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Original article

Rifampicin-resistant *Mycobacterium tuberculosis* complex in Niger: A 5-year retrospective analysis (2017–2022)

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ABSTRACT

Background: Rifampicin-resistant *Mycobacterium tuberculosis* complex is a growing burden globally and is classified as a critical organism. This study aimed to determine the prevalence of Rifampicin-resistant tuberculosis (RR-TB) and associated risk factors in Niger Republic. **Methods:** This was a retrospective study, conducted from January 1, 2017, to December 2022 at GeneXpert sites in Niger. GeneXpert MTB/RIF was used to detect *Mycobacterium tuberculosis* complex (MTC) and the resistance to rifampicin. Multivariate logistic analysis was performed to identify risk factors for rifampicin resistance in Niger. **Results:** A total of 12970 patients were enrolled. The median age of patients was 39 years, with male predominant, sex ratio of 2.70. The overall, prevalence of MTC was 37.69% (4889/12970), among this 4.45% (210/4889) were children. Out of 4889 MTC positive cases, 479 (9.79%) were rifampicin-resistant, all from pulmonary tuberculosis: 111 (23,57%) new cases, 195 (41,40%) therapeutic failure, 153 (32,48%) relapsed cases, 12 (2,55%) treatment abandonment. Based on the univariate analysis, therapeutic failure (p=0.001), relapsed cases (p=0.001), and treatment abandonment (p=0.005), were significantly related to rifampicin resistance in Niger. Based on the multivariate analysis, only therapeutic failure (AOD: 6.62, 95%CI: 5.17-8.51, p<0.001) and relapsed cases (AOD: 3.08, 95%CI: 2.39-3.98, p<0.001) were the independents factors associated with rifampicin resistance. **Conclusion:** The prevalence of MTC resistance to rifampicin was relatively high in Niger. Therapeutic failure and relapsed cases represented the major factors favoring rifampicin resistance.

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Introduction

Tuberculosis (TB) is an infectious, contagious disease caused by *Mycobacterium tuberculosis* complex. TB remains a recurrent public health concern leading to the second cause of death from a single infectious agent worldwide in 2022, after COVID-19 [1]. According to the World Health Organization (WHO), globally in 2022, TB caused an estimated 1.30 million deaths [1]. These burdens are particularly worrying for drug-resistant tuberculosis. Rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB) affected 450 000 and 77 000 patients in the WHO African region, in 2023 [2]. To guide research, discovery, and development of new antibiotics, recently, the WHO updated a global bacterial priority pathogen list, divided into three categories according to the urgency of the need for new antibiotics: critical, high, and medium priority [3]. In this list, RR *Mycobacterium tuberculosis* is classified as a critical organism [3].

Rifampicin is an ansamycin antibiotic made by the soil bacterium *Amycolatopsis rifamycinica* [4]. Rifampin exerts by inhibiting DNA-dependent RNA polymerase by sterically obstructing the path of the elongating RNA at its 5′ end or by reducing the RNAP's affinity for short RNA transcripts, resulting in bactericidal activity [5]. Moreover, Rifampicin is an antipruritic, particularly effective in cholestatic diseases [5]. Resistance to rifampicin depends on the species. The resistance can occur via (i) ADP ribosylation of rifampicin (ii) efflux, (iii) mutation of RNA polymerase, or (iv) mutation of the *rpoB* promoter [6,7]. Rifampicin is on the WHO essential medicines List, widely available as a generic [8].

Detection of RR-TB has been improving with Xpert diagnostics. Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, California, United States) improved RR results as well as a higher sensitivity for smear-negative tuberculosis cases resulting from tuberculosis and HIV coinfection [9,10].

In Niger, through the National TB Program (NTP) and its partners, the country has set up specialized structures such as National Reference Laboratory for TB (NRL/TB) and tuberculosis centers over the country for diagnosis and management of tuberculosis. The NTP has integrated the fight against multidrug-resistant TB (MDR-TB) into its priority activities and encourages the use of GeneXpert MTB/RIF assay for the detection of MTC as well as RR. The first Xpert MTB/RIF was installed in 2011 and by May 2024 there were 348 installed modules.

