Short Communication

When a Deadly Disease Ironically becomes Desirable: Insights from 2023 Antimalarial Therapeutic Efficacy Studies in Nigeria

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Abstract

Malaria continues to cause avoidable suffering and claims hundreds of lives annually, particularly in sub-Saharan Africa. The disease responds to antimalarials, but regular monitoring of the efficacy of the drugs and surveillance for parasite resistance are critical to having positive outcomes in case management. Nigeria, the country with the highest burden of the disease globally, conducted another antimalarial therapeutic efficacy studies (TES) in 2023 in four different zones in the country. Seeing the unusually pleasant way their children (study participants) were treated, caregivers' perception of malaria as a deadly disease changed to that of a "desirable" malady. The clinical trial, done in a near-perfect environment, demonstrated that the disease is not indomitable after all. In this paper, we describe our experience at the trial and posit that, with a health system thinking approach and inclusive malaria interventions, Nigeria can overcome malaria and end mortality attributed to it soon.

Keywords: Malaria, Therapeutic Efficacy Studies, TES, Nigeria.

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Introduction

A disease usually causes discomfort and engenders unease, stress and anxiety for the affected and their caregivers. As a result, no one ordinarily wishes to be ill, and certainly not with malaria - a disease with an estimated 249 million cases and 608,000 deaths in 2022 alone.[1] The morbidity and mortality associated with malaria are largely attributable to a country's weak health system that cannot guarantee adequate prevention, prompt diagnosis, and timely and effective treatment for its residents, especially those on the negative side of the social determinants of health.[2] Whether uncomplicated or severe malaria, there is no certainty about the outcome of the disease in the face of poorly equipped and largely unregulated treatment outlets, paucity of trained health personnel, fake drugs, and inability to pay for quality service in the absence of health insurance.[3–8] These are the common denominators in many resource-limited countries such as Nigeria where the disease is still debilitating and killing in large numbers.

The therapeutic efficacy studies (TES) present a different state of affairs in the management of malaria.[9] These, being clinical trial, are a situation where everything is in place and works seamlessly to test, treat, and track malaria in line with the WHO T3 policy.[10] During TES, children suspected of having uncomplicated malaria are diagnosed using malaria rapid diagnostic test (mRDT) and positive cases are confirmed for enrollment with malaria microscopy which enables parasite identification, speciation, and quantification.[11] Cases that meet strict criteria including the age range of 6 months to 8 years; malaria parasite density 2000/μL to 200,000/μL; and absence of danger signs are enrolled for supervised treatment with selected quality-assured artemisinin-based combination therapies (ACTs) in use in the country. They are then followed up for drug efficacy and safety over 28 to 42 days depending on the antimalarial drug being studied.[9] Finally, molecular studies are conducted on the specimen of blood collected from the participants in the course of the study to determine whether apparent treatment failures are due to recrudescence of the earlier infection or reinfection. Molecular studies also help to determine polymorphisms of known drug-resistant markers.[9]

Therapeutic efficacy studies are microcosm of a health system and typify the interconnectedness of the WHO six building blocks of a health system – service delivery; health workforce; health information systems; medicines, vaccines and technology; financing; and leadership/governance.[12] The 2023 TES in Nigeria were conducted in four states representing four geopolitical zones of the country: Anambra (South East), Bayelsa (South South), Oyo (South West) and Yobe (North East). The preliminaries including advocacy visits to the selected states started in February 2023 and enrollment/data collection occurred concurrently in all the sites from July to November 2023. The study facility in each state was selected through a rigorous process to ensure that each facility had basic infrastructure and equipment needed for the study. Whatever was not available was supplied to ensure a hitch-free study.

The study teams were also carefully selected based on preset qualifications and experience and were reasonably motivated to conduct the study. The data generated on screening, enrollment and follow-up of study participants were entered real-time on a customized WHO spreadsheet and a data management software (REDCap®) by trained data clerks, while a central data manager conducted real-time monitoring of the collected data and provided feedback for immediate action where required. The diagnostic materials and medicines were procured centrally from certified manufacturers and necessary tests were conducted to assure their quality. Money was not a barrier to accessing services by study participants. In line with health research ethics, the cost of participating in the study by patients was borne by the sponsor and the tests, drugs, and follow-up visits (FUVs) were done at no direct cost to the caregivers. In addition, the caregivers were given a reasonable transport fare for follow-up visits and their children were given full-cream milk (as a fatty meal to facilitate absorption of artemether-lumefantrine) and biscuits as an incentive. A governing structure was in place to manage the study (Figure 1). This included the National Coordinator of the National Malaria Elimination Programme (NMEP), the TES core team consisting of all the partners involved, and the Technical Coordinator who oversaw the study at all the sites. Each site had a Principal Investigator (PI) that supervised the study and reported to the Technical Coordinator. Each governing unit met periodically for updates and discussed matters relating to the performance of the sites. This enabled prompt remedial actions to be taken whenever problems were identified.

