Fatunla et al. *Afr. J. Clin. Exper. Microbiol.* 2023; 24 (2): xxxx https://www.afrjcem.org

African Journal of Clinical and Experimental Microbiology. ISSN 1595-689X Apr 2023; Vol.24, No.2
AJCEM/2254. https://www.ajol.info/index.php/ajcem

Case Series **Open Access**

Malaria treatment failure after Artemisinin-based combination therapy: A case series of children managed at a private tertiary hospital in southwest Nigeria

[1,2*†]Fatunla, O. A. T., [3,4†]Irek, E. O., [1,2]Oyebanji, A. H., [2]Adisa, S. O., [5]Jesulana, T. E., and [2]Ajibola, T. O.

[1]Department of Paediatrics, Faculty of Clinical Sciences, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Nigeria
[2]Department of Paediatrics, Afe Babalola Multi-System Hospital, Ado-Ekiti, Nigeria
[3]Department of Medical Microbiology and Parasitology, Faculty of Basic Clinical Sciences, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Nigeria
[4]Department of Medical Microbiology and Parasitology, Afe Babalola Multi-System Hospital, Ado-Ekiti, Nigeria
[5]Department of Internal Medicine, Afe Babalola Multi-System Hospital, Ado-Ekiti, Nigeria
*Correspondence to: odunayofatunla@abuad.edu.ng; +2348034397539; ORCiD: https://orcid.org/0000-0002-2839-1491
[†]Contributed equally to the study

Abstract:

Malaria treatment failure is the inability to clear parasitaemia after antimalarial drug administration. There are reports of treatment failure with artemisinin-based combination therapy (ACT) in Nigeria but few reported among children. We report three paediatric cases of treatment failure with ACT admitted at a private tertiary hospital in Nigeria in early 2022. All three were 'under-fives' admitted for open-heart surgery, major flame burns, and cerebral malaria respectively. They had symptomatic *Plasmodium falciparum* infection but one had mixed *P. falciparum* and *Plasmodium vivax* infections. Cases 1 and 2 were initially given oral artemether-lumefantrine while case 3 received intravenous artesunate. Despite appropriate antimalarial drug compliance, all the 3 still had fever with heavy parasitaemia. They subsequently received intravenous quinine, with improvement within the first 24 hours of therapy, and no longer had fever at the fourth week of follow-up. Although ACT resistance was not established, poor drug quality may have contributed to treatment failure. There is a need for pharmacovigilance of anti-malarial in Nigeria.

Keywords: Artemisinin; Quinine; Malaria; *Plasmodium vivax*; Treatment failure; Nigeria

Received Feb 21, 2023; Revised Mar 6, 2023; Accepted Mar 7, 2023

Échec du traitement du paludisme après une polythérapie à base d'artémisinine: une série de cas d'enfants pris en charge dans un hôpital tertiaire privé du sud-ouest du Nigeria

[1,2*†]Fatunla, O. A. T., [3,4†]Irek, E. O., [1,2]Oyebanji, A. H., [2]Adisa, S. O., [5]Jesulana, T. E., et [2]Ajibola, T. O.

[1]Département de Pédiatrie, Faculté des Sciences Cliniques, Collège de Médecine et des Sciences de la Santé, Université Afe Babalola, Ado-Ekiti, Nigéria
[2]Département de Pédiatrie, Hôpital Multisystème Afe Babalola, Ado-Ekiti, Nigéria
[3]Département de Microbiologie Médicale et de Parasitologie, Faculté de Sciences Cliniques Fondamentales, Collège de Médecine et des Sciences de la Santé, Université Afe Babalola, Ado-Ekiti, Nigéria
[4]Département de Microbiologie Médicale et de Parasitologie, Hôpital Multisystème Afe Babalola, Ado-Ekiti, Nigéria
[5]Département de Médecine Interne, Hôpital Multisystème Afe Babalola , Ado-Ekiti, Nigéria
*Correspondance à: odunayofatunla@abuad.edu.ng; +2348034397539; ORCiD: https://orcid.org/0000-0002-2839-1491
[†]A contribué à parts égales à l'étude

Résumé:

