

## Performance of Diagnostic Methods for Detection of Drug Resistance Among New Cases of *Mycobacterium tuberculosis*

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### ABSTRACT

**OBJECTIVE** The increasing incidence of new cases of drug resistant-TB (DR-TB) infection is worrisome, with high rates of new pulmonary morbidities occurring mostly among the vulnerable populations. The performance of diagnostic methods of GeneXpert MTB/RIF assay and phenotypic Drug Susceptibility Test (pDST) for detection of drug resistance among new cases of *Mycobacterium tuberculosis* (MTB) infections was evaluated.

**METHODS** Sputum samples (n = 546) from newly suspected MTB cases were analysed for phenotypic drug resistance using BACTEC MGIT (B-MGIT) and genotyped with xpert MTB/RIF assay. The predictive performance of B-MGIT culture-based methods and xpert MTB/RIF assay for MTB detection were determined.

**RESULTS** Of the collected sputum samples (n = 546), the highest rates of phenotypic drug resistance (66.7%) were AFB3+ smear positive and MTB with detection rates of 98.2% and 92.7%, respectively, with B-MGIT and Xpert MTB/RIF ( $p = 0.63$ ). B-MGIT detected higher resistance rates to isoniazide (*inh*) and rifampicin (*rif*) of more than 60.0%, and less than 20% resistance to ofloxacin (*ofx*) and protionamide (*proth*) compared to Xpert ( $p < 0.05$ ). B-MGIT had a higher detection rate (98.2%), sensitivity (87.8%), specificity (91.4%), positive predictive value (PPV) (95.8%) (95%CI: 0.778-1.04;  $p = 0.001$ ) and likelihood of detection of rifampicin resistance (OR:5.76;95%CI:1.01-7.56) compared to Xpert MTB/RIF methods. B-MGIT provided higher AUC-rifampicin of 0.9339 (95%CI: 0.8398 to 1.000) than gene xpert (AUC-rifampicin = 0.9019 [95%CI: 0.7899 to 1.000]). B-MGIT is needed for further confirmation of new cases of MTB identified from acid-fast bacilli (AFB) smear positive sputum.

**CONCLUSIONS** The inclusion of B-MGIT examination of sputum in new TB cases would enhance early detection of drug resistant MTB, mostly from rifampicin negative sputum investigated with GeneXpert and mostly in low resource settings.

**KEYWORDS** acid-fast bacilli, tuberculosis, MDR-*Mycobacterium tuberculosis*, rifampicin, resistance predictor

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## INTRODUCTION

Tuberculosis (TB), caused by the *Mycobacterium tuberculosis* (MTB), remains a global health challenge. Continuing health campaigns, detection and treatment have improved in several specific locations in developing countries, particularly in Nigeria (1). In 2020, Nigeria was ranked first in Africa with a rising death rate of up to 1.5 million and 4<sup>th</sup> globally in reported TB cases (1, 2). The increasing incidence of new cases of drug-resistant TB (DR-TB), resistant to either or both of the 2 first-line drugs, isoniazid and rifampicin, among vulnerable Nigerian populations continues to complicate the TB infection prevalence as well as TB treatment. New *Mycobacterium tuberculosis* complex (MTBC) infections characterized with multidrug-resistance pose challenges to both local and global TB control (3). There are few reports of baseline resistance globally among new TB cases, but resistance is becoming a worrisome situation with a record of one out of five new cases showing resistance (4). DR-TB is defined as a laboratory-confirmed resistance to one or more of the first-line anti-TB drugs, indicating a mono- or poly-resistance pattern (5, 6).

