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## Trends in rifampicin resistance among patients with presumptive TB in the pre-COVID and COVID-era

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### ABSTRACT

**Background:** The COVID 19 pandemic has had its impact on tuberculosis notification, incidence, and management, particularly in the context of rifampicin-resistant TB. We set out to determine the trends in rifampicin resistant tuberculosis between the pre-COVID and COVID era in a resource-constrained setting.

**Methods:** This was a retrospective review of single early morning sputum from presumed tuberculosis between January 2016 and May 2022 in a regional TB referral and treatment centre in South-western, Nigeria. We used a molecular beacon to detect *Mycobacterium tuberculosis* (MTB) and mutations in the *rpoB* gene using a real-time polymerase chain reaction (PCR).

**Results:** We analyzed 19,892 of 20,589 presumptive TB with complete data. Most subjects were in the age group 18–45 years (10,594; 53.3 %) and were males (11,492; 57.8 %). Of the 19,892 presumptive TB, 4,526 (22.8 %) were in pre-COVID-19 era (Jan 2016–December 2019) and 15,366 (77.2 %) cases were in COVID-19 era (Jan 2020–May 2022). The MTB notification declined during the COVID-19 era compared with the pre-COVID-19 era (10.5 % vs 12.9 %,  $p < 0.001$ ). The annual prevalence of MTB rose from 5.6 % (2016) to a peak of 23.2 % in 2019 (pre-COVID-19 era), followed by a decline to 12.8 % in 2020 and 8.6 % in 2022 (COVID-19 era),  $p = < 0.001$ . The overall incidence of RR-TB was 3.8 %. The incidence of RR was higher during pre-COVID-19 than the COVID-19 era, 9.5 % vs 2.5 %,  $p = < 0.001$ . The incidence of RR-TB declined substantially from 28.0 % in 2016 to 1.6 % in 2021 but rose exponentially to 5.4 % in 2022. After controlling for confounders, only the pre-COVID-19 status was associated with increased odds for RR (adjusted odds ratio 3.3, 95 % confidence interval, 2.049, 5.421).

**Conclusion:** This study found a progressive decline in MTB notification since the COVID-19 pandemic's outbreak. Furthermore, RR-TB notification decreased gradually in the pre-COVID-19 era, with a resurgence in 2022. In the era of COVID-19, there is an urgent need to increase intervention efforts in order to halt the decline in MTB detection rates and the resurgence of RR-TB.

### 1. Introduction

The 2019 coronavirus disease pandemic (COVID-19) continues to pressure healthcare systems around the world, with varying impacts [1]. Despite the progress documented in the early stages of the pandemic, the current outbreak of COVID-19 in parts of China and North Korea reflects

the ongoing threat to global health [2,3]. As at June 14, 2022, the World Health Organization (WHO) real-time dashboard shows a total of 533,816,957 confirmed cases of COVID-19 with more than six million deaths [4].

Although, the severe form of COVID-19 is often accompanied by multiorgan dysfunction syndrome, a more significant impact is felt in

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the respiratory system [5]. Being an infectious disease with its primary mode of acquisition via the respiratory route, it presents predominantly with varying severity of pneumonia [6]. Pneumonia caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19 may be indistinguishable from Tuberculosis and rarely the two diseases entity may co-exist [7]. In addition, both infections are associated with high mortality, with COVID-19 ranked as the world's leading killer infectious disease in May 2021 [8,9].

Containment and management of COVID-19 in the early phase of the pandemic hinged on various measures such as lockdown, isolation, quarantine, and in-hospital management of the very sick individuals [10]. The above measures with the introduction of vaccines brought progress in the global effort at curtailing the COVID-19 pandemic [11].

The progress in the COVID-19 is at the expense of the health care systems and the chronic respiratory diseases such as tuberculosis (TB) management [8,9,12]. Hence, the earlier concern and subsequent confirmation of the drawback on the progress towards global control of tuberculosis [8,9,12,13]. The notification, and access to treatments for tuberculosis were reduced in most high-burdened countries. Due to these, more deaths were recorded during the pandemic [12]. The WHO 2021 global TB report indicated a significant decline in the newly diagnosed cases of TB from 7.1 million in 2019 to 5.8 million in 2020, with more deaths than in prior years [8,9,12]. The situation in Nigeria also looks similar with a multi-centered study in Nigeria showing a progressive decline in clinic attendance, presumptive TB identification, and treatment [14,15].