L'échec du traitement du paludisme est l'incapacité à éliminer la parasitémie après l'administration d'un médicament antipaludique. Il y a des rapports d'échec de traitement avec la thérapie combinée à base d'artémisinine (ACT) au Nigeria, mais peu ont été signalés chez les enfants. Nous rapportons trois cas pédiatriques d'échec de traitement avec ACT admis dans un hôpital tertiaire privé au Nigeria au début de 2022. Tous trois étaient des « moins de cinq ans » admis pour une chirurgie à cœur ouvert, des brûlures graves par la flamme et un paludisme cérébral, respectivement. Ils avaient une infection symptomatique à Plasmodium falciparum mais un avait des infections mixtes à P. falciparum et Plasmodium vivax. Les cas 1 et 2 ont initialement reçu de l'artéméther-luméfantrine par voie orale tandis que le cas 3 a reçu de l'artésunate par voie intraveineuse. Malgré une bonne observance des médicaments antipaludiques, tous les 3 avaient encore de la fièvre avec une forte parasitémie. Ils ont ensuite reçu de la quinine par voie intraveineuse, avec une amélioration dans les 24 premières heures de traitement, et n'avaient plus de fièvre à la quatrième semaine de suivi. Bien que la résistance à l'ACT n'ait pas été établie, la mauvaise qualité des médicaments peut avoir contribué à l'échec du traitement. Il y a un besoin de pharmacovigilance des antipaludéens au Nigeria.

Mots clés: Artémisinine; Quinine; Paludisme; *Plasmodium vivax*; Échec du traitement; Nigeria

Introduction:

Malaria treatment failure poses a threat to malaria control and global eradication. Treatment failure in malaria is the inability to clear malaria parasitaemia or prevent recrudescence in an individual after administration of an antimalarial (1). Early treatment failure is parasitaemia with symptoms of malaria occurring within three days of commencement of treatment while late clinical failure is presence of parasitaemia with symptoms of malaria occurring on any day between day 4 and day 28 in patients who did not meet criteria for early treatment failure (2). The symptoms include fever (axillary temperature of $\geq$37.5^{o}C), danger signs or features of severe malaria (2,3). If an individual still has parasitaemia on any day between day 7 and day 28 but without fever, it is termed late parasitological failure parasitaemia (2).

There are many factors that can cause malaria treatment failure, these include incorrect dosing, poor drug compliance, poor drug quality, drug interactions and drug resistance (1,4). There are reports of resistance to all the groups of anti-malarial drugs including artemisinins recommended by the World Health Organization (WHO) for the treatment of uncomplicated malaria (1,5). In Nigeria, reports of malaria treatment failure with artemisinin-based combination therapy (ACT) have been documented (1,6–8), but there are very few reported incidences among children, who have the highest malaria burden.

Between January and March 2022, three paediatric patients were managed for malaria treatment failure associated with artemisinin-based combination therapy (ACT) at the Afe Babalola University Multi-System Hospital, Ado-Ekiti (AMSH), a privately owned tertiary facility in Southwest Nigeria. We report these cases and the management challenges, and suggest ways of circumventing treatment failure of malaria in children.

Case presentations:

Case 1:

Case 1 is KO, a 7-month-old boy who had open heart surgery for tetralogy of Fallot in January 2022 in AMSH. He had blood transfused intra-operatively and was noticed to have developed intermittent fever a week after the surgery while on admission. He was conscious and other wise clinically stable post-operatively except for fever that ranged from 37.5^{o}C to 38.9^{o}C. Blood film for malaria parasite revealed presence of trophozoites of *Plasmodium falciparum.* He weighed 5kg and was therefore administered oral combination of artemether 20mg and lumefantrine 120mg at 0 hour, then 8 hours after first dose then twice daily for a total duration of 3 days. Fever still persisted despite completion of antimalarial. Blood culture sample was obtained but yielded no growth.

Four days after the completion of the oral ACT, a quick bedside rapid diagnostic test (Onsite® Rapid Test, CTK Biotech, USA) done was positive for *P. falciparum* and *P. vivax.* This was corroborated by microscopic blood film that revealed trophozoites of mixed species of *P. falciparum* and *P. vivax,* with a parasite density of 5,820 parasites/µL [white blood cell (WBC) count of 9,700 cells/µL]. He was then commenced on intravenous (IV) quinine 50mg 8-hourly delivered in intravenous 10% dextrose in water. Fever subsided within 12 hours of commencement of quinine and no parasite was seen in the repeat blood film performed afterwards. He received six IV doses of quinine and was discharged on oral quinine 50mg three times a day to complete 21 doses (including the IV formulations). He was followed up for four weeks and remained fever-free throughout the period.

Case 2:

Case 2 is TA, a 33-month-old girl who was on admission for major flame burns with inhalational injury in February 2022, developed intermittent fever on the 7th day of admission with highest temperature reading of 37.8°C at that time. She was conscious with an estimated weight of 15kg and was given oral combination of artemether 40mg and lumefantrine 240mg at 0 hour, then 8 hours after first dose then twice daily for a total duration of 3 days. The fever subsided from the second day of commencing the ACT until the last dose of ACT was taken.

