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Primaquine in African Children: PAC study

Submission date
17/03/2017

Recruitment status
No longer recruiting

Registration date
09/05/2017

Overall study status
Completed

Last Edited
20/10/2025

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Malaria is a disease that is spread by mosquito bites. It causes flu-like symptoms but can also cause serious illness and death. Malaria is a major problem in tropical areas like Africa. Research has shown that a drug called primaquine can reduce the malaria offspring in mosquitos which can then reduce malaria transmission. However, primaquine has a major disadvantage as it changes to act like bleach in the body. This is problematic to people who have naturally weak red blood cells and are lacking an enzyme that makes the chemicals that counteract bleach and drug metabolites called glucose 6 phosphate dehydrogenase (G6PD). The less G6PD in the red cells, the more damaging primaquine's is. It can cause red cells may burst open (haemolysis) which creates many health problems. Many malaria control programmes are unwilling to use primaquine because they think it is too dangerous and they cannot afford the cost, training or equipment to test for G6PD levels. Although the World Health Organisation (WHO) recommends using low dose primaquine even in malaria patients with G6PD deficiency, primaquine is not being used due to a lack of research, concerns about tests for G6PD and issues providing the medication to children. The aim of this study is to provide evidence that a low dose of primaquine is safe in G6PD deficient kids in order to reduce malaria rates and benefit communities.

Who can participate?
Children aged six months to 11 years old who have malaria.

What does the study involve?
Participants are allocated to one of two groups. Those in the first group have a deficiency in G6PD and those in the second group have normal G6PD levels. Participants in each group are then randomly allocated to one of four dosing treatments which include primaquine and combination treatments and two placebo primaquine treatment. The doses vary with each participant’s age and weight and are given daily for three days. The placebo group only receives the medication once. Participants are followed up for 42 days to measure their iron deficiency level in their blood.

What are the possible benefits and risks of participating?
Participants may benefit from knowing the status of their G6PD levels and from receiving information and counseling. There are risks with primaquine as it can cause anaemia (low blood iron).

Where is the study run from?
1. Kinshasa Mahidol Oxford Tropical Medicine Research Unit (Democratic Republic of Congo)
2. The Mbale Regional Referral Hospital (Uganda)

When is the study starting and how long is it expected to run for?
Feburary 2017 to November 2020

Who is funding the study?
DFID/MRC/Wellcome Trust (UK), grant reference number: MR/P006973/1

Who is the main contact?
Dr Bob Taylor

Contact information

Type(s)
Public

Contact name
Dr Bob Taylor

Contact details
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Additional identifiers

Protocol serial number
BAKMAL1606, 106698/Z/14/Z

Study information

Scientific Title
Assessing the tolerability and safety of single low dose primaquine in African children with acute uncomplicated falciparum malaria and glucose 6 phosphate dehydrogenase deficiency in Africa

Acronym
PAC study

Study objectives
The aim of this study is to provide evidence for drug policy on the safety of the WHO recommended SLDPQ regimen when used under close to routine conditions to G6PDd African children with acute uncomplicated P. falciparum.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxford Tropical Research Ethics Committee, 01/03/2017, ref: 53-16

Study design
Multi-centre double-blind open randomized parallel safety trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Uncomplicated falciparum Malaria, G6PD deficiency, Single low dose primaquine (SLDPQ)

Interventions
Participants are allocated to either the G6PDd group or the G6PD normal group based on their the results of a G6PD rapid diagnostic test (RDT).

Participants are then randomly allocated as to which dosing group they receive using a computer generated randomisation list generated for each site. Treatment allocation is placed in a sealed envelope which is opened once participants receive their study number. The treatment allocation described the Artemisinin based combination treatment (ACT) to be given and the number of PQ/placebo pack.

The four dosing groups are the following:
1. Artemether Lumefantrine (AL) + single low-dose primaquine (SLDPQ)
2. Artemether Lumefantrine (AL) + single low-dose primaquine (SLDPQ) placebo
3. Dihydroartemisinin-piperaquine (DHAPP) + single low-dose primaquine (SLDPQ)
4. Dihydroartemisinin-piperaquine (DHAPP) + single low-dose primaquine (SLDPQ) placebo

The dosages for primaquine depends vary with age and the dosing for AL vary with weight (in kg). DHAPP+SLDPQ dosages are given daily for three days and vary with body weight (in kg). Those who receive the primaquine/placebo receive it once only at baseline. Follow up continues until day 42.