While the significant decline in newly diagnosed cases of tuberculosis appears to be easily quantifiable, a hidden impact that poses a more serious challenge is the issue of drug resistance, which could be a major setback, particularly in resource-constrained settings such as Nigeria. The efficacy of anti-tuberculosis treatments is jeopardised by a rising treatment failure rate caused by patients' inability to obtain prescriptions as a result of various pandemic measures [16]. The implication on treatment is the emergence and worsening of TB drug resistance [17]. There appears to be a paucity of literature on trends in the incidence of tuberculosis comparing the pre-COVID and COVID-eras as they pertain to rifampicin-resistant tuberculosis in resource constrained settings. The limited data on rifampicin resistance in our environment hampers evidence-based decision-making [17]. As a result, we hypothesised that the COVID-19 pandemic may have impacted the trends of tuberculosis and rifampicin resistance in our health facility. Hence, we aimed to examine the trend in tuberculosis prevalence and incidence of rifampicin-resistant TB between the pre-COVID and COVID eras using Xpert MTB/RIF assay in South-western, Nigeria.

## 2. Methods

### 2.1. Study design and location

This was a retrospective cross-sectional analytical study of early morning sputum samples from presumptive TB patients at the TB Referral and Treatment centre located in a tertiary mission hospital in Southwest, Nigeria from January 2016 to May 2022.

### 2.2. Study population

The study included all children and adults with a presumptive diagnosis of TB at the hospital or referred from primary health care centres, general hospitals, and tertiary health care facilities from neighbouring states. Although, suspected TB-HIV co-infection was given precedence when Xpert MTB/RIF was first used for TB diagnosis in the programme, it has subsequently become the primary diagnostic technique for all presumed TB cases. We excluded subjects with indeterminate or incomplete results from the final analysis.

**Table 1**  
Patients' demographic and HIV status of the Presumptive Tuberculosis.

Variables	n = 19,892 (%)	Pre-COVID- 19 (2016 to 2019) n = 4526 (%)	COVID-19 era (2020 to May 2022) n = 15366 (%)	$\chi^2$	p
<b>Age groups</b>					
<18	1104 (5.5)	349 (7.7)	755 (4.9)	166.217	<0.001
18–45	10,594 (53.3)	2051 (45.3)	8543 (55.6)		
>45 years	8194 (41.2)	2126 (47.0)	6068 (39.5)		
<b>Sex</b>					
Males	11,492 (57.8)	2247 (49.6)	9245 (60.2)	158.567	<0.001
Females	8400 (42.2)	2279 (50.4)	6121 (39.8)		
<b>HIV Status</b>					
Positive	991 (5.0)	756 (16.7)	235 (1.5)	2962.434	<0.001
Negative	7256 (36.5)	2443 (54.0)	4813 (31.3)		
Unknown	11,645 (58.5)	1327 (29.3)	10,318 (67.2)		

### 2.3. Sample collection and laboratory analysis

Each presumed case of TB submitted a single early morning sputum or gastric washing sample in a 25-ml leak-proof, wide-mouthed screw-cap cup. The material was diluted 1:2 (v/v) with carbonic acid buffer, mixed thoroughly, and maintained at room temperature for 10 min to complete liquefaction for polymerase chain reaction (PCR). The supplied cartridge port loaded a 2 ml aliquot of the diluted sample into the GeneXpert machine (GeneXpert® Sunnyvale, CA, USA) via the supplied cartridge port. The DNA was liberated during the ultrasonic lysis of the mycobacterium. The GeneXpert uses an integrated microfluidic system to extract, purify, amplify, and measure DNA using real-time PCR technology. It also uses a molecular beacon to detect mutations in the *mpoB* gene linked to rifampicin resistance TB (RR-TB). The results were then read after two hours and quality control was established by calibrating the equipment to the standard using a probe check control. The sample processing control system improved internal quality control even more. Those who proved positive were referred to the hospital's TB treatment centre, supported by the Damien Foundation, for further treatment.

