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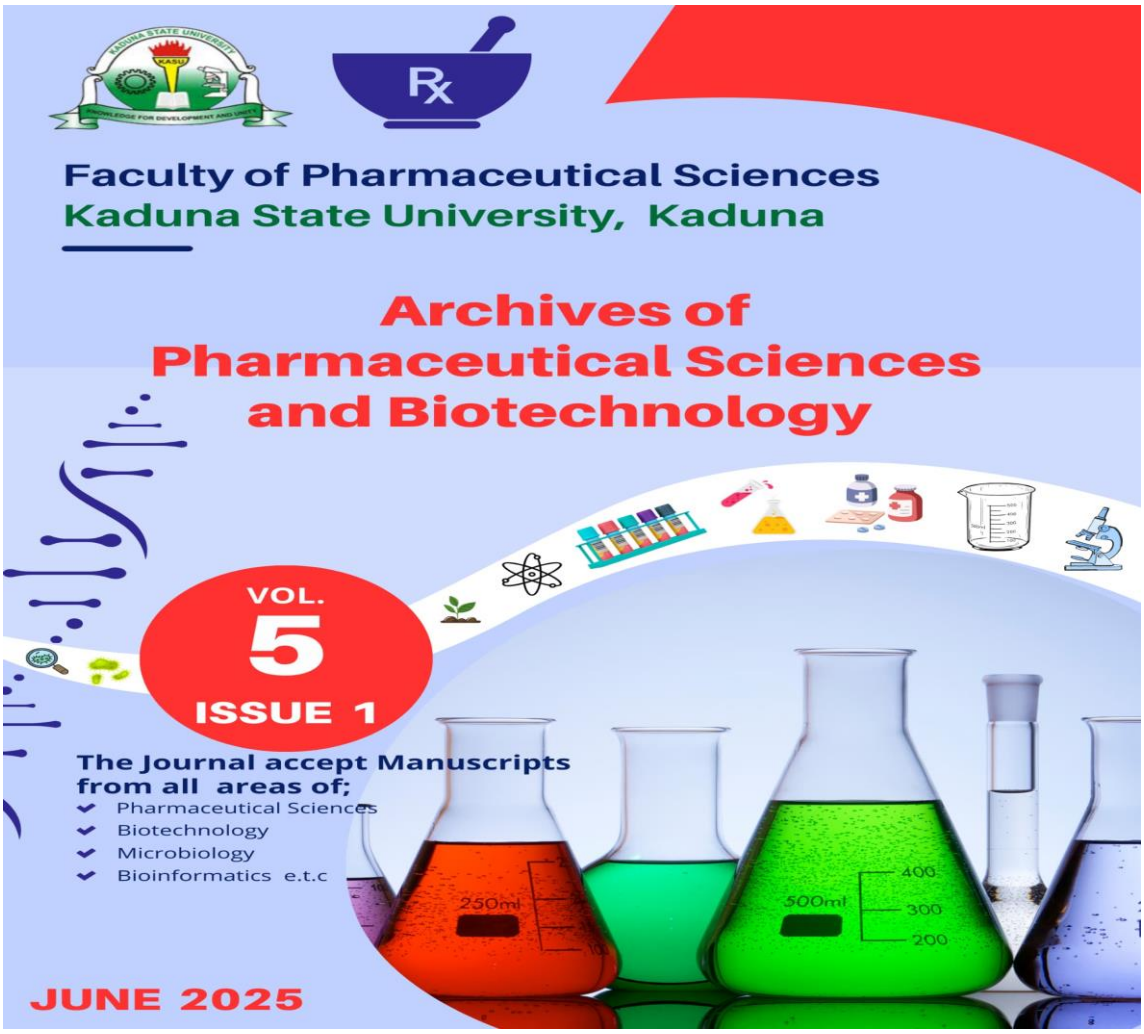


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# RETROSPECTIVE STUDY OF THE PREVALENCE OF RIFAMPICIN RESISTANCE AMONGST TUBERCULOSIS PATIENTS IN A HOSPITAL IN KADUNA

**Moroof, M.B.[1]*, Abdullahi, M.G.[1], Igwe, J.C., [2]Musa, F.M[3]**

[1]Department of Applied Biology, College of Science and Technology, Kaduna Polytechnic

[2]Department of Pharmaceutical Microbiology and Biotechnology, Kaduna State University