Three days afterwards, on the 12th day of admission, she developed fever again with a temperature range of 37.8°C to 40.0°C. Repeat blood film revealed trophozoites of *P. falciparum* and was given three doses of IV artesunate 40 mg at 0, 12th and 24th hour. Blood culture sample taken at this time yielded growth of *Escherichia coli* sensitive to piperacillin-tazobactam, imipenem and levofloxacin, and was consequently given IV imipenem 250mg 6hrly. Nevertheless, fever still persisted after the third dose of IV artesunate, and despite IV antibiotics temperature was as high as 40.0°C. Another blood sample was then obtained for blood film microscopy which still revealed >10 parasites/high power field trophozoites of *P. falciparum,* with a parasite density of 20,849 parasites/μL (WBC count of 16,100 cells/μL). Subsequently, IV quinine 150mg 8hourly was administered in IV 10% dextrose in water. Fever subsided after the second dose of IV quinine. She received 6 doses intravenously and 15 oral doses of syrup quinine 150mg three times a day. She spent another four weeks on admission for burns but remained fever-free throughout.

Case 3:

Case is IJ, a 19-month-old boy referred to AMSH in March 2022. He had been on admission at the referring health facility for a week, where he had presented with a week history of fever, and had one episode of generalized tonic-clonic seizure that lasted for 15 minutes which was aborted at the referring facility. He subsequently lapsed into unconsciousness and remained so at presentation in AMSH. The referral note stated that he had microscopy done that revealed hyper parasitemia, for which he was given IV artesunate 30mg stat, at 12th and 24th hour and then daily for six days. His cerebrospinal fluid (CSF) was also analyzed but was said to be normal, nonetheless, he was given IV antibiotics at the referring facility.

At admission in AMSH, he was still unconscious, with a Glasgow Coma Score (GCS) of 8, febrile with a temperature of 39.1°C and weighed 8kg. There was no evidence of raised intracranial pressure and no sign of meningeal irritation. Thick blood film showed trophozoites of *P. falciparum,* with parasite density of 30,562 parasites/μL (WBC count of 23,600 cells/μL) but the CSF findings were essentially normal. His cranial magnetic resonance imaging (MRI) revealed only cerebral oedema.

He was nursed as an unconscious patient and managed for cerebral malaria with IV quinine 160mg loading dose then 80mg 8hourly, administered in 10% dextrose water. Fever began to subside after six hours of commencement of quinine and GCS improved to 10 within 24 hours of therapy. He remained fever-free and regained full consciousness on the fourth day of admission after receiving 9 doses of intravenous quinine, and was subsequently commenced on oral quinine 80mg three times a day to complete a total of 21 doses of quinine. However, he had some neurologic deficits including cortical blindness and cortical deafness with regression of previously attained milestone that resulted from cerebral malaria. On the eighth day of admission, there were improvements with his vision and hearing and he was subsequently discharged home. He maintained normal temperature even at the fourth week of follow-up.

Clinical and laboratory characteristics of the patients:

The blood films for malaria parasites of all the three patients were made and read by one of the authors (a consultant medical microbiologist at AMSH). Cases 1 and 3 had early treatment failure while case 2 had late clinical failure. The blood glucose measurements of all the patients were normal during parenteral quinine administration and thereafter. One of the cases who could communicate verbally (this excludes the infant and the patient managed for cerebral malaria), did not complain of tinnitus or hearing impairment. All the three cases had auditory assessments that were grossly normal, besides the case with cerebral malaria who had cortical deafness that improved over time. None of the cases had history to suggest glucose-6-phosphate dehydrogenase (G6PD) deficiency, neither did any of them exhibit clinical features to suggest hemolysis induced by quinine administration.

Discussion:

This case series is a report of three cases of malaria treatment failure managed at the department of paediatrics of a private tertiary hospital in southwest Nigeria. These cases

were managed within the first three months of the year 2022, during the dry season, when malaria transmission is supposedly low (9). All three patients were younger than five years but only one of them had severe malaria. This buttresses the observation that the burden of malaria is high among the 'under-fives' (10).

