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Assessment of baseline molecular markers of sulfadoxine-pyrimethamine resistance in Ebonyi and Osun states, Nigeria: Toward implementation of perennial malaria chemoprevention

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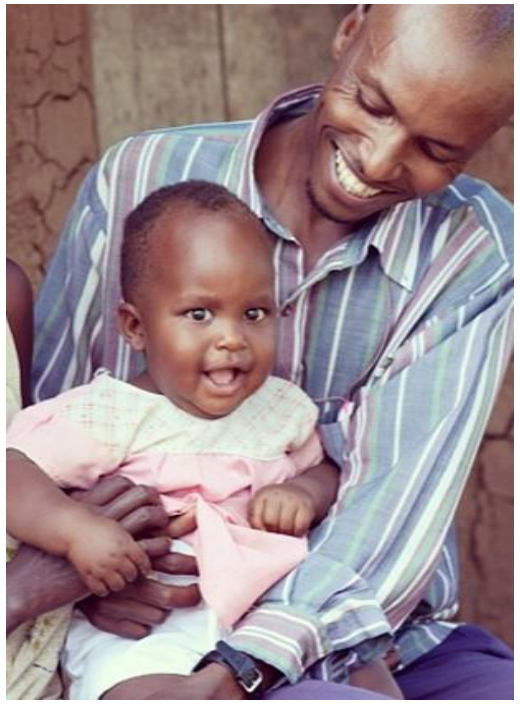
Contents



Background

- Nigeria accounts for 27 percent of global malaria deaths.[1]
- Between 2008 and 2018, the mortality rate for children under five dropped by 15.9 percent (from 157 to 132 per 1,000 live births); however, reduction in the infant mortality rate (IMR) was minimal at 10.7 percent (from 75 to 67 per 1,000 live births).[2]
- Nigeria intends to deploy perennial malaria chemoprevention (PMC) — formerly intermittent preventive treatment in infants (IPTi) — to contribute to the reduction in IMR.
- This study was conducted to determine the prevalence of molecular markers of sulfadoxine-pyrimethamine (SP) resistance (dhps K540E) and confirm state eligibility prior to PMC implementation.

1. World Health Organization. World malaria report 2020: 20 years of global progress and challenges. Geneva: World Health Organization; 2020.
2. National Population Commission (NPC), Nigeria and ICF. Nigeria demographic and health survey 2018. Abuja and Rockville, Maryland: NPC and ICF; 2019.

Background

- The protective efficacy of SP-IPTi is dependent on the antimalarial efficacy of SP.
- The World Health Organization (WHO) recommends SP-IPTi in areas with less than 50 percent prevalence of pfdhps 540 mutation in the *Plasmodium falciparum* parasite.[3]
- Mutation at codon 540 of dhps is associated with SP resistance
  - dhps-540K: wild-type variant
  - dhps-540E: resistant variant
  - dhps-540K/E: any sample carrying both variants (the mixed variant).
- There has been increasing parasite resistance in most parts of Africa.

3. WHO Global Malaria Programme; Department of Immunization, Vaccines & Biologicals; and UNICEF. Intermittent preventive treatment for infants using sulfadoxine pyrimethamine (SP-IPTi) for malaria control in Africa: Implementation field guide. Geneva: WHO; 2011.

Methods

- Pre-intervention assessment of the prevalence of molecular markers of SP resistance was conducted in Ebonyi and Osun states, Nigeria, from September to December 2021.
- These non-seasonal malaria chemoprevention (SMC) states were selected as they have the highest malaria incidence rate among children under five, and the highest infant mortality rate.
- A two-stage cluster sampling method was used to select 12 local government areas (LGAs) — six in each state.
- Nigerian Institute of Medical Research (NIMR) researchers facilitated collection of dried blood spot (DBS) samples from mRDT*-positive patients aged six months and above who had fever/history of fever in the 24–48 hours preceding presentation at the health facility.

