

Research Article

# Factors Associated with Multidrug-Resistant Tuberculosis in Patients Diagnosed in the Centre Region, Burkina Faso, 2020-2022

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## Abstract

**Introduction:** The emergence of multidrug-resistant tuberculosis (MDR-TB) is a challenge for disease control and prevention worldwide. **Objective:** To study factors associated with MDR-TB in patients diagnosed in the Centre region, from 2020 to 2022. **Methods:** We conducted a retrospective unpaired case-control study on data from January 1, 2020 to December 31, 2022. The variables used were grouped into sociodemographic, clinical, paraclinical and therapeutic characteristics. We calculated crude and adjusted odds ratios (aOR) at a 95% confidence interval (CI), with a significance level  $\alpha = 5\%$ . **Results:** Factors associated with multidrug-resistant tuberculosis were history of TB treatment [OR=7.36;  $p < 0.0001$ ]; place of residence [OR=6.04;  $p = 0.0001$ ]; alcohol consumption [OR=4.20,  $p = 0.002$ ]; Acid-Fast Bacillus (AFB)  $\geq 3+$  [OR=3.37,  $p = 0.008$ ]; hospitalization during treatment [OR=5.20; IC95%=1.79,  $p = 0.002$ ]; DOTS knowledge [OR=6.53;  $p < 0.0001$ ]. **Conclusion:** Our study identified several factors associated with multidrug-resistant tuberculosis, those related to behavior in both patients and caregivers being: history of TB treatment; alcohol consumption; and lack of knowledge of the DOTS strategy. Which means that future studies should aim to understand the impact of patient behavior/knowledge or caregiver attitudes so that the results can guide the use of scarce resources to optimize their impact.

## Keywords

Tuberculosis, Risk Factors, Multidrug-resistant Tuberculosis

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## 1. Introduction

The emergence of multidrug-resistant tuberculosis (MDR-TB) is a challenge for disease control and prevention worldwide [1, 2]. It is the most severe form of tuberculosis. In addition, the Covid 19 pandemic has had a negative impact on tuberculosis control, and the number of people diagnosed with multidrug-resistant or rifampin-resistant TB (MDR/XDR-TB) has risen from 206,030 cases in 2019 to 450,000 cases in 2021 [3, 4], with around 2.14 deaths per 10 million occurring [5].

In Burkina Faso, the number of notified MDR/XDR-TB cases rose from 78 in 2019 to 85 in 2021 (unpublished data). In order to effectively combat tuberculosis and drug-resistant tuberculosis, and move towards its elimination worldwide by 2035 in line with the Sustainable Development Goals (SDGs), the Stop TB Strategy has been drawn up by the World Health Organization (WHO). The emergence and spread of multidrug-resistant and extensively drug-resistant tuberculosis is exacerbated by inadequate detection and inappropriate treatment. People become infected with MDR-TB either when they are exposed to a resistant strain, or when treatment leads to the selection of a resistant strain [5]. Indeed, according to the WHO, ensuring comprehensive, high-quality care will also benefit global health security. There is therefore a crucial need to ensure good prevention of MDR-TB if we are to achieve our objectives.

Prevention, an important element in the fight against multidrug-resistant tuberculosis, requires knowledge of the disease's risk factors. In the literature, several authors have identified factors associated with MDR-TB [2, 6]. Among these studies, in Burkina Faso three (03) cross-sectional studies were carried out, and the results showed that there were also some discrepancies between the results presented (unpublished data). Indeed, of these cross-sectional surveys, only the latest study by Diandé et al. on the 2016 - 2017 prevalence survey found that only history of TB treatment was statically significantly associated with MDR-TB. In order to go further in the search for levels of evidence, we undertook a case-control study whose aim was to identify factors associated with MDR-TB so that patients with a high profile of MDR-TB could be identified early and policy recommendations aimed at reducing the occurrence of MDR-TB in them could be formulated.

