms were also observed. There was no severe adverse event.

Conclusion: The present study revealed that chloroquine remains an effective drug for the treatment of uncomplicated *P.vivax* and has a rapid clearance of parasitaemia and fever; haemoglobin improvement and clinical resolution. No severe adverse events were recorded. Therefore, chloroquine should continue as a first-line drug to treat uncomplicated *P.vivax* malaria in the study area.

Keywords: *Plasmodium vivax*, Therapeutic efficacy, Shewa Robit, Ethiopia

1. INTRODUCTION

1.1. Background

Malaria remains the most prevalent and fatal vector-borne disease in the world. It is a disease caused by a protozoan parasite belonging to the genus *Plasmodium* and is transmitted by the female anopheles mosquito through a blood meal. In humans, the disease is caused by species of *Plasmodium falciparum (P.falciparum), Plasmodium vivax (P.vivax), Plasmodium malariae (P. malariae), Plasmodium ovale (P.ovale),* and *Plasmodium knowlesi (P.knowlesi)* (Basu and Sahi, 2017). The majority of the reported severe and often fatal cases have been attributed to *P. falciparum*, which is the most prevalent species in Africa, while *P.vivax* is more common in countries outside the African continent. *P.vivax* can also cause severe and fatal malaria (Baird, 2013).

Malaria is still a major cause of death and severe illness in most of the world. Currently nearly half of the world's population is at risk of malaria, with Africa having the biggest portion of cases and deaths of any continent (~ 90%). In 2019 alone, there were an estimated 229 million reported cases of malaria worldwide with 409,000 malaria-related deaths. The World health organization (WHO) African Region accounted for 215 million cases and 384,000 deaths. The percentage of total malaria deaths among children aged under 5 years was 67% (WHO, 2020).

Plasmodium vivax is the most prevalent human malaria parasite found in many parts of the tropical and subtropical regions of the world. A recent estimate, integrating national prevalence surveys, surveillance data, and geospatial mapping, have reviewed the global burden to ~14.3 million cases in 2017 (Battle *et al.*, 2019). The highest burden of *P. vivax* infection is seen throughout the country of Southeast Asia, South America, and sub-Saharan Africa (WHO, 2015).

In Ethiopia, two-thirds of the population (~66 million people) lives in areas at risk of malaria infection. *P. falciparum* accounts for 60% of malaria cases and the remaining 40% of malaria cases were caused by *P.vivax* (WHO, 2015). Also in some areas of Ethiopia, *P. vivax* is becoming gradually increasing from year to year (File *et al.*, 2019). A survey conducted in the current study area in 2019/20 showed that malaria was reported throughout the year with a prevalence of 7.8% in major transmission seasons and 13% in the minor transmission season

Malaria transmission is speeding up due to human migration, urbanization, and agricultural development. Apart from human factors, the emergence of drug-resistant *Plasmodium* parasites and the presence of insecticide-resistant vectors are major obstacles in the control of malaria in Ethiopia and worldwide (FMoH, 2012).

Currently, anti-malarial resistance has been a major concern in treating malaria patients. Chloroquine (CQ) was the drug of choice in treating both *P. vivax* and *P. falciparum* infections for many years. It has been the most widely used anti-malaria drug, because of its safety, price-related factors and it is also considered as the safest of malaria drugs to use during pregnancy (WHO, 2009). It has additional antipyretic and anti-inflammatory properties which increase its importance (O'Neill *et al.*, 2012). After long-term extensive use, widespread resistance to CQ has been identified in malaria parasites including *P. falciparum* and *P. vivax*. In a systematic review in *The Lancet Infectious Diseases* that involved 179 study sites in Asia, Africa, and South America, Ric Price and colleagues conclude that CQ resistance has spread across most countries endemic for *P vivax* (Price *et al*., 2014).

Chloroquine is still extensively used as an antimalarial agent in vivax malaria. Its use in combination, or not, with primaquine, acts on the *Plasmodium* liver stage preventing relapses is the first choice in the majority of endemic areas of *P. vivax* (WHO,2011). CQ treatment failure and resistance with failures of primaquine as anti-relapse therapy for *P. vivax* malaria have also been reported in some parts of Southwestern and Northeastern regions of India (Singh, 2000) and also in Ethiopia (Yeshiwondim *et al.,* 2010). In many regions of the world somewhere chloroquine resistance (CQR) to *P. vivax* is seen, artemisinin combination therapy along with primaquine is used as an alternative treatment strategy (WHO, 2015).

In Ethiopia, CQ is the first-line treatment for *P. vivax,* and CQ plus primaquine for radical cure is for malaria elimination targeted woredas (FMoH, 2018). However, The emergence of *P. vivax* resistance to CQ threatens the efficacy of *P.vivax* treatment in the country (Getachew *et al.*, 2015). WHO strongly recommends and encourages that the continuous and regular monitoring of first and second-line antimalarial drug efficacy study should be conducted at least in 24 months (every two years) interval in all endemic areas as it would help early detection and prevention of the spread of resistant parasite populations (WHO, 2009). Therefore, conducting continuous drug

efficacy studies in malaria-endemic sites is important to informing antimalarial interventions as prompt treatment is one of malaria case management (WHO, 2015).

1.2. Literature Review

1.2.1. Antimalarial Drugs

Currently, most antimalarial agents are targeting the asexual phase of malaria infection that causes symptomatic illness. Malarial treatment based on natural products, semi-synthetic, and synthetic compounds developed since the 1940s (Burrows *et al*., 2014). The existing antimalarial agents are grouped into three main classes: quinolone–derivative, an antifolate, and artemisinin derivatives. Emphasis is on one of the quinolone-derivative chloroquine, which currently serves as first-line treatment for non *P.falciparum* malaria species, in most African countries including Ethiopia (WHO, 2015).

Chloroquine, which is a 4-aminoquinolone alkaloid, was made widely available in the early 1950s. Although it was introduced as early as 1934 (Cooper and Magwere, 2008). The first development of CQ treatment with humans occurred in 1936 (Coatney, 1963). Patents for sontochin and CQ were discovered in the United States by Wiselogle, and CQ was more effective and better tolerated (Lobe *et al*, 1946). The name CQ was formally registered in the United States in March 1946, after one month the influential paper published by Loeb *et al* on the activity of CQ against *P.falciparum* and *P.vivax* malaria and they recommended 1.5 g of base over 48 h for the treatment of acute *P.falciparum* or *P.vivax* malaria and 0.3 g of base weekly for prophylaxis (Lobe *et al*, 1946).

1.2.2. Chloroquine Resistance

Globally *Plasmodium vivax* Chloroquine resistance (Pvcr) was first noticed in Papua New Guinea in 1989 on two soldiers administered prophylaxis with 300 mg chloroquine base and were not protected against *P. vivax* malaria (Rieckmann *et al.*, 1989). And subsequently, resistance was also seen in most endemic places in Southeast Asia. The highest prevalence of CQ-resistant to *P. vivax* was reported in the Northeastern coast of Indonesian Papua. The incidence of therapeutic failure was 84 % (Sumawinata,2003).To date, there is evidence of CQ-resistant *P. vivax* in many other countries (Awab *et al.*, 2017). On the other hand, there is an efficacious result that showed the effectiveness of the drug conducted in Afghanistan which was 99.5% of treatment success (Shafiqullah,2017).

In Africa, the study conducted in Madagascar that represents the whole area of the country the treatment failure rate was 5.1% with area-specific 0 in the south, 1 in the west, and 14.8% were in the foothills of the central highlands, the age of participants those have gotten treatment failure were 4 are children and 1 was adult (Barnadas *et al.*, 2008). Another study conducted for the first time in the West Africa Saharan zone in Mauritania based on WHO standard per-protocol efficacy study the treatment response of CQ was 100% effective. Fever and parasite clearance after treatment was rapid the drug has an important role play treating vivax malaria in the study area (Salem *et al.*,2015).

In Ethiopia, The first report of CQ resistance in *P.vivax* from Africa was reported in Debre Zeit, Ethiopia which was 4.6% of CQ treatment failure observed during the follow-up period (Teka *et al*., 2008). The study conducted in Halaba district in 2009 with 28 follow-up days showed the highest number (13%) of CQ treatment failure for *P.vivax* when compared with the previous study in Ethiopia and Africa (Ketema *et al.*, 2011). Another study conducted in Jimma zone Serbo town in 2008 supports the emergence of resistance, which was 3.6 % failure, all those who showed treatment failure were children's (Ketema *et al.*, 2009). In the east Shewa district a prospective open-label randomized comparison of CQ with CQ+ PQ study, CQ alone showed 5.76% failure within 28 days follow up period (Yeshiwondim *et al.*, 2010).

In another area of the country, there was evidence that strengthens the emergence of CQ resistance *P.vivax* strain, in studies conducted in Debrezeit and Nazareth towns, the cumulative incidence of treatment failure was 7.5 % (Yohannes *et al.*, 2011). Moreover, a study was conducted in southern Ethiopia on four different sites (Shele 3.8 %, Guba 21.9 %, Batu 5.9 %, Shone 9.2%). collectively three of them show the reduced CQ efficacy with the highest or severe result in Guba (21.9 %) (Getachew *et al.*, 2015). Though some studies indicate the emergence of CQ resistance, there are controversial results reported from other studies that confirmed the efficaciousness of the CQ to treat *P.vivax*, and still, it remains the drug of choice.

A one-arm 28-day follow-up in vivo therapeutic efficacy study was conducted at hosanna in 2014, among 60 patients only 2 treatment failures were detected (Assefa *et al.*, 2015). An in vivo prospective drug efficacy study was conducted in Jimma town in 2011. Only 2.7% of treatment failure was recorded (Kanche *et al.*,2016). Another 28 days follow-up therapeutic clinical

efficacy study conducted in Metekel in Northwest Ethiopia in 2014 showed the efficacious of the drug, among 69 patients only 2 children (2.7 %) showed the treatment failure (Beyene *et al.*,2016). These findings strengthen by the study conducted in the Guragae zone, the treatment failure was detected only 2.5 % (Shumbej *et al.*, 2019).

Consequently, in Ethiopia there was a report of failure alarm for CQ (Abreha *et al.*, 2017); on the other hand, some results reveal CQ is still now efficacious drug to *P.vivax* in some parts of the country. To support such reports further studies are needed especially in the Amhara region there is no satisfactory such type of study on CQ even though the region is one of the malarious sites in the country. Therefore, as aimed to assess the therapeutic efficacy of CQ against *P.vivax*, conducting this study will give updated information about the states of CQ treatment on *P.vivax* in Shewa Robit Health Center.

1.3. Statement of the Problem

The development of antimalarial drug resistance is the main challenge in the prevention, control and elimination of malaria in all endemic areas. The emergence of chloroquine resistance (CQR) strains to *P.vivax* has been reported in different parts of the world; Indonesia (WHO,2007), Myanmar (Fryauff *et al.*, 1989), Madagascar (Barnadas *et al.*, 2008), Ethiopia (Ketema *et al.*, 2011) since the first treatment failure due to CQR was documented in 1989 from Papua New Guinea (Rieckmann *et al.*, 1989).

