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Original Article **Open Access**

Bridging diagnostic gaps of drug-resistant pulmonary tuberculosis with clinical diagnosis in a low-and middle-income state, southwest Nigeria: A secondary data analysis

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Abstract:

Background: Drug-resistant tuberculosis (DR-TB) poses a significant challenge to global TB control efforts, particularly in low- and middle-income countries (LMICs) where diagnostic resources are limited, thereby widening treatment gap. This has increased morbidity and mortality due to TB in Sub-Saharan Africa. We sought to evaluate the role of clinical diagnosis in identifying DR-TB in pulmonary TB cases missed by the sputum GeneXpert MTB/RIF assay in Ekiti State, Nigeria.
Methodology: A secondary data analysis was conducted using the 2024 National Tuberculosis, Leprosy and Buruli Ulcer Control Programme (NTBLCP) register in Ekiti State. Data on demographics, diagnostic methods, and resistance patterns were extracted and analyzed using descriptive statistics.
Results: Among 28 DR-TB cases identified, GeneXpert MTB/RIF assay detected only 53.6% (n=15), missing 46.4% (n=13) which were subsequently identified through clinical suspicion followed by Line Probe Assay. MDR-TB accounted for 46.4% (n=13), rifampicin mono-resistance for 39.3% (n=11), and isoniazid mono-resistance for 14.3% (n=4). Two cases of pre-XDR TB were observed among people living with HIV, both of whom had false-negative GeneXpert results. The average diagnostic delay from GeneXpert testing to LPA-based diagnosis was 16 days.
Conclusion: Clinical evaluation is critical in bridging diagnostic gaps created by false-negative GeneXpert results, ensuring timely identification and treatment of DR-TB.

Keywords: Diagnostic gaps, Nigeria, GeneXpert, Tuberculosis

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Combler les lacunes diagnostiques de la tuberculose pulmonaire pharmacorésistante par le diagnostic clinique dans un État à revenu faible et intermédiaire du sud-ouest du Nigéria: Une analyse de données secondaires

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Résumé:

Contexte: La tuberculose pharmacorésistante (TB-DR) représente un défi majeur pour la lutte mondiale contre la tuberculose, en particulier dans les pays à revenu faible et intermédiaire (PRFI) où les ressources diagnostiques sont limitées, ce qui creuse l'écart de traitement. Cette situation a entraîné une augmentation de la morbidité et de la mortalité liées à la tuberculose en Afrique subsaharienne. Nous avons cherché à évaluer le rôle du diagnostic clinique dans l'identification de la TB-DR chez les patients atteints de tuberculose pulmonaire non détectés par le test GeneXpert MTB/RIF sur expectorations dans l'État d'Ekiti, au Nigéria.
Méthodologie: Une analyse secondaire des données a été réalisée à partir du registre 2024 du Programme national de lutte contre la tuberculose, la lèpre et l'ulcère de Buruli (NTBLCP) de l'État d'Ekiti. Les données démographiques, les méthodes diagnostiques et les profils de résistance ont été extraits et analysés à l'aide de statistiques descriptives.
Résultats: Parmi les 28 cas de tuberculose pharmacorésistante (TB-DR) identifiés, le test GeneXpert MTB/RIF n'en a détecté que 53,6 % (n = 15), manquant ainsi 46,4 % des cas (n = 13), qui ont été ultérieurement identifiés grâce à la suspicion clinique, suivie d'un test de génotypage par sonde linéaire (LPA). La tuberculose multirésistante (TB-MR) représentait 46,4 % des cas (n = 13), la monorésistance à la rifampicine 39,3 % (n = 11) et la monorésistance à l'isoniazide 14,3 % (n = 4). Deux cas de tuberculose pré-ultrarésistante (pré-TB-XDR) ont été observés chez des personnes vivant avec le VIH ; ces deux cas présentaient des résultats GeneXpert faussement négatifs. Le délai diagnostique moyen entre le test GeneXpert et le diagnostic par LPA était de 16 jours.
Conclusion: L'évaluation clinique est essentielle pour pallier les lacunes diagnostiques dues aux résultats faussement négatifs du test GeneXpert, garantissant ainsi une identification et un traitement précoces de la TB-DR.