Patients with presumptive TB had their HIV-1 and HIV-2 tested simultaneously using Determine® Kits (Alere Medical, Matsuhidai, Matsudo-shi, Chiba-ken Japan) and Uni-Gold® HIV (Trinity Biotech, Wicklow, Ireland), with a tie-break using STAT-PAK® (Chembio Diagnostic System, Medford NY, USA).

### 2.4. Data analysis

The Statistical Package for Social Sciences (version 23) was used to analyze the data. Using the frequency table, we summarised the demographic variables (age groups, and sex) and HIV status. The proportion of subjects with mycobacterium tuberculosis (MTB) and rifampicin resistance tuberculosis (RR-TB) detected using the Xpert MTB/RIF assay was estimated. We compared the pre-COVID period (data extracted from January 2016 till December 2019) with the COVID-19 era (from January 2020 till May 2022) using chi-square test for linear trends and odds ratio with its 95 % confidence interval. Lines graphs depict the yearly proportions of MTB and RR-TB notified. The p-value for statistical significance was set at <0.05.

The research followed the Declaration of Helsinki and was approved by the Bowen University Health Research Ethics Committee (HREC)

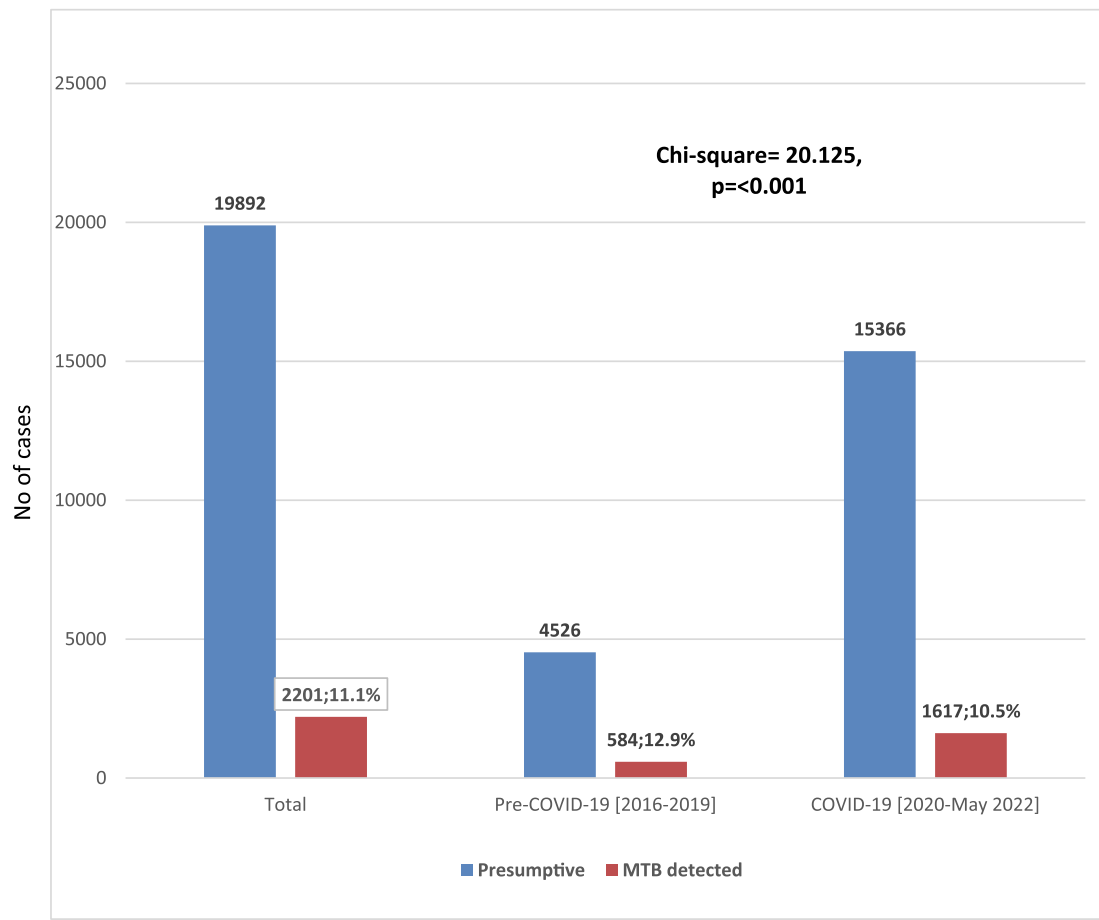


Fig. 1. Prevalence of Mycobacterium Tuberculosis detected by GeneXpert among the presumptive cases.

