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Emerging threat of drug-resistant tuberculosis and trends in the era of COVID-19: A descriptive study from northwestern Nigeria

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ABSTRACT

Background: Mycobacterium tuberculosis with resistance to first line and second line anti tuberculous drugs is a serious setback in the treatment of tuberculosis (TB). The COVID-19 pandemic constitutes a serious threat that could unwind the recent gains made thus far in the control of tuberculosis. This study aims to explore the pattern of drug resistant tuberculosis (DRTB) in our institution. We also aimed to explore the changing trends of TB in the era of the COVID-19 pandemic.

Methods: This descriptive study included all DRTB patients admitted and managed in the hospital between January 2018 and December 2020. We compare TB case detection in the facility before and after COVID-19 pandemic. Drug susceptibility testing were expressed as frequencies and percentages.

Results: The study found that there was 66.03%, 45.09% and 77.78% drop in case detection of drug-sensitive TB (DSTB), DRTB and Fluoroquinolone (FQ) resistant TB respectively in the year 2020 compared to 2019. The drop in cases was similar when the year 2020 was compared to 2018. Among the 132 patients in the cohort, resistance to isoniazid, fluoroquinolones and second-line injectable agents were reported as 23.48%, 12.88%, and 31.06% respectively.

Conclusion: We question the potential reason why a drop in tuberculosis cases was observed in the year 2020 and we alert the Nigerian authorities that COVID-19 control efforts going hand-in-hand with intensified TB case finding and surveillance efforts and initiating proper TB treatment for persons with active TB are urgently needed.

1. Introduction

Tuberculosis (TB) is the most important killer infectious disease worldwide[1]. The causative agent called *Mycobacterium tuberculosis* (MTB) has infected one third of the world's population with 10.4 million incident cases occurring in 2015[2,3]. In the same year, 60% of the global TB burden was in Nigeria, South Africa, Indonesia, China, India and Pakistan[3]. The Nigeria TB prevalence survey conducted in 2012 reported that the TB prevalence rate of bacteriologically confirmed TB cases was 524 per 100,000 population aged 15 years and over[4].

The emergence of drug-resistant tuberculosis (DRTB) poses a serious public health threat in sub-Saharan Africa and globally[5–7]. In 2019, about 500, 000 people worldwide developed rifampicin-resistant tuberculosis (RR-TB) and 78% of them had multidrug-resistant tuberculosis (MDRTB)[5]. In Nigeria, the prevalence rate of any DRTB among new and previously treated TB cases was reported as 32% and 53% respectively[8]. The prevalence rate of MDRTB in Nigeria among new and previously treated TB cases was reported as 6% and 32%

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respectively[8].

The emergence of coronavirus disease 2019 (COVID-19) in Wuhan [9], China in December 2019, has raised questions especially with regards to the preparedness of developing countries in handling the pandemic[10]. The disease which was declared a pandemic by the World Health Organization, has the potential to cause havoc especially in countries with weak health systems [11]. The COVID-19 pandemic constitutes a serious threat that had unwind the recent gains made thus far in the control of tuberculosis [5]. The pandemic has severely impacted TB services worldwide [5].

The aim of this study is to explore the pattern of DRTB in our institution. This information is useful to stakeholders involved in the control of DRTB in Nigeria. We also aimed at providing information on the changing trends of DRTB in the institution in the era of the COVID-19 pandemic.

2. Methods:

2.1. Study design and patients:

This was a retrospective study conducted at the Infectious Disease Hospital, Kano Nigeria. We included all patients admitted and managed in the hospital with a diagnosis of drug resistant tuberculosis (DRTB) between January 2018 and December 2020.