Mots-clés: Lacunes diagnostiques, Nigéria, GeneXpert, Tuberculose

Introduction:

Drug-resistant tuberculosis (DR-TB) is drug-resistance of *Mycobacterium tuberculosis* to any of the most effective medications used in treatment regimens of TB. DR-TB can be grouped as secondary drug resistance when it results from an on-going resistance acquisition or primary drug resistance when it is from person-to-person transmission in a treatment-naive (new) patient (1). It can also be categorized as mono-drug resistance, in which there is resistance to only one drug used for treatment. Poly-drug resistance is resistance to at least two drugs used for TB treatment but not isoniazid and rifampicin. Multidrug-resistance (MDR-TB) is resistance to at least isoniazid and rifampicin, the most effective first-line TB treatment drugs. Another form of DR-TB is pre-extensively drug-resistant TB (pre-XDR TB) where *M. tuberculosis* is resistant to isoniazid, rifampicin and a fluoroquinolone. The last form of DR-TB is extensively drug-resistant TB (XDR TB) which has a resistance profile to isoniazid and rifampicin, a fluoroquinolone, and either bedaquiline or linezolid (1–3).

The initiative for eliminating TB cannot be successful until DR-TB is adequately stemmed (4). DR-TB is part of the broader framework of global antimicrobial resistance (AMR) occurrence which is estimated to accrue more morbidity and mortality in Africa (5). DR-TB is estimated to cause 13% of all AMR-attributable deaths worldwide (6). Nigeria is recently ranked 6th among 30 high-burden TB countries globally and 14th among countries with DR-TB based on estimated incidence of MDR-TB while the national MDR-TB burden is estimated to be 21,000 annually (7). Further, the prevalence of MDR-TB in Nigeria is estimated at 4.3% among new TB cases (treatment-naive) and 25% among previously treated cases (8). A pooled Southwestern region prevalence in Nigeria of MDR-TB in 2023 was about 13.8% (9) despite the pragmatic approach of combating DR-TB in Ekiti State with early identification and management of DR-TB cases.

Diagnostic and treatment gaps appear to worsen the present situation, deterring the achievement of the end TB strategy (4). Initial diagnosis of pulmonary TB (PTB) is majorly by sputum GeneXpert MTB/RIF assay (7). Although this diagnostic has an impressive predictive value, it could still present with false-negative results in some circumstances (10). This would require heightened clinical evidence to bridge the apparent diagnostic gap to achieve a good clinical outcome. We therefore identified the relevance of clinical diagnoses in supplementing diagnostic gaps of DR-TB in Ekiti State, Nigeria.

Materials and method:

A secondary data analysis was conducted using the 2024 register of the National Tuberculosis, Leprosy and Buruli Ulcer Control Programme (NTBLCP) in Ekiti State, Nigeria. The register included patients diagnosed with DR-TB across various local government areas within the State. Data extracted from the register included patient demographics (age, sex),

HIV status, mode of TB diagnosis (GeneXpert MTB/RIF assay, line probe assay [LPA], and/or culture), drug-resistant patterns, TB treatment category (new or previously treated), and diagnostic timelines. Only confirmed DR-TB cases recorded in the 2024 register were included. Incomplete entries or unverified diagnoses were excluded from analysis.

Ethical approval for this study was obtained from the Ekiti State Ministry of Health and Human service Ethics Committee**.** Approval number MOH/EKHREC/EA/P/139**.** No individual identifiers were collected. Dataset was stored a pass-worded computer and could only be accessed by authors for analysis.