All the patients were initially given artemisinin-based medications as first line treatment according to the WHO recommendation, even in the management of *P. vivax* infection (5). The poor responses to this first line treatment in this case series may be due to various factors including the use of poor-quality medicine. Poor-quality drugs (counterfeit or sub -standard) have been documented as causes of treatment failure and development of resistance (5). In addition to this, some practices such as the indiscriminate use of ACT for malaria prophylaxis as observed in a rural community in southwest Nigeria (11) or the over-diagnosis and presumptive treatment of clinical malaria (5) may contribute to development of resistance to artemisinins. There are several studies that have inferred a possibility of artemisinin resistance in Nigeria (6–8), nonetheless, artemisinin-resistance is yet to be established in this part of the world (5). There is a need for effective pharmacovigilance in the community to curb the development of artemisinin resistance, based on possible adulteration of antimalarials.

There are alternatives to the use of ACTs, which include primaquine, combination of full doses of parenteral artesunate and parenteral quinine for severe malaria, and new combinations of artesunate and pyronaridine (5). Primaquine is known to achieve radical cure in cases of *P. vivax* and to clear gametocyte stages of *P. falciparum* very rapidly (2,5,12). Unfortunately, this drug is not routinely prescribed in Nigeria (13) and was not available for use at the time. Primaquine unavailability may be due to lack of diagnostic tools for *P. vivax* and reduced expertise, hence under-diagnosis of non-falciparum plasmodia species.

The new combination of artesunate and pyronaridine was not available either, hence quinine (initially parenteral then oral) was administered to all the three patients that demonstrated malaria treatment failure to artemisinin-based treatment and good responses were achieved. Besides, this new combination is also an ACT and there is a possibility of cross-resistance if this drug was used assuming genetic mutations in ACTs were responsible for the treatment failure. There is a need for molecular analyses for artemisinin-resistance in Nigeria so that policies regarding malaria treatment failure can be reviewed as necessary.

Although, chloroquine has good coverage of *P. vivax*, its use for malaria treatment is prohibited in Nigeria (14,15) because of drug resistance. It may become imperative to cautiously review the role of chloroquine in the treatment of *P. vivax* infection given the recent increasing reports of *P. vivax* infection in Nigeria (16–19). Quinine, on the other hand, is an antimalarial that has been in use for over a century, yet there is dearth of reports of quinine-resistance in recent times since the early observations during the first world war (20). Perhaps side effects of quinine, such as bitter taste of the oral formulation, hypoglycaemia, tinnitus, hearing impairment, among others and the cumbersomeness of IV administration deter the abuse of this medication. In addition, the WHO recommendation of the artemisinins as first line antimalarial may have preserved the effectiveness of quinine in the treatment of malaria. All the patients in this case series tolerated quinine therapy with good response and none had any untoward side effect. This case series supports the use of quinine in the treatment of children with malaria treatment failure as recommended by the WHO (4,5).

Conclusion:

This case series reports malaria treatment failure among three children managed at a private tertiary hospital in Nigeria, one of whom had mixed *P. falciparum* and *P. vivax* infection. There were remarkable clinical and parasitological improvements with the use of quinine in managing malaria treatment failure in the three children. Although, inherent drug resistance to ACTs administered could not be ruled out completely, there is a possibility that poor drug quality via adulteration contributed to the treatment failure seen in these patients.

There is a need for pharmacovigilance in the country, to promptly mitigate factors that contribute to malaria treatment failure. There should be more studies to review the effectiveness of ACTs in the treatment of malaria especially in the wake of reports of treatment failures. There is also a need to ease the availability of primaquine for the increasing prevalence of *P. vivax* infections in Nigeria.

Consent for publication:

Written informed consent for publication was obtained from the parents of the three children.

Acknowledgements:

The authors appreciate the contributions

of the staff of the Afe Babalola University Multi-System Hospital, Ado-Ekiti, towards the management of the patients in this case series.

Authors' contributions:

All authors have made substantial contributions to this manuscript. OATF, EOI and AHO designed the study. OATF drafted the manuscript and all authors were involved revising it. EOI prepared and interpreted all the peripheral blood films. All authors were involved with data retrieval. All authors read and approved the final version of the manuscript, and agree to be personally accountable for their respective contributions.

Source of funding:

Funding is by Afe Babalola University, Ado-Ekiti, Nigeria.