In the recent past, multidrug-resistant tuberculosis (MDR-TB) has become a leading cause of pulmonary morbidity and death, particularly among the populace with declining socio-demographic status (7, 8). Self-medication for respiratory infections without diagnosis among various age groups and both genders further enhances drug resistance patterns, mostly among lower economic status populations, thereby intensifying resistance to MTB and isoniazid (9, 10). Despite the use of acid-fast bacilli (AFB) microscopy in several locations, the reliability of that method is fast declining due to the variability of its sensitivity, inadequate expertise and poor-quality controls, leading to misdiagnosis of TB cases (11). A culture-based method is the gold standard for detection of TB, one which would also provide testing for drug resistance. That would, however, require expensive laboratory infrastructure and expertise (12). The continuing emergence of drug resistance MTB among new cases is a challenge to public health. Application of rapid molecular methods for diagnosis and identification of rifampicin resistance such as the GeneXpert (Xpert) MTB/RIF system is considered an effective di-

agnostic method. This system is currently employed for pulmonary TB detection among the Southwest Nigerian population. The use of MTB resistance as a surrogate marker for GeneXpert MTB/RIF assay and the phenotypic Drug Susceptibility Test (pDST) in Bactec mycobacteria growth indicator tube (B-MGIT) provide precise and reliable detection for new TB cases with resistance (13).

The application of a trained the receiver operating characteristic curve (ROC) model for predictive performance of commonly GeneXpert MTB/RIF and B-MGIT at designated centres, mostly in rural communities in Southwest Nigeria, needs to be evaluated. Evaluation of the comparative performance of these diagnostic tools would help prevent inconsistencies between phenotypic detection (pDST) and genotyping (Gene Xpert), would better inform clinical management of new resistance cases, and would reduce ineffective treatment. To that end, this study aims to review and evaluate the performance of the diagnostic methods GeneXpert MTB/RIF assay and pDST using B-MGIT for detection of drug-resistant *M. tuberculosis* infections among new TB cases.

## METHODS

### Ethical approval

Approval for the study protocols and collection of the samples was obtained from the Covenant Health Research Committees, Covenant University, Ota, Nigeria (CHREC/055/2022) and the Federal Medical Centre, Abeokuta (FMCA/470/HREC/02/2022). These Institutional Review Boards granted ethical approval with the caveat of the exclusion of the patient's personal data and identifiers. All personal information about the participants was treated confidentially.

### Sample collection

Between February 2022 and June 2023, a total of 546 AFB positive sputum samples were collected from both suspected and clinically diagnosed MTB patients at the outpatient clinic of the Federal Medical Centre, Abeokuta, which serves as referral facility for the management and treatment of respiratory infections in Southwest Nigeria. This facility also received samples from two annexed DOT-TB Treatment centers and 23 Primary Health Care facilities providing health services to rural communities in southwest

Nigeria. Patients were initially screened for TB at various adjoining facilities using ZN-AFB sputum smear microscopy. For smear-positive new cases collected using a generalized and randomized method, further confirmation was performed with Xpert MTB/RIF assay and phenotypic drug sensitivity testing (pDST Bactec MGIT) at referral centre. This study has limitations related to insufficient data from adjoining facilities, mainly due to difficulty with diagnostic regents, patients' unwillingness and/or inability to provide sputum and inadequate access to required equipment (GeneXpert) in some communities.

### **Xpert MTB/RIF assay**

AFB smear-positive samples received were further analysed for MTBC and Rifampicin (rif) drug resistance using GeneXpert (Cepheid Inc., Sunnyvale, CA, USA) as previously discussed (14, 15). Briefly, each sample maintained in a leak-proof sputum collection container was analysed with GeneXpert MTB/RIF sample reagent in a 2:1 (v/v) ratio (14). The mixture was transferred to a GeneXpert cartridge containing the required solution for nucleic acid amplification which simultaneously detects MTB complex DNA and the *rpoB* gene associated with MTB resistance (15, 16).