Prior to site initiation and commencement of the study, and while the studies were in progress, the essential community structures were engaged and mobilised. Community mobilisation involved meeting with the gatekeepers and opinion leaders of the communities - traditional rulers, women's association leaders, religious leaders, and chairmen of community development committees. Health facilities in the catchment area of the study facilities and the ubiquitous proprietary and patent medicine vendors (PPMVs) who are usually the first port

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of call for many community members for malaria treatment in rural Nigeria[13] were also engaged. We introduced the study to them and sought their cooperation in referring eligible children to the study facilities.

Such was the setting in which 2023 TES were conducted in all the four selected sites, and it is no wonder that the responses were positive. Caregivers willingly and enthusiastically brought their children/wards to the facilities for care. Those that were enrolled spread the message of the care received and soon enough the facilities thronged with children with suspected malaria as well as well children. There were cases of caregivers pleading for their children to be enrolled, especially when the mRDT was positive but other criteria were not met. Not meeting the inclusion criteria, these children were treated gratis but were not enrolled – a situation that was deeply disappointing to the caregivers. There was a case of marital disharmony in one of the sites caused by a controversy between the parents about who should take the child to the facility for follow-up because of the agreeable transport incentive of two thousand naira (₦2000) - an equivalent of USD2.4 - per FUV. Those on artemether-lumefantrine (AL) needed seven FUVs while those on dihydroartemisinin-piperaquine (DHP) or pyronaridine-artesunate (PA) had to make nine FUVs. For many caregivers, especially those living in the vicinity of the study facilities, TES was a godsend. So, in the light of receiving quality care from trained health staff that were always available, at no direct cost and with transport fare that "enriched" many caregivers given the economically disadvantaged populations where the studies were conducted, malaria became a disease many desired for their children. TES thus demystified malaria as a killer disease and caregivers could see that it is a disease that can be easily treated, and that with prompt presentation at a functional health facility, no child needs to suffer or die from it. This should be the objective reality of everyone affected by the disease including those in rural communities. Unfortunately, many treatment outlets in Nigeria still practise presumptive treatment of malaria without testing[13,14] leading to over-diagnosis of the disease.[14] The febrile illnesses, wrongly treated as malaria, may however be due to other causes. In addition, the antimalarials wrongly given may be perceived as ineffective while the missed diagnosis could worsen and end in mortality. Another concern is that there is no guarantee that the drug given is quality-assured with reports of widespread availability of fake and substandard drugs.[8,15]

The TES scenario is not prescribed nor expected in everyday management of malaria, but for a country that bears the highest burden of the disease globally, accounting for 27% of cases and 31% of deaths,[1] the WHO system building blocks need to be in place and quickly so if Nigeria is to achieve the targets set in its National Malaria Strategic Plan 2021-2025[16] and accelerate the realisation of the targets of the Global Technical Strategy for Malaria 2016-2030.[17] Efforts should be intensified to rapidly increase access to testing at every treatment point whether private or public and in rural as well as urban centers. Negative cases should be thoroughly evaluated and investigated for other febrile illnesses and referral made as required. The antimalarial drug market should be sanitized to rid it of counterfeit drugs and ensure that only quality-assured recommended ACTs are available. With the reports of possible imminent resistance to artemisinin in Africa,[18] surveillance needs to be heightened and TES must be regularly conducted in all the six geopolitical zones of the country for rapid detection and action. One overarching goal that must be vigorously pursued is the attainment of universal health coverage (UHC), which will solve most of the problems militating against optimal case management of malaria in Nigeria. With many households in the country not adequately covered by preventive measures,[13] cases of malaria may remain high for a long time but with UHC and a strong health system, the cases can be effectively managed, transmission markedly reduced (artemisinins are gametocidal), and mortality from the disease reduced to zero in the near future.