## 2. Materials and Methods

### 2.1. Study Framework

This study took place in the Centre region, whose capital is Ouagadougou, the capital of Burkina Faso. The Centre region covers an area of 2,805 km<sup>2</sup> with a population of 3,030,384, or 14.8% of the total population of Burkina Faso. In terms of health, it is subdivided into five (05) health districts: Baskuy, Boulmiougou, Nongremassom,

Sig-Noghin and Bogodogo, each with a tuberculosis diagnosis and treatment center (DTC). In this region, diagnosis and management of MDR-TB cases are carried out at the National Center for Tuberculosis Control (NCTBC), Paul VI Paul 6 hospital, University Hospital Yalgado OUEDRAOGO, University Hospital Bogodogo, and the Boulmiougou district, all of which have GeneXpert MTB/RIF tools at their disposal. NCTBC receives patients from all over the country. Over the last 5 years, 284,463 people have left Burkina Faso compared to 300,906 who have entered. It is noted that 68.6 per cent of emigration is directed to Côte d'Ivoire, 8.2 per cent to Mali and 7.2 per cent to Ghana. In addition, the United States and France are the other main destinations with 0.8% and 0.7% of emigration respectively. In addition, in view of the security context in the country, as of February 28, 2023, 1,999,127 internally displaced persons in the country. In the central region, there are 59,822 internally displaced people, or 3% (CONASUR, February 28, 2023).

### 2.2. Type and Period of Study

We conducted an unmatched case-control study on data from January 1, 2020 to December 31, 2022, i.e. over a period of three (03) years.

### 2.3. Study Population and Sampling

#### 2.3.1. Study Population

The study population consisted of all patients with tuberculosis confirmed bacteriologically by smear microscopy, culture or GeneXpert MTB/RIF examination diagnosed in the Centre region from January 1, 2020 to December 31, 2022.

*Case definition:* A case was defined as any tuberculosis patient with a test (culture or molecular including GeneXpert MTB/RIF examination confirming infection with *Mycobacterium Tuberculosis*, resistant to rifampicin alone (RR-TB) or associated with isoniazid (MR-TB), diagnosed in the Centre region, between January 1, 2020 and December 31, 2022.

*Control definition:* Controls were people diagnosed bacteriologically (Microcopy, GeneXpert MTB/RIF, culture) with drug-susceptible tuberculosis, treated and declared cured. Controls must have been diagnosed at the same time and in the same health facility as cases in the Centre region, between January 1, 2020 and December 31, 2022.

#### 2.3.2. Inclusion and Non-inclusion Criteria

Inclusion criteria

Cases

- 1) Any patient at least 15 years of age;
- 2) All forms of tuberculosis, rifampin-resistant (RR-TB)

or multidrug-resistant (MDR-TB), confirmed by mycobacteriological culture or GeneXpert MTB/RIF, already treated or under treatment;

3) Diagnosed in the Centre region during the study period.

#### Controls

Controls included were those:

- 1) With bacteriologically confirmed (microscopy or culture or GeneXpert MTB/RIF) drug-susceptible TB.
- 2) And who had negative results (microscopy or culture or GeneXpert MTB/RIF test) during the last month of treatment and had been diagnosed and cured in the Centre region.

#### Non-inclusion criteria

##### Cases:

Were not included in the study:

- 1) Patients whose clinical condition would not allow answers to the questions;
- 2) Patients whose clinical records could not be used;
- 3) Patients who did not give their consent;
- 4) Patients who could not be reached or who had died.

#### Controls

The following were not included in the study:

- 1) Patients whose clinical records could not be used.
- 2) Patients who did not give their consent.
- 3) Patients who could not be reached or who had died.

### 2.3.3. Sample Size

To obtain our sample size, we calculated it using SAS® 9.4 statistical software, with a matching of 1 case to 2 controls. Considering that 45% of the controls had been exposed to risk factors for MDR-TB, and taking our research hypothesis that history of TB treatment is associated with MDR-TB, i.e. a odds ratio = 3, and a risk of error alpha of 0.05, we obtained 204 patients. With a margin of error of 10%, we included a total of 225 patients, i.e. 75 cases and 150 controls.

### 2.3.4. Sampling Procedure

#### Cases

The group of cases in our sample (N1=75 cases) was allocated proportionally to the average annual weight of multidrug-resistant tuberculosis cases in each diagnostic and treatment center from the registers of confirmed multidrug-resistant tuberculosis cases recorded. In each facility we adopted simple random sampling using Microsoft Excel to generate a random selection from data recorded in a spreadsheet until the required size was reached. This is a national database collected by the national tuberculosis control program from which we extracted patients diagnosed in the central region.

