



Recurrence of *Falciparum* Malaria under Coartem Treatment in the City of Mâncio Lima, Acre, Brazil: A Retrospective Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ARS and MSN conceived the study and designed the study protocol. Authors ARS, RAA, FMA, RN, CBB, BWBA, MNS, TMP, SASM and ACM identified recurrent events and revised data. Authors ARS and LFML wrote the manuscript under the supervision of MSN. All authors critically revised the manuscript for intellectual content. Author MSN is the guarantor of the paper. All authors read and approved the final manuscript.

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ABSTRACT

Background: Malaria remains a health problem in the Amazon and since 2005 the state of Acre has high incidence of malaria. Treatment with Coartem® for cases of *falciparum* malaria was introduced in Acre in August 2012. In Brazil, there is still no published study on the effectiveness of Coartem in endemic areas.

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Methods: This study was conducted in Mâncio Lima, Acre, in the western Brazilian Amazon region. All malaria cases notified in Mâncio Lima between August 01st, 2012 and October 31st, 2013 were revised. The therapeutic response to Coartem in Mâncio Lima, Acre, was evaluated. A recurrence of *falciparum* malaria was defined as a malaria case occurring in the same patient in a maximum interval of 40 days between the day treatments was started and the day the next diagnosis was made.

Results: All malaria cases (7,171) notified between August 2012 and July 2013 were revised. About 23.72% (n = 1,701) were *falciparum* malaria. There were six cases of recurrent *falciparum* malaria that can be classified as treatment failure. All cases had low parasitemia. The minimum and maximum interval between the first and the recurrent malaria episode was 17 days and 33 days. Age range was 9 to 50 years. Two patients were from rural areas, while all others were from riverine areas.

Conclusion: Possible failure to Coartem treatment was identified, however causes are not clear. Further studies are needed.

Keywords: Amazon; coartem; *Plasmodium falciparum*; recurrent malaria.

1. INTRODUCTION

Malaria remains a health problem in the Brazilian Amazon. Data for the year 2011 indicate that 260,356 cases of malaria were reported in the Amazon. In this year, the state of Acre accounted for 8.43% of reported cases of malaria in the Amazon (21 957 cases), and since 2005 the state of Acre has the highest Annual Parasite Index (API) of Brazil (136.6 cases / 1000 inhabitants in 2006 and 68.6 / 1000 inhabitants in 2007) [1]. In 2006, there was an increase of 362% in the number of total case notification in Acre when compared to the previous year, corresponding to an increase of 662% of cases of *P. falciparum* and an increase of 46% in hospital admissions due to malaria) [2].

The Acre region that contributed most to this increase in malaria was the Jurua Valley, where the cities of Cruzeiro do Sul, Mâncio Lima and Rodrigues Alves are located. In 2006, 42,841 malaria cases were reported in Cruzeiro do Sul, 16 125 cases in Mâncio Lima and 7894 cases in Rodrigues Alves [3]. Cases occurred in urban, rural and coastal areas. After intensive efforts to control malaria, cases decreased in 2010: There were 5,722 cases in Mâncio Lima, and only 350 were *falciparum* malaria. In 2011, there were 4850 cases of malaria and 642 cases of *P. falciparum* registered in Mâncio Lima. There was an increase in the number of cases in 2012, with 5,271 malaria cases and 858 cases of *falciparum* malaria. Another important increase in the number of malaria cases in Mâncio Lima occurred in 2013, with 7290 notifications and 2,029 cases of *falciparum* malaria, an almost six-fold increase over 2010.

The Ministry of Health introduced artemether + lumefantrine treatment (Coartem) for cases of

falciparum malaria uncomplicated in Brazil since 2006, however in the municipalities of Mâncio Lima, Cruzeiro do Sul and Rodrigues Alves this drug was adopted only in August 2012. Before that these municipalities used as first-line treatment the artesunate + mefloquine scheme.

Treatment failure of *Plasmodium falciparum* evidenced by the persistence or increase in parasitaemia, with or without symptoms [4]. The World Health Organization recommends that monitoring and definition of treatment failure for *falciparum* malaria uses a 28-day interval at minimum, but preferably for 42 days [5]. According to WHO, response to treatment can be classified as early treatment failure (briefly, presence of symptoms and parasitaemia between day 1 and 3 of treatment), late clinical failure (danger signs or severe malaria in the presence of parasitaemia between day 4 and 28 or presence of parasitaemia with fever between day 4 and 28), late parasitological failure (presence of parasitemia on any day between day 7 and 28 with axillary temperature <37.5 C) and adequate clinical response (absence of parasitaemia on day 28 (or day 42) irrespective of axillary temperature), all four criteria being exclusive.