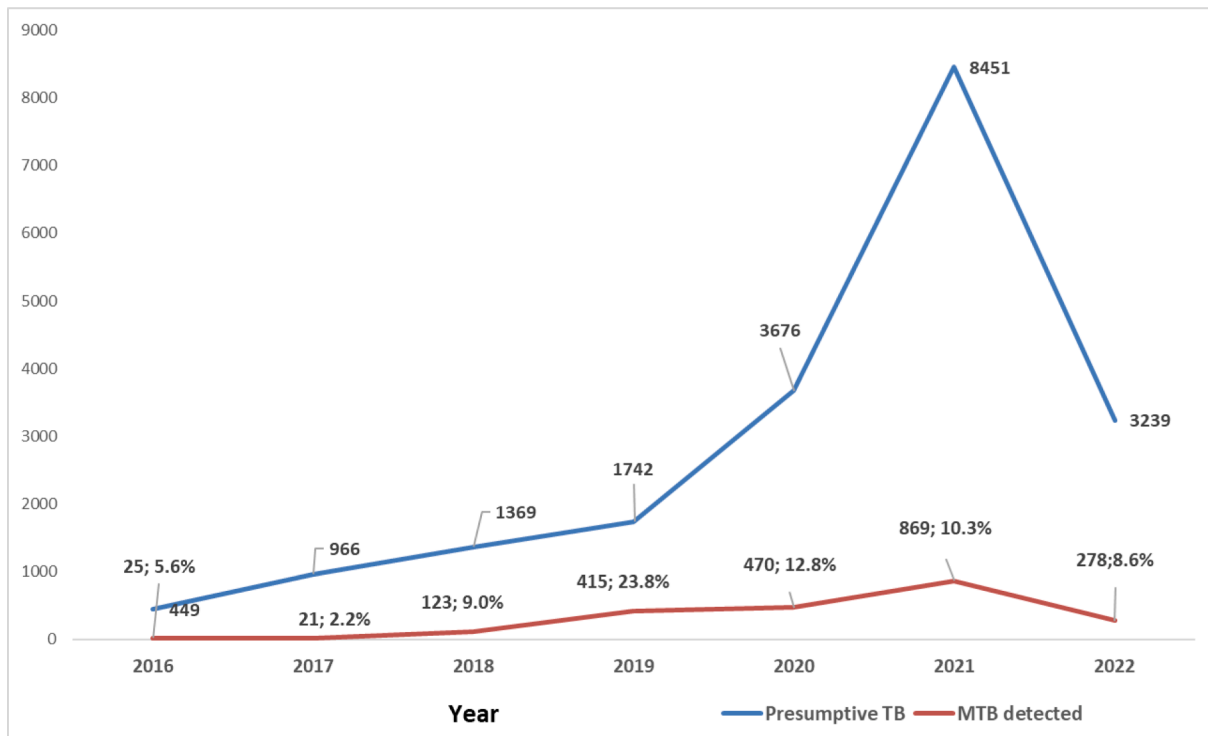


Fig. 2. Trends of prevalence of MTB detected during pre-COVID-19 (2016 to 2019) and COVID-19 era (2020 to 2022).