[3]Department of Microbiology, Faculty of Life Sciences, Kaduna State University

**Correspondence email: munirabadaruu@gmail.com, Phone number:08033908872**

## ABSTRACT

**Background:** The prevalence of tuberculosis is second to COVID- 19 as the leading cause of death from a single infectious agent with mortality rates doubling that of HIV/AIDS. Drug resistant tuberculosis remains a public health crisis, a health security threat and a limiting factor to the WHO end TB strategy of 2030. Drug resistance TB results in treatment failure, increasing morbidity and mortality rates. Nigeria ranks 11th among the 27 high multi- drug-resistant countries killing 268 people every day. Rifampicin is one of the first line antitubercular drugs used in combination with isoniazid (INH) for the treatment of tuberculosis. However, Rifampicin (RIF) resistance is a predictor of multidrug resistant tuberculosis (MDR-TB) because resistance to RIF, in most instances, co-exists with resistance to isoniazid (INH). With six years to the end of 2030 TB strategic plan as implemented by WHO, it is imperative to determine the current burden of rifampicin resistance amongst diagnosed TB patients within Kaduna state.

**Aim**: The aim of this study is to determine the prevalence of rifampicin resistance among tuberculosis patients in a hospital within Kaduna metropolis.

**Study Design**: Four years retrospective study

**Study Area and Period of Study:** The study was carried out in the Direct Observed Treatment (DOT) unit of a teaching hospital within Kaduna Metropolis. .

**Methods**: Tuberculosis record registers from January 2020 - October 2024 were used to identify all patients who were confirmed TB patients at the Hospital. Data on age, sex, year of treatment and drug susceptibility test (DST) results were collected. The data collected was subjected to statistical analysis using Microsoft Excel.

**Results**: A total of 1396 cases were reported within the period under review, and 3.3% (46) cases were rifampicin resistant. Demographic assessment showed that 65% (30) of patients that had rifampicin resistant TB cases in the hospital were male and 35% (16) were females. While 96.7% (1350) were susceptible to Rifampicin with 54% (729) being males and 46% (621) females. The prevalence rate of rifampicin resistance increased from 1.8% in 2020 to 5.39% in 2022. However, there was a decrease in the year 2023 and 2024 with prevalence rates of 4.18% and 2 .99% respectively. The pooled prevalence rate over the five-year period was 3.29%.

**Conclusions**: This study observed an increased prevalence of rifampicin resistance from 1.8% in 2020 to 5.39% in 2022 with a decrease to 4.18% in 2023 and 2.99% in 2024 respectively. The number of cases of tuberculosis and rifampicin resistant tuberculosis was more in males (65%) than females (35%). The highest number of recorded cases of TB fell within the age groups of 21-30 while the least number of cases was found within the age groups of > 60. With six years to the WHO end TB strategy of 2030, further studies are needed to determine the national burden of drug resistance tuberculosis within Nigeria so as to meet the targets set by the WHO end TV strategy of 2030.

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**Keywords**: Rifampicin, prevalence, tuberculosis, Kaduna, End TB strategy 2030, rifampicin resistant

## INTRODUCTION

Tuberculosis (TB), is an extremely contagious disease caused by *Mycobacterium tuberculosis* (MTB) and transmitted via aerosol droplets. It comes second to COVID- 19 as the leading cause of death from a single infectious agent with mortality rates doubling that recorded from HIV/AIDS [1]. More than 10 million people all over the world continue to fall ill from TB every year [2]. Over 3,500 people lose their lives to TB each day, translating to 1.3 million deaths each year [3]

Globally, in 2021 the African region came second with 23% of the global burden of tuberculosis [1]. Nigeria has the highest TB burden in Africa and sixth globally [4]. About 245,000 Nigerians die from tuberculosis (TB) yearly and about 590,000 new cases occur (of these, around 140,000 are also HIV-positive) [4]. TB is reported to be responsible for 10%of all deaths in Nigeria with thirty persons dying every hour [4]. The world health Organisation (WHO) reported that tuberculosis afflicted 452,000 persons in Nigeria in 2020[4]. More so, in 2022 an estimated 479,000 persons in Nigeria contracted the disease with 97,900 deaths [5]. This represents an average of one person developing TB every minute in the country and one person dying from TB every five minutes [5], even when the disease is preventable and treatable.