World health organization regularly updates therapeutic study protocol for high transmission and low to moderate transmission areas. Based on this, more studies are needed to monitor the therapeutic efficacy of CQ against uncomplicated *P.vivax* in malaria-endemic areas. This will help to trace the development of CQR due time as well as monitoring of clinical response, side effects, and adverse events of the drug. There are few studies conducted on the therapeutic efficacy of CQ for treatment of *P.vivax* in malaria-endemic areas of Ethiopia (Assefa *et al*., 2015; Beyene *et al*.,2016; Shumbej *et al,* 2019), and some of the studies didn't measure full clinical response of the drug.

Failure to early detecting the emergence and spread of malaria drug resistance could lead to the spread of drug-resistant malaria and hinder the malaria control and elimination strategies. To combat the development and spread of antimalarial drug resistance, a continuous monitoring and surveillance system is needed. However, there are limited studies in Shewa Robit, East Shewa, which is one of the malaria-endemic areas and Sentinel site for malaria drug resistance monitoring. A study conducted seven years ago reported (93.4% efficacy) of CQ against uncomplicated *P.vivax* in the same area (Seifu *et al.*, 2017).

Even if the result shows an indication to failure of CQ treatment and the authors recommended further study, since then no other studies of this sort were conducted on the site. Therefore, the present study gives updated information about the status of therapeutic efficacy of CQ for the treatment of uncomplicated *P.vivax* in the study area. The study result will support malaria elimination program in Ethiopia and beyond for policy decision.

1.4. Significance of the Study

This study assessed the therapeutic efficacy of chloroquine against uncomplicated *Plasmodium vivax* in malaria patients visiting Shewa Robit Health Center. The information generated maybe used by policymakers for informed decision-making purposes. It also provides information for clinicians on the clearance of clinical signs and symptoms after CQ treatment. It gives information on the haemoglobin level before and after treatment. It may also provide information on an adverse event happening during CQ treatment. Finally, it can be used as baseline data for scholars for further study.

2. OBJECTIVES

2.1. General Objective

- To assess the therapeutic efficacy of chloroquine against uncomplicated *Plasmodium vivax* infection in Shewa Robit Health Center northeast Ethiopia

2.2. Specific Objectives

- To determine the cure rate of chloroquine against uncomplicated *P. vivax*
- To determine the clinical sign symptoms of patients after chloroquine treatment
- To determine haemoglobin level before and after chloroquine treatment
- To evaluate the incidence of adverse events following chloroquine treatment

3. METHODS AND MATERIALS

3.1. Study Area

This study was conducted in Shawa Robit Health Centre, located in Shawa Robit town administration, North Shawa Zone, Amhara Regional State, northeast Ethiopia at 225 km Northeast of Addis Ababa. The area is located at a longitude of $10^{0}060$N 39^{0} 590 E and latitude of 10.1^{0}N39.983^{0} E., The total population, which resides in four urban and 5 rural kebeles of the district, was 60,234. Concerning the climate of the district, nearly 100 % is Qola (1288 meters above sea level). There are one government health centre, one primary hospital, one private primary hospital, eight private medium clinics, two lower private clinics, five government health posts, and ten private drug shops. The area receives high rainfall during the main rainy season (June to September) and is characterized by markedly unstable seasonal malaria. Malaria is one of the top ten diseases in the town and is reported throughout the year (SRHC, 2020).

3.2. Study Design

Health Center-based a one-arm *in vivo* prospective design was used to evaluation of clinical and parasitological responses to directly observed chloroquine treatment for uncomplicated *P.vivax* malaria.

3.3. Study Period

The study was conducted during the malaria transmission season, from November 2020 to March 2021

3.4. Source Population

All malaria suspected individuals attending at Shewa Robit Health Centre during the study period were the source population.

3.5. Study Population

Patients with confirmed uncomplicated *P. vivax* malaria mono-infection attending the outpatient department (OPD) of Shewa Robit Health Centre and who fulfil the inclusion criteria were the study population.

3.6. Sample Size Determination

The sample size was determined according to the WHO (2009) protocol; by using the single population proportion formula and calculated assuming 5% margin of error, 95% confidence interval (CI), and treatment failure of 5% and 20% loss to follow-up rate. Accordingly, a minimum of 73 patients should be enrolled.

$n = (z/d)^2 P (1-P) = (1.96/0.05)^2 0.05 (1-0.05) = 73$

Assuming an additional 20% loss to follow-up rate and withdrawal of consent (15 patients) during the study, at least 88 (73 + 15) patients should be required to bring about a representative sample size

$n= (1+0.2) 73= 88$

Where, n= sample size

P = the expected treatment failure (5%)

z = confidence interval (95%)

d = margin of error (5%)

The study participants were selected from malaria suspected symptomatic patients who visited the health centre. All adult and children (above 6 months) age who fulfilled the inclusion criteria and signed an informed consent/assent was eligible for the study.

3.7. Sampling Technique and Data Collection

About 90 study participants confirmed with *P.vivax* mono-infection on blood film examination and who fulfilled the inclusion criteria stated by WHO were recruited (WHO 2009). Patients treated with onsite CQ for *P.vivax* were monitored for 28 days. The follow-up was consisting of a fixed schedule of check-up visits and corresponding clinical and laboratory examinations. The data was collected during 28 day follow-up period using a standardized drug efficacy record form, on days 0, 1, 2, 3, 7, 14, 21 and 28. The proportion of patients experiencing therapeutic failure during the follow-up period was used to estimate the efficacy of the study drug.

3.8. The study variables

3.8.1. Dependent Variable

Therapeutic efficacy of Chloroquine for the treatment of uncomplicated *P.vivax*

3.8.2. Independent Variables

- Age
- Sex
- Residence
- Clinical characteristics
- Haemoglobin determination
- Parasite density

3.9. Operational Definitions

Adequate clinical and parasitological response: The absence of parasitaemia on day 28, irrespective of auxiliary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure.

Adverse event: An adverse event is defined as any unfavourable, unintended sign, symptom, or disease that develops or worsens with the use of a medicinal product, regardless of whether it is related to the medicinal product.

Early treatment failure: Danger signs or severe malaria occurred on day1, 2, or 3 in the presence of parasitaemia, parasitaemia on day 2 higher than on day 0, irrespective of auxiliary temperature, parasitaemia on day 3 with auxiliary temperature $\geq$ 37.5ºC and parasitaemia on day 3 $\geq$ 25% of count on day 0.

Late clinical failure: Danger signs or severe malaria in the presence of parasitaemia on any day between day 4 to day 28 in patients who did not previously meet any of the criteria of early treatment failure and presence of parasitaemia on any day between day 4 and day 28 with auxiliary temperature $\geq$ 37.5 ºC in patients who did not previously meet any of the criteria of early treatment failure.

Late Parasitological Failure: Presence of parasitaemia on any day between day 7 to 28 and axillary temperature: < 37.5 ºC in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

Per protocol analysis: participants who couldn't complete a 28 day follow up period (withdrawn and lost to follow-up) were removed from the denominator.

Primary outcome: The 28 days treatment outcome of the participants whether treatment failure (ETF, LCF, and LPF) or adequate clinical and parasitological response (ACPR).

Secondary outcome: The clinical and parasitological outcomes following chloroquine treatment (parasite, fever and gametocyte clearance rate, incidence of drug adverse events)

Serious adverse event: Is defined as any untoward medical occurrence that at any dose; results in death/ life-threatening, requires hospitalization or prolongation of hospitalization and results in a persistent or significant disability

Uncomplicated *Plasmodium vivax*: A patient who presents with symptoms of malaria and positive parasitological test, but with no features of severe malaria

3.10. Inclusion and Exclusion Criteria

3.10.1. Inclusion Criteria

The study was conducted according to the WHO revised protocol (WHO 2009) for malaria drug therapeutic efficacy study. On admission, patients showing signs/symptoms of malaria were screened for the following selection criteria:

- Both sexes ≥6 months of age
- Bodyweight >5 kg
- Fever (axillary temperature ≥37.5 ^{0}C) or history of fever within the previous 48 hours
- Mono infection with *P.vivax* confirmed by microscopic blood smear with asexual parasitemia >250/µl of blood
- Non-pregnant or breast-feeding women
- Patients living within the health centre catchment area (10 km radius of the health centre)

- Informed consent by the patient or by caregivers for children under 12 years old and agreed to return for all scheduled visits (Annex XII)
- Ability and willingness to comply with the study protocol for the duration of the study and to comply with the study visit schedule

3.10.2. Exclusion Criteria

- Mixed or mono-infection with other than *P.vivax* species
- Haemoglobin level ≤ 5.0 g/dl
- Intake of antimalarial drug within 2 weeks before enrolment
- Unable to take oral medication or continuous vomiting
- Known hypersensitivity to the study drug
- Evidence of severe malaria or other danger signs according to WHO definition for severe malaria (not able to drink or breast-feed, vomiting (i.e. more than twice in past 24 hours), the recent history of convulsions (i.e. more than once in past 24 hours), unconscious state, unable to sit or stand)
- Presence of severe malnutrition (defined as a child who had a mid-upper arm circumference < 110 mm)
- Presence of febrile conditions due to diseases other than malaria (e.g. measles, acute lower respiratory tract infection, severe diarrhoea with dehydration) or other known underlying chronic or severe diseases (e.g. cardiac, renal, and hepatic diseases, HIV/AIDS)
- Regular medication may interfere with the study drug pharmacokinetics

3.11. Loss to Follow-Up

Loss to follow-up occurs when, despite all reasonable efforts, an enrolled patient does not attend the scheduled visits and cannot be found. No treatment outcomes were assigned to these patients. These patients were classified as lost to follow-up and excluded from the analysis.

3.12. Patient Discontinuation or Protocol Violation

Study participants who meet any of the following criteria were classified as

- Withdrawal of consent. A patient may withdraw consent at any time, without prejudice

for further follow-up or treatment at the study site

- Failure to complete treatment, due to:
  - ✓ Persistent vomiting of the treatment; a patient who vomits the study medication twice was withdrawn from the study and given rescue treatment
  - ✓ Failure to attend the scheduled visits during the first three days; or
  - ✓ Serious adverse events necessitating termination of treatment before the full course is completed. A patient was discontinued from the study due to an adverse event. In this case, information on the adverse event and symptomatic treatment given was recorded on a case report form.
- Enrolment violation:
  - ✓ Severe malaria developed within 24 hours after the beginning of the treatment; or
  - ✓ Erroneous inclusion of a patient who does not meet the inclusion criteria.
- Voluntary protocol violation:
  - ✓ Self- or third-party administration of the antimalarial drug (or antibiotics with antimalarial activity)
- Involuntary protocol violation:
  - ✓ Occurrence during follow-up of concomitant disease that would interfere with a clear classification of the treatment outcome;
  - ✓ Detection of mono-infection with another malaria species during follow-up; or
  - ✓ Misclassification of a patient due to a laboratory error (parasitaemia), leading to administration of rescue treatment. However, no treatment outcome was assigned to these patients and they were censored or excluded from the analysis. The reasons for discontinuation or protocol violation were recorded on the case report form.