Descriptive statistics, including frequencies and percentages were used to summarize the data. Trends in diagnostic outcomes and resistance patterns were also described. Graphical representations were generated for geographic distribution and DR-TB categories.

Results:

A total of 28 people were diagnosed with drug-resistant TB in 2024, with female to male ratio of 9 to 19 and mean age of 38±13.8 years. Only four patients (14.3%) were people living with HIV/AIDS (PLWHA) and were on anti-retroviral medications as at DR-TB diagnosis. Of these, 1 was a new case, while the other 3 were previously treated TB cases (relapse or treatment after follow-up). Furthermore, 2 of the 4 (50%) PLWHA had false-negative sputum GeneXpert MTB/RIF assay.

Sputum GeneXpert MTB/RIF assay identified 15 (53.6%) of the 28 patients as DR-TB and missed 13 (46.4%). These 13 sputum GeneXpert MTB/RIF assay-negative cases were evaluated on clinical premise with(out) radiology, which necessitated further sputum analysis using line probe assay (LPA). LPA was positive in all the 28 DR-TB cases (sputum GeneXpert MTB/RIF assay positive and negative) with highest identification as MDR-TB (13/28, 46.4%), followed by rifampicin mono-resistant TB (11/ 28, 39.3%) and isoniazid mono-resistant TB (4/28, 14.3%) (Fig 2). In addition, LPA identified the second line anti-TB drug resistance in 2 HIV-positive patients showing intermediate susceptibility to both fluoroquinolones and aminoglycosides in one and only fluoroquinolones in another, indicating pre-XDR.

For those with false-negative sputum GeneXpert MTB/RIF assay, the timeline difference between a negative sputum GeneXpert MTB/RIF assay and a positive LPA, which necessitated initiation of DR-TB medications, was averagely 16±23 days. Of the 9 (32.1%) patients who had subsequent culture of sputum for further analysis, only 4 (44.4%) were culture positive. Only one patient (3.6%) died from this pool of patients managed as DR-TB in 2024.

Fig 1 displayed the distribution of the DR-TB cases by Local Government Areas in Ekiti State, with Ado-Ekiti having the highest frequency of cases (35.7%, n=10) in the State. Fig 2 displayed the frequency of the DR-TB patients' category with drug-resistance patterns using LPA, with MDR-TB mostly seen in persons who has been previously treated for TB. Fig 3 displayed the distribution of sputum GeneXpert MTB/RIF assay results among DR-TB patients' category, with false-negative sputum GeneXpert MTB/RIF assay prevalent in previously treated TB cases (61.5%, n=8/13).

Fig 4 presented the prevalence of DR-TB in Ekiti State over the three-year period of the study, which showed an initial high rate of 5.1% (n=23/450) in 2022, followed by a decline to 2.9% (n=15/515) in 2023 and a rise to 3.5% (n=28/781) in 2024.

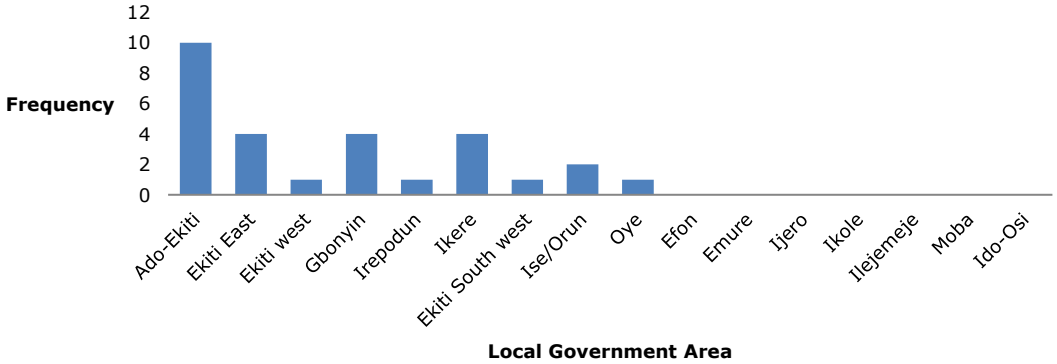

Fig 1: Distribution of drug-resistant tuberculosis (DR-TB) cases by Local Government Areas in Ekiti State, Nigeria, 2024.