Treatment of tuberculosis basically involves the use of antibiotics that are combined to reduce the risk of bacilli developing resistance. Anti-tuberculosis drugs are classified into first- and second-line drugs. The first-line drugs for tuberculosis (TB) are isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin. Second-line drugs include: bedaquiline, linezolid, moxifloxacin, levofloxacin, clofazimine, cycloserine, Para-aminosalicylic acid (PAS), Propylthiouracil, and amikacin [6]. According to WHO [6] report the treatment success rate for people treated for TB with first-line regimens is 86%.

In spite of the successes recorded from the treatment of tuberculosis with antibiotics, Renee in 1950, predicted that the bacteria would eventually develop resistance to antibiotics through random mutations and natural selection.

Drug-resistant TB is defined as tuberculosis in which *Mycobacterium tuberculosis* is resistant to at least one of the effective drugs used in the treatment of TB. Depending on the antibiotics to which resistance is observed, resistance is classified as mono-resistance: resistance to one first-line anti-TB drug only (isoniazid or rifampicin). Poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin. Multidrug resistance (MDR): resistance to at least both isoniazid and rifampicin, this usually occurs when the first line drugs are misused. Extensive drug resistance (XDR): resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin) in addition to multidrug resistance. Rifampicin resistance (RR) is resistance to rifampicin detected using phenotypic or genotypic methods with or without resistance to other anti-TB drugs [6]. Rifampicin (RIF) resistance is a predictor of MDR-TB because resistance to RIF, in most instances, co-exists with resistance to Isoniazid (INH) [7].

The World Health Organization (WHO) endorsed the Xpert MTB/RIF in 2010 for

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use in tuberculosis (TB) endemic countries [8]. The test which simultaneously detects *Mycobacterium tuberculosis* complex (MTBC) and resistance to rifampin (RIF) in less than 2 hours contributes to the rapid diagnosis of TB disease and drug resistance [9], [10]. In comparison, standard cultures can take 2 to 6 weeks for *Mycobacterium tuberculosis* complex to grow and conventional drug resistance tests can add 3 more weeks [9].In developing and resource limited countries like Nigeria, the Xpert MTB /RIF test allows for rapid confirmation of tuberculosis and drug resistance among presumptive TB patients, allowing patients to start effective treatment quicker and preventing unnecessary presumptive management and isolation of non-tuberculosis patients.

Drug resistant tuberculosis remains a public health crisis, a health security threat and a mitigating factor to the WHO end TB strategy of 2030.About 464,000 global cases of rifampicin-resistant TB, 78% of which were MDR-TB was noticed at global in 2019 [4] and approximately 25% of deaths related to TB can be attributed to antimicrobial drug resistance[11].In 2021, there were an estimated 450,000 cases of multi drug resistant tuberculosis MDR-TB, representing a 3.1% increase from the previous year [5]. Globally in 2022, the estimated proportion of multidrug or rifampicin resistant TB (MDR/RR-TB) cases with pre-XDR TB (i.e. resistance to any fluoroquinolone for which testing was done) was 18% [5]. Nadeer *et al* [12] reported a pooled global prevalence of single drug-resistant TB, Rifampin - resistant TB, isoniazid resistant TB, multi drug resistant TB and extensive drug resistant TB as 11.8%, 9.4%, 15.7%. 11.6% and 2.5% respectively.

Drug resistance TB cases are continuously being reported both in developed and developing countries, it is more widespread in developing countries with low standards of living [14]. Africa, carries approximately 24% of the global TB burden [2]. Unlike other geographical areas which harbor single to few lineages of the *Mycobacterium tuberculosis* complex (MTBC), West Africa harbors all the six major lineages of the MTBC including two West Africa restricted lineages [15] with some genotypes associated with drug resistance as well as specific drug resistance -conferring and/or associated mutations [15], [16]. According to WHO [1] there is an estimated 77000 multi drug resistant tuberculosis in Africa region, of these cases 53% are from Nigeria and South Africa. Data on prevalence of drug resistance in most developing countries is limited due to lack/inadequate diagnosis, therefore submitted reports doesn't reflect the true epidemiologic situation [17].

Nigeria has the highest TB burden in Africa and ranks 11$^{th}$ among the 27 high multi-drug-resistant burden countries, killing 268 people in the country every day [1]. The MDR/RR TB burden in Nigeria is estimated to be 21,000 annually. With the suboptimal case notification in Nigeria, this value does not reflect the actual MDR-TB burden. The case notification rate in 2019 was 11% with only 2,384 cases diagnosed [2]. In 2021 WHO reported a pooled rifampicin prevalence rate of 4.6% was in Nigeria [1].