2.2. Study setting, patient diagnosis and management:

The infectious disease hospital (IDH) is in Fagge, Kano Metropolis. It is a 150-bed secondary health care facility dedicated for the management of infectious diseases. The hospital provides primary care, tuberculosis treatment, HIV care, in-patient care for epidemic-prone infections and treatment for other infectious diseases. The DRTB center for the state is located in the hospital and was upgraded in 2012 by the Kano State government with support from donor agencies. The center serves as referral center for DRTB for Northwestern States.

Based on the guidelines of the Nigerian National Tuberculosis and Leprosy Control Program (NTBLCP)[12], all presumptive TB patients, submit sputum sample for Gene Xpert assay. Patients that turn out to have rifampicin resistance based on Gene Xpert assay, submit sputum sample for culture (on solid and liquid media) and drug susceptibility testing (DST) by line probe assay for first- and second-line drugs at a zonal reference laboratory located at Aminu Kano Teaching Hospital.

At the period of the study, based on the guidelines of the Nigerian National Tuberculosis and Leprosy Control Program (NTBLCP)[12], patients diagnosed to have rifampicin resistant tuberculosis (RR-TB) and MDRTB could be managed on outpatient basis if they are clinically stable and do not require in-patient care. However, if these patients are not clinically stable, they were admitted for a period of 4 months during which they are stabilized and started on antituberculosis medication. All patients with resistance to any of the second line antituberculosis medication, were admitted for a period of 4 months irrespective of clinical stability. During the period of admission, patients were commenced on antituberculosis medication. Ancillary drugs, baseline and follow-up laboratory evaluation, feeding, monthly stipend and transport allowances were provided with support from the Global Fund NFM Grant for DRTB patient care.

Data for the last one-third of the study period (2020), was recorded at the time when COVID-19 transmission and control activities began in the State. COVID −19 was first reported in Nigeria on 27th February 2020[13] and in Kano State on 11th April 2020[14]. The public health measures instituted to halt the transmission of COVID-19 were associated with disruption of daily activities, livelihoods, socioeconomic and sociocultural activities. For instance, on 30 March 2020, a nationwide lockdown was introduced in three states of the Federation of Nigeria: namely Abuja, Ogun and Lagos [15]. On 27th April 2020, the lockdown was extended for further two weeks period and Kano State was included [15]. On 2nd July 2020, Kano State government announced the easing of the lock down measures, however, a nationwide curfew continued between 22:00 to 04:00 local time. Although hospitals remained open during the lockdown, public transportation system was shut down, markets were closed, and non-essential workers were requested to stay home. The IDH was not designated for the treatment of COVID-19.

2.3. Data collection and ethical approval:

We retrieved data for all patients admitted at the DRTB ward of the Infectious Disease Hospital, Kano, between January 2018 and December 2020. The demographic, clinical and drug susceptibility information of the patients was retrieved from patients case files.

This retrospective study was approved by the Health Research Ethics Committee of Kano State Ministry of Health with approval reference number MOH/Off/797/T. I/2124.

2.4. Statistical analysis:

Baseline demographic, clinical information and results of drug susceptibility testing were expressed as frequencies and percentages. Chi-square analysis was used to examine the difference in DRTB patterns prior to COVID-19 and after COVID-19. Data from the case files were entered into Microsoft Excel spreadsheet (Version 2013; Microsoft Corporation, Redmond, WA, USA) and cleaned. All analysis was done using JMP Pro (JMP Version 12.0.1, SAS Institute Inc., Cary, N. C., USA) statistical software.

3. Results:

3.1. Trend in TB and HIV cases during the study period (2018–2020):

As shown in Fig. 1, the total number of patients diagnosed to have all forms of tuberculosis(TB) during the study period was 2097. Of the 2097 patients with all forms of TB, 132 (6.29%) had drug resistant tuberculosis (DRTB), while the remaining 1965 (93.71%) had drug susceptible tuberculosis (DSTB). Overall, among the 132 patients with DRTB, 15 (11.36%), 17 (12.88%), and 100 (75.76%) patients had MDRTB, FQ-resistant TB and other forms of DRTB respectively. Compared to previous years, the hospital noticed a sharp drop in DSTB and DRTB cases in the year 2020 during which COVID-19 transmission and control activities began in the State (Fig. 2). For instance, the total DSTB cases seen in the hospital in 2018, 2019 and 2020 were 845, 836, and 284 respectively. The total DRTB cases seen in the hospital in 2018, 2019 and 2020 were 53, 51 and 28 respectively. Nonetheless, there was a progressive increase in HIV cases seen from 2018 to 2020.