To differentiate the cases of *falciparum* malaria recurring in the same individual between treatment failure and reinfection, WHO recommends the use of genotyping [5]. However, such molecular tool is usually available only as part of research studies and is not a feature available in all endemic areas. Therefore, the Ministry of Health of Brazil defines as therapeutic failure the presence of a positive slide for *P. falciparum* within 40 days after the start of treatment [4].

The therapeutic response to Coartem was studied in various countries in recent years, and most studies showed efficacy greater than 95% [6,7,8,9]. In Brazil, there is still no published study on the effectiveness of Coartem in endemic areas.

In this study, we evaluated the therapeutic response to Coartem in the municipality of Mâncio Lima, Acre, between 2012 and 2013.

2. MATERIALS AND METHODS

2.1 Study Area and Population

This study was conducted in Mâncio Lima, Acre, in the western Brazilian Amazon region. Mâncio Lima is 5,453 km² in area and has 16,795 inhabitants living in urban (57.3%), rural or riparian (37.9%), and indigenous (4.8%) areas [10]. The city, located 38 km from Cruzeiro do Sul and 650 km northwest of Rio Branco, borders the municipality of Cruzeiro do Sul and Rodrigues Alves to the east, Amazonas state to the north, and Peru to the west (Fig. 1). Mâncio Lima is an equatorial region surrounded by palm trees and rainforests [11]. Its monsoon season occurs from November to April, with an annual rainfall of 1,600–2,750 mm. The city's annual temperature ranges between 20°C and 32°C, and the annual relative humidity is 80–90%. In 2010, the human development index was 0.625. The economy's main sources of income are cattle-raising, fishing, and producing and selling banana and cassava products.

In 2010, there were 5,729 autochthonous malaria cases within a total population of 16,795, resulting in an incidence rate of 34.11%. About 40% of those cases occurred in the urban areas of the city. In 2013, Mâncio Lima registered 6,936 cases of malaria, of which 29.1% were *falciparum* malaria and 70.3% *vivax* malaria; only 0.6% of the cases were of mixed species [1].

2.2 Case Selection

All malaria cases notified in Mâncio Lima between August 01st, 2012 and July 31st, 2013 were revised. Due to SIVEP-Malaria system requirements, the variables were extracted in two steps: in the first step, date of notification and patient's name was obtained and names were compared. Notifications with the same patient's name or very similar names (e.g. Jose da Silva and Jose da Silva Santos) were selected for further analysis. In the second step, patient's name and address, age, mother's name, malaria species and parasitemia, treatment and date of treatment were obtained. Cases were matched again using patient's name, address, age and mother's name. Only cases that matched patient's name, mother's name and at least one more criteria (age or address) were considered to have occurred in the same patient. In situations where mother's name was missing, a match of patient's name, age and address was required in order to consider the cases to belong to the same patient. A recurrence of *falciparum* malaria was defined as a malaria case occurring in the same patient in a maximum interval of 40 days between the day treatment was started and the day the next diagnosis was made.

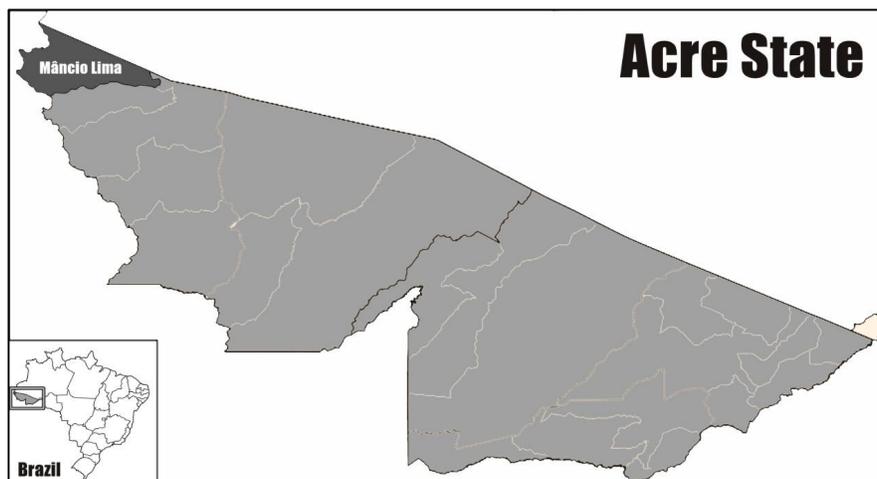


Fig. 1. Map of Brazil showing the location of the state of acre in the smaller box and the location of Mâncio lima within the state of acre in the larger box

3. RESULTS

There were 7,171 malaria cases notified between August 2012 and October 2013 in Mâncio Lima. About 23.72% (n = 1,701) were *falciparum* malaria, 75.69% were *vivax* malaria (n = 5,428) and 0.58% were mixed infection (*P. vivax* and *P. falciparum*).