#### Controls

A “2 controls for 1 case” approach was adopted. And controls were selected in a simple random fashion from consultation registers (N2 =150).

## 2.4. Data Collection: Collection Techniques, Tools and Variables

We conducted face-to-face or telephone interview and reviewed the literature, “Kobocollect®” tool, using a semi-structured questionnaire configured for individual interviews and a secondary data extraction grid, to collect the dependent variable (Multidrug-resistant TB); the explanatory variable of interest (History of TB treatment) and the explanatory variables. These later are:

Sociodemographic characteristics: age, age range, sex, marital status, educational level, occupation, religion, place of residence, number of people living in the same household, distance between place of residence and DTC, stigma, social support, prison stay, eating habits and lifestyle: alcohol consumption, smoking.

Clinical and paraclinical features: clinical signs (cough, dyspnea, weight loss, chest pain, hemoptysis, fever, nocturnal sweating), location of disease, sputum smear results, hospitalization during treatment, date of diagnosis, date of start of treatment, comorbidities such as HIV, diabetes and other pathology.

Therapeutic characteristics: history of TB treatment, number of previous treatment episodes, classification according to history (new case, relapse, treatment failure, lost to follow-up, previously treated), family history of TB, history of close contact with MDR-TB patients, knowledge of MDR-TB, knowledge of Directly Observed Treatment Sort-course (DOTS), treatment irregularity, momentary interruption of treatment and adherence to medication schedule.

The reasons for using AFB <3+ is used as the threshold value are as follows:

Patients with sputum smear results with  $\geq 3+$  AFBs are the most contagious and are full of enough bacilli. So, if the treatment is inadequate, poorly followed, for example, they may take longer to negative, which could increase the risk of developing MDR-TB. However, if the sputum smear of acid bacilli contains less BAAR ( $\leq +1$ ) the patient is more likely to negative quickly and therefore to recover.

## 2.5. Data Management and Analysis

### 2.5.1. Data Processing

The data collected were returned to the Kobotoolbox® server instantly. At the end of data collection, we exported the single database in Excel® format. We then cleaned the database, correcting missing data, extreme data, inconsistencies and duplicates. We then recoded the variables and imported the database into SAS® 9.4 for the analysis.

### 2.5.2. Data Analysis

Analyses were performed with SAS® 9.4

#### Descriptive analysis

This involved a descriptive analysis of the so-

cio-demographic, clinical, paraclinical and therapeutic characteristics of cases and controls. Qualitative variables were described in the form of proportions. These measures were accompanied by their p-value, and compared as modalities of a variable using the Chi2 test. For quantitative variables, we expressed means and compared the quantitative variable between cases and controls by Student's t test.

#### *Etiological analysis*

The aim of the analysis was to verify whether there was an association between *the history of TB treatment* or all other independent variables with multidrug-resistant tuberculosis.

To investigate the factors associated with multidrug-resistant tuberculosis, which is a qualitative binary yes/no variable, we performed logistic regression.

First we performed univariate logistic regression, to calculate crude Odds Ratios (ORb) of association between our main independent variable and the different factors with MDR-TB. These ORs were tested by the Mantel Haenszel test at the 20% threshold. The 95% confidence interval (CI) was also estimated.

Next we tested for possible interactions between the various confounding variables or effect modifiers such as age range, gender, HIV serology and diabetes with our main independent variable (history of TB treatment). There was no statistically significant interaction between the variable of interest and the other co-variables.

Finally, variables associated with MDR-TB with a  $p < 20\%$  in univariate analysis were retained for the multivariate model. In addition to these variables, we forced our main independent variable and the other confounding variables found in the literature. Adjusted ORs and their confidence intervals (IC95%) were estimated. For variable interpretation, the significance threshold  $\alpha < 0.05$  was used.

#### *Model fit*

Model fit was assessed using the Hosmer-Lemeshow test. Model adequacy was achieved when the  $p$ -value of the Hosmer-Lemeshow test was  $> 5\%$ .

### 3. Ethical Considerations

Before conducting the study, we obtained authorization from the General Secretariat of the Ministry of Health and Public Hygiene, the regional directorate of health and public hygiene for the Centre region, the executive management of the Paul VI, Saint Camille and CHU-YO hospitals,

and the various managers of tuberculosis diagnosis and treatment centers in the five (05) districts and NCTBC. Patient confidentiality and anonymity were respected during data collection and during data entry, taking into account their registration number. Verbal or written informed consent was obtained from patients.