Therefore, there was 66.39%, 47.17% and 66.67% drop in case detection of DSTB, DRTB and FQ resistant TB respectively in the year 2020 compared to 2018. Furthermore, there was 66.03%, 45.09% and 77.78% drop in case detection of DSTB, DRTB and FQ resistant TB respectively in the year 2020 compared to 2019.

3.2. Demographic and clinical characteristics of the patients (2018–2020):

The demographic characteristics of the 132 study patients with DRTB are shown in Table 1. The mean age of the patients was 33.28 years (+/-13.264) with majority below 29 years of the age. There were more males 63.63% than females 36.37%. Of the 132 patients, 74 (56.06%), came from urban areas. As shown in Fig. 3, the patients were mostly from northern states of Kano (59.09%), Katsina (13.64%) and, Jigawa (8.33%).

Out of the 132 patients in the cohort, 22 (16.67%) were HIV positive and 52 (39.39%) do not have a history of having been diagnosed or treated for tuberculosis. However, 35 of the patients had exposure to second-line anti TB medication for TB treatment in the past (Table 2).

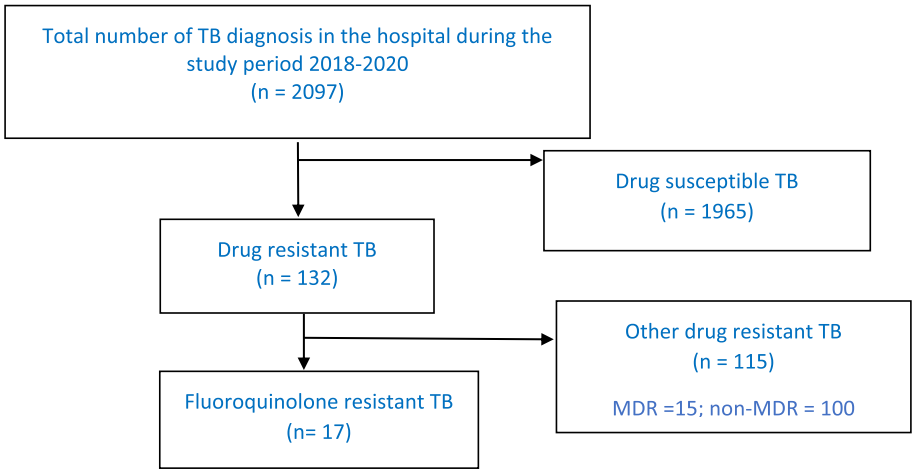

Fig. 1. Tuberculosis cases that presented to the hospital during the study period 2018–2020.

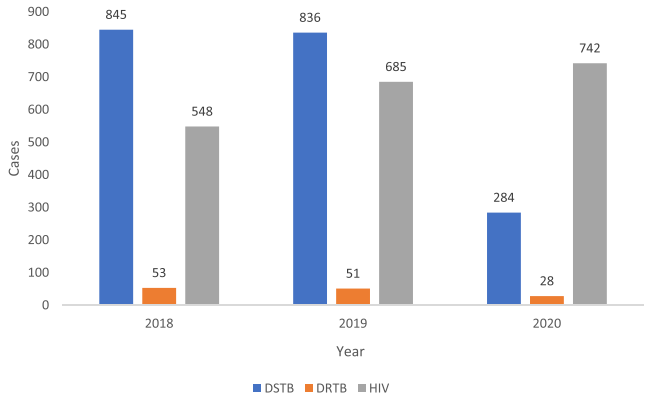

Fig. 2. Distribution of tuberculosis and new HIV cases by year (2018–2020).