There were 10 patients with two episodes of *falciparum* malaria identified in an interval of 42 days. In four of them, the initial treatment was not provided in the notification form. Therefore, they were not included in the analysis.

Table 1 shows the characteristics of six patients with *falciparum* malaria that fulfilled the Ministry of Health operational criteria for treatment failure. In one case, the initial thick smear revealed the presence of gametocytes of *P. falciparum*. All cases had low parasitemia (up to $\frac{1}{2}$ cross or the equivalent of up to 300 parasites/mm³), (Ministério da Saúde, 2010), [4] both in the initial episode as well in the second episode. Two patients presented gametocytes of *P. falciparum* in the second malaria episode. The minimum interval between the first and the second malaria episode was 17 days, and the maximum interval was 33 days. It was not possible to investigate the presence of symptoms at the time of diagnosis because not all notification forms included such information. There were five women and one man; age range was 9 to 50 years (only one child). Two patients were from rural areas, while all others were from riverine areas.

4. DISCUSSION

The efficacy of Coartem has been studied in several countries before, and a high efficacy was reported. Assefa et al. [7] performed a study about treatment failure for Coartem in Ethiopia, with 85 patients followed according to WHO guidelines (2003) for 28 days. Late clinical failure was 1.2% and late parasitological failure was 2.4% before PCR correction. After genotyping, late parasitological failure decreased to 1.2%, showing a high efficacy of Coartem four years after its introduction in Ethiopia. Nambozi et al. [12] studied AL treatment in children from Zambia, followed up to 42 days. The frequency of treatment failure at day 28 was 25.6% before genotyping correction and 6.7% after excluding new infections defined by PCR. No recrudescences were found after day 28 of follow-up. Ebstie et al. [8] also reported a 1.5 %

treatment failure (late parasitological failure) with AL in 128 children over 5 years old from Ethiopia in 2012 between the seventh and 14th day of follow-up and at the end (day 28), 98.5 % participants showed adequate clinical and parasitological response.

Data from SIVEP-Malaria shows that the number of cases of *P. falciparum* increased a lot in Mâncio Lima between 2012 and 2013 [1]. The rise in *falciparum* malaria cases started in October 2012, two months after Coartem was introduced as the first choice for treatment, and remained high until late 2013. The reasons for that are not clear: it could be an epidemic of *Falciparum* malaria occurring at the same time the drug was changed, or even reflect an inadequate drug usage for *falciparum* malaria treatment. However, if we consider that all six cases of *P. falciparum* recurrences identified in this study were recrudescences, and that all 1701 cases of *falciparum* malaria notified between 2012 and 2013 were treated with Coartem, the frequency of recrudescence would be 0.35%, much lower than reported by most of the studies in Africa and Asia.

Although the number of cases of malaria recurrence under Coartem treatment was small in Mâncio Lima, there were three distinct features: All cases were late recurrences, all of them occurred in rural or riverine areas, and all of them had an initial low parasitemia.

Late recrudescences with Artemether-Lumefantrine (AL)/ (Coartem®) are reported in the literature. Aydin-Schmidt et al. [6] investigated recurrent *P. falciparum* infections in children after artemether-lumefantrin treatment in Tanzania, between 2009 and 2010. From 53 subjects treated with Coartem and followed with PCR and RDT, one had a recurrence at day 14 of follow-up, 4 at day 21, 2 at day 28 and 3 at day 35. Therefore, all of them were late recurrences. A clinical trial performed in Cameroon, Côte d'Ivoire and Senegal [13] and another in Tanzania [14] failed to find early recrudescences when using AL as well.

While *P. falciparum* in Africa affects mainly children and usually present with high parasitemia, in Latin America both children and adults are equally infected, but parasitemia tend to be low [15,16]. So, the presence of low parasitemia among those recurrences identified in Mâncio Lima may represent only the common spectrum of the disease in this endemic setting.