The continuous emergence and spread of drug-resistant strains of *Mycobacterium tuberculosis* amongst the populace will result in treatment failure, translating to increased morbidity and mortality rates and a hindrance to the actualization of the End TB strategy by 2030. Ole *et al* [16] reported that the global treatment success rate of extensively drug-resistant tuberculosis is 44.2% which is far below the WHO's target rate of 75%; uncomplicated TB is 85%; MDR/RR-TB, which is more expensive is

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reduced to 60%. Pre-XDR/XDR-TB is far worse and requires using relatively more expensive drugs compared to MDR-TB [18], [19]. This retrospective study was conducted to determine the prevalence of rifampicin resistance (RR-TB) using Xpert MTB/RIF from January 2020- October 2024 among TB patients attending the Directly Observed Treatment (DOT) unit of a teaching hospital within Kaduna metropolis.

## MATERIAL AND METHODS

### Study Area

The study Center is a government owned hospital, within Kaduna metropolis. The center has a directly observed treatment (DOT) tuberculosis unit that serves as a major referral center for all presumptive tuberculosis patients within Kaduna metropolis. The unit performs testing of presumptive patients using Xpert/ MTB machine to detect tuberculosis and rifampicin resistance. Other services offered by the unit include counseling and administration of drugs to tuberculosis patients.

### Data Collection

Tuberculosis record registers were utilized to identify all patients who had confirmed TB cases at the hospital between January 2020 and October 2024. The data on the register was reviewed. Data on age, sex, year of treatment and drug susceptibility test (DST) results were collected and analyzed. The data collected was subjected to statistical analytics using Microsoft Excel.

## RESULTS

### Prevalence of Rifampicin Resistance

The prevalence of rifampicin resistance from January 2020 - October 2024 among diagnosed TB patients is shown in (Table 1). The prevalence rates increase from 1.8% in 2020 to 5.39% in 2022. However, there was a decrease in the year 2023 and 2024 with prevalence rates of 4.18% and 2.99% respectively. The pooled prevalence rate over the period of the study was 3.29%.

**Table1: Prevalence of rifampicin resistance among TB patients (Jan. 2020 – Oct. 2024).**

| Year | MTB detected/ Rifampicin susceptible | MTB detected/ rifampicin resistant | Total | Prevalence rates (%) of rifampicin resistance |
|---|---|---|---|---|
| 2020 | 327 | 6 | 333 | 1.80 |
| 2021 | 230 | 6 | 236 | 2.54 |
| 2022 | 228 | 13 | 241 | 5.39 |
| 2023 | 306 | 13 | 319 | 4.18 |
| 2024 | 259 | 8 | 267 | 2.99 |
| Total | 1350 | 46 | 1396 | 3.29 |

**Key: MTB – *Mycobacterium tuberculosis***

### Annual Rifampicin Resistance

The annual prevalence of rifampicin resistant TB cases from January 2020 -October 2024 is shown in (Fig 1). In 2020 and 2021 prevalence rates of 1.8 and 2.54 % cases was reported

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respectively. There was an exponential increase in 2022 and 2023 with prevalence rates of 5.39% and 4.18% respectively. In 2024 however, prevalence rates of 2.99% was reported.