Table 1
Demographic characteristics of patients with drug-resistant tuberculosis (2018–2020).

Variable	Number	Percentage
Age (years)		
<29	60	45.45
30–39	39	29.55
40–49	14	10.61
>50	19	14.39
Sex		
Male	84	63.64
Female	48	36.36
Setting		
Rural	58	43.94
Urban	74	56.06

3.3. Antimicrobial resistance among the Mycobacterium tuberculosis isolates in the studied patients (2018–2020):

Table 3 summarizes the result of susceptibility testing for both first line and second-line drugs. All MTB isolates were resistant to rifampicin. However, resistance to isoniazid, fluoroquinolones and second-line injectable agents were reported as 23.48%, 12.88%, and 31.06% respectively.

As shown in Table 4, majority of the patients studied had rifampicin mono-resistance (44.7%), while 11.36% had MDRTB. Pre-extensively drug resistant tuberculosis was observed in 7.58% (second-line injectable anti TB resistance) and 4.55% (fluoroquinolone resistance). The remaining 23.48% and 8.33% were in addition to rifampicin resistance, also resistant to a second-line anti TB and fluoroquinolone respectively.

3.4. Pattern of presentation of DRTB patients before COVID-19 (2018/2019) and during COVID-19 (2020):

As shown in Table 5, there is a statistically significant difference in pattern of presentation of DRTB before and during COVID-19 in terms of gender with females more likely to be admitted with DRTB during COVID-19 period compared to the male gender (P = 0.033). However, there is no statistically significant difference in pattern of presentation of DRTB before and during COVID-19 in terms of age-group, state of residence, setting of residence, type of patient, use of second-line anti TB in the past and HIV status.

4. Discussion:

This report describes the epidemiology of DRTB in the era of COVID-19 at a referral center in a resource limited setting showing a sharp drop in all forms of TB cases seen at the center in the year 2020 compared to previous years 2019 and 2018. The demographic characteristics of the 132 patients with DRTB revealed that majority were below 29 years of age, males, and from urban areas. We found that all the isolates were rifampicin resistant. The study also highlights the influence of COVID-19 disruption on case identification and management.

In our center, a sharp drop in TB cases was noted in 2020 during which COVID-19 spread in the country. This is true for both DSTB and DRTB cases. The WHO has shown that TB notifications from countries with high TB burden have sharply dropped in 2020[5]. In the year 2020, mathematical modelling suggests that up to 400 000 additional deaths due to TB could occur as a result of 50% drop in TB case detection over a period of 3 months [5]. A reduction in reported cases of TB/DRTB has been reported by various regions of Nigeria, Africa and the globe as a whole. Adewole reported reduction in both presumptive and confirmed cases of TB in Ile-Ife, western Nigeria in the first half of 2020 compared to the same period in 2019[16]. Similarly, the TB surge intervention implemented across 61 high volume facilities in nine Nigerian states including Kano State reported a progressive decline in clinic attendance, presumptive TB identification, TB case detection and treatment initiation since the onset of the COVID-19[17]. The same finding was reported by the wellness on wheels (WoW) campaign in Kano [17]. Gidado and colleagues have reported their experience with integrated COVID-19 testing built on existing TB structure through a multi stakeholder collaboration [18]. In Sierra Leone, a drop in both presumptive and confirmed cases of TB was recorded in the year 2020 compared to the preceding year [19]. Certain areas of Brazil reported a decline in reported cases of TB during the COVID-19 pandemic compared to the