### **Phenotypic drug sensitivity testing (DST)**

Drug susceptibility of the identified MTB/RIF isolates was determined using MTB using the Bactec MGIT 960 system (B-MGIT). Briefly, LJ-culture positive MTB/RIF isolates were sub-cultured and 100 µL aliquot suspension of the isolate was prepared and cultured in an MGIT 960 system. Preparations of reconstituted antibiotics from lyophilized drugs were made into a different final concentration of MTB, 1.0 µg/mL, following previously described protocol (17). To the control tubes, 0.5 mL of Growth Control working solution was added and labeled as drug-free MGIT, and the other drug-containing tubes were labeled S, I, R and E. The results were interpreted in growth units (GU). As the growth control (GC) reached a minimum value of 400 and the GU values of both DST sets were read and recorded. Quality control was observed by testing the batch of MGIT medium, SIRE Kit and PZA kit with *M. tuberculosis* H37Rv strain (18). Safety precautions taken in-

cluded that the liquid culture using the BACTEC MGIT system assay was performed in a biosafety cabinet (BSL-2<sup>+</sup>) with appropriate personal protective equipment (PPE). All procedures were conducted in accordance with specific protocols approved by the Covenant Health Research Ethics Committee, Covenant University, Ota, Nigeria (CHREC/055/2022), and the Federal Medical Centre, Abeokuta (FMCA/470/HREC/02/2022). Strict aseptic techniques were employed to prevent contamination and aerosolization. All biological waste was decontaminated before disposal.

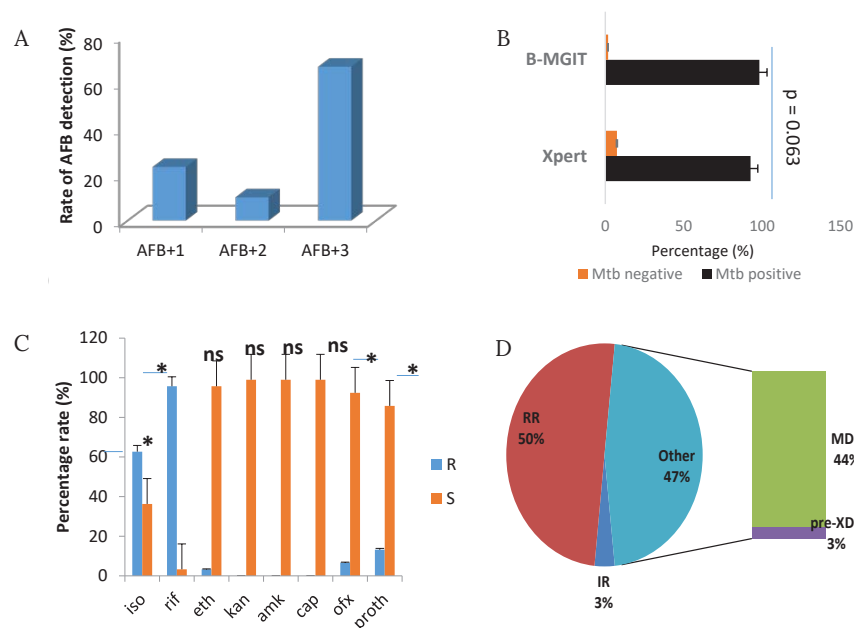
### **Data analysis**

Independent variables from the hospital database, including age and gender (male or female), smear AFB reports and DR-TB patterns, were categorized and analysed using descriptive tools. Comparative evaluation of the detection rate of the Gene Xpert and MGIT960 culture-based method was used to determine the positive predictive values (PPV) at 95% confidence interval ( $p < 0.05$ ). GeneXpert and MGIT960 outcomes for new cases were analysed using multivariate regression for likelihood detection of resistance to MTB and estimation of odds ratios at the 95% confidence interval (CI), establishing a significant association at a  $p < 0.05$ . Predictive performance was determined using the area under the curve (AUC) of the receiver operating characteristic curve (ROC). The ROC, which operates on the coding of the strain as susceptible and resistant at the susceptibility level used for the phenotypic DST, was derived from the co-ordinates and reliability provided by the AUC. drawn at values closer to 1 and unreliable at 0.50 or less were considered (19).