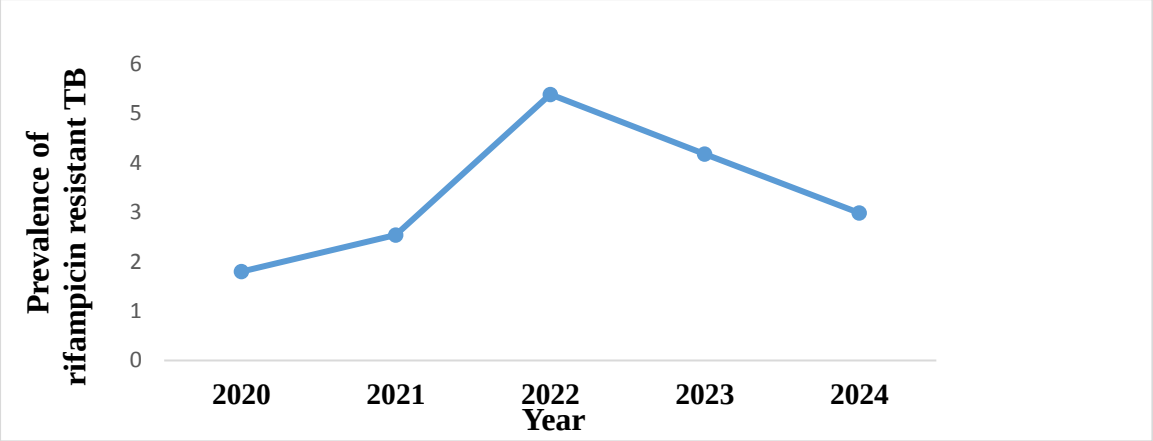


**Fig 1: Prevalence rates of rifampicin resistant Tb from January 2020-October 2024**

**Sex Distribution of TB Cases**

The distribution of rifampicin susceptible and resistant TB cases by sex is shown in (Fig 3). Out of the 1396 cases diagnosed from 2020 to 2024, 1350 were susceptible to rifampicin with 54% (729) males 46% (621) females. Forty-six (46) cases of rifampicin resistant TB were reported with 65% (30) males and 35% (16) females.

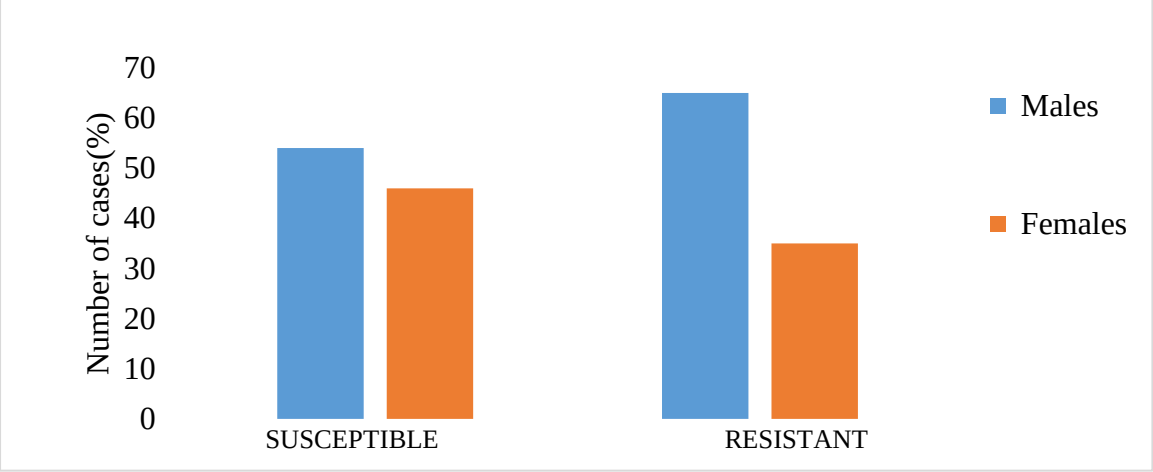


**Fig 2: Sex distribution of rifampicin susceptible and resistant TB cases**

**Disaggregation of TB cases by age**

The age distribution of TB cases is shown in (Fig 4), the highest number of cases was found in age group of 21-30, while the age group of > 60 years had the least number of reported cases.

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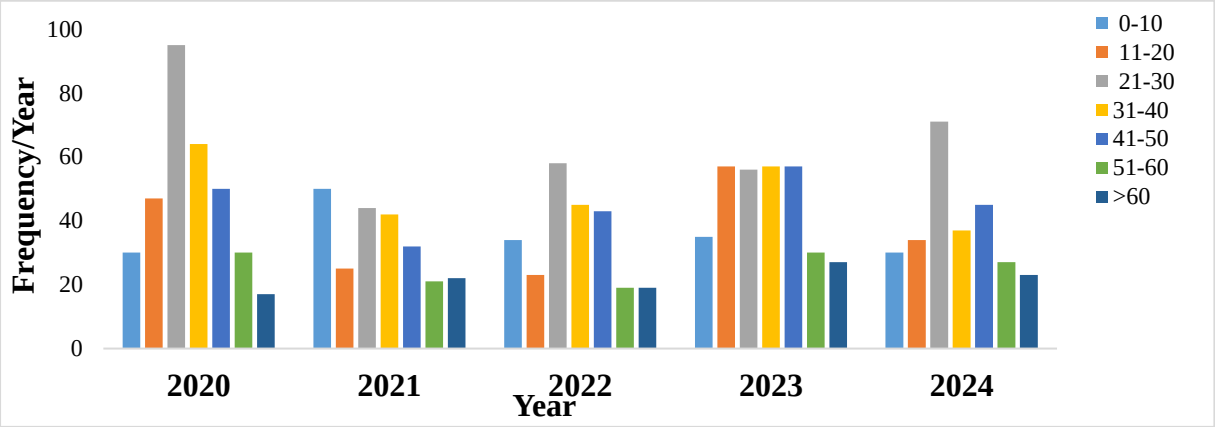