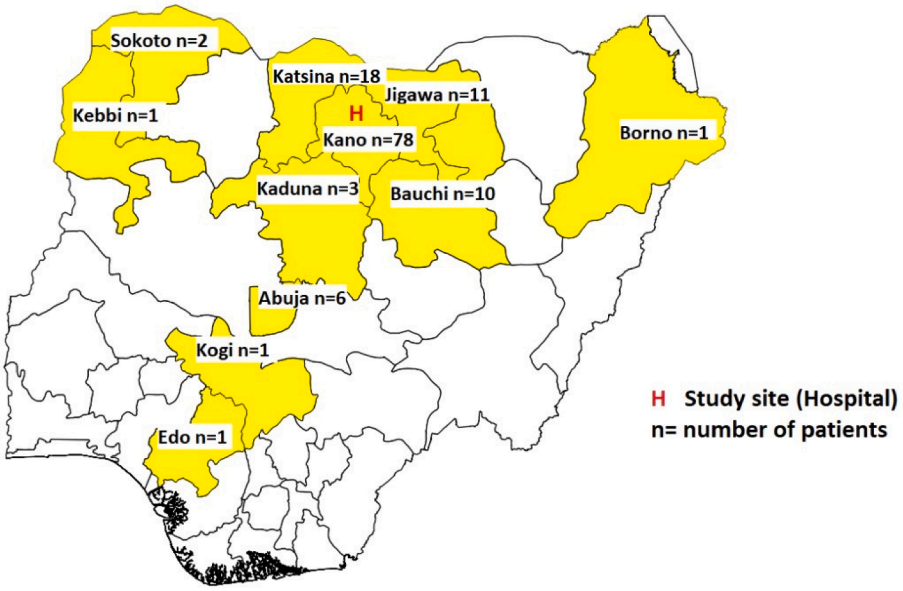

Fig. 3. Geographical distribution of patients with Drug-resistant TB and location of the treatment center (2018–2020).

Table 2
Clinical characteristics of patients with drug-resistant tuberculosis(2018–2020).

Variable	Number	Percentage
HIV status		
Yes	22	16.67
No	110	83.33
Category of patient		
New	52	39.39
Relapse	38	28.79
Treatment after failure	42	31.82
Second-line drug use in the past		
Yes	35	26.515
No	80	60.606
Missing	17	12.879

Table 3
Antimicrobial resistance in patients with drug-resistant tuberculosis (2018–2020).

Antibiotic	No. of resistant isolates/no. tested	Percentage
Rifampicin	132/132	100
Isoniazid	31/132	23.48
Fluoroquinolone	17/132	12.88
Second-line injectables	41/132	31.06

Table 4
Classification of antimicrobial resistance among patients with drug-resistant tuberculosis(2018–2020).

Variable	Number	Percentage
Rifampicin mono-resistance	59	44.70
MDR (Rifampicin plus Isoniazid resistance)	15	11.36
Rifampicin resistance plus resistance to a second-line injectable agent	31	23.48
Rifampicin resistance plus resistance to a fluoroquinolone	11	8.33
Pre-extensibly drug-resistance – injectable (MDR plus resistance to a second-line injectable agent)	10	7.58
Pre-extensibly drug-resistance – fluoroquinolone (MDR plus resistance to a fluoroquinolone)	6	4.55

Table 5
Examining for difference in pattern of DRTB in 2018/2019 (Prior to COVID-19) and 2020 (during COVID-19) in Chi-square analysis.

Predictor	Category	DRTB (2018/2019)	DRTB (2020)	Pearson $\chi 2$ or Fishers exact test	P value
Age group	<35	32/104	11/28	0.729	0.393
	>36	72/104	17/28		
Sex	Male	71/104	13/28	4.548	0.033
	Female	33/104	15/28		
State	Other	47/104	7/28	3.721	0.054
	Kano	57/104	21/28		
Setting	Rural	49/104	9/28	2.008	0.157
	Urban	55/104	19/28		
Type of patient	Retreatment	66/104	14/28	1.674	0.198
	New	38/104	14/28		
Second line anti TB use in the past	Yes	23/87	12/28	2.698	0.100
	No	64/87	16/28		
HIV status	Yes	19/104	3/28	0.906	0.341
	No	85/104	25/28		

period before COVID-19[20].