3.13. Treatment and Dosing Procedure

The correct drug dosage was determined according to the national malaria treatment guideline of Ethiopia (FMoH, 2018) and revised WHO protocol (Weight-based guideline) (Annex VII). Accordingly, enrolled patients were treated with the standard Chloroquine phosphate 250 mg coated tablet, (Manufacturer Rimedica Ltd Aharnon Str, Limassol Industrial Estate,3056 Limassol, Cyprus, EU, batch number 80368 and expiry date 02/2024) was administered daily for three consecutive days in the health centre under direct supervision of qualified clinicians. The

study patients were observed for 30 min after medicine administration for vomiting. Any patient who vomits during this observation period was re-treated with the same dose of medicine and observed for an additional 30 min. If the patient vomits again, he or she was withdrawn and offered rescue therapy. At the end of the 28 follow-up days, PQ was administered for radical cure as per the national malaria treatment guideline.

3.14. Concomitant Treatment and Medication

Fever over 38 °C was treated with a standard dose of 10 mg per kilogram paracetamol tablets every 6 hours until the symptoms subsided (WHO 2009). Prior treatment with antimalarial drugs was considered an exclusion criterion however, during follow-up if infections other than malaria require the administration of medicines with antimalarial activity; the patient was withdrawn from the study. Patients are given tetracycline as an eye ointment was not being excluded (Annex VIII). Patients were withdrawn from the study in the case of self-medication or if an antimalarial drug or an antibiotic with antimalarial activity is administered by a third party.

3.15. Baseline Evaluation

Potential participants were assessed further for adherence to the rest of the inclusion criteria. Base-line physical, clinical examinations with particular attention to any danger signs or symptoms associated with severe malaria were thoroughly assessed by a clinician (Annex III). Febrile patients were treated with an appropriate dose of paracetamol. History and demographic data were taken; axillary temperature and body weight were measured. Patients who meet the selection criteria at this stage was assigned with a patient identification number and referred to the laboratory again for further laboratory investigation and sample collection:

- determination of Hb to exclude severe anaemia (Hb $\leq$ 5.0 g/dl);
- Collection of a finger-prick blood sample for repeated thick and thin blood smears before the patient enrolled and treated with antimalarial drug

3.16. Study End Points

The study end-point is the classification assigned to a patient. Valid study end-points include treatment failure (early treatment failure, late clinical failure, and late parasitological failure)

completion of the follow-up period without treatment failure (adequate clinical and parasitological response), loss to follow-up, withdrawal from the study including protocol violation. At all times, the well-being of the patient was taken priority over his or her continuation in the study (WHO, 2009).

3.17. Classification of Treatment Outcomes

Treatment outcomes were classified based on an assessment of the parasitological and clinical outcomes of antimalarial treatment according to the latest WHO guidelines. Thus, all patients were classified as having early treatment failure, late clinical failure, late parasitological failure, or an adequate clinical and parasitological response.

3.18. Clinical Evaluation

All patients were evaluated clinically as described below

3.18.1. Physical Examination

A standard physical examination was performed at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21, and 28. A complete medical history, including prior and concomitant medication, demographic information, and contact details were recorded at baseline.

3.18.2. Bodyweight

Body weight was recorded on day 0 to the nearest kilogram on a Salter scale or a hanging scale for young children. The scales were properly calibrated. The reliability of the scales was verified before the study begins and checked at regular intervals. Patients were not wearing excessive clothing while being weighed as this can overestimate their true weight. All young children were only wearing undergarments while being weighed. The screening weight was used to satisfy the inclusion or exclusion for nutrition status as well as to calculate the dose (number of tablets) to be administered.

3.18.3. Body Temperature

Axillary temperature was measured at baseline (day 0 before dosing) and on days 1, 2, 3, 7, 14, 21and 28. The temperature was measured with a thermometer that has a precision of 0.1 °C. If

the result is < 36.0 °C, the measurement was repeated. The same route was used throughout the study. The quality of the temperature-taking technique and the thermometers was assessed regularly. A thermometer was tested in a water bath of known temperature before the study begins.

3.19. Laboratory Procedures

3.19.1. Microscopic Blood Film Examination

Thick and thin blood films for parasite counts were obtained and examined at screening on day 0 to confirm adherence to the inclusion and exclusion criteria. Thick blood films were examined by well-trained laboratory personnel on days 2, 3, 7, 14, 21, and 28. Specimens were labelled anonymously. The screening number or the patient study number, the date, and the day of follow-up were labelled on the frosted edge of the slide.

A fresh Giemsa stain dilution was prepared at least once a day and possibly more often, depending on the number of slides to be processed. Giemsa-stained thick and thin blood films were examined with a magnification power of 100 x objective to identify the parasite species and to determine the parasite density. At screening, three blood slides per patient were obtained: two thick blood smears and one thin blood smear for species confirmation if needed. One thick blood smear with the screening number was stained rapidly with 10% Giemsa for 10–15 min for initial screening and then for the second staining 3% Giemsa for 45-60 min to provide definitive parasite count.

The thick blood smear for initial screening was used to count the numbers of asexual parasites and white blood cells in a limited number of microscopic fields. The adequate parasitaemia for enrolment is at least one parasite for every six white blood cells, corresponding to approximately 1000 asexual parasites per microliter or ≥ 250/µl.

The second blood smear with the study number was used to calculate the parasite density, by counting the number of asexual parasites in a set number of white blood cells (typically 200) with a hand tally counter. Once a field has been started, it must be counted to completion; the final number of white blood cells was therefore rarely being exactly 200. If more than 500 parasites have been counted before 200 white blood cells have been reached the count was

stopped after the reading of the last field has been completed. Parasite density expressed as the number of asexual parasites per µl of blood was calculated by dividing the number of asexual parasites by the number of white blood cells counted and then multiplying by an assumed average white blood cell density (8000 per µl) (Annex X).

$$\text{Parasite density (per µl)} = \frac{\text{number of parasites count} \times 8000}{\text{Number of leukocytes counted}}$$

The same technique was used to establish the parasite count on each subsequent blood film. When the number of asexual parasites is less than 10 per 200 white blood cells in follow-up smears, counting was done against at least 500 white blood cells (i.e. to completion of the field in which the 500^{th} white blood cell is counted).

A blood slide was considered negative when examination of 1000 white blood cells or 100 fields containing at least 10 white blood cells per field reveals no asexual parasites. The presence of gametocytes on an enrolment was recorded, but this information was not contributed to basic evaluation.

In addition, 100 fields of the second thick film at day 0 were examined to exclude mixed infections; in case of any doubt, the thin film was examined for confirmation. If examination of the thin film is not conclusive, the patient was excluded from the analysis. Two qualified microscopists were read all the slides independently, and parasite densities were calculated by averaging the two counts. Blood smears with discordant results (differences between the two microscopists in species diagnosis, in parasite density of > 50% or the presence of parasites) were re-examined by a third person, independent microscopist, and parasite density were calculated by averaging the two closest counts.

3.19.2. Measurement of Blood Haemoglobin Level

Haemoglobin level was measured from finger-prick blood samples using a portable spectrophotometer (HemoCue Hb 301 Sweden Analyser) (Annex XI) on the day, 0, 14, and 28 to observe improvements in blood Hgb level after treatment and classify the level of anaemia. Anaemia is defined according to the WHO classification, Hgb 7-9.9 g/dl for <5, and 8-10.9 g/dl moderate anaemic for 5-15, and >15 of age respectively. Hgb 10-10.9 g/dl, 11-11.9g/dl and 11-

12.9g/dl mild anaemic for <5, 5-15 and non-pregnant women and adult male respectively, and Hgb >11g/dl for <5,>11.5g/dl for 5-15 and non-pregnant women and >13g/dl classified for adult male. Hb≤5.0 g/dl was considered as severe anaemia and an exclusion criterion (WHO 2009).

3.20. Follow Up Protocol

Table 1. Follow-up methods of study participants treated with chloroquine at Shewa Robit Health Center, northeast Ethiopia from November 2020 to March 2021

Days	0	1	2	3	7	14	21	28
Clinical examination	X	X	X	X	X	X	X	X
Treatment with Chloroquine	X	X	X					
Blood film for Parasitemia	X		X	X	X	X	X	X
Haemoglobin	X					X		X

3.21. Safety Assessment

Safety was assessed by recording the nature and incidence of adverse events and serious adverse events. Adverse events were assessed by direct questioning. All adverse events were recorded on the case report form (Annex IV) and the series of adverse events were also recorded on the series adverse report form (Annex IX).

3.22. Data Management and Analysis

The study protocol was ensured that adhered to and all data are collected and recorded correctly on the case report form. Laboratory and clinical data were recorded daily on the case record form designed for the study. Any change or correction to a case record form was dated and explained. All case record forms were checked for completeness.

All data from recruited patients were imported into the WHO Excel sheet (double entry) which is designed for analysis of therapeutic efficacy study data. Data was also entered into IBM SPSS

(version-20) software to calculate descriptive statistics (mean, median, standard deviations, range). One-Way ANOVA and independent sample t-tests were used to compare baseline temperature and parasitaemia between age groups, and paired sample t-test was used to compare mean Hgb level between D0 and D14, D0 and D28, D14 and D28. All comparisons were performed at 95% CI and a significance level of 0.05.

Kaplan Meier (K-M) survival analysis and per-protocol (PP) analysis were used for estimation of primary outcomes and the PP analysis method was used to analyze secondary outcomes. The K-M survival analysis method provides a better approximation of cure rates as it incorporates probabilities for censored data (incomplete observations due to LFU and withdrawals) into the analysis. The WHO excel sheet is designed for estimation of cure rate based on the K-M survival estimator analysis method.

3.23. Dissemination of Results

At the end of the study, the result will be submitted to Bahir Dar University, College of Medicine and Health Sciences, Department of Medical Laboratory Science and will be disseminated to Amhara regional state health bureau furthermore it will be presented at conferences and the manuscript will be submitted to peer-reviewed journals for publication. Also, this report will be shared through EPHI with the national malaria control program and the Ministry of Health and will allow to formulate recommendations and to enable the Ministry of Health to make informed decisions about whether the current national antimalarial treatment guidelines should be updated.

3.24. Ethical Consideration

Ethical clearance for the study was obtained from the Ethical Clearance Committee of Bahir Dar University (BDU) Institutional Review Board (IRB) (protocol number: 162/2021) and the Ethiopian Public Health Institute (EPHI) (protocol number: 294/2020) before its initiation. In addition, permission was obtained from Shewa Robit Health Centre. Written informed consent was obtained from adult patients while for children, informed assent was secured from their parents or guardians. Details about the study and its benefits and potential risks were explained. Confidentiality of the result was maintained and patients had the right to stop or withdraw from the study at any time (Annex X).