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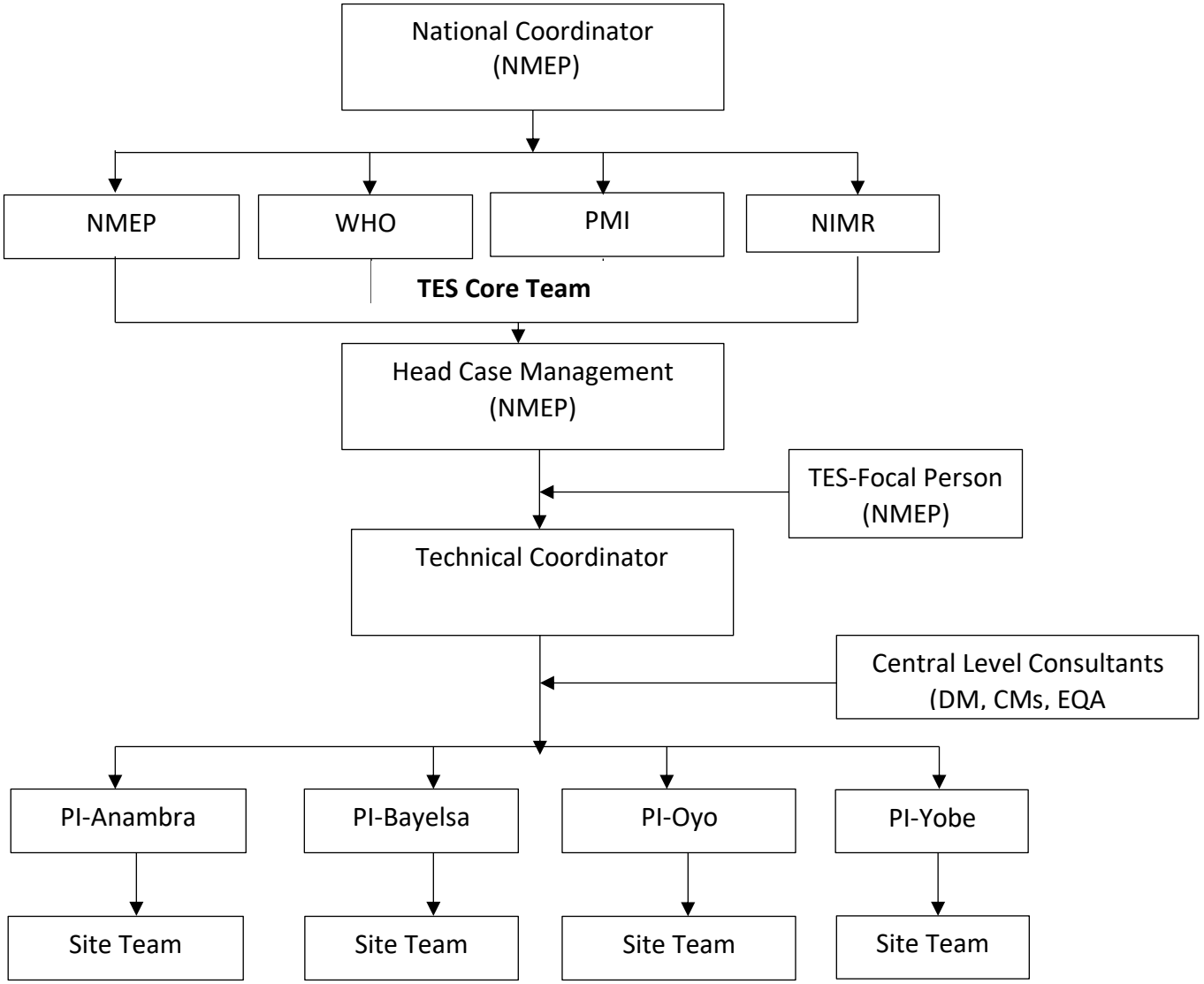

NMEP: National Malaria Elimination Programme; **WHO:** World Health Organization; **PMI:** President's Malaria Initiative; **NIMR**: Nigerian Institute of Medical Research; **DM:** Data Manager; **CM:** Clinical Monitor; **EQA:** External Quality Assessment; **PI:** Principal Investigator

Figure 1: Organogram of 2023 Therapeutic Efficacy Studies

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Conclusion

The 2023 therapeutic efficacy studies were conducted in four states in the country to determine the therapeutic efficacy of AL, DHP, and PA in treating uncomplicated malaria. The caregivers of children (the study participants) were pleased that their children received quality treatment from caring health professionals at no direct cost to them. In addition, they were adequately reimbursed for their trips to the study sites. All of this made the deadly malaria look like an innocuous disease such that other caregivers wished their children could suffer from the disease and be enrolled to receive the same unprecedented care. No Nigerian child needs to die from malaria! The country can soon get to this state where a preventable and curative disease like malaria would no longer be a killer. But for this to happen, a strong health system and universal health coverage are a sine qua non.

Declarations

Ethical Consideration: Ethical approval for the Therapeutic Efficacy Studies was obtained from the National Research Ethics Committee of Nigeria: NHREC/01/01/2007-12/04/2023B

Authors' Contribution: AO was a Principal Investigator (PI) and conceptualised this perspective; KO, AO, CE, AT, and JA were PIs/Co-PIs. They provided insights from their sites and contributed to the first draft of the manuscript; FO and AD (Clinical Monitors); GN, NO, SI, LO, and OB (members of the TES Core Team); CF (Technical Coordinator). All authors reviewed the first and subsequent drafts of the manuscript as well as approved the final manuscript.

Conflict of interest: The authors declare no conflict of interest.

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List of Abbreviations

ACT	Artemisinin-based combination therapy
AL	Artemether-lumefantrine
DHP	Dihydroartemisinin-piperaquine
FUV	Follow-up visit
mRDT	Malaria rapid diagnostic test
PA	Pyronaridine-artesunate
PI	Principal Investigator
PPMV	Proprietary and patent medicine vendor
TES	Therapeutic efficacy studies
UHC	Universal health coverage
WHO	World Health Organization

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