Conflicts of interests:

Authors declare no conflict of interests

References:

1. World Health Organization. Artemisinin resistance and artemisinin-based combination therapy efficacy. Geneva Switzerland; 2018 https://apps.who.int/iris/handle/10665/274362.
2. World Health Organization. Methods for surveillance of antimalarial drug efficacy. Geneva, Switzerland: World Health Organization. 2021: 90. https://appshttps://www.who.int/docs/default-source/documents/publications/gmp/methods-for-surveillance-of-antimalarial-drug-efficacy/pdf?sfvrsn=29076702_2.who.int/iris/handle/10665/342169. (Accessed Mar 7 2022)
3. Centers for Disease Control and Prevention C. CDC - Malaria - About Malaria - Disease. 2019. https://www.cdc.gov/malaria/about/disease.html. (Accessed Mar 7, 2022)
4. Bloland, P. B., and World Health Organization. Anti-Infective Drug Resistance Surveillance and Containment Team. Drug resistance in malaria. Switzerland: World Health Organization. 2001. https://apps.who.int/iris/handle/10665/66847
5. World Health Organization. WHO Guidelines for malaria. Geneva, Switzerland. 2022. https://www.who.int/publications/i/item/guidelines-for-malaria
6. Ebohon, O., Irabor, F., Ebohon, L. O., and Omoregie, E. S. Therapeutic failure after regimen with artemether-lumefantrine combination therapy: a report of three cases in Benin City, Nigeria. Rev Soc Bras Med Trop. 2019; 52: e20190163.
7. Umar, R. A., Jiya, N. M., Hassan, S. W., Abdullahi, K., Ahmed, J. M., and Nata`ala, U. Apparent Drug Failure Following Artesunate Treatment of *Plasmodium falciparum* Malaria in Sokoto, Nigeria: Three Case Reports. Trends Med Res. 2007; 2: 113–116.
8. Ajayi, N. A., and Ukwaja, K. N. Possible artemisinin-based combination therapy-resistant malaria in Nigeria: a report of three cases. Rev Soc Bras Med Trop. 2013; 46 (4): 525–527.
9. Samdi, L., Ajayi, J., Oguche, S., and Ayanlade, A. Seasonal Variation of Malaria Parasite Density in Paediatric Population of North Eastern Nigeria. Glob J Hlth Sci. 2012; 4 (2): 103–109.
10. United Nations Children's Fund. Malaria in Africa. UNICEF Data. 2021. https://data.unicef.org/topic/child-health/malaria/. (Accessed 11 Mar 2022).
11. Fatunla, O. A. T., Olatunya, O. S., Ogundare, E. O., et al. Malaria prevention practices and malaria prevalence among children living in a rural community in Southwest Nigeria. J Infect Dev Ctries. 2022; 16: 352–361.
12. Tsuung, A. B., Pitmang, S. L., and Dassak, F. L. Effect of Primaquine on Gametocyte Carriage in the Case-Management of Uncomplicated Falciparum Malaria with ACTs: Nigerian Perspective. Adv Infect Dis. 2018; 8 (2): 39–53.
13. World Health Organization. Nigeria - Malaria profile; African region. World malaria report 2018. https://www.who.int/malaria/publications/country-profiles/profile_nga_en.pdf?ua=1. (Accessed Mar 11, 2022).
14. Olokor, F. FG bans chloroquine, artemisinin monotherapy Punch Newspapers. 2017. https://punchng.com/fg-bans-chloroquine-artemisinin-monotherapy/. (Accessed Mar 11, 2022).
15. United Nations Office for the Coordination of Humanitarian Affairs. Nigeria: Chloroquine malaria treatments to be phased out - health minister - Nigeria ReliefWeb. 2005.https://reliefweb.int/report/nigeria/nigeria-chloroquine-malaria-treatments-be-phased-out-health-minister. (Accessed Mar 11 2022).
16. Oboh, M. A., Badiane, A. S., Ntadom, G., et al. Molecular identification of *Plasmodium* species responsible for malaria reveals *Plasmodium vivax* isolates in Duffy negative individuals from southwestern Nigeria. Malaria Journal. 2018; 17 (1): 439.
17. Oboh, M. A., Singh, U. S., Ndiaye, D., et al. Presence of additional Plasmodium vivax malaria in Duffy negative individuals from Southwestern Nigeria. Malaria Journal. 2020; 19 (1): 229.
18. Oboh, M. A., Oyebola, K. M., Idowu, E. T., Badiane, A. S., Otubanjo, O. A., and Ndiaye, D. Rising report of *Plasmodium vivax* in sub-Saharan Africa: Implications for malaria elimination agenda. Sci Afr. 2020; 10: e00596.
19. Okoh, F. N., Akoma, O. N., Ezeonu, I. M., and Iwuagwu, E. O. Is *Plasmodium vivax* becoming more prevalent in parts of Nigeria? A molecular evaluation of the parasite from persons living in Ishielu, South-East Nigeria. Nig J Parasitol. 2021; 42 (2): 220–227.
20. da Silva, A. F. C., and Benchimol, J. L. Malaria and Quinine Resistance: A Medical and Scientific Issue between Brazil and Germany (1907–19). Med Hist. 2014; 58 (1): 1–26.