Research Article

Biotech and biopharmaceutical drug-resistant malaria - an *in vivo* assessment using chloroquine®, camoquine® and Maldox® for uncomplicated *Plasmodium falciparum* infection

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ABSTRACT

Malaria burden is on the increase among Gokana communities in Rivers State in the Niger Delta of Nigeria. All the 67 patients enrolled in the research were infected with the parasite *Plasmodium falciparum*; the causative agent of malaria. The anti-malarial Drug efficacy test in a 14 days in vivo assessment of chloroquine® Camoquine® (Amodiaquine hydrochloride) and Maldox® (Sulfadoxine Pyrimethiamine)shows early Treatment Failure rate, late treatment failure and late parasitological failure respectively. Though drug resistance is responsible for treatment failure, but in the drugs resistant malaria research in Gokana communities, not all the treatment failure was due to resistance. Incorrect dosing, non-compliance with duration of dosing regimen, poor drug quality, drug interaction, poor or erratic absorption and misdiagnosis are among the factors responsible. Despite these factors chloroquine shows an adequate Clinical and Parasitological Response of 75% of the total patients treated with it, Camoquine® and Maldox® shows 85% and 95% of the total patient treated with each respectively. Confirming these drugs still remains an effective drug for the treatment of non-complicated infection of *Plasmodium falciparum* in Gokana, more importantly considering the Economic state of the people.

Key Words: Malaria, *Plasmodium*, antimalaria drugs, dosing, drug resistance, drug regimen

INTRODUCTION

Malaria is an illness caused by the bite of an infective female anopheles mosquito which transfers the parasites called Plasmodium. Four (4) Plasmodium species exist (*P. falciparum, P. malariae, P. vivax and P. ovale*) but only of (*P. falciparum*) is significance in disease transmission in Gokana, Rivers state of Nigeria. Malaria comes with fever (most important symptom in Children), malaise, body pain, headache and vomiting. Though the symptoms may vary in individuals and according to presentation, malaria represents one of the major causes of ill health and death throughout Nigeria. It also reduces economic productivity.

Malaria is the cause of one in four deaths in infants (¼) and young children and worse still for every ten (10) women that died during childbirth, one is caused by malaria (Roll back malaria Nigeria, 2005). In Nigeria about half of Nigeria adults have at least one episode of malaria each year while malaria occurs in younger children up to three (3) to four (4) times a year (National malaria and vector control division, Nigeria Health centers/clinic, Hospital).

Malaria particularly hurts under-five (<5) children and pregnant women due to the lessened immunity seen in both groups. It thereby contributes to both poverty and under development for the nation, community, family and individual because people spend a large part of their yearly income on its prevention and treatment. Reducing the burden of malaria is a cost effective way of promoting development and reducing poverty. Drug resistant malaria has become one of the most important problems in malaria control in recent years. Drug resistance necessitates the use of drugs which are more expensive and may have dangerous side effects. In Gokana, Nigeria; chloroquine drugs are the first line of treatment, and are used indiscriminately for self treatment of suspected

uncomplicated malaria - so we can expect to see malaria form resistant to chloroquine.

The problem of drug resistance can be attributed primary to increase selection on *P. Falciparum* in particular, due to indiscriminate and incomplete drug use for self treatment (Zucker, 1992). In areas such as the Niger Delta, mosquitoes of the *Anopheles* species spread the drug resistant parasites. These mosquitoes adapt their biting activity to human behavior patterns, and maintain it in transmission.

Drug resistance was first reported in Thailand in 1961 (Kevin *et al*., 1994). Various *Plasmodium falciparum* 'strains' have attained resistance to all commonly used and generally available antimalarial drugs. In man the problem of resistance to the common antimalarial drugs such a chloroquine and pyrimethamine, and the decreasing effectiveness of quinine are mainly limited to *P. falciparum* infection. Several mechanisms can account for change in drug sensitivity in the malaria parasites, for example, physiological adaptations due to none genetic changes, selection of previously existing drug resistant cells from a mixed population under drug pressure, spontaneous mutation of extra nuclear genes, or the existence of plasmid-like factor.

This research therefore evaluate the therapeutic efficacy of chloroquine, amodiaquine hydrochloride and sulfadoxine antimalarial drugs used for treating uncomplicated falciparum malaria in Gokana Local Government Area of Rivers State and also to look for the factors responsible for human host antimalaria drugs resistance and recommend measures for combating with the parasite plasmodium falciparum.