4. RESULTS

4.1. Characteristics of Study Participants

4.1.1. Socio-Demographic Characteristics

A total of 2090 malaria suspected patients were screened, and females accounted for 54.1%. About 8% (167/2090) of the participants were found to be slide positive for malaria, of which 147 (88%) of the cases were attributed to *P. vivax.* Ninety (61%) of the *P. vivax* mono-infection cases fulfilled the inclusion criteria were recruited. The majority of the study participants 83 (92.2%) were urban residents.

Among the 90 enrolled participants, males took the highest number yielding a male to female ratio of about 2 (58/32). The median age of the study participants was 18 years, ranging from 1.4 - 60 years, and under-five children accounted for 11.1%. About 50 (55.6%) of the participants had access to a bed net, with a proper bed net utilization rate of 56%. Among 78 (86.8%) of the participants who had a previous history of malaria attack, three-quarters took chloroquine and the remaining 11 (12.2%) were treated with Arthemeter Lumefantrine. Of the enrolled participants, four participants couldn't complete the 28-day follow-up and were therefore excluded. A participant developed hypersensitivity to the study drug on day 0, two others withdrew the consent on day 1 and day 2, and one participant left the study site on day 21 (Figure 1).

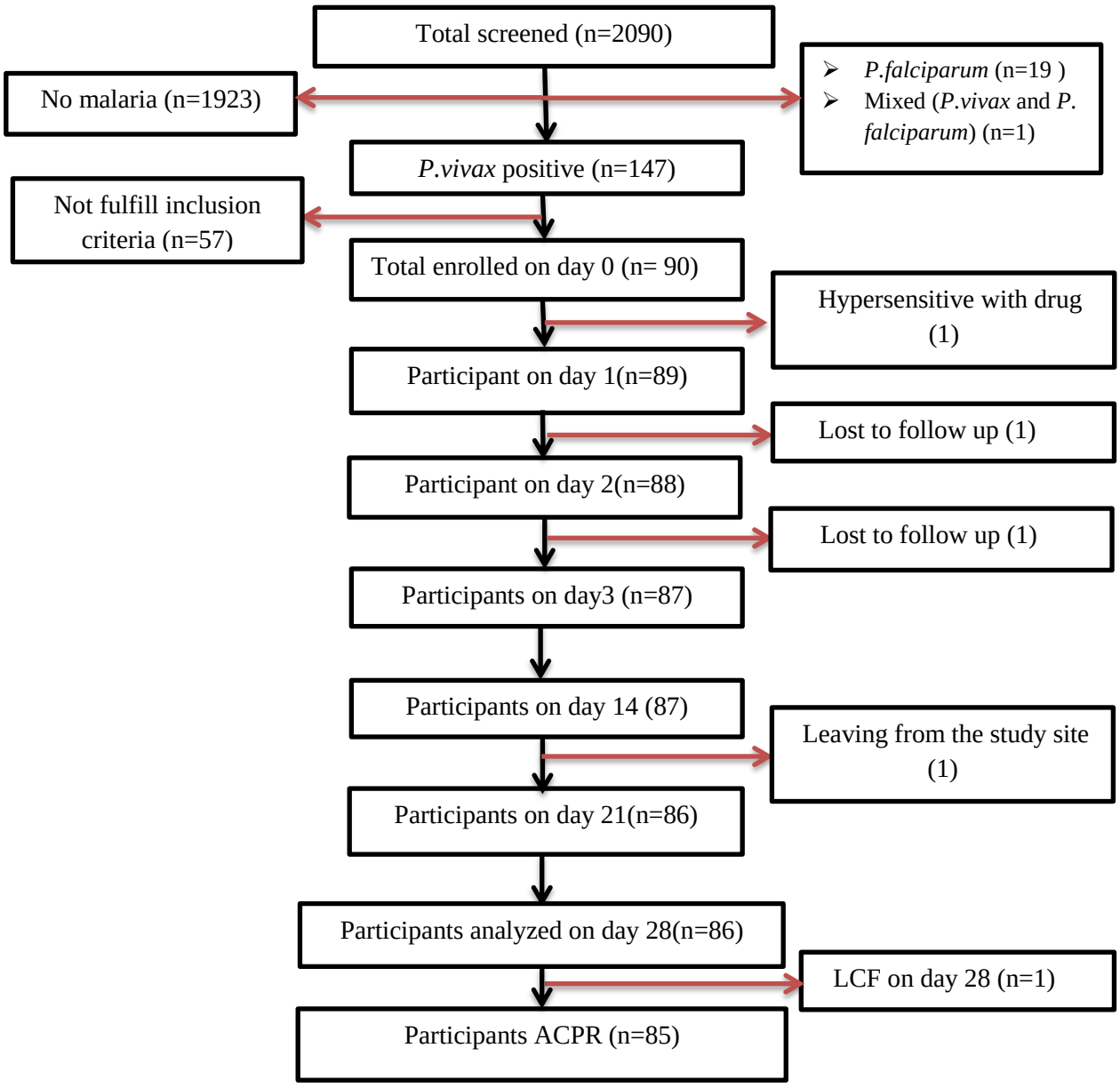


Figure 1. Flow chart of study participants recruitment and follow-up for Chloroquine efficacy in Shewa Robit Health Centre, northeast Ethiopia from November 2020 to March 2021

4.1.2. Baseline Clinical Characteristics

From the total 90 included participants, about 8.9% of the participants had a history of fever in the previous 48 hrs, 55.5% had both histories of fever in the last 48 hrs and fever at the time of enrolment, and the remaining 35.6% were febrile at the time of enrolment. The baseline mean ± SD body temperature was 38.8±1^{0}C (males 38.8±0.9 ^{0}C, females 39±1.2 ^{0}C) with no significant difference (*P=0.427*). The highest mean body temperature was recorded for under-5 children (39.3±0.1 ^{0}C). Headache, vomiting and nausea were the major clinical signs/symptoms reported on the first day (D0). Headache was the most common symptom 69 (80.2%). The average weight and height were 41.1 kg and 145.7 cm, respectively.

The baseline geometric means parasitaemia was 5368 with a significant difference (*P=0.001*) between all age groups and (*P=0.015*) between age groups 5-15 vs >15. Overall gametocyte carriage at baseline was 87/90 (96.7%). The baseline means haemoglobin level of the study participants was 13 g/dl, with 11.5, 11.9, and 13.8 g/dl for <5, 5-15, and >15 age groups, respectively. The prevalence of anaemia was 26.7% (18.9% mild and 7.8% moderately anaemic) (Table 1).

Table 2. Baseline characteristics of the study participant with chloroquine treatment in Shewa Robit Health Centre, northeast Ethiopia from November 2020 to March 2021

Variables		**Sex**		**Residence**		**Total**
		Male	**Female**	**Urban**	**Rural**	
No (%)		58 (64.4)	32 (35.6)	83 (92.2)	7 (7.8)	90 (100)
Mean Temp (^{0}C)		38.8	39	38.8	39.4	38.8
Mean Hgb(g/dl)		13.4	12.4	13	14	13
Anaemia status	**Mild**	8 (13.8)	9 (28.1)	15 (18.1)	2(28.6)	17(18.9)
	Moderate	4 (6.9)	3 (9.4)	7 (8.4)	0 (0)	7 (7.8)
	Total	12 (20.7)	12 (37.5)	22 (26.5)	2 (28.6)	24 (26.7)
Mean (Geo) Para/µl		5097	5895	5261	6810	5368
Gametocyte carriage n (%)		56 (96.6)	31(96.9)	80 (96.4)	7 (100)	87 (96.7)
<10000 parasitaemia n (%)		45 (77.6)	22 (68.8)	62 (74.7)	5 (71.4)	67 (74.4)
>10000 parasitaemia n (%)		13 (22.4)	10 (31.2)	21 (25.3)	2 (28.6)	23 (25.6)

Geo=Geometric, Hgb= Haemoglobin, Para=Parasitaemia, Temp=Temperature

Age and parasitaemia were inversely correlated; parasite load was higher in children than adults (day of admission) (r^2=*0.115*, (*P=0.001*) (Figure 2)

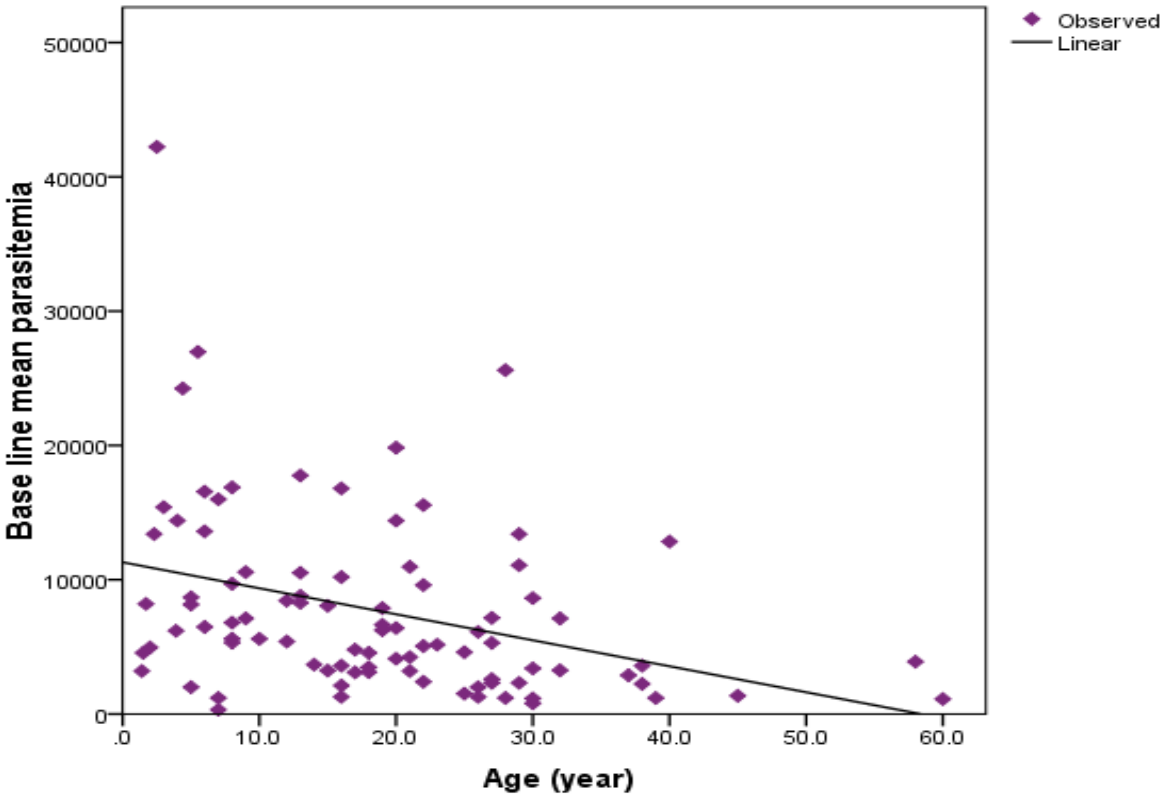


Figure 2. Relation between age and parasite counted at baseline of study participants in Shewa Robit Health Centre, northeast Ethiopia from November 2020 to March 2021

4.2. Primary Outcomes

4.2.1. Cure Rate of Chloroquine

Based on the per-protocol analysis method, the overall cure rate of chloroquine was 98.8 % (95% CI: 95.3%-100%). During the 28 days follow-up, a recurrence of *P.vivax* was found on day 28 and classified as LCF 1.2% (95%CI:0.0%-4.7%) (Table 2).