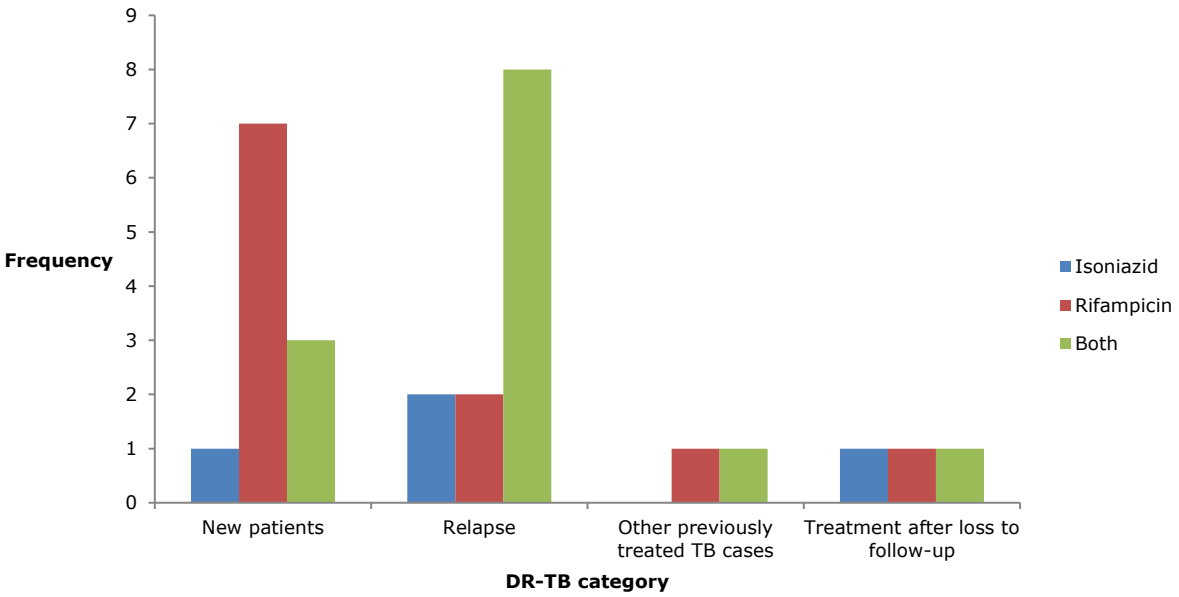

Fig 2: Distribution of drug-resistant tuberculosis (DR-TB) patients with drug-resistance patterns using LPA in Ekiti State, 2024

