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Efficacy of the antimalarial drugs recommended by the National Malaria Control Programme in Madagascar

Submission date	Recruitment status
11/05/2009	No longer recruiting
Registration date	**Overall study status**
29/05/2009	Completed
Last Edited	**Condition category**
10/01/2020	Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
MDG-304-G05-M

Study information

Scientific Title
Assessment of the efficacy of antimalarial drugs recommended by the National Malaria Control Programme in Madagascar in Plasmodium falciparum and Plasmodium vivax malaria: a randomised open-label active-controlled parallel-assignment efficacy trial

Study objectives
Despite major efforts made by national and international health organisations, malaria remains the most widespread infectious parasitic diseases and one of the most serious global health problems in the world. In sub-Saharan African, the main problem is Plasmodium falciparum drug-resistance, especially with the spread of the parasite resistance to the inexpensive and widely used drugs, such as chloroquine (CQ) or sulphadoxinepyrimethamine (SP), and the major consequence is the use of ineffective antimalarial drugs leading to the increasing malarial incidence and mortality.

Therefore, substantial efforts have been made to encourage the monitoring and the evaluation of the antimalarial drugs resistance in the endemic countries for assessing regularly their antimalarial drug policies and ensuring a continued coverage of effective antimalarial treatment.

In Madagascar, since 2005, antimalarial treatment is in transition with the elaboration and the implementation of the new national policy for the fight against malaria. The main modifications in term of drugs use has been the withdrawal of CQ in favour of artemisinin combination therapies (ACTs), as first-line (artesunate plus amodiaquine combination, ASAQ) and second-line treatment (artemether plus lumefantrine combination), and the use of the SP for intermittent preventive treatment for pregnant women (IPTp). This choice was guided by the recommendations of World Health Organization (WHO) and unpublished data from a clinical trial conducted on the island of Sainte Marie in 2004, which show 36.9% of treatment failure over the 14-day follow-up period, unadjusted by genotyping. However, with regards to the home treatment of presumed malaria in children (HMM), it has been decided to continue to use pre-packaged chloroquine, either PaluStop® sold by the NGO "Population Service International" (PSI) or Ody Tazomoka® freely distributed at primary public health facilities by Malagasy Ministry of Health (Mal-MoH), as transitory measure until ACTs were available at community level. At present, the implementation of the ACTs as first-line treatment at health centres level is complete on the east coast of Madagascar, with the result that only 24% (31/131) of the health districts in Madagascar are using ACT. Since 1999, the antimalarial drug resistance surveillance system in Madagascar is supported by a national network for the surveillance of malaria resistance (named RER - Réseau d'Etude de la Résistance). The RER was formed as a collaborative effort between the MalMoH and the Malaria Research Unit of the Institut Pasteur de Madagascar (IPM). The strategy of monitoring was initially based on the use of the in vitro assessment of P. falciparum sensitivity to antimalarial drugs and the evaluation of the frequency of genetic markers associated with P. falciparum drug resistance. In vivo studies were also carried out, but these studies were limited geographically, the sample sizes were small and used only a 14-day follow-up period, a series of constraints which may have significantly underestimated the true risk of treatment failure. No data concerning the susceptibility of P. vivax to SP is available.

In order to improve the monitoring of antimalarial drug resistance in Madagascar, a new RER was set up in 2006, with the support of the Global Fund. According to the WHO recommendation, this network was based on sentinel sites located within public or private health facilities and

selected to be representative of the range of ecological and epidemiologic conditions. This multi-site randomised clinical trial aims to assess the therapeutic efficacy of antimalarial therapies recommended by the National Malaria Control Programme.

Ethics approval required
Old ethics approval format

Ethics approval(s)
National Ethics Committee of the Ministry of Health of Madagascar approved in February 2006 (ref: 007/SANPF/2007)

Study design
Randomised open-label active-controlled parallel-assignment efficacy trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Malaria (P. falciparum and P. vivax)

Interventions
P. falciparum clinical trial:
All patients aged between 6 months and 15 years were eligible to be enrolled and were screened for malaria at the primary health centres in the sentinel sites on the basis of history of febrile illness. Once written informed consent was given, patients were enrolled in the study and assigned consecutive patient numbers.

Randomisation to treatment group was performed in blocks of three or four, and treatment regimens were allocated by an independent individual, not involved in the analysis of the study. Patients were administered either CQ (10 mg/kg on days 0 and 1, and 5 mg/kg on day 2), AQ (10 mg/kg on days 0, 1, and 2), SP (25 mg/kg sulphadoxine and 1.25 mg/kg pyrimethamine as a single dose on day 0) or ASAQ (AS: 4 mg/kg on days 0, 1, and 2 and AQ:10 mg/kg on days 0, 1, and 2). Patients were directly observed for 30 minutes after treatment, and the dose was readministered if vomiting occurred. Patients who repeatedly vomited their first dose of study medication were excluded from the study. Patients were assessed on days 1, 2, 3, 7, 14, 21 and 28, and any intervening day they were unwell for malaria infection. Blood was obtained by finger prick on all follow-up days and on any unscheduled day to use for analysis of thick and thin blood smears and for storage on filter paper. Thick and thin blood slides were examined by light microscopy for parasites on any day during the 28-day follow-up. Blood slides were read by a microscopist blind to treatment allocation. All slides were controlled by a second microscopist

also blind to treatment group and previous diagnosis. Discordant slides were read, blind to treatment group and previous diagnosis, by a third microscopist. Haemoglobin was measured on Day 0 and Day 28 using a HemoCue® haemoglobinometre (HemoCue AB, Sweden).