### 4. Results

#### 4.1. Descriptive Analysis

##### 4.1.1. Socio-demographic Data

A total of 75 cases and 150 controls were included in our study. The majority of cases (44%;  $p < 0.001$ ) were diagnosed in 2020. The mean age was  $39.09 \pm 13.46$  for cases and  $41.39 \pm 15.44$  for controls ( $p = 0.187$ ). We observed that 36% of cases versus 26% of controls consumed alcohol.

Our study revealed that the majority of MDR-TB cases studied resided in urban areas, with 57.3% of cases and 73.3% of controls ( $p = 0.022$ ) (Table 1).

**Table 1.** Socio-demographic characteristics of cases ( $n=75$ ) and controls (150) diagnosed with multidrug-resistant tuberculosis in the Centre region, Burkina Faso, 2020-2022.

Variables	Cases, n = 75 n (%)	Controls, n = 150 n (%)	p
Region of origin			0.0007
Central	37 (49.3)	109 (72.7)	
Other	38 (50.7)	41 (27.3)	
Age range			0.366
15-24	8 (10.7)	21 (14.0)	
25-44	44 (58.7)	69 (46.0)	
45-64	19 (25.3)	47 (31.3)	
> 65	4 (5.3)	13 (8.7)	
Gender			0.494
Female	14 (18.7)	35 (23.3)	
Male	61 (81.3)	115 (76.7)	

Variables	Cases, n = 75 n (%)	Controls, n = 150 n (%)	p
Profession			0.587
Job	58 (77.3)	107 (71.3)	
Health worker	1 (1.3)	5 (3.3)	
Unemployed	16 (21.3)	38 (25.3)	
Religion			0.170
Christian	21 (28.0)	59 (39.3)	
Muslim	53 (70.7)	87 (58.0)	
Other	1 (1.3)	4 (2.7)	
Place of residence			0.022
Urban	43 (57.3)	110 (73.3)	
Rural	32 (42.7)	40 (26.7)	
Level of education			0.555
Educated	29 (38.7)	51 (34.0)	
Illiterate	46 (61.3)	99 (66.0)	
Distance from residence to DTC			0.600
≤ 5km	58 (77.3)	121 (80.7)	
> 5km	17 (22.7)	29 (19.3)	
Number of people living in the same household			0.041
≤ 4	19 (25.3)	18 (12.0)	
5-10	35 (46.7)	86 (57.3)	
> 10	21 (28.0)	46 (30.7)	
Prison stay			0.336
No	72 (96.0)	148 (98.7)	
Yes	3 (4.0)	2 (1.3)	
Social support			0.024
No	23 (30.7)	25 (16.7)	
Yes	52 (69.3)	125 (83.3)	
Stigma			0.004
No	51 (68.0)	128 (85.3)	
Yes	24 (32.0)	22 (14.7)	
Alcohol consumption			0.124
No	48 (64.0)	111 (74.0)	
Yes	27 (36.0)	39 (26.0)	
Smoking			0.381
No	45 (60.0)	99 (66.0)	
Yes	30 (40.0)	51 (34.0)	

DTC: Diagnostic and Treatment Center.

#### 4.1.2. Clinical, Paraclinical and Therapeutic Features

Cough was the most common symptom reported by cases (88.00%) and controls (96.67%) ( $p=0.017$ ). Among patients in our study, more than half (85.3%) of cases were hospitalized during treatment, compared with 34% of controls ( $p=0.002$ ).

Only 45.6% of cases and 24% of controls had more than 3 AFB in their sputum ( $p=0.0037$ ). The proportion of patients with a history of tuberculosis treatment was 41.33% in cases and 16% in controls ( $p<0.0001$ ). The mean number of days of hospitalization was  $21.05 \pm 20.30$  for the cases and  $6.08 \pm 3.20$  for the controls. (Table 2).

**Table 2.** Clinical, paraclinical and therapeutic characteristics of cases ( $n=87$ ) and controls ( $n=174$ ) diagnosed with multidrug-resistant tuberculosis in the Centre region, Burkina Faso, 2020-2022.