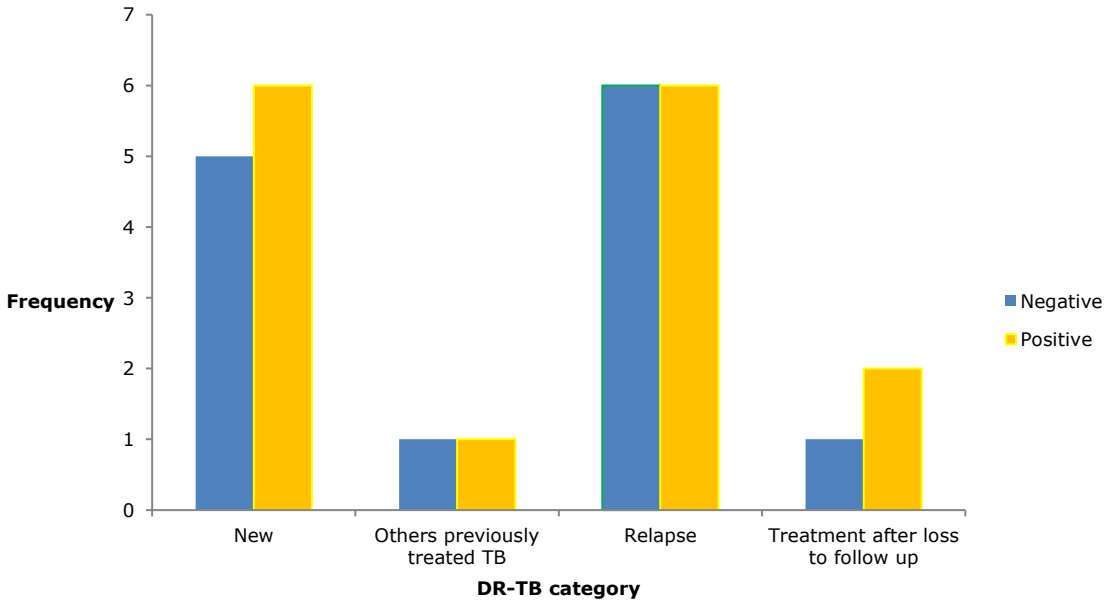

Fig 3: Distribution of sputum GeneXpert results among drug-resistant tuberculosis (DR-TB) patients' category

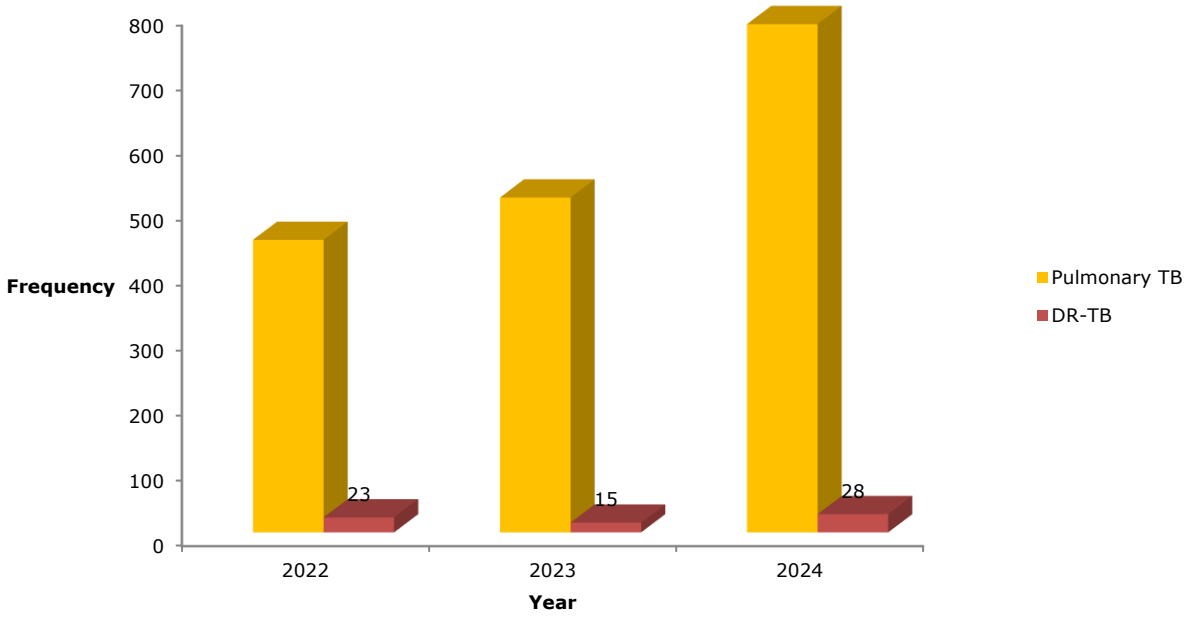

Fig 4: Frequency of pulmonary and drug-resistant tuberculosis in Ekiti State, Nigeria, over a 3-year period