P. vivax clinical trial:
All patients included were weighed and their medical histories (including previous antimalarial medication) recorded. Clinical examination, including axillary temperature recording and Giemsa staining of serial thick and thin blood films, was carried out on days 0, 1, 2, 3, 7, 14, 21, and 28. Thick and thin films were read by a skilled microscopist. Patients were treated with the standard CQ regimen (25 mg/kg of body weight per day for 3 days) or the standart SP regimen (25 mg/kg sulphadoxine and 1.25 mg/kg pyrimethamine as a single dose on day 0) and monitored for 28 days. Patients were directly observed for 30 min after treatment, and the dose was readministered if vomiting occurred. Patients who repeatedly vomited their first dose of study medication were excluded from the study. Blood was blotted onto filter paper during follow-up and was stored at 4°C for DNA analysis. The haemoglobin concentration was determined on days 0 and 28 (HemoCue AB, Sweden).

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
P. falciparum:
Treatment outcomes were assessed according to WHO 2003 guidelines as Early Treatment Failure (ETF; danger signs or complicated malaria or failure to adequately respond to therapy on days 0 - 3), Late Clinical Failure (LCF; danger signs or complicated malaria or fever and parasitaemia on days 4 - 28 without previously meeting criteria for ETF), Late Parasitological Failure (LPF; asymptomatic parasitaemia on days 4 - 28 without previously meeting criteria for ETF or LCF), and Adequate Clinical and Parasitological Response (ACPR; absence of parasitaemia on day 28 without previously meeting criteria for ETF, LCF, or LPF). Overall Treatment failure (OFT) was considered as the sum of the ETP, LCT and LPF. Patients classified as having suffered treatment failure were treated with quinine (10 mg/kg three times daily for seven days); however, their response to repeat therapy was not assessed.

P. vivax:
Treatment outcomes were assessed according to WHO 2001 guidelines as "treatment failure" (TF; clinical deterioration due to P. vivax illness requiring hospitalisation, with parasitaemia and an axillary temperature of greater than or equal to 37.5°C any time between days 3 and 28, or parasitaemia on any day between days 7 and 28, regardless of clinical condition) or "adequate clinical and parasitological response" (ACPR; absence of parasitaemia on day 28 without the criteria for TF having been met previously). Patients with TF were treated with artesunate (4 mg /kg on days 0, 1, and 2) plus amodiaquine (10 mg/kg on days 0, 1, and 2), but their response to rescue therapy was not assessed.

Secondary outcome measures
No secondary outcome measures

Overall study start date
01/02/2006

Completion date
31/07/2007

Eligibility

Key inclusion criteria
P. falciparum trial:
1. Both males and females, aged between six months and 15 years
2. Monoinfection with P. falciparum at a parasitaemia between 1,000 and 200,000/µl
3. Axillary temperature greater than or equal to 37.5°C
4. Body weight greater than 5 kg
5. Absence of severe malnutrition (defined as a child whose weight-for-height is below 3 standard deviations of less than 70% of the median of World Health Organization [WHO] reference values, or who has symmetrical oedema involving at least the feet)
6. Absence of febrile conditions caused by diseases other than malaria
7. Absence of 'danger signs' (inability to stand, breastfeeding or drink; recent convulsions; lethargy or persistent vomiting) and of severe and complicated malaria
8. Haemoglobin (Hb) greater than or equal to 5 g/dl
9. Informed written consent of parents/guardians
10. Ability to attend stipulated follow-up visits
11. Absence of history of hypersensitivity reactions to any of the drugs being evaluated

P. vivax trial:
1. Both males and females, aged greater than 6 months
2. Monoinfection with P. vvax at a parasitaemia above 250/µl
3. History of fever during 48 hours prior to time of recruitment
4. Ability and willingness to participate based on information given to parent or guardian and access to health facility
5. Informed consent

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Months

Upper age limit
15 Years

Sex
Both

Target number of participants
P. falciparum trial: 1,434; P. vivax trial: 120

Key exclusion criteria

P. falciparum trial:
1. Aged less than 6 or greater than 16 years
2. Severe malnutrition (defined as a child whose weight-for-height is below 3 standard deviations of less than 70% of the median of WHO reference values, or who has symmetrical oedema involving at least the feet)
3. No slide confirmed infection with P. falciparum or a mixed infection that includes a non P. falciparum species
4. Initial parasite density less than 1,000 or greater than 200,000 asexual parasites per microlitre
5. Presence of general danger signs among children less than 5 years (inability to stand, breastfeeding or drink; recent convulsions; lethargy or persistent vomiting) and of severe and complicated malaria
6. Measured axillary temperature less than 37.5 °C
7. Inability to attend stipulated follow-up visits
8. Unwilling to provide informed consent provided by parent/guardian
9. History of hypersensitivity reactions to any of the drugs being evaluated

P. vivax trial
1. Presence of clinical condition requiring hospitalisation
2. Presence of severe malnutrition
3. Pregnancy
4. Significant concomitant febrile illness which would interfere with follow-up
5. Chronic infectious diseases other than malaria (e.g., tuberculosis)
6. Known allergy and/or intolerance to drug(s) being tested

Date of first enrolment
01/02/2006

Date of final enrolment
31/07/2007

Locations

Countries of recruitment
Madagascar

Study participating centre
Institut Pasteur de Madagascar
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Sponsor information

Organisation
Ministry of Health (Madagascar)

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Sponsor type
Government

Website
http://www.sante.gov.mg

ROR
https://ror.org/05d0mtf30

Funder(s)

Funder type
Other

Funder Name
The Global Fund to Fight AIDS, Tuberculosis and Malaria (Switzerland) - Round three grant (ref: MDG-304-G05-M)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	therapeutic response results	26/02/2008		Yes	No
Results article	baseline data results	04/04/2008		Yes	No

Results article	clinical efficacy results	01/12/2008	Yes	No