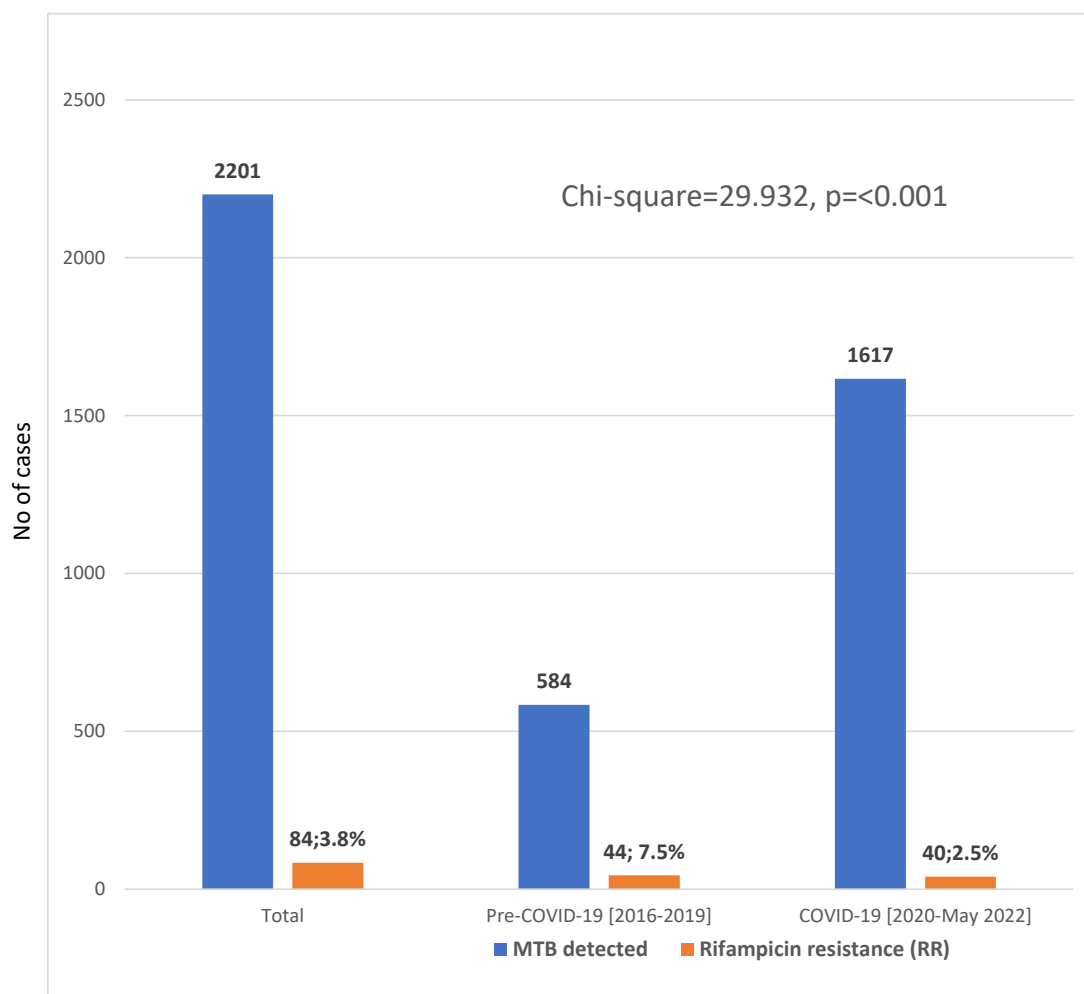


Fig. 3. Incidence of Rifampicin resistance (RR) among the patients with MTB detected.

with approval number BUTH-REC - 047.

### 3. Results

Out of 20,589 cases extracted from the registry, a total of 19,892 (96.6 %) cases of presumptive TB had complete data and were analyzed. Of the total cases of presumptive TB analyzed, 4,526 (22.8 %) were managed before the COVID-19 pandemic (pre-COVID-19 period-January 2016 to December 2019), while 15,366 (77.2 %) cases were seen from January 2020 till May 2022 (COVID-19 era). Overall, there were more males (11,492; 57.8 %). Most of the cases were in the age group 18–45 years (10,594; 53.3 %). Of all the cases, 5.0 % (991) tested positive for HIV, 7256 (36.5 %) were seronegative and the remaining, HIV status was unknown. There were significant differences in the age groups, sex distribution, and HIV status between the pre-COVID-19 period and the COVID-19 era (Table 1).

The overall prevalence of MTB detected by GeneXpert was 11.1 % (2201/19,892). The prevalence of MTB detected also declined during the COVID-19 era compared with the pre-COVID-19 period (12.9 % vs 10.5 %,  $p < 0.001$ ) as shown in Fig. 1. On the annual trend analysis, the prevalence of MTB detected increased from 5.6 % in 2016 to a peak of 23.2 % in 2019 (pre-COVID-19 era), followed by a decline to 12.8 % in 2020 and 8.6 % in 2022 in the COVID-19 era as shown in Fig. 2.