Discussion:

The occurrence of DR-TB is a global challenge, and its burden is more observed in Sub-Saharan Africa due to many factors such as inadequate TB diagnostics, limited access to quality healthcare and relative inaccessibility to anti-TB medications amidst other social factors (9,10). This has contributed to ineffective drug uptake of DR-TB medication by about 40% (11). Clinical diagnosis of TB has apparently increased presumptive cases of TB where diagnostic gap exists. Further confirmation with more specific TB diagnostics such as line probe assay and or culture would be helpful in early identification and commencement of anti-TB medications. Hence, diagnostic and treatment gaps ensue when the initial TB diagnostics fail.

In our study, Ado-Ekiti had the highest number of DR-TB cases (n=10, 35.7%) in the State. Being the state capital and urban area with population density estimated about 1,100/km^2 (12), Ado-Ekiti may be over-crowded according to the minimum density for such a landscape (13). Over-crowding is a known factor for person-to-person transmission of pulmonary TB (9). DR-TB was identified mostly in TB-relapse patients and secondarily in new patients (treatment–naive). The global proportion trend of DR-TB shows similar occurrence where DR-TB is seen in previously treated patients than in new patients (2). While the TB-relapse patient had a high rate of MDR-TB (i. e. resistance to both isoniazid and rifampicin), the new patients had rifampicin mono-resistance (RMR) as most prevalent drug-resistant pattern. MDR-TB still remains the major drug-resistant pattern observed in TB (2,14) and their occurrence in previously TB treated patients is not unexpected due to inadequate drug compliance, or drug pharmacokinetics in the individuals (1,5).

The diagnosis of RMR is usually done with LPA which was adopted by the WHO for testing DR-TB (6,15). This increasing RMR is gaining global attention, although studies are sparse on its occurrence, it has been noted to be associated with HIV and with poorer clinical outcomes (15–17). A recent study in south-western region of Nigeria identified a proportion of 6.7% among DR-TB patients (8). This rate is lower than our findings of 39.3% (11/28). This may require more extensive studies on a larger premise to further evaluate these discrepancies.

The only mortality recorded in our study was identified as RMR which concurs with poor clinical outcomes as noted by aforementioned studies. PLWHA in our study were not identified with RMR, contrary to prevalent studies (16,17) where a quarter of PLWHA were diagnosed with RMR in South Africa (17). Our negative finding from PLWHA may be due to the small sample of PLWHA in our pool of

dataset analysis. Isoniazid-resistant TB in our dataset was less than a quarter of all DR-TB patients. Global rate of this resistant pattern is about 17%, with 7.1% as new cases and about 10% in previously treated TB cases (2), which is in tandem with our study. Olabiyi et al., (8) reported a prevalence of isoniazid-resistant TB among DR-TB of about 4%. In Taiwan, the total proportion of isoniazid-resistant TB was about 1:20 persons (18). These figures are notwithstanding lower than rate obtained in our study. Therefore, Ekiti State may be harbouring more isoniazid-resistant TB than presently identified if extensively studied. Inappropriate use of isoniazid preventive therapy as TB preventive treatment among contacts of pulmonary TB or TB prophylaxis for PLWHA might be a reason for the occurrence of such resistance pattern (19).

HIV has been a duet with TB in common occurrence (10). Less than 1 in 20 of the DR-TB patients in our dataset were PLWHA. These patients were nonetheless on anti-retrovirals and were judged to be adherent on medications. Only one of PLWHA was a new case. This patient was likely to have had a lower CD4+ count at the commencement of anti-retrovirals and perhaps not placed on tuberculosis preventive therapy. Two of PLWHA had false-negative sputum GeneXpert MTB/RIF assay results and were both identified to be Pre-XDR TB on LPA. False-negative sputum GeneXpert MTB/RIF assay in PLWHA is quite common (6,10) and they are predisposed to worse forms of DR-TB due to relative immune anergy (20). From Southeast (21) to Southwestern Nigeria (22), the prevalence of pre-XDR has ranged from 7.1% to 16.7% respectively whereas our dataset just identified two (2/28, 0.07%).