Table 3. Per protocol treatment outcome of study participants following chloroquine treatment on day 28 at Shewa Robit Health Center, northeast Ethiopia from November 2020 to March 2021

Outcome	<5	5-15	>15	Sex		Total
				Male	Female	
ETF n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LCF n (%)	1 (10)	0 (0)	0 (0)	0 (0)	1 (3.2)	1(1.2)
LPF n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ACPR n (%)	9 (90)	25 (100)	51 (100)	55 (100)	30 (96.8)	85 (98.8)
Total analysed n (%)	10 (100)	25 (100)	51(100)	55 (100)	31(100)	86 (100)

The K-M survival analysis on the 28-day follow-up period showed survival and failure rate of 98.8% and 1.2% respectively (Table 3).

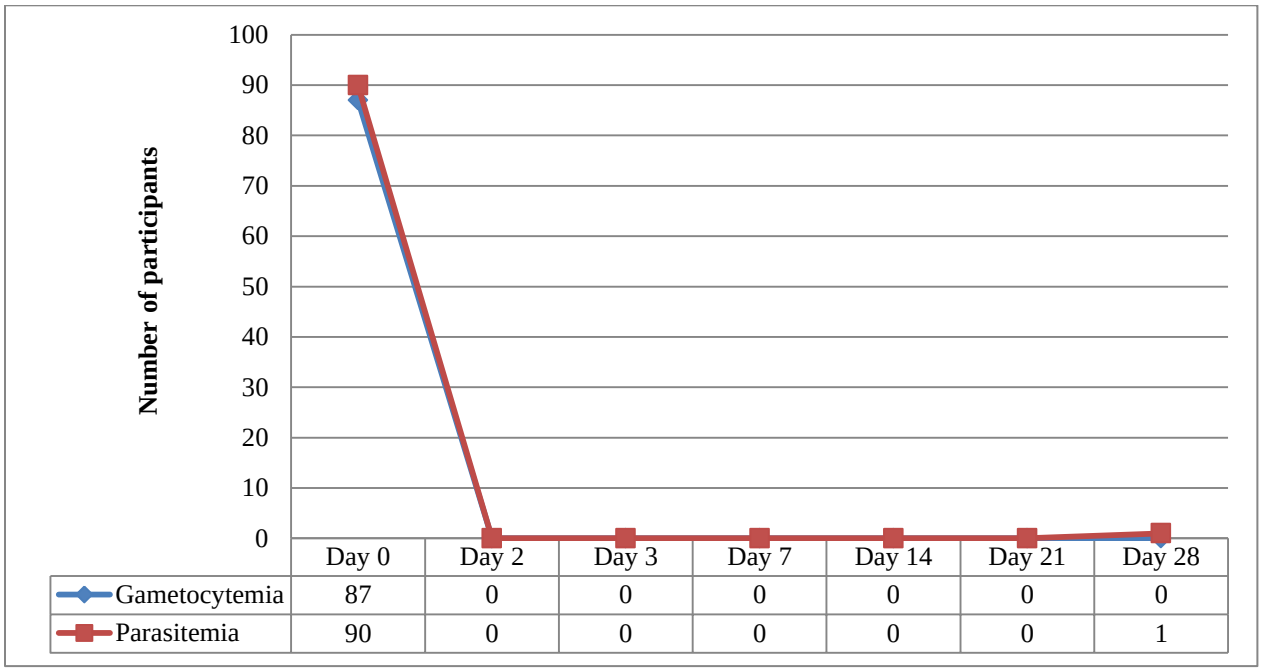
Table 4. Chloroquine treatment outcome of study participants based on K-M analysis in Shewa Robit Health Center, northeast Ethiopia from November 2020 to March 2021

Follow up days	At-Risk	Censored	Failure	Survived	K-M survival rate	K-M Failure rate
0	90	1	0	90	1	0
1	89	1	0	89	1	0
2	88	1	0	88	1	0
3	87	0	0	87	1	0
7	87	0	0	87	1	0
14	87	1	0	87	1	0
21	86	0	0	86	1	0
28	86	0	1	85	**0.988372**	**0.011628**

4.3. Secondary Outcome

4.3.1. Parasite Clearance

All asexual stages and gametocytes were cleared within 48 hrs (day 2 of the follow-up period). A 1.5 years old age female child had a late clinical failure with a parasitaemia of 1760/µl of blood on day 28. However, the parasitaemia level of the patient with treatment failure on the 28 day of infection (1760/µl) was lower than the day of admission (4560/µl), giving a parasite reduction ratio (PRR) of 2.6/µl (Figure 4).



	Day 0	Day 2	Day 3	Day 7	Day 14	Day 21	Day 28
Gametocytemia	87	0	0	0	0	0	0
Parasitemia	90	0	0	0	0	0	1

Figure 3. A pattern of parasite and gametocyte clearance following CQ treatment in Shewa Robit Health Centre, northeast Ethiopia from November 2020 to March 2021

4.3.2. Temperature Clearance

Of the 86 participants that completed the study 79 (91.9%) patients had a body temperature ≥ of 37^0C and the rest had a history of fever in the last 48hrs on day 0. However, 57 (66.3%) participants cleared the fever on days 1, 74 (86%), and 78 (90.7%) on days 2 and 3 respectively. Nearly all participants cleared the fever on day 7 (Figure 4).

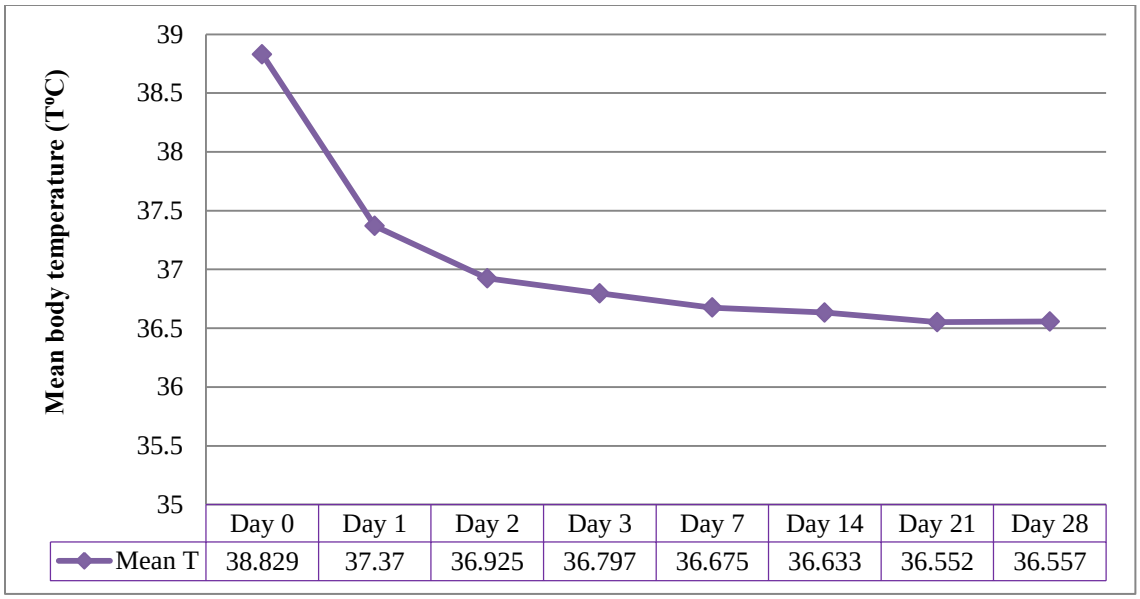


Figure 4. Mean axillary temperature on the day 0 to 28 follow up among chloroquine treated *P. vivax* infected participants in Shewa Robit Health Center, northeast Ethiopia from November 2020 to March 2021

4.3.3. Haemoglobin Determination

There was a significant recovery of haemoglobin across the days of follow-up; days 0, 13±1.8 and 14 13.3±1.5 (*P=0.032*), 0 and 28 13.7±1.5 (*P<0.001*), and 14 and 28 (*P=0.005*). On the day of recruitment (day 0), about 19.8% and 8.1% of the participants were mildly and moderately anaemic respectively. Of the total 24 mild and moderate anaemic patients only 12.5% of patients had no previous history of malaria attack and they recovered totally on day 28. The remaining 87.5% of anaemic patients had a history of repeated malaria infection and 81% of them recovered; the rest 19 % of patients couldn't show improvement in haemoglobin level even on day 28. Allover the number of anaemic patients declined from day 0 before CQ treatment 24 (27.9%) to 14 (16.3%) and 4 (4.7%) on days 14 and 28 respectively following CQ treatment (Table 4).

Table 5. Anaemia status among study participants following chloroquine treatment in Shewa Robit Health Center, northeast Ethiopia from November 2020 to March 2021

Variables			**Follow up days**		
Age			**Day 0**	**Day14**	**Day 28**
group	**<5 (n=10)**	Mean Hgb level	11.5	11.8	12.4
		Mild n (%)	2 (20)	2 (20)	0 (0)
		Moderate n (%)	1 (10)	1 (10)	2 (20)
	5-15 (n=25)	Mean Hgb level	11.9	12.6	13.1
		Mild n (%)	6 (24)	1 (4)	0 (0)
		Moderate n (%)	3 (12)	2(8)	0 (0)
	>15 (n=51)	Mean Hgb level	13.8	13.9	14.3
		Mild n (%)	9 (17.6)	7 (13.7)	1 (2)
		Moderate n (%)	3 (5.9)	1 (2)	1 (2)
Sex	**Male (n=55)**	Mean Hgb level	13.3	13.6	14
		Mild n (%)	8 (14.5)	7 (12.7)	1 (1.8)
		Moderate n (%)	4 (7.3)	1 (1.8)	1 (1.8)
	Female	Mean Hgb level	12.3	12.8	13
	(n=31)	Mild n (%)	9 (29)	3 (10)	0 (0)
		Moderate n (%)	3 (10)	3 (10)	2 (6.5)
Total		Mean Hgb (g/dl)	13	13.3	13.7
		Mild n (%)	17 (19.8)	10 (11.6)	1 (1.2)
		Moderate n (%)	7 (8.1)	4 (4.7)	3 (3.5)
		All anaemic n (%)	**24 (27.9)**	**14 (16.3)**	**4 (4.7)**
Mean difference			**Day 0 and 14**	**Day 0 and 28**	**Day14 and 28**
			P=0.003	*P<0.001*	*P=0.005*

4.3.4. Clinical Sign Symptoms and Adverse Events Following Chloroquine Treatment

One 19-year-old male patient developed recurrent vomiting, fatigue, and weakness 4 hrs after taking CQ, and was therefore excluded from the study. At baseline (before treatment) fever, headache, and vomiting were the most encountered signs/symptoms, accounting for 80.2%, and 36%, respectively. Adverse events observed following chloroquine treatment were mouth ulcers (11.6%) and blurred vision (2.3%). The number of patients with abdominal pain and cough also showed increment from the baseline (1.2% vs 9.3% & 2.3% vs 11.6%, respectively). However, all clinical symptoms and adverse events declined on day 7 and thereafter (Table 5).