The overall incidence of RR-TB was 3.8 % (95 % confidence interval 3.1 to 4.6 %) among the MTB cases. The incidence of RR-TB during pre-COVID-19 (2016–2019) was 9.5 %, which was higher than 2.5 % during the COVID-19 era (2020 to May 2022),  $p < 0.001$  (Fig. 3). The incidence

of RR-TB declined substantially from 28.0 % in 2016 to 1.6 % in 2021 and rose exponentially to 5.4 % in 2022 (Fig. 4).

Factors that were associated with the diagnosis of MTB from presumptive cases included the age groups [18–45 years (adjusted odds ratio 1.6 (95 % confidence interval 1.270–2.095), >45 years (adjusted odds ratio 2.1, 95 % confidence interval 1.657–2.731), male (1.6, 95 % confidence interval 1.463, 1.773), pre-COVID-19 era (adjusted odds ratio 1.2, 95 % CI 1.161, 1.447) and those with HIV status unknown (Table 2).

The demographic characteristics-age and sex were not associated with RR-TB (Table 3). Although being HIV negative and those with status unknown were associated with higher odds for RR-TB on bivariable analysis, after controlling for confounder, only the pre-COVID-19 status was associated with higher odds for RR-TB (adjusted odds ratio 3.3, 95 % confidence interval, 2.049, 5.421) as shown in Table 3.

### 4. Discussion

The devastating impact of COVID-19 remains a critical challenge that has not only slowed the progress but also reversed the previous gains in the global drive to eradicate TB [8,9]. Despite the increased disease screening based on the National TB Leprosy and Buruli Ulcer Control Programme's TB diagnosis and treatment guidelines, this study found a 2.4 % decrease in MTB notification during the COVID-19 pandemic compared to the pre-COVID-19 era [12,18]. During the COVID-19 pandemic in Nigeria, a comparable drop in case notification was reported in a multi-region multi-site engaged in intensive TB case search