BACKGROUND OF THE STUDY AREA

Gokana Local Government Area is one of the Local Government Areas of Rivers State in Nigeria. It occupies a total area of about 1.046,36 square kilometers. It is bordered in the North by Tai and South by Andoni, in the east by Khana and West by Bonny Local Government Areas respectively.

The Gokana people are one of the many indigenous people in the Niger Delta region of South-South Eastern part of Rivers State Nigeria. They number about half a million people. They are also referred to as Ogoni in Ogoniland. Gokana is made up of seventeen (17) villages with chiefs (*Menebon*) and the *Gberemene* as the overall chief.

RELIGION

Christianity and African Traditional Religion (ATR) are the only two religious practices by the people of Gokana. However, Christianity is predominant religion in the area.

CULTURE AND TRADITION

The people's culture and tradition is directly influenced by Christianity and African traditional religion respects for the elders are widely practiced. The predominant languages are Ogoni Language (Gokana dialect). Their marriage customs is according to Christianity and Traditional procedures.

CLIMATE

Gokana forms part of the coastal region of the country Nigeria. Gokana has a long rainy season with dry season that last for about five to six (5-6) months. Its coldest month is November and December while the hottest period is January.

EDUCATION

Gokana area is not left behind in terms of western education. The areas have some prominent functionaries in both private and public sectors in the state and the country at large.

HEALTH FACILITIES

The area has about 50 dispensaries, 5 maternities, 12 Health Centers, and 4 cottage Hospitals, 2 General Hospital at Bodo and Terabor respectively.

ECONOMIC ACTIVITY

The people of Gokanaa Local government Area are merely commercial and predominant farmers. Those communities at the upland, produces food in a large quantity and sell it to other Local government Areas such as Andoni and Opodo Nkoro Local government Area. Other communities which are in river line area sell their product (fish) to Local Government Areas Despite these occupations, the Gokana people engage in petty trading and white collar jobs.

SCOPE OF THE STUDY

The research work "Drug resistance malaria in Gokana Communities: An in Vivo Assessment using chloroquine, Camoquine®-Amodiaquine hydrochloride and maldox® sulfaoxine pyrimethiamine for uncomplicated plasmodium falciparum infection covers the Panumu Districts of Gokana. The Panumu district is made up of seven (7) villages namely: Mogho, Gbe, Lewe, Bomu, Kpor, Bodo and Kegbara Dere. The choice of Panumu district is because the Gokana Local Government Area is large (17communities) and it will be difficult to cover considering the period required completing the project, also from available data from the Health Records and Statistics Unit of the Gokana Council, the Panumu is malaria endemic zone of Gokana.

STATEMENT OF PURPOSE

The purpose of the research "Drug Resistant malaria in Gokana Community: An *In vivo* Assessment using chloroquine, Amodiaquine Hydrochloride and sulfadoxine pyrimethiamine for uncomplicated *Plasmodium falciparum* infection is to evaluate the therapeutic efficacy of chloroquine, Amodiaquine, hydrochloride and sulfadoxine pyrimethiamine antmalarial drugs use for treating uncomplicated falciparum malaria and

also to provide minimum information essential for programmatic decision making.

Also the research evaluates the clinical and parasitological response to directly observed treatment for uncomplicated malaria and from basis of a surveillance system capable of monitoring drug efficacy changes over time.

BROAD OBJECTIVES

The aim of this study is to evaluate the therapeutic efficacy of a range of antimalaria drugs used for treating uncomplicated falciparum malaria in an in vivo assessment among Gokana Communities of Rivers State and to provide minimum information essential for programmatic decision making.

SPECIFIC OBJECTIVES

1. To determine the therapeutic efficacy of chloroquine in an uncomplicated plasmodium falciparum
2. To access the efficacy rate of camoquine® for uncomplicated falciparum malaria in Gokana.
3. To access the rate of antimalaria drugs efficacy; maldox® sulfadoxine pryimethiamine for the treatment of uncomplicated faliciparum malaria in Gokana.

RESEARCH QUESTIONS

Question 1:

What is therapeutic efficacy of chloroquine in uncomplicated plasmodium patients?