It is therefore necessary to ensure that appropriate measures are implemented to reach out to the 2.9 million people infected with TB and not accessing care including those people infected with DRTB[5]. There is an urgent need to intensify TB prevention efforts summarized by the acronym 6Is vis Immunization i.e., BCG given at birth, Intensified TB case finding and surveillance, Initiating proper TB treatment for persons with active TB, Isoniazid preventive therapy, Instituting ART for the HIV patient, and Infection control measures[21]. These preventive efforts need to be integrated in the COVID-19 pandemic response especially in developing countries with weak healthcare system. Furthermore, the national TB data should be examined in order to identify the changing trends in TB cases that might result from the COVID-19 pandemic.

Similar to our findings, the majority of patients with DRTB in Ethiopia are male, and most patients live in urban areas[22]. As in our report, a Canadian study found that the majority of DRTB patients were those in the age group 15–34 years[23]. Male patients may be at greater risk of TB acquisition due to other risk factors they might have such as cigarette smoking, and seasonal migration[24,25]. Seasonal migrants are exposed to poor living conditions such as overcrowding predisposing them to TB acquisition and they are also more likely to interrupt TB

treatment with attendant risk of DRTB acquisition[26,27]. Bajehson et al reported 16.3% of all DRTB patients having HIV in a retrospective cohort in northwestern Nigeria[28]. This is similar to our cohort where HIV/DRTB coinfection constitutes 16.6% of DRTB patients. This finding is important given the high mortality associated with HIV/DRTB coinfection reported in previous studies[29–31].

Our finding that up to 12.88% of the DRTB patients had FQ resistance is a serious concern given the importance of FQ in the treatment of DRTB. This finding is much higher than 11.8% and 4.3% FQ resistance reported in Southwestern Nigeria and Samara region of Russia respectively[32,33]. The differences between the two studies may be due to differences in population prevalence of FQ resistance and differences in the study designs.

The finding in our study that females were more likely to be admitted with DRTB during COVID-19 period compared to the male gender ($P = 0.033$) might be related to gender differences in health seeking behavior. The lack of difference in pattern of presentation of DRTB before and during COVID-19 in terms of age-group, state of residence, setting of residence, type of patient, use of second-line anti TB in the past and HIV status suggest that the drop in DRTB cases witnessed during the COVID-19 pandemic affected the entire community with no predilection to a particular segment of DRTB patients or a particular geographical location.

The major limitation of our study is that it's a single center study. Another limitation is that the study included only patients accessing facility based DRTB care, community DRTB patients are being followed up by another program and not included in the analysis. Despite these limitations we have described the pattern of DRTB at an isolation center in northwestern Nigeria during the COVID-19 pandemic.

The growing emergence of DRTB among TB patients in Nigeria should be urgently addressed. We question the potential reason why a drop in tuberculosis cases was observed in the year 2020 and we alert the Nigerian authorities that COVID-19 control efforts going hand-in-hand with intensified TB case finding and surveillance efforts and initiating proper TB treatment for persons with active TB are urgently needed.

CRediT authorship contribution statement

Farouq Muhammad Dayyab: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Garba Iliyasu:** . **Bashir Garba Ahmad:** Data curation, Writing – review & editing. **Ibrahim Aliyu Umar:** Data curation, Writing – review & editing. **Nura Musa Shuaib:** Data curation, Writing – review & editing. **Mamman Bajehson:** Data curation, Writing – review & editing. **Ibrahim Muhammad Daiyab:** Conceptualization, Validation, Visualization. **Oji Akpala:** Data curation, Writing – review & editing. **Olaoye Remilekun:** Data curation, Writing – review & editing. **Abdulrazaq Garba Habib:** Data curation.

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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