Variables	Cases $n=87$ (%)	Controls $n=174$ (%)	P
Cough			0.017
No	9 (1.00)	5 (3.33)	
Yes	66 (88.00)	145 (96.67)	
Dyspnea			0.467
No	70 (93.33)	135 (90.00)	
Yes	5 (6.67)	15 (10.00)	
Fever			0.204
No	33 (44.00)	80 (53.33)	
Yes	42 (56.00)	70 (46.67)	
Haemoptysis			0.267
No	68 (90.67)	142 (94.67)	
Yes	7 (9.33)	8 (5.33)	
Chest pain			0.0007
No	52 (69.33)	133 (88.67)	
Yes	23 (30.67)	17 (11.33)	
Weight loss			0.016
No	51 (68.00)	124 (82.67)	
Yes	24 (32.00)	26 (17.33)	
Night sweats			0.632
No	67 (89.33)	137 (91.33)	
Yes	8 (10.67)	13 (8.67)	
Hospitalization during treatment			0.002
No	11 (14.67)	99 (66.00)	
Yes	64 (85.33)	51 (34.00)	
Localisation of disease			0.276
Pulmonary	69 (92.00)	129 (86.00)	
Extrapulmonary	6 (8.00)	21 (14.00)	
Diabetes			0.278
No	72 (96.00)	145 (96.67)	
Yes	3 (4.00)	5 (3.33)	

Variables	Cases n=87 (%)	Controls n=174 (%)	P
HIV			0.837
No	65 (86.67)	108 (85.04)	
Yes	10 (13.33)	19 (14.96)	
Sputum smear results			0.0037
AFB <3+	31 (54.39)	114 (76.00)	
AFB =3+	26 (45.61)	36 (24.00)	
history of TB treatment			<0.0001
No	44 (58.67)	126 (84.00)	
Yes	31 (41.33)	24 (16.00)	
Number of history of TB treatment			0.055
0-1	66 (88.00)	143 (95.33)	
≥2	9 (12.00)	7 (4.67)	
TB history classification			0.0002
New cases	43 (57.33)	126 (84.00)	
Relapse	5 (6.67)	4 (2.67)	
Treatment failure	13 (17.33)	7 (4.67)	
Lost to follow-up	5 (6.67)	7 (4.67)	
Already treated	9 (12.00)	6 (4.00)	
TB history in family			0.281
No	64 (85.33)	118 (78.67)	
Yes	11 (14.67)	32 (21.33)	
DOTS knowledge*			<0.0001
No	35 (46.67)	30 (20.00)	
Yes	40 (53.33)	120 (80.00)	
MDR-TB knowledge			<0.0001
No	43 (57.33)	139 (92.67)	
Yes	32 (42.67)	11 (7.33)	
Treatment irregularity			1.000
No	57 (76.00)	115 (76.67)	
Yes	18 (24.00)	35 (23.33)	
Respect for dosing times			0.168
Yes	60 (80.00)	131 (87.33)	
No	15 (20.00)	19 (12.67)	

HIV: Human Immunodeficiency Virus, TB: tuberculosis, DOTS: Directly observed treatment, TB-MR: Multidrug-resistant tuberculosis, AFB: Acid-Fast Bacillus.



## 4.2. Etiological Analysis: Multivariate Analysis

In multivariate analysis, the factors associated with multi-drug-resistant tuberculosis were history of TB treatment [OR=7.36; IC95%=(2.75-19.68),  $p=0.0001$ ]; place of resi-

dence (rural) [OR=6.04; IC95%=(2.39-15.27),  $p=0.0001$ ]; alcohol consumption [OR=4.20; IC95%=(1.66-10.60);  $p=0.002$ ]; sputum smear result with AFB = 3+ [OR=3.37; IC95%=(1.36-8.36),  $p=0.008$ ]; hospitalization during treatment [OR=5.20; IC95%=(1.79-15.41);  $p=0.002$ ]. (Table 3).

**Table 3.** Factors independently associated with MDR-TB in patients diagnosed in the Centre region, Burkina Faso, 2020-2022.