Table 6. Common malaria clinical sign symptoms and adverse events following Chloroquine treatment in Shewa Robit Health Centre, northeast Ethiopia from November 2020 to March 2021

Adverse events/clinical symptoms	**Follow up days**							
	Day 0	**Day 1**	**Day 2**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**
Headache n (%)	69 (80.2)	41 (47.7)	20 (23.3)	9 (10.5)	4 (4.7)	0 (0)	0 (0)	0 (0)
Anorexia n (%)	8 (9.3)	6 (7)	6 (7)	3 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea n (%)	19 (22.1)	5 (5.8)	4 (4.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting n (%)	31 (36)	15 (17.4)	3 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain n(%)	1 (1.2)	2 (2.3)	5 (5.8)	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhoea n (%)	3 (3.5)	0 (0)	1 (1.2)	1 (1.2)	1 (1.2)	0 (0)	0 (0)	0 (0)
Cough n (%)	2 (2.3)	3 (3.5)	4 (4.7)	3 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)
Behavioral change n (%)	6 (7)	1 (1.2)	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness n (%)	2 (2.3)	1 (1.2)	2 (2.3)	3 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)
Mouth ulcer n (%)	0 (0)	2 (2.3)	3 (3.5)	4 (4.5)	1(10.2)	0 (0)	0 (0)	0 (0)
Blurred vision n (%)	0(0)	0 (0)	1 (1.2)	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)

5. DISCUSSION

Antimalaria drug resistance has been a major concern in malaria prevention, control, and management. In Ethiopia, chloroquine (CQ) has been extensively used as a first-line drug for the treatment of uncomplicated *P.vivax* since the drug is cheap and effective. However, some recent data showed that CQ resistance has been reported in different areas of the country (Teka *et al*., 2008; Ketema *et al.*, 2011; Seifu *et al.*, 2017), and elsewhere (Awab *et al.*, 2017).

The adequate clinical and parasitological response of the present standard treatment of CQ at the end of the 28 follow-up days showed a therapeutic efficacy of 98.8% (95% CI: 95.3%-100%) in the present study. It is consistent with findings from different parts of Ethiopia; Hossana, 96.7% (Assefa *et al.*, 2015), Metekel, 97.3% (Beyene *et al*.,2016), Jimma, 97.3% (Kanche *et al.*,2016), Wolkite, 97.5% (Shumbej *et al*, 2019), and elsewhere 99.5% (Shafiqullah, 2017).

Treatment failure was observed on day 28 1.2% (95% CI: 0.0%-4.7%) in this study. A load of parasitaemia on the day of recurrence (1760/µl) was lower than the day of admission (4560/µl) parasite reduction ratio (PRR) of treatment failure case was 2.6/µl, which is similar to the study carried out in different areas of Ethiopia (Ketema *et al.*, 2011; Seifu *et al.*, 2017; Shumbej *et al*, 2019).

Contrary to the current finding, higher treatment failure of CQ was found in some areas of Ethiopia including the same study site 6.6% (7 years ago) (Seifu *et al.*, 2017), Halaba district, 13% (Ketema *et al.*, 2011), Debrezeit and Nazareth towns, 7.5% (Yohannes *et al.*, 2011), Southern Ethiopia, 9.4% (Getachew *et al.*, 2015), and elsewhere Madagascar 5.1% (Barnadas *et al.*, 2008). Variation in the efficacy of CQ might be due to recurrent parasitaemia, malabsorption, and other patient/drug-related factors,(not all treatment failure is due to drug resistance) (Bloland and WHO, 2001). Complementary laboratory tests such as measurement of CQ and Desethylchloroquine (DCQ) concentration levels in blood and genotyping would be helpful.

In the present study a child was reported to have treatment failure. agreement with earlier studies in the country (Ketema *et al.*, 2009; Beyene *et al.*,2016; Seifu *et al.*, 2017) and Madagascar (Barnadas *et al.*, 2008), in which the majority of treatment failures was children, However,

previous studies in Ethiopia couldn't demonstrate a significant association of age with treatment failure (Kanche *et al*, 2016; Shumbej *et al.*, 2019).

There was a significant reduction and rapid clearance of parasite density in the study participants after two days of CQ administration. This could be a strong host defense response post-treatment of CQ, the efficacy of CQ to cure *P.vivax* (White, 2017), and rapidly and completely absorbance of CQ in the gastrointestinal tract after oral administration (Ducharme and Farinotti, 1996).

The quick parasite clearance results in a subsequent relief of fever and other malaria symptoms. Fever clearance time is one of the crude methods to assess the therapeutic efficacy of chloroquine in the treatment of *P.vivax*. In the present study, 91.9% of patients had fever at starting day, as malaria fever is elevated due to the cyclical release of merozoite and malaria toxins during schizont rupture of red blood cells, which induce endogenous pyrogens (Romanovsky *et al.*, 2005). After CQ treatment, more than 90 % of the participants cleared fever within 3 days follow up period. A very recent study showed similar fever clearance (Yeshanew *et al.*, 2021). This rapid clearance of fever could be due to the anti-pyrogenic effect of CQ (Jang *et al.*, 2006) in addition to inhibition of malaria hemozoin crystal formations (Slater, 1993).

Age and parasitaemia were negatively correlated in our study; parasite load was higher in children than adults. These findings are similar to the previous study in Serbo (Ketema *et al.*, 2011), and Shewa Robit (Seifu *et al.*, 2017). This might be partially explained by the fact that previous exposure to *P.vivax* infection leads to partial immunity and subsequent reduction in parasite density in adults (White, 2017). The other reason might be young children produce a lower concentration of pro-erythropoietin cytokine in response to the inflammatory process (Nussenblatt *et al*., 2001) and have low expression of complement regulatory protein on their red blood cells (Waitumbi *et al*., 2004). These age-related factors make it more likely that malaria in children might lead to more parasitaemia and severe clinical course.

The total mean haemoglobin level of the study participants was improved significantly, similar to the study conducted in Wolkite (Shumbej *et al.*, 2019) which was improved from 11.8 g/dl days 0 to 13.8 g/dl on day 28 and elsewhere12.5g/dl to 13.2g/dl (Shafiqullah, 2017).

Destruction of infected red blood cells (RBCs) and removal of high number of uninfected RBC results in malaria-related anaemia (Collins *et al.*, 2003). In the present study, there was no severe anaemia recorded. Finding in Wolkite showed a similar result (Shumbej *et al.*, 2019). The possible mechanism involved in severe malaria anaemia is a cumulative loss of RBCs due to mixed infection, lysis of uninfected RBCs in the circulation, and impaired RBC production (Anstey *et al* 2009; Fendel *et al*., 2010).

In the present study, the majority of mild and moderately anaemic patients who had a previous history of malaria and those all anaemic patients who had no previous history of malaria attack recovered on day 28; the rest few anaemic patients who had a history of repeated malaria infection couldn't show improvement in haemoglobin level even on day 28. Selvam and Baskaran showed that repeated malaria infection and relapse can lead to impairment of haemoglobin level (Selvam and Baskaran, 1996).

Chloroquine can cause side effects or intensify symptoms already present such as fever, headache, anorexia, nausea, vomiting, abdominal pain, diarrhoea, cough, behavioural change, and dizziness (WHO, 2015). In the current study, most of the observed adverse events were similar to the common symptoms of malaria mentioned above and disappeared following treatment within 7 days. But the frequency of some adverse events such as abdominal pain and cough increase following CQ treatment. A similar result was reported by Martins and colleagues in Brazil (Martins *et al.*, 2017). Mouth ulcers and blurred visions were also observed after CQ treatment in this study. However, the proportion of blurred vision observed in this finding is much lower 2/86(2.3%) as compared to 27/50 (54%) patients from Brazil (Martins *et al.*, 2017).

There were no severe adverse events observed in the study. Only a patient developed hypersensitivity after 4 hrs of CQ (100mg) treatment, and encounter vomiting on the first day of treatment. He was referred to a nearby hospital, diagnosed with dyspepsia, and treated with cimetidine 400 mg IV, Artusinate 120 mg IV at 0, 12, and 24 hrs for 05 days with other treatment and maintenance fluid. He was finally recovered from malaria and other complications.

6. CONCLUSION

The present study revealed that the cure rate of CQ remains high for the treatment of *P.vivax* with rapid clearance of parasitaemia and fever; haemoglobin improvement and good clinical resolution. There is no severe adverse event recorded during the follow-up period. Our study result supports the current use of CQ for the treatment of uncomplicated *P. vivax* by the national and regional malaria elimination program.

7. RECOMMENDATION

Based on our findings, we commend that CQ should continue as a first-line drug in the treatment of uncomplicated *P.vivax* in the study area. Large-scale continuous and strong surveillance of therapeutic efficacy studies on CQ is needed for early detection and effective control of measures on the possible emergence and spread of drug resistance in the study area and the country at large.