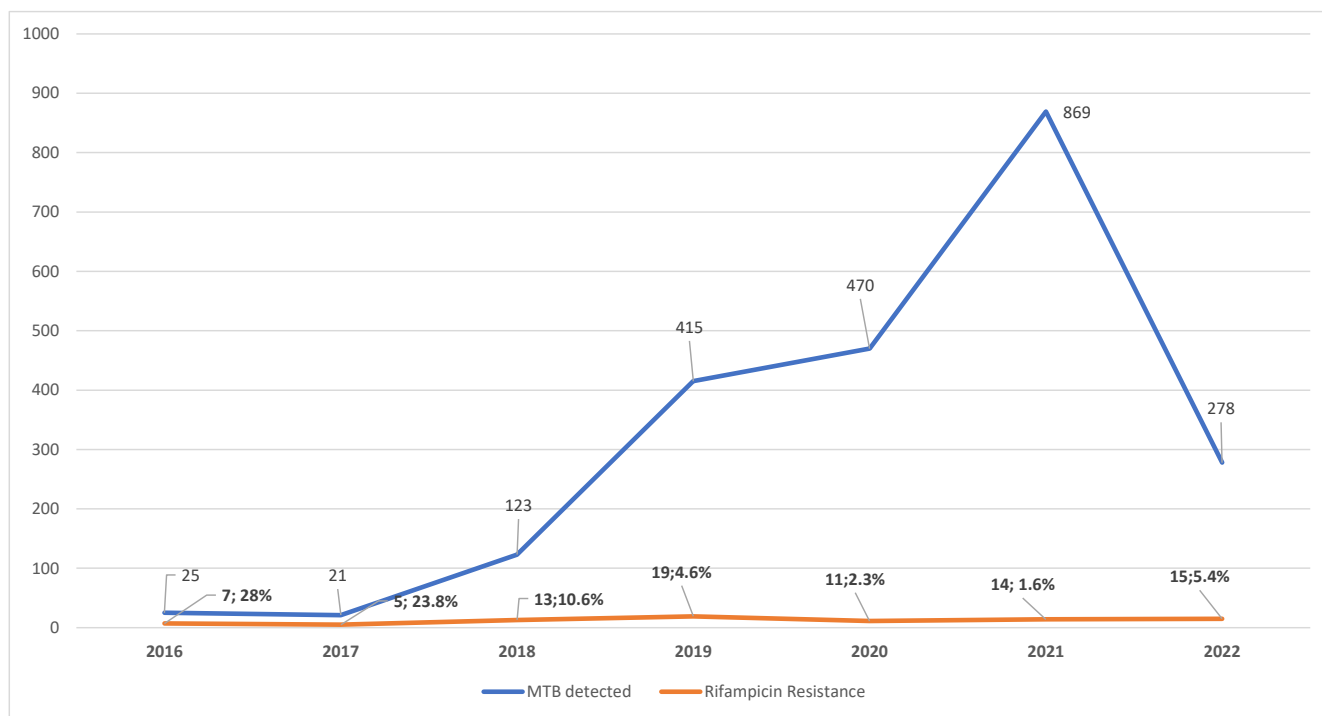


Fig. 4. Trends of Rifampicin resistance (RIF) during pre-COVID-19 (2016 to 2018) and COVID-19 era (2019 to 2022).

**Table 2**  
Factors associated with MTB detection amongst the presumptive Tuberculosis.

Variable	Sub-categories	(MTB positive) n = 2201	OR	95 % CI	Adjusted OR	95 % CI	P value
<b>Age</b>	<18	71	1				
	18–45	1043	1.589	1.239, 2.038	1.631	1.270, 2.095	<0.001
	>45 years	7107	2.225	1.735, 2.854	2.127	1.657, 2.731	<0.001
<b>Sex</b>	Females	698	1				
	Males	1503	1.660	1.510, 1.825	1.610	1.463, 1.773	<0.001
<b>HIV status</b>	Positive	77	1		1		
	Negative	941	1.769	1.388, 2.254	1.749	1.357, 2.231	0.156
	Unknown	1183	1.342	1.056, 1.707	1.389	1.079, 1.789	0.011
<b>Era</b>	COVID-19	1617	1				
	Pre-COVID-19	584	1.260	1.139, 1.394	1.296	1.161, 1.447	<0.001

MTB-Mycobacterium Tuberculosis; OR-Odds ratio; CI-Confidence interval;

**Table 3**  
Factors associated with Rifampicin resistance (RR) amongst the MTB detected cases.

Variable	Categories	(RR) positive) n = 84	OR	95 % CI	Adjusted OR	95 % CI	P value
<b>Age</b>	<18	2	1		1		
	18–45	43	0.674	0.160, 2.841	0.624	0.147, 2.656	0.524
	>45 years	39	0.779	0.184, 3.293	0.691	0.162, 2.958	0.619
<b>Sex</b>	Females	28	1		1		
	Males	56	1.080	0.680, 1.715	0.794	0.489, 1.288	0.350
<b>HIV status</b>	Positive	7	1		1		
	Negative	38	2.376	1.024, 5.516	1.562	0.657, 3.713	0.313
	Unknown	39	2.933	1.266, 6.794	1.406	0.575, 3.441	0.455
<b>Era</b>	COVID-19	40	1		1		
	Pre-COVID-19	44	3.212	2.071, 4.984	3.333	2.049, 5.421	<0.001

MTB-Mycobacterium Tuberculosis; OR-Odds ratio; CI-Confidence interval; RR-Rifampicin resistance.

[15,17]. The observed reduction in MTB notification during the COVID-19 pandemic from the present study is consistent with the global reduction in reported TB cases since the COVID-19 pandemic's outbreak. While this drop is close to the 2.5 % recorded for the WHO Africa region, it is substantially lower than the 9–20 % reduction reported for the WHO Western Pacific region [8,9,19]. These data imply that more people were unable to receive a TB diagnosis and treatment as a result of the outbreak. The observed MTB trend indicated a steady improvement until the COVID-19 pandemic, with a subsequent decline in 2020. The observed pattern of decreased MTB case notification in the current study is tandem with recently published trends from the 2021 Global TB report, with a higher representation from high-burden countries [8,9]. Given that TB is a chronic disease that received less attention in the early phases of the pandemic than COVID-19, which was associated with a large burden and mortality rate, this result is not surprising [8,9]. The decline in MTB notification in this study is also likely due to healthcare service disruptions, lack of access to diagnostic for suspected cases, fear of stigmatisation, patients' aversion to visiting health care facilities in the aftermath of the pandemic, various levels of restrictions, and lockdown implemented during the COVID-19 pandemic's curtailment, all of which may have had a negative impact on TB control in Nigeria. While this represents a setback in TB control, a more pragmatic strategy, including rigorous case finding, training, and increased accessibility, is required to provide a feasible catch-up programme. This will keep the country on track to meet the end TB strategy goal of reducing new cases by 80 % and putting an end to new deaths [20].