This study aimed to determine the prevalence, patterns, and of and factors associated with RR-TB in Niger Republic.

Methods

Design and setting

This retrospective observational study was conducted in the National Reference Laboratory for Tuberculosis of Niger Republic. This laboratory administers oversight of TB diagnostic networks in Niger and coordinates routine laboratory-based TB surveillance using testing data including rifampicin resistance by GeneXpert MTB/RIF. The study analyzed clinical and laboratory data collected between January 2017 to December 2022.

Study population

The study population was all TB presumptive patients with clinical symptoms and signs suggestive of TB who visited selected TB diagnostic units during the survey period.

Inclusion and exclusion criteria

A patient was included in the survey if (i) he/she was present as a presumptive TB case (new cases); (ii) cases of tuberculosis therapy failure, relapse, and treatment abandonment; RR-TB retreatment and patients with ultra-resistant-TB were excluded.

Definitions

WHO definitions were used for new cases, failure, and relapse [11]; (i) New cases: if the patients have never been treated for TB or have taken anti-TB drugs for less than 1 month [11]; (ii) treatment failure was defined as when treatment was terminated or at least two anti-TB drugs were permanently changed due to either a positive culture after ≥ six months of treatment (except for an isolated positive culture), or at least 2 consecutive positive sputum smears with grade ≥ 2 + after ≥ six months of treatment (if cultures were not available) [11]; (iii) Relapse was declared if patients had a positive culture during a 12-month follow-up after cure or completion, except if molecular tests showed reinfection [11]; (iv) RR-TB is defined as tuberculosis caused by M. tuberculosis complex strains resistant to rifampicin, susceptible or resistant to isoniazid [11].

Statistical analyses

Data were exported to R Studio version 4.0.4. for analysis. Categorical variables were summarized using frequencies and percentages. As the missing data in key variables did not exceed 5%, data imputation was not performed. Univariate and multivariate analyses were used to assess risk factors of RR. Risk factors exhibited significant associations in univariate analyses and were re-analyzed by the multivariate logistic regression model. Multivariable logistic regression was used with backward elimination of variables based on a p-value cutoff of 0.05 to select variables to obtain an adjusted odds ratio (AOR). The level of significance at all analyses was considered at *p*- value < 0.05.

Results

Baselines characteristics of patients

A total of 12970 presumptive TB patients were included in this study. Male patients predominated with 9451 cases (72.87%) and a sex ratio of 2.70. The median age of patients was 39 years, with extremes of 0 and 100 years. Most patients were new cases (n=9132, 70.41%), followed by relapsed cases (n=2094, 16.14%). Among the 12970 patients, 1731 (13.34%) had a known and documented HIV status. Of these 1731, 449 (25.93%) were HIV-positive**.** HIV typing (HIV1 or HIV2) was not specified **(Table 1).**

Prevalence of rifampicin resistant *Mycobacterium tuberculosis*

The GeneXpert MTB/RIF assay test for the detection of MTB was positive in 4889 (37.69%) samples and negative in 7665 (59.10%) samples. Of the positive samples, the prevalence of RR TB was 9.79% (n=479). Among samples with RR TB, 2.24% (n=110) had primary RR TB **(Table 2).**

Analysis of risk factors associated with rifampin resistance

In univariate analysis, the risk of RR TB was significantly higher in patients with therapeutic failure (OR 9.35, 95%CI: 5.15-17.81), relapsed cases (OR 3.29, 95%CI: 1.69-6.59), and treatment abandonment (OR 6.47, 95%CI: 1.58-23.01) **(Table 3).**

In multivariate analysis, only therapeutic failure (OR 9.35, 95%CI: 5.15-17.81) and relapsed cases (OR 3.29, 95%CI: 1.69-6.59) were significantly higher in patients with RR TB **(Figure 1).**

Table 1. Patients' characteristics.