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9. ANNEXES

Annexe I: Patient screening form

1	Patient aged 6 months and over	Yes:□	No:□
2	The patient has severe malnutrition	Yes:□	No:□
3.	The patient has mono-infection with *P.vivax*	Yes:□	No:□
4.	Bodyweight 5 kg or more	Yes:□	No: □
5.	Patient with fever or history of fever in the previous 24 hours	Yes: □	No:□
6.	Non-pregnant or breast-feeding female	Yes:□	No:□
7.	Residents living within 10 km radius of the health centre	Yes:□	No:□
8.	12. Evidence of concomitant febrile illness f "YES", indicate illness. If "NO", leave blank. Pneumonia/RTI □ Measles□ Otitis Media □ UTI □ Gastroenteritis □ Other: □	Yes:□	No: □
9.	Evidence of severe malaria/danger signs If "YES" indicates criteria. If "NO", leave blank □Unarousable coma (if after convulsion, > 30 min) □Repeated convulsions (> 2 within 24 h) □Recent convulsions (1-2 within 24 h) □Altered consciousness (confusion, delirium, coma) □Lethargy □Unable to drink or breastfeed □Vomiting everything □Unable to stand/sit due to weakness	Yes:□	No:□

Annexe II: Enrollment form

Age……..	Gender/Male……Female……	Weight……
1. Study Number:--------	2. Number of tablets--------	3. Start Date ----------
4. Patients Full name:		
5. Family head:		
6. Mother's/Wife's (if married) name:		
7. Caregiver's name and relationship:		
8.Kebele/Street:		
9. Home parish:		
10. LC1/village:		
11. Home address and localizing features/Owners name/Direction:		
Phone number (s) and the owner(s):		
12. Previous malaria attack: Yes _____No _____ 13. Previous antimalarial intake: Yes _____No _____ If yes, CQ____SP____ AL? 14. Hold Bed net: Yes ___No If yes, Bed net use Yes ____ No ___-____ _____		

Annex III: Case screening form

Case screening form	
Health centre name Locality District Province	Study number ---------- Patient screening number ---------- Date of visit ----------
Demographic data	
Age ---------- in a month---------- in a year---------- Height ---------- Sex ---------- If the female is the patient pregnant? Yes ---------- No--------- If pregnant, provide the date of the last menstrual period ----------	
Pre-treatment temperature	
History of fever in previous 24 hr? Yes ---------- No ---------- Temperature ------ ^{0}C axillary----------	
Thick and thin blood smear for estimation of *p.vivax* parasite counts	
Species: *P.falciparum*------- *P.vivax*---------- Were species other than *P.vivax* present? Yes --------- No ---------- (if yes, the patient is not eligible) An approximate number of *P.vivax* asexual parasites: Presence of 1-100 parasites / 3-6 white blood cells? Yes-------- No ----------(if no, the patient is not eligible) Presence of *P. vivax* gametocytes? Yes ---------- No ---------- Has a blood sample for PCR been collected? Yes ------- No --------- Haemoglobin ----------g/dl Haematocrit ----------%	
Urinary analysis (pregnancy test for female patients)	
Result of pregnancy test: Positive ---------- Negative --------- (If positive, the patient is not eligible)	
Does the patient meet any of the exclusion criteria? Yes -------- No -------- (If yes, the patient is not eligible)	
If Yes, please specify the reason for exclusion:	
Patient informed consent and assent	
Consent form signed Yes --------- No ------- Assent form signed Yes ---------- No -------	Patient identity number ---------- Date ----------

Annexe IV: Case Record Form

PIN…… No. of Tablets ……. Name……

Follow up day	**0**	**1**	**2**	**3**	**7**	**14**	**21**	**28**	**Extra day**
Date									
Successes of treatment *	1 ------	2 ------	3 -----						
Axillary T^0									
Parasite asexual									
Gametocyte count									
Haemoglobin									
Adverse event **									
Concomitant treatment									
Reason for withdrawal									
Remarks									
Completed by (initials0									

*1. Observed by the health professional and successfully took medication

**1) Headache 2) Anorexia 3) Nausea 4) Vomiting 5) Abdominal pain 6) Diarrhea 7) Cough 8) Behavioral Change 9) Dizziness 11) Mouth ulcer 12) other, specify

Annexe V: Laboratory Request Form

Client details

Study participant ID _____ Study arm CQ ----------

Age---------- Sex Male -------- Female ----------

Follow-up visit

☐ Day 0 ☐ Day 1 ☐ Day 2 ☐ Day 3

☐ Day 7 ☐ Day 14 ☐ Day 21 ☐ Day 28

☐ Day 35 ☐ Day 42 ☐ Unscheduled Day

3. Laboratory tests

☐ Hgb g/dl
☐ Blood Film(P/µL)
☐ DBS
☐ HCG

☐ Urine Colour (1-10)

Requested by (Study Clinician)
Name :_____
Date :_____
Signature :_____

Performed by (Laboratoty Professional)
Name :_____
Date :_____
Signature :_____

Annex VI: Patient follow–up card

Patient Follow-up Card

Patient Identification Number: _____

Name----------

Scheduled visit day

Day	0	1	2	3	7	14	21	28
Appointment date								

Note:

Annex VII: Weight-Based Administration of Chloroquine

A total of 25mg base per kg over 3 days (10 mg base/kg on Days 1 and 2, and 5 mg base/kg on Day 3), 500 mg tablets, and 10mg/ml syrup formulations

Weight (kg)	**Day 1**	**Day 2**	**Day 3**
5–6	¼ tablet (5 ml syrup)	⅛ tablet (5 ml syrup)	⅛ tablet (2.5 ml syrup)
7–10	¼ tablet (7.5 ml syrup)	¼ tablet (7.5 ml syrup)	¼tablet (5 ml syrup)
11–14	½ tablet (12.5 ml syrup)	½ tablet (12.5 ml syrup)	¼ tablet (7.5 ml syrup)
15–18	½ tablet (15 ml syrup)	½ tablet (15 ml syrup)	½ tablet (15 ml syrup)
19–24	¾ tablet (20 ml syrup)	¾ tablet (20 ml syrup)	½ tablet (15 ml syrup)
25–35	1¼ tablet	1¼ tablet	½ tablet
36–50	1½ tablet	1½ tablet	1 tablet
> 50	2 tablet	2 tablet	1 tablet

Annex VIII: Medications (with anti-malarial activity) that should not be used during the study period

- Amodiaquine
- quinine, quinidine
- Mefloquine, halofantrine, lumefantrine
- Artemisinin and its derivatives (artemether, Lumefantrine arteether, artesunate, dihydroartemisinin)
- Proguanil, chlorproguanil, pyrimethamine
- Sulfadoxine, sulfalene, sulfamethoxazole, dapsone
- Primaquine
- Atovaquone
- Antibiotics: tetracycline*, doxycycline, erythromycin, azithromycin, clindamycin, rifampicin, trimethoprim
- Pentamidine

*Tetracycline eye ointments can be used

Annexe IV: Series adverse event form

Series adverse event report form	
Health centre name:---------- Locality:---------- District:---------- Province:----------	Study number:---------- Patient identity number:---------- Date of visit (dd-mmm-yyyy): ---------- Follow-up day:----------
Demographic data	
Date of birth (dd-mmm-yyyy): or estimated age:------ in months---------- or years---------- Height (cm): Weight (kg): Sex: Male----- Female--------- If female, is the patient pregnant? Yes------ No -------- Not sure--------- If pregnant, provide the date of the last menstrual period (dd-mmm-yyyy):----------	
Series adverse events	
Type of event: Death Life-threatening Hospitalization or prolongation of hospitalization Permanent disability Congenital anomaly or birth defect Date of occurrence (dd-mmm-yyyy):	
Describe the serious adverse event (include all relevant laboratory results):	

Describe how the reaction was treated:

Serious adverse event report form

Comments (e.g. relevant medical history, drug allergies, previous exposure to similar drugs, other laboratory data,
whether reaction abated after stopping the drug, whether reaction reappeared after reintroduction):

Outcome

Recovered completely ------
Not yet recovered -------
Recovered with long-term consequences-----
If the patient recovered, provide date of recovery (dd-mmm-yyyy):----------

Medicines (list the medicine suspected of causing the serious adverse event as well as all concomitant medicines)

Brand name, batch number, manufacturer name (list suspected medicine first)	Daily dose	Route	Start date	End date	Indications for use

Reporting officer

Name:
Qualification:
Address:
Phone:
Fax:
Email:
Signature: ----------Date:----------

Annex X: Standard Operating Procedures for Blood Film Preparation, Staining, and Examination

1. Explain the procedure to the patient and gain informed consent
2. Label pre-cleaned slides (preferably frosted-end) with the patient ID number
3. Clean the lobe of the finger using cotton moistened with 70% alcohol
4. Using a sterile lancet, prick the finger and Wipe away the first drop of blood with clean gauze
5. Add a 2uL of blood to the centre of the slide /for thin-film/ and a 6uL of blood for the thick film to the nearest of the frosted adage
6. Immediately spread the thin film using a smooth-edged slide spreader and spread the large drop of blood using the corner of another slide circular pattern to make a one-centimetre diameter thick smear
7. Allow the blood to air-dry with the slide in a horizontal position and place in a safe place.
8. Apply a small drop of absolute methanol for fixing thin film, making sure the methanol doesn't touch the thick film
9. Gently pour 3% or 10% Giemsa working solution in the staining jar
10. Put the slides in a rack inside the staining jar; the slides should be fully submerged /covered with the stain
11. Stain for 30-45 minutes and 10-15minutes for 3% and 10% Giemsa working solutions, respectively
12. Pour clean water gently into the jar to float off the iridescent scum on the surface of the stain. Alternatively, gently immerse the whole jar in a vessel filled with clean water
13. Gently pour the remaining stain, and rinse slides again in clean water for a few seconds. Pour water off
14. Wipe the back of each slide with paper towels
15. Dray the slides in a vertical position with the thin film downwards
16. Place the stained slid on the microscope stage, switch on the light and adjust the light source optimally by looking through the ocular and the 40x objective.
17. Place the drop of immersion oil on the dray-stained slide. To avoid cross-contamination, ensure that the immersion applicator never touches the slide

18. Slowly change to the oil immersion objective, and a thin film of oil will form between the slide and the lenses
19. Adjust the light source optimally by looking through the 10x ocular (eyepiece) and the 100x objective and use the fine adjustment knob to focus the lens should not be allowed to touch the slide
20. Examine the slide in a systematic fashion. Start at the left end of the thick film and begin reading at the periphery of the ground and finish at the other end. When the field is read, move the slide right to examine adjacent fields
21. Scan the thick film under oil immersion objective (100x) and ascertain whether a smear is positive or negative
22. Use the WHO bench job aids in the diagnosis of Plasmodium infections
23. If positive, determine all species and stages present in the slide
24. Read a minimum of 100 oil immersion fields before declaring a slide negative. If time permits, scan the whole thick film
25. When species is doubtful on the thick film or mixed infections are suspected, a careful examination of the parasite morphology should continue on the thin smear for verification
26. Select a part of the thick film, under oil immersion objective, where the white cells are evenly distributed and the parasites are well stained
27. Using tally counter, count parasites while simultaneously counting WBCs in each field covered
28. Count asexual parasites on the thick film against 200 or 500 WBCs
29. Stop counting after counting 200 WBCs if the asexual parasites counted are reached 150
30. Continue counting up to 500 WBCs if parasites are less than 10 after 200 WBCs have been counted
31. All parasites in the final field must be counted even if a count of 200 or 500 WBCs have been exceeded. Record actual number of parasites and WBCs counted.
32. Compute for the number of parasites/ul of blood using the formula:

$$\text{Parasite density (per µl)} = \frac{\text{number of parasites count} \times 8000}{\text{Number of leukocytes counted}}$$

Annexe XI: Standard Operating Procedures for Measuring Haemoglobin from Capillary Blood

Principle of the Method and Procedure

The micro cuvette serves both as a pipette and as a measuring cuvette and is for single-use only. A blood sample of approximately 10 µL is drawn into the cavity by capillary action. Measurement takes place in the analyzer, which measures the absorbance of whole blood. Analyzer measures transmittance at two wavelengths to compensate for turbidity. The haemoglobin level is calculated and presented. The system is factory calibrated against the international reference method for haemoglobin determination.

Always wear protective gloves. Handle blood with care, as it may be infectious. Follow local safety procedures for disposal of used micro cuvettes.