The discrepancies noted with false-negative TB have been a global problem and have perpetuated diagnostic and treatment gaps (10). About half of the patients in our dataset diagnosed of DR-TB had a false-negative sputum GeneXpert MTB/RIF assay. GeneXpert MTB/RIF assay is the mainstay of diagnosis of TB in Nigeria (7) hence, thorough clinical evaluation with (out) radiologic evidence of pulmonary TB (24) can supplement for patients with false-negative sputum GeneXpert MTB/RIF assay result to further investigate the patient with either LPA with/out culture. Traditional symptoms such as chronic cough with (out) haemoptysis, weight loss, night sweats are not exclusive of pulmonary tuberculosis. Therefore, identifying this constellation of symptoms especially in patients who have previously been treated for TB or in PLWHA should heighten clinical suspicion of DR-TB as rightfully highlighted in the national guidelines (7,8).

Unfortunately, diagnostic gap in a very contagious disease such as Pulmonary TB could lead to rapid person-to-person transmission. As these patients with false-negative results could infect close contacts leading to an overt community transmission. In this study, it took an average of 16 days to make up for the diagnostic gap and commence DR-TB medication. Since one active untreated pulmonary TB patient have the capacity of infecting 15-20 persons per year (2), it can be deduced from our study that an average of one contact each of the initial missed cases could have been infected during the 16-day diagnostic gap. This is alarming based on the estimation of the reduction proportion of the end TB strategy (4) .

A three-year assessment of the prevalence of pulmonary TB with DR-TB in Ekiti from 2022 to 2024 shows an increase in total pulmonary TB in the state, however, there was an initial reduction of DR-TB from 2022 to 2023, while 2024 saw a gradual increase in prevalence compared to 2023. This might be due to the added clinical diagnosis that bridged the diagnostic gap as was seen in a study in Nigeria by Oga-Omenka et al., (25). Nigeria has been experiencing a gradual but constant rise in incidence of DR-TB (26) whereas global trend of DR-TB observed a plateau of incidence within 2020-2023 (2). This global trend could change if low-and middle-income countries increase clinical suspicion to further identify DR-TB.

Our study has some limitations. First, the small dataset limits generalizability and statistical inference. Second, there are inadequate important clinical and socioeconomic variables in the dataset, precluding multivariate analysis of risk factors for specific drug-resistant patterns. Third, reliance on programmatic data as with ours may have introduced reporting biases. Lastly, the absence of long-term treatment outcome data limits assessment of clinical effectiveness and mortality trends.

Conclusion:

Nigeria remains a high-burden country for DR-TB with diagnostic limitations potentially leading to underreporting and delayed treatment. This study highlights the importance of integrating clinical judgment supported by radiologic evaluation and confirmatory assays such as LPA to obtund diagnostic and treatment gaps especially in previously treated TB patients and PLWHA with false-negative sputum GeneXpert MTB/RIF assay. This is imp-

ortant to reduce diagnostic timeline and curb community transmission to finally enable national and global targets for DR-TB control and elimination.

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Contributions of authors:

EOI conceptualized the study; EOI, AOI, and JAO were involved in study investigation; EOI was involved in methodology; EOI and AOI were involved in formal analysis; EOI wrote the original manuscript draft: EOI, AOI, and JAO reviewed and edited the manuscript. All authors approved the manuscript submitted for publication.

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Authors declare no competing interests

Disclosure:

Part of the entire set of findings in this study have been presented in a conference as a poster presentation in World Conference on Lung Health 2025, Copenhagen, Denmark.

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