Variables	Frequencies	Percentages	95% CI
Age (years)			
0 - 5	34	2.78	[1.04-4.52]
6 - 18	812	6.55	[4.85-8.25]
19 - 40	5657	45.64	[44.34-46.94]
41 - 65	4310	34.77	[33.35-36.19]
> 65	1271	10.25	[8.58-11.92]
Sex			
Male	9451	72.87	[72.10-73.63]
Female	3501	26.99	[26.24-27.76]
No information	18	0.14	[0.9-0.22]
Type of specimen			
Sputum	12779	98.53	[98.31-98.72]
Bronchoalveolar fluid	1	0.01	[0.00-0.04]
Gastric aspiration	19	0.15	[0.09-0.23]
Biopsy	2	0.02	[0.00-0.06]
Cerebrospinal fluid	3	0.02	[0.01-0.07]
Pus/effusion fluid	165	1.27	[0.56-3.98]
Urine	1	0.01	[0.00-0.04]
HIV			
Negative	1282	9.88	[9.38-10.41]
Positive	449	3.46	[3.16-3.79]
Not tested/unknown	11239	86.65	[86.06-87.23]
Therapeutic status			
New cases	9132	70.41	[65.62-67.25]
Relapsed cases	2094	16.14	[15.14-17.25]
Therapeutic Failure	1234	9.51	[8.79-10.33]
Treatment abandonment	226	1.74	[0.04-3.44]
No information	284	2.19	[1.95-2.46]
Sputum smear microscopy			
Positive	4077	31.43	[30.00-32.86]
Negative	2990	23.05	[21.54-24.56]
No information	5903	45.51	[44.64-46.36]

Table 2. Distribution of patients according to GeneXpert MTB/RIF results.

Variables	Frequencies	Percentages	95% CI
MTC detection			
Non detected	7665	59.10	[58,25-59,94]
Detected	4889	37.69	[36,86-38,53]
Error	416	3.21	[2,92-3,52]
Pattern of RIF			
Sensible	4338	88.73	[87,81-89,59]
Resistant	479	9.79	[9,00-10,66]
No information	72	1.47	[1,17-1,85]
Resistance type			
Secondary resistance	362	7.40	[4,70-10,10]
Primary resistance	110	2.24	[1,53-6,01]
No information	72	1.47	[1,17-1,85]