1. Make sure that the patient's/blood donor's hand is warm and relaxed. Use the middle or ring finger for sampling. Avoid fingers with rings on.
2. Clean fingertip with disinfectant and allow drying.
3. Using your thumb, lightly press the finger from the top of the knuckle towards the fingertip to stimulate blood flow.
4. Sample at the side of the fingertip for best blood flow and comfort.
5. Press lightly towards the fingertip and puncture using a lancet.
6. Wipe away the first 2 or 3 drops of blood. Press lightly towards the fingertip until another drop of blood appears.
7. When the blood drop is large enough, fill the micro cuvette in one step (approximately 10µl). Do not refill. If a second sample is to be taken, this must be done after the measurement of the first sample is complete. Do not let more than 40 seconds pass between step 7 (filling) and step 9 (starting the measurement).
8. Wipe off the specimen from the outside of the micro cuvette; make sure no specimen is drawn out from the open end. Visually inspect the micro cuvette. If the micro cuvette is not filled with blood, or if there are air bubbles, discard and fill a new micro cuvette. Small bubbles around the edges can be ignored.

9. Place the micro cuvette in the cuvette holder and start measurement by gently sliding the cuvette holder to the Measuring position
10. Whilst measuring will be displayed after ≤3 seconds, the hemoglobin value is displayed. The result is displayed as long as the cuvette holder is in measuring position.
11. Discard the micro cuvette after measurement. Micro cuvettes are for single use only. If needed, repeat the measurement with a new micro cuvette. If not in use, an analyser operated on batteries will automatically turn off after 5 minutes.

Annex XII: Consent/Assent Form

Informed consent form (for adult consent and parental permission for child six years and under), and assent form (for child 7-17 years), for enrolment for malaria in the Vivo efficacy study

Contact Person:

Habtamu Belay, Bahir Dar University

Bahir Dar, Ethiopia

Mobile: + 251912242624

Participation Duration: 28 days

Anticipated Number of Subjects: 90 *(Participation is Voluntary)*

Purpose

The purpose of this research study is to find out how well the treatment for malaria is working in Ethiopia. This will help us to treat malaria better in the future. We are asking you to be part of this study because you have malaria. This study is supported by the Ministry of Health (MOH) and the Ethiopia Public Health Institute (EPHI).

The study aims to evaluate the efficacy of CQ and CQ as common treatments of malaria in Ethiopia. The study results will help the country to better manage and treat diseases caused by malaria.

Risks

There may be risks or discomforts if you take part in this study.
The drugs can cause an upset stomach, vomiting, diarrhoea, headache, dizziness, mild skin rash, and itching. But these are mostly mild and soon go away.

Benefits

You may or may not get personal (direct) benefit from taking part in this study but you will not get paid for participating in the study.

There are possible benefits of taking part in this study which follow:
You will not have to pay fees for any of the clinic visits during this study including any visits for other illnesses during the 28 days of follow-up. You or your child will be closely followed for the next 28 days to see how well the drugs are working.

There will be someone here at the clinic every day. You may come for a visit at any time if you feel that you are ill, even on nights or weekends or in-between visits.

This study will also help Ethiopia learn which drugs work best in this region. This may help you or someone you know in the future.

Injuries

Staff members will assist you in obtaining medical treatment, including emergency treatment, hospital care, and follow-up care as needed. Any hospital stay which occurs during the 28 day follow-up period will be paid for.

You do not give up any of your legal rights by signing this consent form.

Compensation

You will receive 100 Ethiopian Birr for each visit to pay for your travel to the clinic

Participation

Taking part in this study is your choice. You can decide not to take part in or stop being in the study at any time. Your choice will not affect the treatment you receive for malaria. Also, none of the treatments you receive will be affected. You may leave the study at any time. This will not affect your health care, and you will still receive malaria treatment for free.

If a staff member needs to take you out of the study for any valid reason, then we will not continue to follow you. If you are removed from the study before the treatment is complete, or if the medicine did not make you better, then you will be referred to the clinic and treated with another treatment as noted in Ethiopia malaria treatment guidelines.

Statement of Consent

By signing or placing my thumbprint below, I am saying that:

I have read this form, or it has been read to me; I have been able to ask questions about it, and my questions have been answered.

For adults: I understand that my or my child's participation is voluntary and that I can leave the study at any time without it affecting my care.

For a child aged 7-17 years: I understand that my participation is voluntary and that I can leave the study at any time without it affecting my care. My decision to participate is supported by my parent/ guardian but not forced by him/her.

For a child aged 7-11 years: Read the assent addendum below.
I agree to enter this study. I agree to report any unexpected or unusual symptoms.
I have received a copy of this form.
Signing this form does not waive any of my legal rights.
Person Obtaining Consent/Assent
Name of participant _____ Signature _____ Date _____
Witness: I confirm that the participant has given consent freely
Name of witness _____ Signature _____ Date _____
Name of investigator _____ Signature _____ Date _____

የታካሚዎች ስምምነት ቅፅ

የጥናቱ መሪ ስም- ሀብታሙ በላይ

ባህርዳር ዩኒቨርስቲ

ባህርዳር ኢትዮጰያ

ስልክ +251912242624

በጤና ባለሙያ በተደረገሎት የጤና ምርመራ የወባ በሽታ ታማሚ መሆንዎ የተረጋገጠ ሲሆን በዚህም ምክንያት በኢትዮጵያ የጤና ጥበቃ ሚኒስቴር እውቅና ያለውን የወባ መድሀኒት መዉሰድ ያለብዎት መሆኑ ይታወቃል። በዚህ ጥናት ላይ እንዲሳተፉ በከፍተኛ ደረጃ እያበረታታን መሳተፍ የማይፈልጉ ከሆነ ዉሳኔዎትን የምናከብር ሲሆን መድሃኒቱን በነፃ የምናቀርብ መሆኑን እንገልፃለን።

ይህ ጥናት በመደበኛ ሁኔታ በየአመቱ በኢትዮጵያ የጤና ጥበቃ ሚኒስቴር ስር የሚካሔድ ሲሆን ለወባ በሽታ አገልግሎት ላይ የሚውሉ መድኒቶች ያላቸዉን ውጤታማነት ለማጥናት የሚረዳ ነው። ከላይ እንደተገለጸው በዚህ ጥናት ላይ እንዲሳተፉ በከፍተኛ ደረጃ የምናበረታታ ሲሆን በጥናቱ መሳተፍዎ መድሃኒቱ በበሽታው ላይ ያለዉን ዉጤት ለመረዳት ትልቅ አስተዋፅዎ ያደርግልናል።

በዚህ ጥናት ላይ ስድስት ወርና ከዚያ በላይ የሆኑ የወባ በሽታ ታማሚዎችን እንዲሳተፉ እንጋብዛለን።በዚህ ጥናት ላይ ለመሳተፍ ከተስማሙ ለሶስት ቀናት የወባ መድሀኒት እንክብሎችን ይወስዳሉ። ይህ ጥናቱ ላይ ባይሳተፉም ከሚሰጥዎት ጋር ተመሳሳይ ነው። መድሀኒቱ በጤና ተቋም ውስጥ በጤና ባለሙያ የሚሰጥ ይሆናል።ጥናቱ ለ28 ቀናት የሚቆይ ሲሆን ወደ ጤና ተቋም መምጣት ባለብዎት ቀናት ቀን 1፣2፣3፣7፣14፣21፣እና $28^{ተኛ}$ ቀናት በጤና ተቋም ውስጥ መገኘት አለብዎት።በተጨማሪም የህመም ስሜት ካለዎት፣አዲስ የበሽታ ምልክት ካዩ እና ካልተሻሎት ወደ ጤና ተቋም መምጣት አለብዎት።ለክትትል ወደ ጤና ተቋም ሲመጡ የትራንስፖርት ወጪዎት የሚሸፈን ሲሆን በየጊዜዉም ከጣት ላይ የደም ናሙና የሚወሰድ ይሆናል።

የወባ መድሀኒት የጎንዮሽ ጉዳት ሊኖረው ይችላል፤ነገር ግን የቅርብ ክትትል የሚደገረ ይሆናል።ታማሚው በክትትሉ ወቅት ከባድ የጤና ችግር ካጋጠመው እስከሚሻላቸው ድረስ ከጥናቱ ነጻ ይደረጋል።በጥናቱ ወቅት በሚደረጉ ማንኛውም ውሳኔዎች ላይ የጤና ባለሙያው ሙሉ ሀላፊነቱን ይወስዳል።

በዚህ ጥናት ላይ ያለዎት ተሳትፎ በእርስዎ ሙሉ በጎ ፈቃደኝነት ላይ የተመሰረተ ሲሆን በጥናቱ ላይ አለመሳተፍም ሆነ በማንኛውም ሰዓት ማቋረጥ የሚችሉ ሲሆን በጥናቱ ላይ ባለመሳተፍም ወይም በማቋረጥዎ ከጤና ተቋም የሚያገኙትን መደበኛ አገልግሎት በመደበኛው መቀጠል ይችላሉ።

በዚህ ጥናት ላይ መሳተፍ ከወሰኑ ስምዎት የማይጠቀስ ሲሆን ማንኛውም የሚሰጡት መረጃ በሚስጥር የሚያዝ ይሆናል።

የተጻፈውን ነገር ተረደተዋል? ማንኛውም ጥያቄ ካለዎት መጠየቅ ይችላሉ።

ጥናቱን የተመለከተዉን መረጃ አንብቤ/በቋንቋዬ ተነቦልኝ፣ ይዘቱን በዉል ተገንዝቤ መረጃዉን ካነበብኩ/ከተነበበልኝ በኋዋላ ያልገባኝን ነገር ካለ ጠይቄና ተረድቼ በጥናቱ ለመሳተፍ በፈቃዴ ተስማምቻለሁ።

ለወላጆች ፡ የኔ ወይም የልጄ በጥናቱ መሳተፍ ሙሉ ለሙሉ በፈቃደኝነት የተመሰረተ በመሆኑ በማንኛውም ሰአት ከጥናቱ መውጣት እንደምችል ተረድቻለሁ።

ከ 12_17 አመት ላሉ ታዳጊዎች፡ በጥናቱ መሳተፍ ሙሉ በሙሉ በፈቃደኝነት የተመሰረተ በመሆኑ በማንኛውም ሰአት ከጥናቱ መውጣት እንደምችል ተረድቻለሁ። ይህም በወላጆቼ የተደገፈ ነው

ተሳታፊ ለመሆን ተስማምቼያለሁ እንዲሁም ያልተለመደ ምልክት ባይ አሳውቃለሁ።

የዚህን ኮፒ የተቀበልኩ ሲሆን ይህንን በመፈረሜ የትኛውም ሀጋዊ መብቴ ላይ ችግር እንደማያስከትል ተረድቻለሁ።

ስምምነቱን የሚያስሞላው ባለሙያ

ስም፡----------ፊርማ----------

ቀን----------

የተሳታፊው ስምምነት

ስም፡----------ፊርማ----------

ቀን----------

ከ 12-17 አመት ላሉ ስምምነት

ስም፡----------ፊርማ----------

ቀን----------