Intervention Type
Drug

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
Artemether, lumefantrine, dihydroartemisinin, piperaquine, primaquine

Primary outcome(s)
1. Profound anaemia (Hb concentration < 4g/dL) is measured using the HemoCue machine during the first days 21 days of follow up

2. Severe anaemia (Hb <5g/dL) with clinical features of severe malaria is measured using the HemoCue machine during the first 21 days of follow up

Key secondary outcome(s))
1. Fractional change in haemoglobin on day seven vs. baseline, measured by HemoCue® at baseline and day seven
2. Proportion of patients with a fractional change of ≥ 25% measured by HemoCue® over the follow up period of 42 days
3. Determinants of changes in HemoCue® measured haemoglobin over the follow up period of 42 days
4. G6PD genotype (hemizygous male, homo-, heterozygous female, normal) and selected G6PD variants (e.g. G6PD A- 202 mutations) are assessed by polymerase chain reaction (PCR) at baseline
5. G6PD enzyme activity is measured using a quantitative spectrophotometric method at baseline
6. Genotypes of other inherited blood disorders are assessed by polymerase chain reaction (PCR) at baseline
7. Incidence of adverse events are measured using clinical and laboratory records over the follow up period of 42 days
8. Pharmacokinetic characteristics of PQ and carboxyPQ by measuring drug concentrations at baseline and at hours one, one and a half, two, three, four, six, eight, ten, 12, 24 hours
9. Pharmacokinetic characteristics of lumefantrine and piperaquine are measured using their drug concentrations at baseline, day three, seven and 28
10. CYP 2D6 genotypes are assessed by polymerase chain reaction (PCR) at baseline
11. Asexual parasitaemia clearance time and half life are measured using malaria slide results at days one, two and three
12. Therapeutic efficacy of AL and DHAPP is measured using the WHO criteria at day 42
13. Gametocytaemia over time is measured using thick blood films at baseline and days one, two, three, seven, 14, 21, 28, 35 and 42
14. Proportion of patients with gametocytes over time is measured using those with a positive thick blood film at baseline and on days one, two, three, seven, 14, 21, 28, 35 and 42

Completion date
02/11/2020

Eligibility

Key inclusion criteria
1. Aged 6 months to 11 years old
2. Clinically uncomplicated disease
3. Fever (≥37.5ºC aural) or history of fever within the previous 72 hours
4. Positive malaria RDT (Uganda only)
5. Positive malaria slide for P. falciparum (mono or mixed infection) of any parasitaemia (Kinshasa only)
6. Informed consent provided by patient or relative/legal guardian

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
6 months

Upper age limit
11 years

Sex
All

Total final enrolment
1137

Key exclusion criteria
1. Malaria danger signs, sign(s) of severe malaria, or decompensated anaemia, including: an inability to take or retain fluids or oral medications, confusion, prostration, convulsions, respiratory distress, passing of red or cola-coloured urine (putative “blackwater fever”)
2. Severe anaemia (Hb <6 g/dL)
3. Comorbid illness that requires treatment in hospital (physician’s judgement)
4. Patients on drugs known to cause haemolysis in G6PDd e.g. dapsone, nalidixic acid
5. Known to be allergic to PQ, AL, or DHAPP
6. Previous enrolment in the current trial or current enrolment in another trial

Date of first enrolment
17/07/2017

Date of final enrolment
07/10/2019

Locations

Countries of recruitment
Congo, Democratic Republic

Uganda

Study participating centre
Kinshasa Mahidol Oxford Tropical Medicine Research Unit
The Kinshasa School of Public Health
University of Kinshasa
Avenue Tombalbaye 68-78
Kinshasa
Congo, Democratic Republic
1015

Study participating centre
The Mbale Regional Referral Hospital
Mbale Clinical Research Institute
Mbale Regional Referral & Teaching Hospital
Mbale
Uganda
209

Sponsor information

Organisation
The University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Other

Funder Name
DFID/MRC/Wellcome Trust

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		30/11/2022	05/12/2022	Yes	No
Results article		20/10/2023	20/10/2023	Yes	No
Results article		01/07/2025	02/07/2025	Yes	No

Results article	Plasma folate dynamics in Plasmodium falciparum-infected African children treated with artemisinin combination therapy and single low-dose primaquine or placebo	15/10/2025	20/10/2025	Yes	No
Other publications	Age-based dosing regimen development	18/01/2018	21/10/2021	Yes	No
Other publications	Pharmacokinetics	25/09/2023	09/06/2025	Yes	No
Participant information sheet	version V2	14/02/2017	01/06/2017	No	Yes
Participant information sheet	version V2	14/02/2017	01/06/2017	No	Yes
Protocol file	version 2	01/09/2018	22/08/2022	No	No