Question 2:

To what extent is the antimalaria drug efficacy of camoquine® in Gokana Community of Rivers State?

Question 3:

To what extent is the antimalaria drug efficacy of maldox® (sulfadoxine Pyrimetiamine) for the treatment of uncomplicated *P. falciparum* malaria in Gokana.

MATERIALS AND METHODS

STUDY DESIGN

The World Health Organization (WHO) standardized *in vivo* Test Protocol was adopted for assessing the response of *Plasmodium falciparum* to anti-malarial Drugs. The fundamental design of protocol is to evaluate the therapeutic Efficiency of anti-malaria drugs used for treating uncomplicated falciparum malaria.

The design is a simple, one-arm, prospective evaluation of clinical and parasitological response to directly observed treatment for uncomplicated malaria. The research evaluates three anti-malarial drugs.

The descriptive statistical tool, percentage was used to analyze the result obtained, as it is an ideal approach in determining the relationship or dependence or discrepancy between two variables. Also the Kaplan Meier protocol was used as it shows the risks of failure on Target days (day's 14 and 28) in patients.

SAMPLE SIZE DETERMINATION

Sample size determination refers to the approach used in the finding the proportion of total population of the study used for finding the factors about drug resistance in malaria in Gokana Communities of Rivers State.

To determine the number of subjects (persons) to be included in the sample so that there is a good chance of the study estimating prevalence to within 10 percentage points of the true value with 95% confidence:

(i) Anticipated population of clinical failure (p): 20%

(ii) Confidence level: 95%

(iii) Precision (d): 10% point

The table shows (see appendix) that p=0.20 and d=0.10. A sample size of 61 would be needed. Sample size adjustment for the follow-up losses and with drawls (expected to be 10% in a study with 14days follow up) n= (1+0.10) x61-67 Therefore the study enrolled 67 patents to take care of the losses and withdrawals.

SCREENING EVALUATION

A rapid screening procedure was used in an outpatient of three Health Centers to identify patients that meets enrolment criteria. The exact procedure used was a clinical and laboratory (Blood test for malaria parasite).

The screening procedure involves rapid identification of all potential patients coming to the health facility (Health Centers) (especially those coming to the pediatric out patients clinic) measurement of temperature and body weight and height and recording of basis demographic information (Name, age, sex and address). Blood was collected for malaria smear Examination from patient whose axillary's temperature exceeds or equal 37.5æ%C. Patients who meet these basic enrolment criteria were treated by Health facility staff in accordance with routine practice.

A case record from (Annex 2) was used to record the general information and clinic observation from each patient passed

from screening into study. Particular care was taken to record detailed instruction on how to find the patients home. This was to ensure that follow-up at home was possible with patients that fail to return to the health facility.

INFORMED CONSENT

Formal informed consent was obtained form all patient meeting the enrolment criteria. The procedure for obtaining consent conforms to WHO guidelines for research on hum subjects. The study potential benefits and risk was fully, explained to patients or parents/guardians (see annex 3)

TREATMENT

Patients meeting all enrolment criteria subsequently received **withMaldox®** 500/25mg tablets combination of sulfadoxine + pyrimethamine (Emzor Ltd, Lagos Nigeria) in one dose, or Camoquine® 200mg tablet + Amodiaquine (Pfizer Afrique – Daka R.P Senegal) over 3 days or chloroquine phosphate 25mg (Phytoriker (GIHOC) Pharmaceutical Ltd- Accra-Ghana, and U.S.A.) oral doses. These days were given under direct supervision. Patients were randomly assigned to their treatment arm. To avoid introduced bias, computer generated randomized list was adopted. Enrolled patients were observed for more than 30 minutes after swallowing to ensue they do not vomit the drug (medicine). Patient with complicated malaria case were referred. All patients who did not show response to treatment were curded with first line treatment. Artesunate + Amodiaquine.

FOLLOW UP

The recommendation for areas of intense transmission (WHO protocol) was also adopted. A minimum of 14 days (see annex 4) schedule table from the day the patients is enrolled and received the first of medicine is designated Day, there after, the schedule calls for clinical reassessment to be on day 1, 2, 3 and 7, then weekly for reminder period (i.e. on any day 14, 21, and 28). Patients were strongly advised to return on any day during the follow-up period when symptom returned and not wait for schedule visit days. Blood films for parasites count was obtained and examined on day 2, 3, 7, 14, 21, and day 28 for parasites. The same fever indicator was used throughout the assessment.