## **RESULTS**

### **Detection of MDR-TB among new cases**

Of the 546 sputum samples, preliminary AFB staining indicated AFB 3+ (66.7%), AFB +2 (10.1%) and AFB +1 (23.2%) as smear positive. A total of 506 (92.7%) were confirmed *M. tuberculosis* positive with Gene Xpert and 534 (98.2%) with B-MGIT with no significant difference in detection rates (Figure 1A and 1B). Overall drug susceptibility testing performed with B-MGIT indicated higher significant resistance rates of more than 60.0%



**Figure 1.** (A) Distribution of AFB smear positive cases recorded in new infections, (B) proportion of confirmed MTB cases, (C) anti-TB resistance rates using the B-MGIT pDST, (D) distribution of the recorded RR, IR, MDR and pre-XDR (R, resistance; S, susceptible; ns, not significant; iso, Isoniazid; RIF, rifampicin; eth, ethambutol; kan, kanamycin; AMK, amikacin; cap, capreomycin; OFX, ofloxacin; proth, protionamide; RR, rifampicin resistance; IR, isoniazid resistance; MDR, multi-drug resistance; XDR, extensive drug resistance. \* $p < 0.01$ ; \*\* $p < 0.05$ ).

to isoniazide (inh) and MTB and less than 20% resistance to ofloxacin (ofx) and Protionamide (proth) (Figure 1C) compared to MTB (RR; 50.0%), isoniazid (IR; 3.0%), MDR (44.0%) and pre-XDR (3%) recorded with GeneXpert (Figure 1D).

### MTB infection demography by gender and age

Among the new culture-confirmed pulmonary TB cases with resistance to anti-TB drugs, a higher percentage (29.7%) showed significant MTB resistance infection (RR) compared to MDR (23.1%) (OR [95%CI:] = 53.1 [42.5-60.2]) among the male subjects. Of the female subjects, 26.4% and 19.8% were infected with MTB resistant-MTB and MDR-MTB (OR [95%CI:] = 48.4 [31.6-61.5]) strains, respectively, while 3.3% pre-XDR were observed (\* $p < 0.01$ ; Figure 2A). Among the newly detected cases, high rates of MTB resistance (RR) (32.9%) and MDR (26.4%) were recorded for age groups 16-30 years (6.6%) (OR [95%CI:] = 3.63 [0.25-5.05]) and 31-50 years (26.4%) (OR [95%CI:] = 3.81 [1.01-7.62]), respectively. More than 3.0% of MDR, RR and pre-XDR strains were recorded among ages 0-15 years (OR [95%CI:] = 3.27 [0.82-7.39]) (Figure 2B).