Variables	Cases, n= 75 n (%)	Controls, n=150 n (%)	aOR [IC (95%)]	p
History of TB treatment				
No	44 (58.7)	126 (84.0)	1	
Yes	31 (41.3)	24 (16.0)	7.36 [2.75-19.68]	0.0001
Place of residence				0.0001
Urban	43 (57.3)	110 (73.3)	1	
Rural	32 (42.7)	40 (26.7)	6.04 [2.39-15.27]	
Knowledge of DOTS				
Yes	35 (46.67)	30 (20.0)	1	
No	40 (53.3)	120 (80.0)	6.53 [2.63-16.21]	0.0001
Alcohol consumption				
No	48 (64.0)	111 (74.0)	1	
Yes	27 (36.0)	39 (26.0)	4.20 [1.66-10.60]	0.002
Sputum smear results				0.008
AFB <3+	31 (54.4)	114 (76.0)	1	
AFB = 3+, YES	26 (45.6)	36 (24.0)	3.37 [1.36 -8.36]	
Hospitalization during treatment,				0.002
No	11 (14.67)	51 (34.0)	1	
Yes	64 (85.3)	99 (66.0)	5.20 [1.79-15.41]	

TB: tuberculosis, DOTS: Directly observed treatment, AFB: Acid-Fast Bacillus.

## 5. Discussion

### Main results

The study identified factors associated with multi-drug-resistant tuberculosis: history of treatment, place of residence, alcohol consumption, sputum smear results and hospitalization during treatment.

### Study strengths

The study has certain limitations. During our study, the cases remembered their exposure better than the controls, which could constitute a memory bias, in the sense of a potential increase in ORs. Data were often incomplete, and attempts to correct them by telephone were unsuccessful as some patients were unreachable.

Despite these limitations, a number of strengths can be

recognized. Unlike other cross-sectional studies commonly carried out in the country, the present study was of the case-control type, enabling us to confirm the association of history of TB treatment with multidrug-resistant tuberculosis. In addition, this study took into account variables that may contribute to MDR-TB, notably sociodemographic, clinical, paraclinical and therapeutic variables. The fact that we carried out the study in the central region, which is a major crossroads for healthcare seeking for the entire population of Burkina Faso, would undoubtedly enable us to generalize our results.

### Weaknesses of the study

#### 1) History of TB treatment

Previous treatment significantly multiplied the risk of having multidrug-resistant tuberculosis by 7.36. This could be due to the fact that inadequate previous anti-tuberculosis



treatment leads to conditions conducive to the multiplication of resistant mutants. Even when cured, a patient who has taken anti-tuberculosis drugs is at risk of endogenous bacillus reactivation. Diandé et al. in 2019 in Burkina Faso (OR[IC95%]=8.01), Sylverken et al. in Ghana in 2021 [OR=5.41; IC95%=(1.69-17.30),  $p=0.004$ ]; and Welekidan et al. in 2020 in Ethiopia [OR=3.75; CI95%=(1.7-2.24),  $p=0.002$ ] found the association of MDR-TB with a history of TB treatment [7-9]. Similarly in China, Pengcheng et al. in 2016 found that history of TB treatment increased the risk of multidrug-resistant tuberculosis by 2.15 times (OR = 2.15; 95% CI: 1.09-4.28) [10]. Takashi Hiramata et al. in Canada in 2020 and Ivan et al. in 2018 in the Netherlands in Europe also endorsed this association with statistically significant  $p$  values and 95% confidence intervals [OR=5.39; CI95%=(2.57-11.3);  $p<0.001$ ]; [OR=40.42; CI95%=(1.46-13.37),  $p<0.001$ ] [11, 12]. However, Sangaré et al. in Burkina Faso in 2010 found no significant association [13]. This difference could be explained by the type and population of the study. Unlike the present study, that of Sangaré et al. was cross-sectional and hospital-based.

#### 2) Place of residence

Living in a rural area multiplied by 6 the chance of having multidrug-resistant tuberculosis. This could be explained by the fact that in this environment, the low socio-economic level would entail obstacles to treatment follow-up. This can be explained by precarious living conditions, promiscuity and insalubrity, and contact with strains that are already resistant [14]. In Burundi, Iradukunda et al. in 2021 found a significant relationship with an odds ratio=1.31. Furthermore, Fanta Desissa et al. in 2018 in Ethiopia found that MDR-TB was strongly associated with area of residence [OR=6; CI95%=(1.06-5.42),  $p=0.001$ ] [1]. In contrast, area of residence was not associated with MDR-TB in a study conducted in Addis Ababa and China [15]. This difference may be due to differences in access to TB services, socioeconomic status, level of awareness and adherence to first-line anti-TB treatment, which probably leads to multidrug-resistant TB.

