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Efficacy and safety of artemether–lumefantrine for the treatment of uncomplicated falciparum malaria at sentinel sites in Mozambique, 2015

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ABSTRACT

The resistance of *Plasmodium falciparum* to anti-malarial drugs continues to challenge malaria control. We assessed the therapeutic efficacy and safety of artemether-lumefantrine (AL), the first-line treatment of uncomplicated *P. falciparum* malaria, in children under five years of age in Mozambique. We conducted a prospective one-arm study to evaluate the clinical and parasitological efficacy of AL over 28 days at four sentinel sites, using the WHO protocol for assessing the efficacy of antimalarial treatment. *msp1*, *msp2* and *glurp* genes were analysed by DNA polymerase chain reaction (PCR) to differentiate recrudescence from re-infection with malaria parasites. Haemoglobin concentration was recorded at baseline and on days 7, 14 and 28. A total of 349 children with uncomplicated falciparum malaria were recruited at the four sentinel sites. Adequate clinical and parasitological response to AL on day 28 follow-up varied from 96.3% to 100% after correction by PCR. The drug was well tolerated, and no adverse event related to the drug was reported. AL, the current first-line treatment for uncomplicated *falciparum* malaria in Mozambique, remains highly efficacious at the study sites. Monitoring of the efficacy of the recommended antimalarial drugs should be continued in order to detect any emerging threat to their efficacy.

Trial registration number: ACTRN12616001680459

1. Introduction

Despite efforts to control malaria, it is one of the main causes of morbidity and mortality around the world, with 212 million (148–304 million) cases and 429 000 (235 000–639 000) deaths of malaria, respectively, reported in 2016 (WHO, 2016a). About 88% of malaria cases were estimated to occur in the WHO African Region. Children under five years are the most frequently affected, with 2.9 million deaths in sub-Saharan Africa. Malaria is also a cause of anaemia in children in sub-Saharan Africa (Korenromp et al., 2004). According to the Ministry of Health and the National Institute of Statistics of Mozambique, in 2015, the prevalence of malaria in children under five years of age was 40%, and that of anaemia was 62% (haemoglobin, < 7 g/dL). *Plasmodium falciparum* is the main species implicated in Mozambique (Instituto Nacional de Estatística ande Ministério da Saúde, 2011).

There are effective strategies to control malaria, and case management – consisting of early diagnosis and prompt, effective treatment – is a vital component of these strategies (WHO, 2015). Resistance of *P. falciparum* to antimalarial medicines is a major obstacle to this strategy, in particular its resistance to the most inexpensive antimalarial medicines, such as chloroquine and sulfadoxine–pyrimethamine. WHO (2001) therefore recommended the use of artemisinin-based combination therapy (ACT) for the treatment of uncomplicated falciparum malaria in countries in which malaria is endemic. Unfortunately, resistance to artemisinins and failure of ACT treatment have been reported in South-East Asia (Dondorp et al., 2009; Leang et al., 2015).

Mozambique adopted ACT for treatment of uncomplicated malaria

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Fig. 1. Map of Mozambique with location of sentinel sites (●) at which the study was conducted.

in 2005, and artemether–lumefantrine (AL) has been used as first-line treatment since 2009. A study conducted in Mozambique in 2011–2012 showed a high cure rate of 96% (Nhama et al., 2014). In line with the WHO recommendation to monitor the therapeutic efficacy and safety of nationally recommended ACTs at least every two years (WHO, 2010), we conducted a study *in vivo* to assess AL for the treatment of uncomplicated *P. falciparum* malaria in children under five in Mozambique.

2. Methods

2.1. Study area

The study was conducted in four health centres in the country: the Centro de Saúde de Montepuez, in Cabo Delgado province; the Centro de Saúde de Moatize, in Tete province; the Centro de Saúde de Dondo in Sofala province and the Centro de Saúde do III Bairro Chókwe, in Gaza province (Fig. 1). All are established sentinel sites for monitoring the efficacy of antimalarial drugs. The study was conducted during the peak season for malaria transmission.

2.2. Study design and population

A one-arm prospective study was conducted between February and May 2015 with the standard WHO protocol for monitoring the therapeutic efficacy of antimalarial medicine (WHO, 2009). The participants were recruited among febrile patients attending the four health centres, with the following inclusion criteria: aged from 6 to 59 months, mono-infection with *P. falciparum* as confirmed by microscopy, parasite density of 1000–200 000 asexual forms per μL, axillary temperature ≥37.5 °C or history of fever for the previous 24 h, ability to swallow the drug and parents or guardians willing to return for the scheduled and for unscheduled visits and provide informed consent. Patients were not enrolled if they had danger signs or severe *P. falciparum* malaria as per the WHO classification: weight < 5 kg, mixed or mono-infection with other *Plasmodium* species, severe malnutrition (mid-upper arm circumference < 110 mm), other diseases such as measles, acute lower respiratory tract infection, severe diarrhoea with dehydration or other chronic diseases (e.g. cardiac, renal or hepatic disease or HIV/AIDS). They were also excluded if they were on regular medication that might interfere with the pharmacokinetics of antimalarial drugs or had a history of contraindications or hypersensitivity reactions to AL.

2.3. Recruitment and follow up

Children who met the inclusion criteria were treated with AL (Novartis, each tablet contains 20 mg artemeter and 120 mg lumefantrine) twice daily for three days, with one tablet for children weighing 5 to < 15 kg, two tablets for children weighing 15 to < 25 kg and three tablets for children weighing 25–35 kg. All doses were given under direct observation by the study team. Each patient was observed for 30 min after treatment; if the patient vomited within that time, the full dose was repeated. If vomiting persisted, the patient was given parenteral quinine, according to the national treatment policy, and was excluded from the study. The day a patient was enrolled and received the first dose of AL was considered as day 0. Each patient was given a personal identification number, and the mother or guardian was invited to return for scheduled visits on days 1, 2, 3, 7, 14, 21 and 28 or any other day if malaria symptom or an adverse event occurred. On follow-up visits, patients underwent clinical and laboratory assessments. Haemoglobin was determined with the Hemocue® apparatus on days 0, 7, 14 and 28. The procedures for blood smear staining, parasite counting, parasite density calculation and quality control of blood slide readings are described in the WHO protocol (WHO, 2009).

2.4. Outcomes

Treatment outcomes were assessed on the basis of parasitological and clinical results and were classified according to the WHO protocol as early treatment failure, late clinical failure, late parasitological failure or adequate clinical and parasitological response (WHO, 2009). The parasite positivity rate on day 3 and loss to follow-up and withdrawal rates were calculated. In order to differentiate recrudescence from re-infection, blood spots were collected on filter paper (Whatman No. 3) from day 7 onwards from participants with recurrent parasitaemia for analysis by polymerase chain reaction (PCR) at the *Centro de Investigação de Saúde da Manhiça* to genotype parasites found on day 0 and on the day of recurrence in the polymorphic variant genes *msp1*, *msp2* (merozoite surface proteins) and *glurp* (glutamate-rich protein). Recurrent parasitaemia was classified as recrudescence if it was due to the same parasite strain as that on day 0 and as a new infection if it was due to a genetically different strain. The secondary outcomes were clearance of parasitaemia and gametocytaemia and haemoglobin recovery.

2.5. Sample size calculation and statistical analysis

On the basis of an assumed efficacy estimate of 95%, a confidence level of 95%, a precision level of 5% and loss to follow-up of 20% on day 28, a minimum 88 patients was calculated for recruitment at each site.