### Comparative performance of Xpert MTB/RIF assay and B-MGIT960 culture-based methods

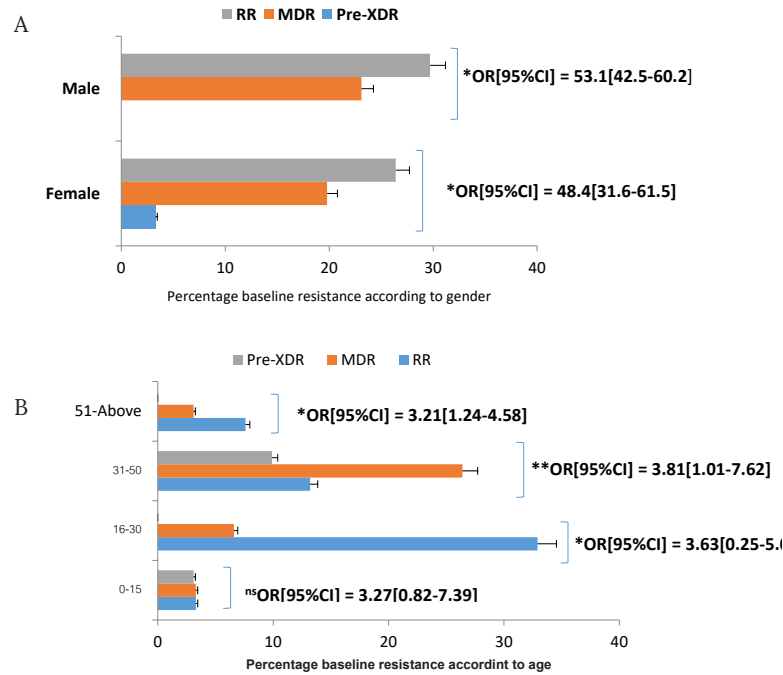
Of the new cases of MTB drug resistance infection, B-MGIT had a higher detection (98.2%), sensitivity (87.8%), specificity (91.4%), and PPV (95.8%) (95%CI: 0.778-1.04;  $p = 0.001$ ) compared to Xpert MTB/RIF methods (Table 1). Likelihood of detection of resistance to MTB by B-MGIT assay was higher (OR: 5.76; 95%CI: 1.01-7.56) compared to Xpert MTB/RIF methods (OR : 2.64; 95%CI: 0.39-6.32) based on multivariate regression analysis (Table 1).

### Predictive performance of B-MGIT and Gene Xpert for detection of resistance

Predictive performance of the assay methods for the detection of resistance was determined based on the calculated ROC, AUC. The predictive performance of B-MGIT using the ROC model was higher for AUC-MTB at 0.9339 (95%CI: 0.8398-1.000) compared to Gene Xpert at 0.9019 (95%CI: 0.7899-1.000) as shown in Figure 3.

### DISCUSSION

The present study considered the comparative performance of Xpert MTB/RIF and B-MGIT for the detection of drug resistant MTB among

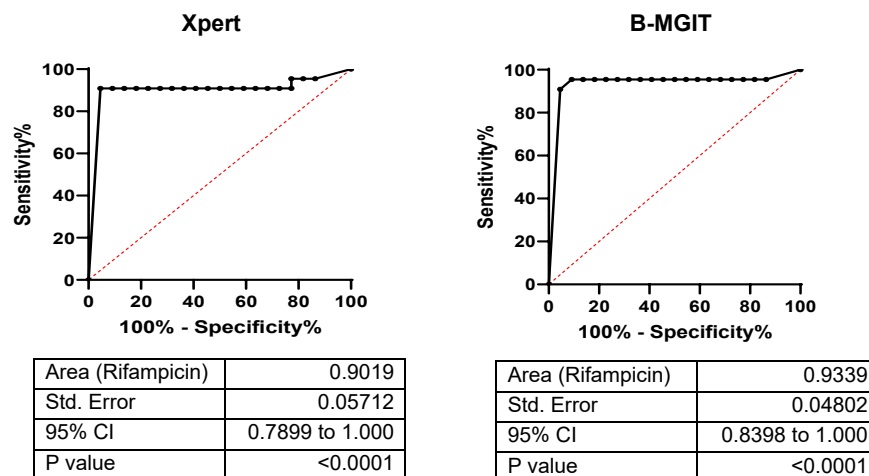


**Figure 2.** (A) Resistant MTB infection rates by gender distribution, (B) proportion of MTB resistance pattern based on age distribution. (ns, not significant; \* $p < 0.01$ ; \*\* $p < 0.05$ , RR, rifampicin resistance; XDR, extensive drug resistance; MDR, multi-drug resistance; mono-DR, mono-drug resistance)