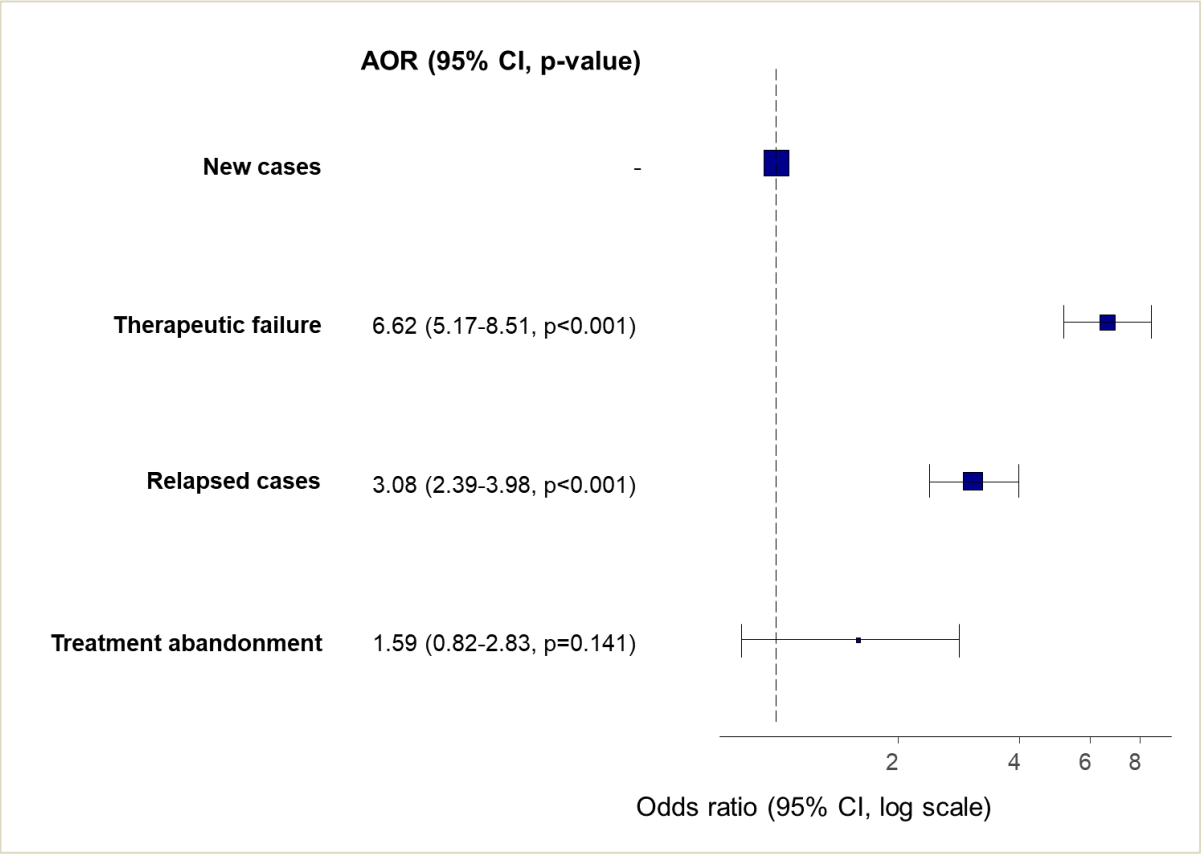
MTC: *Mycobacterium tuberculosis* complex; RIF: Rifampicin ; 95% CI = 95% confidence interval

Table 3. Univariate analysis of risk factors associated with rifampicin resistance.

Variables	Pattern of RR		OR	95% CI	*p*-value*
	No n (%)	Yes n (%)			
Patients HIV Status					
Negative	633 (89,03)	114 (91,94)	1	-	
Positive	78 (10,97)	10 (8,06)	0.72	0.25-1.77	0.500
Treatment history					
New cases	2396 (56,15)	111 (23,57)	1	-	
Therapeutic Failure	636 (14,91)	195 (41,40)	9.35	5.15-17.81	<0.001
Relapsed cases	1072 (25,12)	153 (32,48)	3.29	1.69-6.59	0.001
Treatment abandonment	163 (3,82)	12 (2,55)	6.47	1.58-23.01	0.005
Sex					
Female	839 (19,37)	88 (18,37)	1	-	-
Male	3493 (80,63)	391 (81,63)	0.96	0.54-1.77	0.904
Sputum smear microscopy					
Negative	253 (8,71)	16 (4,21)	1	-	-
Positive	2652 (91,29)	364 (95,79)	1.96	0.60-9.02	0.319
Age (years)					
< 18	185 (4,43)	21 (4,45)	1	-	-
18-40	2415 (57,78)	310 (65,68)	1.23	0.41-4.65	0.730
41-65	1310 (31,34)	118 (25)	0.70	0.21-2.79	0.581
> 65	270 (6,46)	23 (4,87)	0.25	0.03-1.54	0.149

OR= Odds ratio, 95% CI = 95% confidence interval.
95% CI, confident interval at 95%
* Variables with $p < 0.05$ were included in the multivariable regression model

Figure 1. Multivariate analysis of risk factors associated with rifampicin resistance.