Table 1. Characteristics of the 6 cases of malaria and the recurrent episodes in mânico lima, acre - Brazil, during 2012-2013

Date of 1st malaria	Sex	Age	Species of 1st malaria	Parasitemia of 1st malaria	Treatment of 1st malaria	Interval between 1st and 2nd episode	Species of 2nd malaria	Parasitemia 2nd malaria	Treatment 2st malaria	Area of notification of 1st episode
Jan 2013	M	32	F +Fg	1/2+	COARTEM	32 days	F + Fg	1/2+	COARTEM	Riverine
Oct 2013	F	17	F	1/2+	COARTEM	33 days	F	1/2+	COARTEM	Rural
Dec 2012	F	34	F	1/2+	COARTEM	17 days	F	1/2+	COARTEM	Riverine
Nov 2012	F	50	F	<1/2+	COARTEM	37 days	F	<1/2+	COARTEM	Rural
Jun 2013	F	25	F	1/2+	COARTEM	27 days	F	1/2+	COARTEM	Riverine
Dec 2012	F	09	F	1/2+	COARTEM	19 days	Fg	1/2+	COARTEM	Riverine

F= *P. falciparum* merozoites; Fg= *P. falciparum* gametocytes

A study in Zanzibar, performed between 2002 and 2003 found forty-five episodes with recurrent parasitaemia out of 200 children studied, the earliest on day 21. After molecular analysis, from 39 recurrent infections that were genotyped, 28 were classified as reinfection and 11 as recrudescences. After additional pfmsp1 analysis, only 2 out of 11 remained recrudescences, while 7 were reclassified as reinfections and 2 were considered uncertain due to negative PCR outcome with the pfmsp1 marker. The authors concluded that the path to resistance to AL may involve a marked selection of 86N/184F and 86N/1246D haplotypes and may potentially represent a further development towards resistance with increased selection pressure of lumefantrine in Africa. If such resistance is occurring in Brazil is unknown. Ajayi and Ukwaja [17] also reported three cases of possible artemis in-based combination therapy-resistant malaria in Nigeria, one of them treated with Coartem. In India, two cases of AMLF-resistant *P. falciparum* were reported from Orissa [18].

Saha et al. [9] studied 52 patients with *P. falciparum* mono-infection treated with Artemether – Lumefantrine in India, followed up for 42 days to study the clinical and parasitological responses according to the WHO protocol (2009). The crude therapeutic efficacy of AM-LF was 95.9% (47/49), and crude therapeutic failure was 2 (4.1%). Based on msp1 and msp2 genotyping of the parasite on day 0 and the day of recurrence, the two cases were classified as recrudescence. The PCR-corrected 42-day cumulative incidence of failure of AM-LF therapy for *P. falciparum* was 4.1% (95% CI, 0.010 to 0.149), and therapeutic efficacy was 95.9% (95% CI, 0.860 to 0.995). This is a very low recrudescence rate.

Ngasala et al. [14] conducted a prospective study in Tanzania, using children presenting with microscopy confirmed *P. falciparum* parasitaemia, followed by 42 days. On day 7, all patients were afebrile, but 7/244 (2.9%) were still parasitaemic. PCR analysis of these seven patients revealed four reinfections, two recrudescences and one indeterminate result. By day 42, some 141/241 (58.5%) patients had recurrent parasitaemia, of whom 32 (22.7%) presented with fever. Parasite genotyping showed that 118 (84%) were due to reinfection, 14 (10%) recrudescence and 9 (6%) indeterminate results. The PCR corrected cure rates at days 14, 28 and 42 were 97.9%, 95.1%

and 93.0%, respectively. There was no statistically significant difference in median (range) time to recrudescence infections, that is, 21 (7-42) days compared to 28 (7-42) days for reinfections ($p = 0.41$), therefore this was not a good parameter for separating recrudescences from reinfection.

In the same study, a total of 177 of 244 (73%) patients had blood lumefantrine concentrations measured on day 7 after initiation of treatment. The median lumefantrine concentration was significantly lower in patients with recrudescence (97 ng/mL [IQR 0-234]; $n = 10$) than in those with reinfections (205 ng/mL [114-390]; $n = 92$), or no parasite reappearance (217 [121-374] ng/mL; $n = 70$; $p \leq 0.046$). Of the 10 patients with recrudescence infections analysed, eight had lumefantrine concentrations <280 ng/mL. All seven patients with parasitaemia on day 7 had lumefantrine concentration <280 ng/mL. The results from this study showed that intake of unsupervised AL was highly effective and well-tolerated for the treatment of acute uncomplicated *P. falciparum* malaria in children below five years of age, however there was limited post-treatment prophylactic effect of AL. Ngasala et al. [14]. Similar result about lumefantrine concentrations were found in studies in Tanzania and Malawi [19,20].