*malaria rapid diagnostic test

Methods

- DNA extracted from all samples was eluted with 100 µl AE buffer and used immediately or stored at -200°C until use guided by standard operating procedure (SOP) prepared jointly by the London School of Hygiene & Tropical Medicine (LSHTM) and NIMR.
- Confirmation of *P. falciparum* was carried out using an in-house developed cytb-based qPCR (quantitative polymerase chain reaction) assay.
    - The qPCR assay targets a cytb gene present in eight copies of mitochondria of *P. falciparum* (PF3D7_MIT02300).
- Next-generation sequencing amplicon deep sequencing was used for the mutation analysis.
- Prevalence was defined as the percentage of mutant variant (mixed or alone) per total number of samples; while proportion was defined as the total number of mutant variants per total variants in each sample.

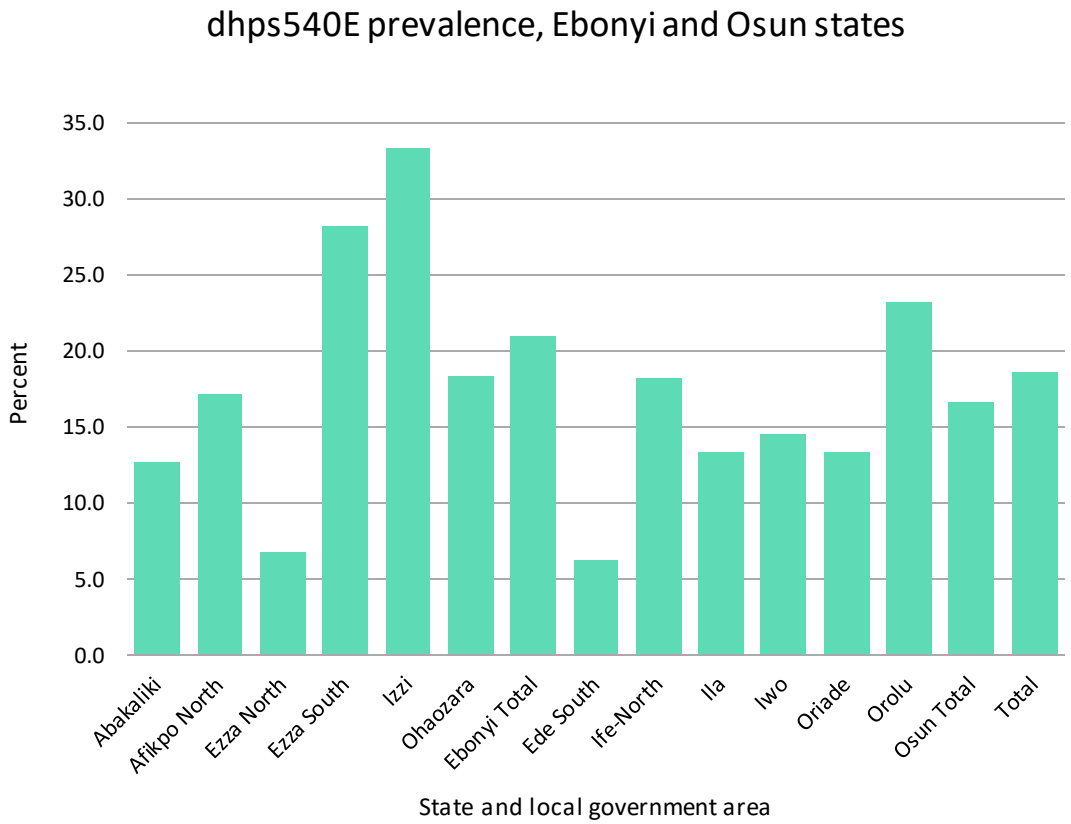
Results

- In total, 1248 samples were collected.
- Of these 1161 (93 percent) were *P. falciparum* positive by qPCR.
- Prevalence was similar in both States: 93.06 percent in Ebonyi and 93.01 percent in Osun .
- We included 969 samples with high sequencing quality for the analysis.

State	Total sample screened	*P. Falciparum* positive	%
Ebonyi	576	536	93.06
Osun	672	625	93.01
Total	1248	1161	93.03