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**Fig 3: Annual disaggregation of TB cases by age from 2020-2024**

## DISCUSSION

Drug resistant tuberculosis isolates have continued to impede the success rate that would have been recorded from the effective control and treatment of tuberculosis. This study x-rayed the prevalence of rifampicin resistant *Mycobacterium tuberculosis* in a hospital within Kaduna metropolis over five years short of two months using retrospective data. Rifampicin resistance was found to be present at different rates throughout the period. Though the prevalence of resistance increased from 2020-2022(1.80% - 5.39%) there was a decrease in 2023 and 2024 (4.18% - 2.99%). The pooled prevalence of rifampicin resistant during the period of study was 3.29%. This is similar to rates reported by Aliyu *et al*, Ahiarakwem *et al* and Olabiyi *et al* [20], [21], [22]. Higher prevalence rate was however reported by Bitrus *et al*, Kome *et al* and Kasimu *et al* [23], [24], [25]. The detection of rifampicin resistance in new cases is an indication that there is a population of rifampicin resistance strains of *Mycobacterium tuberculosis* in circulation within the state. According to WHO [1], there have been an estimated purported increase and surge in the burden of MDR/RR-TB at approximately 3–4% for new cases and 18-21% for acquired cases in the past decade [1]. This translates to the fact that a huge burden of drug-resistant TB is within our community emancipating due to treatment failures. The presence of rifampicin resistant gene in isolates is considered a marker for multidrug resistance tuberculosis because rifampicin resistance co-exist in most cases with resistance to isoniazid; the two most important first line drugs used in the treatment of tuberculosis [7]. The findings of this study further showed that more males than females were diagnosed with tuberculosis and rifampicin resistance TB during the period of study. Similar findings have been reported by Ajide *et al, Olanrewaju et al*, Ugu *et al* and WHO [26], [27], [28], and [1]. Higher TB cases in females than males were however reported by Adeusi *et al* [29] in Ijero local government Area, Ekiti State, Nigeria. According to WHO [30] globally more males than female cases of tuberculosis are reported. In Nigeria, two studies however found no association between gender and drug resistant TB [31], [32]. The high number reported in males can be attributed to lifestyle such as smoking, drug usage resulting in compromised immunity, and

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socioeconomic reasons such as sole bread winner, social network and occupation in informal sector, which increases their risk of exposure, limited access to health care due to cultural barriers imposed on women in the region could be responsible for the low numbers of cases reported in women. Further evaluation showed that the highest number of cases was found in age groups 21-30. This is in concordance with reports by Olabiyi *et al* and Wokem *et al* [22] and [33] and could be attributed to the fact that the youth are the active work force, and are more likely to engage in activities that predisposes them to the disease. The detection of resistance to rifampicin, a core anti-tubercular drugs used in the treatment of tuberculosis is of great concern. The detection of these resistant strains in new cases is an indication that there is a population of rifampicin resistance strains in circulation within the state. It is pertinent to state that one drug resistant TB case, if not detected and treated effectively can result in transmission to fifteen persons [30]. Urgent measures should therefore be taken to detect, treat and curb the transmission of drug-resistant tuberculosis, to enable the actualization of the WHO-end-TB strategy 2030.

## CONCLUSION AND RECOMMENDATIONS

The prevalence of rifampicin resistance in the study center increased from 1.80% in 2020 to 5.39% in 2022 but decreased to 4.18% and 2.99% in 2023 and 2024 respectively. A pooled prevalence of 3.29% was recorded over the period of study. The number of cases of tuberculosis and rifampicin resistant tuberculosis was more in males than females. The highest number of cases was recorded between the age groups of 21-30 while the least cases were recorded among patients > 60 years of age. With six years to the WHO end TB strategy of 2030, there is the need for more awareness campaign, mitigation strategies, comprehensive and periodic surveillance studies, pharmacovigilance studies and research to determine the actual burden of drug resistance tuberculosis across Nigeria, so as to ensure the actualization of the WHO end TB strategy 2030.

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