Measured fever was required for determining whether to collect additional blood smear and for the identifying-potential treatment failure during follow-up.

STUDY END POINTS

A study end-point is the points at which a patient will no longer be follow up within the context of the assessment. Valid study end points include treatment failure, completion of the follow-up period without treatment failure, loss to follow up-withdrawals from study (voluntary and involuntary) and protocol. The number that loss to follow up amounted to 0 while 2 withdrew from the study. There was no loss due to study protocol violation.

DETERMINATION OF STUDY OUTCOME

There were categories for treatment failure treatments, late clinical failure and late parasitological failure) and one treatment success (Adequate clinical and parasitological Response) were used to determine the study outcome.

CLASSIFICATION OF STUDY OUTCOME

(A) Early treatment failure (ETF)

(1) Development of danger signs or severe malaria on day 1, day 2, or day 3 in the presence of parasitemia.

(2) Parasitemia on day 2 higher than day 1 count irrespective of axillary's temperature$^{>}$ 37.5^{0}c

(3) Parasitemia on day 3>25% of count on Day 1

(B) Late Clinical Failure (LTF)

(i) Development of danger signs or severe malaria after Day 3 in the presence f parasitemia without previously meeting any of the criteria of early treatment Failure. Presence of parasitmia and axillary temperature <37.5^{0}c on any of days from day 4 to Day 14, without previously meeting any of the criteria of early Treatment failure.

(C) Late clinical Failure (LTF)

(i) Presence of Parasitemia on day 14 and axillary temperature >37.5^{0}c without previously meeting any of the criteria of Early treatment Late Clinical failure.

(D) Adequate clinical parasitological Response (ACPR)

Absence of parasitemia on day 14 irrespective of axillary temperature and without previously meeting any of the criteria for early treatment failure or late Clinical failure or late parasitological failure.

ETHICAL CONSIDERATIONS

The therapeutic efficacy test was conducted under the direct supervision of medical personnel. At all times the safety and welfare of the individual patient ensured.

DATA MANAGEMENT AND ANALYSIS

There is few analysis techniques used in research of this kind and the choice of any the particular methods used depend on the validity, and scope of the results. It in the study descriptive statistics was used to analyses the data from the Laboratory personnel and data collection forms.

Data collected were presented using textual methods table in percentage (%) as well as figures for easy interpretation and analysis. The results obtained were compared with the facts gathered in the literature reviewed. Care was taken to ensure

that samples were correctly labeled and all Laboratory result was reported correctly and labeled and all laboratory result was reported correctly promptly.

Thee survival analyses which include the use of data from patients who have withdrawn or are lost during following, easy calculation of mean time of failure and calculation of a reasonable unbiased estimates of failure rates was also computed.

TECHNICIAN CONSIDERATION AND QUALITY ASSUANCE

(A) Temperatures

Because outcome classifications are dependent on measured body temperatures, both thermometers and the temperature-taking techniques of the clinical staff were received. Temperatures measured below 36.0^0c were repeated. Thermometer were tested in a water-bath of know temperature before assessment.

(B) Body Weights

The accuracy of scales was verified before use during the study. This was because dosing was based on body weight and it is important to ensure reliability of the scales used in the study.

(C) Blood Slides

Preparation and staining blood slides follows the procedure outlined in malaria microscope. To obtained best result, fresh Gemsa stain dilution was used. The result obtained by staining slides for 45-60 minutes in a 2.5 -3% Giemsa stain solution slides with frosted edge that can be marked were used.

(D) Screening Smears

the microprints in the Kegbara Dere, Health Centre and the that of Tuaka Diagnostic Laboratory Mogho uses semi quantitative system of grading from ½ +++ also indicated the level of parasitemia. As a general rule, it was assumed that" ½ +" is equivalent to about 250 parasite µ 1 and "+ "is equivalent to 500- 200 parasite/ µ 1. This was done in place of calculating parasite densities.

STUDY VALIDITY

Misclassification was below 10% of the total size. Clinical mistake was avoided by adequate training of clinical staff before commencement of the study. Also experienced laboratory techniques were used.