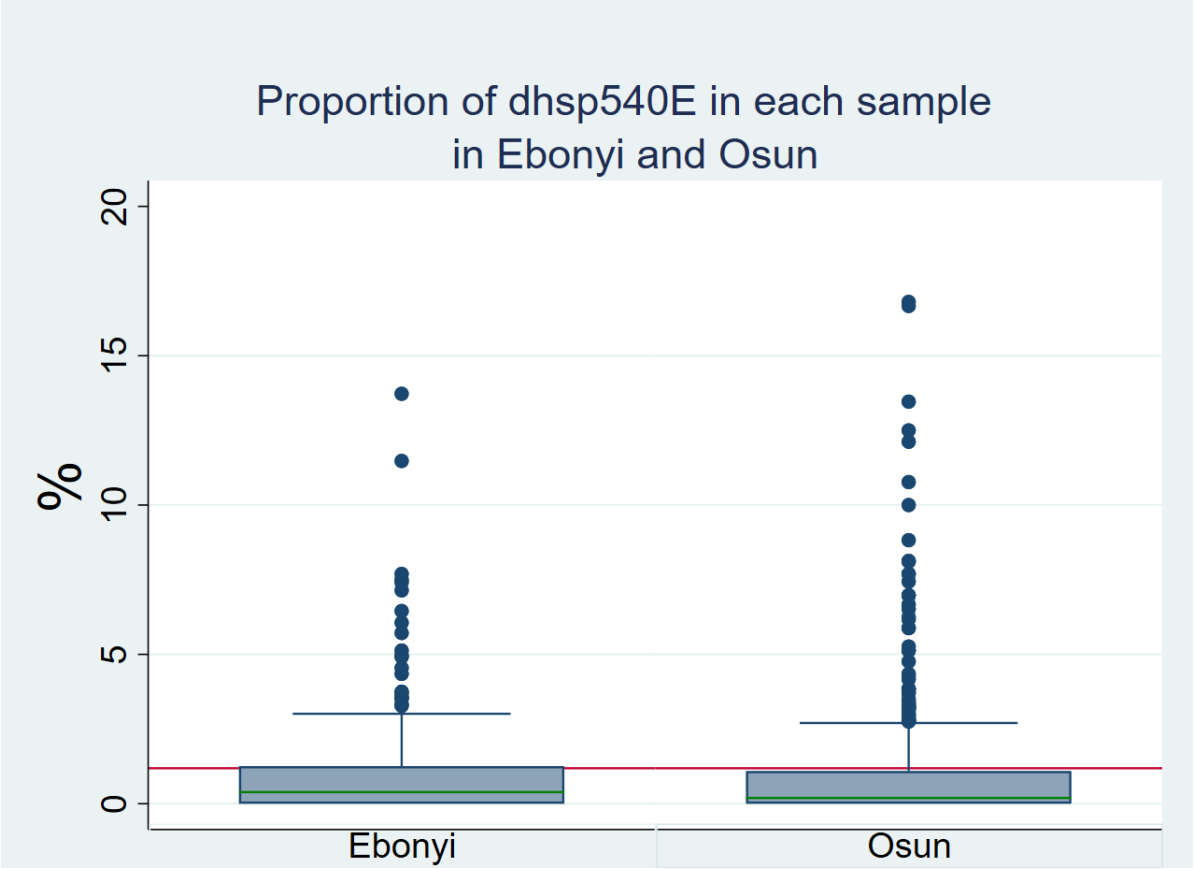
Results

- A higher concentration of the mixed variant was found in Ebonyi than in Osun (21.1 vs 16.5 percent); the difference was not statistically significant (p=0.069, 95% CI 0.52–1.04).
- Highest prevalence of the dhps-K540E variant in Ebonyi and Osun were: Izzi (33.3 percent) and Orolu (23.3 percent), respectively.
- Lowest prevalence: Ezza-North (6.8 percent) and Ede South (6.3 percent), respectively.
- No isolates carried the dhps-540E alone.



Results

- We also investigated dhps-K540E further to determine the proportion of dhps-540E variant in the mixed infection.
- The mean proportion of dhps-K540E (number of 540E variants per sample) circulating in the two states was very low, ranging from one to 16.8 percent (mean= 2.75 percent)
- Mean proportion of mutants per sample was slightly higher in Osun compared to Ebonyi; the difference was not statistically significant.



Conclusion

- The low prevalence of dhps-540E in Ebonyi and Osun is reassuring, and confirms both states are suitable for PMC implementation.
- The parasite prevalence and molecular marker frequency data reported here provide a well-defined baseline against which the impact of scale-up and sustained use of SP as PMC in Nigeria can be assessed.
- Careful monitoring of SP resistance markers will be required during the large-scale administration of SP to children as a chemoprevention strategy.

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