#### 3) Alcohol consumption

Consuming alcohol would increase the chance of having MDR-TB by 4.20 times. Massi in 2011 in Indonesia (OR 4.01, 95%CI 1.28-12.53) and Desissa in 2018 in Ethiopia (OR=4.3; CI95%=(2.29-10.49),  $p<0.001$ ) reported similar findings that a history of alcohol consumption was significantly associated with MDR-TB [1, 16]. Alcoholics would not be very compliant with their treatments, which favors the development of resistance and consequently increases the rate of MDR-TB cases. Several reports, including one from the WHO, have indicated that alcohol consumption increases the risk of developing MDR-TB due to poor treatment compliance. Alcohol consumption is also associated with impaired immune response and increased risk of adverse drug reactions. Alcoholism is a factor in TB reactivation and the selection of resistant mutants.

#### 4) Sputum smear results

Our multivariate analysis showed that sputum smear microscopy positive for more than 3 AFB increased the risk of multidrug-resistant tuberculosis by a factor of 3.37: [OR=3.37; IC95%=(1.36-8.36),  $p=0.008$ ]. In fact, sputum rich in AFB can result in microscopic examination being positive for at least three crosses (3+), and this has the effect of showing the degree of contagiousness of the patient, as well as the severity of the disease. This can lead to a delay in sputum negativation at the end of the intensive phase of anti-tuberculosis treatment, which may result in the selection of resistant strains [17]. In addition, other authors including Bocar Bayaa et al. in Mali in 2019 and Chuchottaworn et al. in 2015 in Thailand found that patients whose sputum smear microscopy was positive for more than 3 AFB were more likely to have MDR-TB, with ORs of 1.98 [OR=1.98; IC95%=(1.13-3.48),  $p=0.02$ ] and OR =13.09 [OR=13.09; IC95%=(4.64-36.91),  $p=0.005$ ] respectively [6, 18]. Careful attention should be paid to patients with more than 3 crosses on microscopy, and whenever possible a sensitivity test should be performed.

#### 5) Hospitalization during treatment

Hospitalization during treatment was associated with MDR-TB with an odds ratio of 5.20 multidrug-resistant TB and this is statically significant with a  $p$  value = 0.002: [OR=5.20; IC95%=(1.79-15.41),  $p=0.002$ ].

In the descriptive analysis, the majority of cases (85.33%) were hospitalized, compared with 34% of controls. Indeed, the decision to hospitalize the patient is most often linked to the patient's general condition when it is altered with alarming clinical signs. Our results differ from those of Bocar Baya et al. in Mali in 2019, who reported that impaired physical condition was significantly less likely to be associated with confirmation of MDR-TB, with an OR = 0.44 [OR=0.44; IC95%=(0.24-0.80),  $p=0.006$ ] [6]. This may be related to the difference in our study populations, where only hospitalized patients were included.

## 6. Conclusion

Our study identified several factors associated with multidrug-resistant tuberculosis (MDR-TB), in particular: history of TB treatment; alcohol consumption; and lack of awareness of the MDR-TB strategy. Targeted action on these modifiable factors, in particular improving public health education and intensifying the community DOTS strategy for all tuberculosis patients, will undoubtedly help reduce cases of resistance. Treatment history is the main exposure variable statistically significantly associated with multidrug-resistant tuberculosis, which includes relapses, treatment failures and dropouts. However, a number of factors play a part in the success of treatment, in particular certain patient behaviours such as compliance, regularity of treatment, adherence to medication schedules and counseling by caregivers. In addition, future studies should aim to understand the impact of patient behavior/knowledge, so

that the results can guide the use of scarce resources to optimize their impact.

## Abbreviations

CDC	Centers for Disease Control and Prevention
DOTS	Directly Observed Treatment Sort-course
DTC	Diagnosis and Treatment Center
NCTBC	National Center for Tuberculosis Control
NTBCP	National Tuberculosis Control Program
MDR-TB	Multidrug-Resistant Tuberculosis
SAS	Statistical Analysis System
TB	Tuberculosis
HIV	Human Immunodeficiency Virus
WHO	World Health Organization

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## Author Contributions

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## Data Availability Statement

The data is available from the corresponding author upon reasonable request.

## Conflicts of Interest

The authors declare no conflicts of interest.

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