RESULTS AND DISCUSSION OF FINDINGS

The study "Drug resistant malaria in Gokana communities: an in vivo assessment using chloroquine Amadiaquine Hydrochloride and sulfadoxine pyrimethaime for uncomplicated plasmodium falciparum infection enrolled 67 febrile patients (Temperature>37^0c(and those with a history of fever within past 45

Hours with microscopically confirmed plasmodium falciparum monoinfection (parasite density 1000-2000 asexual form per µ 1 blood). This excludes pregnant and lactating females, patients with server malaria, those with history of pretreatment and children (<5 years).

The 67 patients enrolled were from three facilities in Gokana communities. See table showing the details from each health facility.Table one indicate 2 out of the 67 patients enrolled for the research, voluntary withdrawn after enrollment.The therapeutic response to chloroquine during the 14 days follow-up is table 2 above. The failure rate with chloroquine® varied from 10% early treatment failure (ETF) to another 10% late treatment failure. 75% of the patient that were treated with chloroquine 250mg/kg has adequate clinical and parasitological response (ACPR).Table 3: summarize the result of in vivo test for sensitivity of camoquine® - (Amodiaquine hydrochloride (200mg) for 3 days). The failure rate varies from 5% early treatment failure (ETF) to 10% late treatment failure (LTF) and 0% Late Parasitological failure (LPF). 85% of the patient treatments with Amadiaquine hydrochloride 200mg/kg have adequate clinical and parasitological response.

The results of Maldox® (pyrimethamine/sulfadoxine) are presented in table 4 above. The failure rate varies from 0%

Table 1: Showing number enrolled at each site

Site number	Name of health facility	Number enrolled	Number withdrawn after enrollment
1.	KegbaraDere Cottage Hospital	22	2
2	Bomu Health centre	22	Nil
3.	Mogho health centre	23	Nil
	Total	67	2

Table2:Result of *in vivo* test with chloroquine (25mg) (over three days) in Gokna communities

Treatment outcome of chloroquine	Number	Percentage
Early Treatment failure (ETF)	2	10%
Late Treatment failure (LTF)	2	10%
Late parasitological failure (LPF)	1	5%
Adequate clinical and parasitological response	15	75%
Total	20	100%

Table 3: Result of *in vivo* test for Camoquine® (200mg. (3days) for treatment of uncomplicated *Plasmodium falciparum* in Gokana communities

Treatment outcome of Camoquine®	Number	Percentage %
Early Treatment failure (ETF)	1	5%
Late Treatment failure (LTF)	2	10%
Late parasitological failure (LPF)	0	0%
Adequate clinical and parasitological response	17	85%
Total	20	100%

for early treatment Failure to 5% Late Treatment to 0% Late Parasitological failure (LPF). 95% of the patient treated with maldox® (pyrimethamine/sulfadoxine (500/25mg) shown adequate clinical parasitological response (ACPR).

Table 4: Results of *in vivo* test with Maldox® (sulfodxine pyrimethamine) (500/25mg) tablets (one dose) for uncomplicated *Plasmodium faliciparum* malaria in Gokana communities

Treatment outcome of Camoquine®	Number	Percentage%
Early Treatment failure (ETF)	0	0%
Late Treatment failure (LTF)	1	5%
Late parasitological failure (LPF)	0	0%
Adequate clinical and parasitological response	19	95%
Total	20	100%

DISCUSSION OF FINDINGS

The present research shows the problem of drug-resistant *P. falciparum* malaria in Gokana Communities of Rivers State of Nigeria. However, the prevalence, therapeutic efficacy, intensity, and evolution of drug resistance are not uniform for chloroquine, Camoquine® and Maldox® (sulfadoxine pyrimethamine) drugs tested.

The result of the present investigation revealed an unacceptable high degree of therapeutic failure after chloroquine treatment of uncomplicated *Plasmodium falciparum* malaria. The failure rate in Gokana communities is 25% during the study. Although there was no previous data from Gokana as to consider it a significant failure rate, the high level of resistance discovered represents a serious problem which calls for concern. A clinical failure rate of 25% within 14days after therapy has been proposed as the upper limit above which treatment should be changed (Bloland *et al*., 1998).