This may be one of the main issues in the efficacy of AL. The absorption of lumefantrine is known to have a high variability and suboptimal drug levels could potentially result from inadequate fat intake [21,22]. Low blood lumefantrine concentrations increase the risk of treatment failure and reinfections [22,23,24]. Ngasala et al. [14] concluded that the risk of recurrent infections after AL treatment was high, especially when fat intake was not adequate, and that the in vivo selection of genetic markers associated with drug resistance confirms that AL is vulnerable to selection of resistance-related polymorphisms in areas of high malaria transmission. This could explain why all possible cases detected in Mâncio Lima are from rural or riverine areas, where fat intake is smaller and malnutrition rates are higher, since communities depend mainly in crops or hunting for food, and the availability of industrialized foods or dairy products is smaller.

There are several limitations of this study. First, it uses data from the surveillance system, and some notification forms were not adequately completed. It is possible that other cases of

inadequate response to treatment were not identified, because of incomplete patients name or lack of mother's name, making it difficult to match cases properly. A national registry based on patient identification using ID numbers would make it easier to surveillance teams to identify such cases, without having to screen all notification forms. Second, it is possible that some residents sought care in neighboring cities, and in this case, we were not able to review his/her case, although if that occurred, it must have been very few cases. Therefore, the number of treatment failure may be higher than what was found. Third, since it is a retrospective study, confirmation of malaria species was not performed. However, microscopical diagnosis were done by experienced microscopists.

Also, there was no confirmation of treatment supervision or drug dosage in all six cases, and genotyping was not performed. Therefore, we cannot differentiate between failure treatment or a new infection according to WHO guidelines. However, while genotyping is widely used to differentiate between recrudescence and reinfection, the appearance of a new genotype does not completely exclude the possibility of a recrudescence, considering that *P. falciparum* infections are usually clonal [25] and clones with very low parasitemia may be undetectable by molecular techniques in the presence of clones with high parasitemia.

At the same time, the operational criteria of 40 days used to identify inadequate response to treatment may exclude some late recurrences, in order to take into account the possibility of new infections. This is a dilemma when performing studies in endemic areas, because defining a new infection based on the day it occurred may not be adequate in all cases, but diagnostic tools for differentiating a treatment failure and a new infection are not widely available in endemic areas.

Hamainza et al. [26] performed a cohort study in Zambia where 171 patients aged more than 6 months old were followed for 28 days after treatment with Coartem. Late parasitological failure, defined as parasitemia on any day from day 7 to 28, was 7%, all occurring under age 15. When genotyping the parasite, these patients presented with a different genotype from the original infection. Based on genotype correction, the authors concluded that there was no treatment failure, although two children

presented with parasitemia at day 3 and 7, despite being a different genotype. The authors concluded that it was not guaranteed that these children were free of treatment failure, since slow parasite clearance to artemisinin was reported in Southeast Asia, thus supporting the idea that slow parasite clearance can occur with artemether as well [27,28]. As molecular techniques advance, further studies may bring new knowledge about drug resistance.

A systematic review of studies about the efficacy of AL confirms that artemether–lumefantrine treatment is an efficacious antimalarial regimen, resulting in a rapid therapeutic response [29]. In more than 90% of patients, fever was resolved and peripheral parasitaemia was cleared within 48 h. Overall, the therapeutic efficacy of artemether–lumefantrine was 97.6% on day 28 and 96.0% on day 42. The dose of artemether–lumefantrine was an independent predictor of recrudescence in Asia but not Africa. The study showed that patients receiving less than 60 mg/kg of lumefantrine accounted for almost 42% of treatment failures in Asia, the effect being most noticeable in young children. Young children receiving lower doses of artemether–lumefantrine had reduced efficacy, particularly in patients from Asia who presented with high parasitaemia and in malnourished patients from Africa. This revision showed that continued surveillance of artemether–lumefantrine efficacy is crucial to assure that appropriate responses to any decline can be implemented to prolong the clinical efficacy of this antimalarial drug in the long term [29].

5. CONCLUSION

Drug surveillance in treatment of malaria is essential for optimal results. Due to the recent introduction of Coartem in Brazil, very few studies about its efficacy have been performed so far. Despite technical limitations, the revision of more than 7,000 notifications identified at least 6 possible cases of treatment failure for Coartem, resulting in a very high drug efficacy. The fact that all of them had an initial low parasitemia, and most of them occurred in riverine areas may suggest low adherence to Coartem treatment, or poor fat intake during drug treatment. Prospective studies are needed in order to evaluate drug adherence and drug efficacy, in order to promote a longer period during which Coartem is effective in the Brazilian Amazon.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this article and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the Ethics Committee for Research with Human Beings at the Federal University of Acre(protocol number 23107.016975/2011-28) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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