**Table 1.** Comparative performance of Xpert MTB/RIF assay and MGIT960 culture-based methods for detection of drug resistance strains among new cases

| Method        | Detection performance            |             |             |         |             |           |
|---------------|----------------------------------|-------------|-------------|---------|-------------|-----------|
|               | Detection rate (%)               | Sensitivity | Specificity | PPV     | 95%CI       | p-value   |
| Xpert MTB/RIF | 92.6                             | 81.6        | 80.1        | 81.3    | 0.812-0.984 | 0.001     |
| B-MGIT        | 98.2                             | 87.8        | 91.4        | 95.8    | 0.778-1.040 |           |
|               | Multivariate regression analysis |             |             |         |             |           |
|               | B                                | SE          | t-value     | p-value | Odds ratio  | 95%CI     |
| Xpert MTB/RIF | 1.43                             | 0.49        | 0.001       | 0.023   | 2.64        | 0.39-6.32 |
| B-MGIT        | 1.57                             | 0.54        | 0.001       | 0.001   | 5.76        | 1.01-7.56 |

PPV, positive predictive value



**Figure 3.** Predictive performance of rifampicin detection by diagnostic method

new TB cases from designated locations in south-west Nigeria. The smear AFB is considered a routine diagnostic method for the early phenotypic detection of MTB in many facilities, most located in rural settings. Due to low detection rates and other limitations of smear microscopy for MTB diagnosis, false TB detection continues to enhance the spread of the infection and misdiagnosis has grave implications for mortality rate, transmission and delay of appropriate therapy (20). As clinical pulmonary morbidity persists among the patients, there is an increase in the use of drugs (antibiotics) to treat any perceived respiratory infections, thereby causing development of more resistance strains (21). This is further substantiated by the high resistance observed among new cases of MTB infections to the first-line anti-TB drugs (MTB and isoniazid), suggesting a new mono-resistance pattern. The recorded MDR and pre-XDR among the newly detected strains is a new report which is similar to that reported in Mumbai, India (22). The observed MDR resistance among the new cases of MTB call for urgent and strategic population-based surveillance, including appropriate control of antibiotic use for pulmonary infections.

The gender and age demography further reveals the infection pattern among the population. Clinically diagnosed new MTB/RIF (Rifampicin resistance *M. tuberculosis*) among male and female subjects could be attributed to the use of antibiotics for the treatment of bacterial infections other than MTB (23, 24). Mono-DR MTB infections among male and female patients in the age groups 16–30 and 31–50 years has similarly been reported (25, 26), suggesting possible spread and transmission of MTB due to the mobility of these age groups, motivated by a desire for socio-economy improvement (27). As the MTB infection rate increases among both genders and various age ranges, there is a need for more precise diagnostic methods.

GeneXpert MTB/RIF assay is as the most rapid test for diagnosis of MTB approved by the WHO (28). It has priority as a diagnostic method because of its speed, reliability, and economic advantages (16). GeneXpert employs a DNA-PCR technology for simultaneous detection of MTB and MTB resistance (*rpoB* gene) (5). Gene Xpert is commonly used in several facilities due to the advantages of being rapid with lower cost, B-MGIT

showing higher detection, sensitivity, specificity and likelihood of the detection of resistance to MTB than the Xpert MTB/RIF methods. Several reports have stated that the GeneXpert MTB/RIF assay has proved to be both sensitive and specific, with considerable PPV for the detection of MTB resistant MTB (29–31). However, the B-MGIT culture-based method with phenotypic DST (pDST) offers accurate and timely pulmonary MTB detection, drug sensitivity testing and effective treatment (32). The assessment of Gene Xpert performance observed in this study indicates it has a lower sensitivity and specificity compare to B-GMIT for detection of new MTB cases. This outcome could be attributed to low abundance of MTB in the submitted samples for Gene Xpert detection. Adequate training and periodic re-training of technical staff handling the genotyping protocol could effectively enhance detection performance. B-MGIT (pDST) is more sensitive and specific, and is available in referral centres for drug resistance detection and estimation. It is not usually distributed to resource-limited communities because it requires advanced laboratory infrastructure, trained staff and adequate quality assurance for detection of low level (smear or Gene Xpert negative) resistant isolates and standardized minimum inhibitory concentration (MIC) evaluation (33).