AOR = Adjusted Odds ratio, 95%; CI = 95% confidence interval; 95% CI, confident interval at 95%

Discussion

RR-TB is categorized as a critical organism by the WHO according to the urgency of the need for new antibiotics [3]. In this study, the prevalence of RR TB detected by GeneXpert assay was 9.79%. This prevalence was found to be lower than a previous report from Niger Republic, which recorded 31.8% (332/1044) [12], but approximately equal to the studies done in Gabon and Ethiopia in which the prevalence of RR TB was 10.9 and 11%, respectively [13,14]. The variation in reported RR TB in Niger may reflect the access to healthcare facilities and the effectiveness of TB control programs. For example, in the previous study carried out in Niger [12], Xpert was mainly used to detect RR among re-treatment cases. Since 2021, Xpert has been used as an initial tool for TB diagnosis. Males were predominantly infected with RR-TB. This is consistent with global trends in TB by gender particularly in low-and middle-income countries [15,16]. The disparity in gender distribution of RR-TB could have been so because men are more exposed to factors that lead to RR such as poor adherence to treatment, smoking, alcoholism, and seeking and accessing TB care which make them more susceptible [16]. The frequency of error Xpert® MTB/RIF results was 3.21%. A similar observation was made in a previous article performed in Nigeria [17]. According to the Xpert manufacturer, a cumulative error rate of >5% is unacceptable and should be investigated and resolved immediately. Most Xpert® MTB/RIF results errors were linked to improper procedures used in specimen collection and sample preparation, as well as faulty modules and cartridges.

RR TB risk factors were widely described in the literature. It has been reported that age [18], educational status of the family [19], residence [19], history of tuberculosis contact [19], type of TB [18], HIV infection [19,20], malnourished status [19,21], duration of cough greater than 3 weeks [19], and weight loss [19,22] were significantly associated with RR TB. This work examined risk factors for RR TB based on demographics, microscopic results, and treatment history. We found therapeutic failure and relapse were significant risk factors for RR TB in Niger. On the contrary, sex, age group, and sputum smear microscopy showed no overt associations with RR TB.

Moreover, of note is the lack of a significant association between rifampicin resistance and HIV infection in this study. However, this association has been reported by several authors [19,20,23]. According to the National Tuberculosis Program (PNLT) statistics, in Niger, the prevalence of tuberculosis among patients living with HIV infection (PLHIV) was estimated at almost 4% in 2019, while the death rate was 21% [24]. These PLHIV may be at higher risk of exposure to RR TB due to their frequent attendance at specialized medical facilities. The use of GeneXpert for both HIV viral load and rifampicin resistance screening could facilitate the management of these patients.

Limitations

This study had several limitations. There were limitations inherent to an observational study design. Missing information was noted for several variables, including HIV infection, mortality, smoking, diabetes mellitus, drug abuse, and alcohol consumption. Moreover, we did not follow up on all patients' clinical outcomes and treatments. However, this study provides valuable information to strengthen the surveillance of RR in Niger.

Conclusion

Tuberculosis remains a major public health concern in Niger. This study reveals a decreasing trend of rifampicin resistance tuberculosis in Niger Republic. Two factors including therapeutic failure and relapse were significantly associated with rifampicin resistance tuberculosis. The study highlights the urgent need to strengthen the surveillance of these risk factors to limit the spread of rifampicin resistance TB in Niger.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Ethical considerations

This study was carried out as part of a medical thesis. Approval from the Dean of the Faculty of Health Sciences at Abdou Moumouni University (n°000845/UAM/FSS) and the head of the National Reference Laboratory were obtained before the study was launched.

Authors' contributions

A.Y contributed to experimental design, routine analyses, data analysis, data interpretation and writing the first draft. N.I.H, I.A.A, T.O collected samples and clinical information and contributed to routine analyses and writing the first draft. N.I.H, B.N and H.H.Z contributed to routine analyses. B.S, B.M.S, A.O, A.S, S.A, D.A, M.Do, M.Da, and S.B contributed to critically reviewing the manuscript and data interpretation. E.A and S.M coordinated and directed the work. All authors have read and agreed to the published version of the manuscript.

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