On the contrary, some authors have suggested that the decrease in TB case notification during the COVID era could also be due to the widespread use of masks as a preventive measure. Nonetheless, the low quality of evidence to support this observation in a systematic review may indicate otherwise [21].

Nigeria has a significant TB burden as well as drug resistance TB, with a low rate of drug resistance treatment access [8,9,12]. As a result, the country cannot afford to fall farther behind in its efforts to reduce drug-resistant cases. This study demonstrates a gradual decline in RR-TB cases until 2022, when a sudden increase to 5.4 % was observed. This finding contradicts the 2021 Global TB report, which revealed a sustained detection and notification of drug-resistant TB case except for the 2020. The difference could be explained by the fact that the WHO report covered the period up to 2021 [8,9]. The global trend of RR-TB notification through 2022 will be known when this report is released in year 2023. The surge in RR-TB observed in 2022 highlighted in this study could be due to the long-term impact of interruption in TB services and possible increase occurrence of drug resistance over time as projected in the earlier studies [13,22,23]. This is because all those who could not access the TB treatment or those without incomplete treatment may have progressively developed drug resistance to TB, and subsequent spread over time. This findings necessitates an urgent intervention and an immediate escalation in the treatment of drug-resistant TB. This strategy will increase the detection of drug-resistant TB patients, provide adequate treatment, and prevent the spread of drug-resistant TB in the country from worsening. This study also found that social demographics and HIV status had no effect on RR detection. However, the COVID-19 era was linked to fewer RR detections through 2022. In contrast, a local study, though limited by sample size (1 3 2) did not observe any differences in drug resistant TB cases between the pre-COVID-19 and COVID-19 eras [17]. Except for 2022, the lower number of drug-resistant TB infections in the COVID-19 timeframe is not surprising, given drug resistance develops over time and spreads. The various COVID-19 containment strategies and disruptions in health care service delivery provide an avenue for missing drug resistance cases, predisposing to default or poor treatment adherence, and limiting access to care among patients infected with TB [22]. The significance of these findings is that efforts to control a highly contagious infectious illness like SARS-CoV-2 should take into account the collateral damage to

control measures for other diseases of public health relevance, such as TB. Innovative measures developed early in the pandemic, such as remote and virtual consultation and the utilisation of adjacent primary health care providers, demonstrated some success in minimising the impact of COVID-19 on TB in Pakistan [24]. These type of measure may have ameliorated the impact of the disruption in health services occasioned by the COVID-19 pandemic and attendant reversal of gains in control of diseases of public important like TB. The large sample size, which spans around 7 years in a well-established TB control programme [25], distinguishes this study from lower middle-income country viewpoints. The use of Xpert MTB/RIF, which has a rapid turnaround time and outstanding sensitivity, lends credence to this work. However, while Nigeria has approved Covid-19 screening and treatment facilities, the centre does not routinely screen for the virus; as a result, a small number of patients may be co-infected, potentially interfering with treatment adherence and outcomes. Furthermore, only data for the first half of 2022 were available for study, but we believe the data is valuable in terms of trends that may not change significantly.

## 5. Conclusion

This study found a continuous decrease in MTB notification since the outbreak of the COVID-19 pandemic. Moreover, RR-TB notification declined gradually from pre-COVID-19 to 2022, when it spiked. In the era of COVID-19, there is an urgent need to scale up intervention strategies to halt the decline in MTB detection rates and the resurgence of RR-TB in order to meet the global goal of ending TB by 2035.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Availability of data and materials.

Data and material from this study is available to the public unhindered.

## Informed Consent.

Informed consent was not sought for the present study because this was a retrospective study.

## Ethical Approval.

This study was a retrospective study, ethic approval was obtained from the Health Research.

Ethical Committee of the Bowen University Teaching Hospital with approval number.  
BUTH/REC/-047.

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