The ability of B-MGIT to predict resistance in MTB is higher (AUC-MTB = 0.9339) compared to Gene Xpert (AUC-MTB = 0.9019). The high predictive power of B-MGIT to infer MTB resistance in new cases of MTB infection could enhance disease prognosis, therapeutic management of pulmonary MTB, reduction in pulmonary morbidity, and identification of resistant mutations at a very early stage and reduce ineffective treatment (34, 35). Because of the discriminatory potential of the ROC model for mono-drug resistance of MTB by pDST and Gene Xpert described in this study, it would be possible to predict the phenotypic and genotypic occurrence of drug-resistant MTB. This improved predictive performance would aid identification of essential diagnostic methods for the prevention of unfavorable resistance outcomes, development of patient-centered prognostic assessment and would also increase the possible chances for MTB cure (36). The application of ROC also provides prediction of potential MTB

resistance in new cases of MTB, and strengthens the prevention of MDR-TB transmission in many communities (37). It would also afford an advantage in the selection of single and combinations of appropriate anti-TB drugs for clinical management and treatment. However, this study has some limitations. Sample size calculation was not employed in the study due to the limited number of patients already presumed to have TB with clinical presentations and smear AFB positivity but with negative Gene Xpert outcomes. This population was over-estimated during clinical assessment, and sputum culture, the gold standard, was not performed at an early stage of the infection, leading to the possible exclusion of some new TB cases.

## CONCLUSIONS

The use of the AFB smear report for assessment of new cases of MTB infections in studied locations is not adequate for MTB diagnosis. Analysis of gender and age demography further support the increasing incidence of resistant MTB among the populace, thereby suggesting a need for more precise diagnostic methods rather than AFB microscopy alone. Further assessment with B-MGIT would enhance detection and provide precise evaluation of drug resistant MTB in new cases of TB infections and supposed negative cases. Sputum outcomes of the GeneXpert MTB/RIF assay deployed to some health facilities may not be sufficient for diagnosis of MTB among AFB smear positive cases which could miss atypical types. Investigation of GeneXpert with B-MGIT examination could further confirm both MTB strains and resistance profiles for more adequate clinical management.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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## AUTHOR CONTRIBUTION

P.A.A.: conceptualization, methodology, data curation, project administration, supervision, investigation, resources, visualization, writing – original draft preparation, software, writing – review & editing; O.E.: methodology, data curation, project administration, supervision, investigation, formal analysis, resources, visualization, writing – original draft preparation, software, writing – review & editing; O.C.A.: methodology, data curation, project administration, visualization, writing – original draft preparation, software, writing – review & editing; K.S.A.: methodology, data curation, investigation, formal analysis, writing – original draft preparation, software, writing – review & editing; J.O.A.: conceptualization, methodology, data curation, resources, visualization, software, writing – review & editing; O.E.O.: data curation, project administration, investigation, formal analysis, visualization, writing – review & editing; C.P.N.: investigation, formal analysis, resources, visualization, software, writing – review & editing; Z.I.A.: data curation, investigation, formal analysis, resources, visualization; A.A.A.: methodology, data curation, investigation, visualization, writing – original draft preparation, software, writing – review & editing; T.T.B.: conceptualization, methodology, project administration, supervision, investigation, formal analysis, resources, software, writing – review & editing

All authors consent to the publication of the identifiable details of the text.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## INSTITUTIONAL REVIEW BOARD STATEMENT

Approval for the study protocols and collection of the samples were obtained from the Covenant Health Research Committees, Covenant Univer-

sity, Ota, Nigeria (CHREC/055/2022) and Federal Medical Centre, Abeokuta (FMCA/470/HREC/02/2022). These Institutional Review Boards granted ethical approval with evidence of the exclusion of the patient's personal data and identifiers.

## INFORMED CONSENT STATEMENT

Informed consent of all the recruited participants was at the commencement of the study. All personal information about the participants was treated confidentially.

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