Another issue of important regarding chloroquine resistance is the large increase in the Early Treatment failure (ETF) rate and its clinical consequences. A very interesting study (Elvall *et al*., 1998) concluded that when chlorouine treatment is associated with a 20% ETF rate, the hemoglobin levels are markedly reduced after 72 hours and recovery is unsatisfactory, even in children with adequate clinical and parasitological Response (ACPR). These are two reasons for anemia increase in children despite chloroquine treatment. The ETF rate for chlorouine in Gokana communities is high 10% with treatment not only proving ineffective but also making matters worse in a relatively uncomplicated case of malaria. A change in the recommendation of chloroquine drug should be considered.

The drug chloroquine® -Amodiaquine hydrochloride (25cm/kg) is still very effective. Its failure rate was 15% and there is hope that its failure rate will not increase significantly if patients completed their treatment regime. It is recommended that Government should control its production, supply and storage. A generalized use of drug could increase the level of its resistance. This has been reported in Malawi, Tanzania and Kenya (Bloland *et al*., 1993; Ogutu, 2000). Although resistance may be inevitable, it probably can be slowed down. WHO recommends an anti-malaria combination therapy based on the synergistic or addictive potential of two or more drugs to improve therapeutic treatment (WHO, 2001- Anit-malaria combination therapy). Some combinations with camoquine® (Artesunate + Amodiaquine) is recommended alternatives and first line treatment in Nigeria and medicine of choice for the treatment of uncomplicated malaria in sub-Saharan countries (RBM-Nig; 2005). A decision to change the first line anti-malaria has to consider different aspect of both the country (epidemiologic and economic) and the drugs (efficiency, affordability, acceptability).

Maldox®- (sulfadoxine Pyrimethamine) (200mg/Kg remains an effective drug against *P. falciparum* malaria in Gokana Communities of Rivers state, Nigeria. The failure rate based on the data gathered is not alarming. (5% Late Treatment Failure - LTF). It is very probable that treatment failures result in part from lack of adherence to the regime because of adverse reactions. All failures were LTF. Therefore, the failure rate is considered even lower. Maldox®-sulfadoxine/ pyrimethamine can be considered an alternative for first line treatment of uncomplicated malaria as it can also be taken to prevent malaria during pregnancy. It has both preventive and curative capacity.

CONCLUSION AND RECOMMENDATIONS

The present investigation revealed drug resistant malaria in Gokana Communities of Rivers State. The research was able to find out the therapeutic efficacy of chloroquine and the antimalarial drugs activities (Camoquine® and Maldox® (sulfadoxine Pyrimethamine) in an *in vivo* test. It also revealed at the factors responsible for the host resistance malaria – malaria treatment failure factors.

Sixty-five (65) persons were sampled for the study, Laboratory report and therapeutic efficacy response of the drugs used confirmed that Chloroquine®, Camoquine® Amodiaquine Hydrochloride) and Maldox® (sulfadoxine pyrimethiamine) still have therapeutic efficacy. These are still drugs of choice especially when the quality of each is maintained, given in its correct dosing-compliance with duration of dosing regimen and adequate diagnosis among others.

Based on the World Health Organization (WHO) classification of the clinical failure rates (WHO, 2001) and in accordance with the result obtained in this research at the three health facilities in Gokana Local Government Areas of Rivers State, Nigeria

(a) Chloroquine® failure rate are in the change period (>25%), and urgent actions is needed

(b) Camoquine® failure rates are in alert period (6-15%) and surveillance must be continued.

(c) Maldox® sulfadoxine-pyrimethamine failure rate are in the grace period (<6%), and the drug can be recommended without hesitancy about its efficacy.

Malaria control and prevention efforts needs to be designed for specific environment in which they will be used and there is the need to consider the local epidemiology of malaria and the level of available resources and political will. There should be aggressive outreach and enlightenment campaigns to educate the uninformed populace on the need for proper environmental sanitation habits and vits to health facilities to avoid preventable deaths due to malaria caused by *Plamodium* species

Malaria is a complex disease that varies widely in epidemiology and clinical manifestation in different part of Nigeria. The variability is the result of factors such as species of malaria parasite that occur in a given area. Their susceptibility to commonly used or available anti-malaria drugs, the distribution and efficiency of mosquito vectors, climates, and other environmental conditions and the behavior and level of acquired immunity of the exposed human population should all be put into consideration.

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