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Research Article

Epidemiological and clinical profile of rifampicin-sensitive and -resistant pulmonary tuberculosis in sites of displaced persons due to the 2022-2024 floods in N'Djamena, Chad

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Abstract

Patients with rifampicin-resistant tuberculosis (RR-TB) may remain a source of infection longer than rifampicin-susceptible tuberculosis (RS-TB). The objective of this study was to detect active cases of rifampicin-susceptible and -resistant tuberculosis in displaced persons sites in the 9th District of N'Djamena.

This observational, cross-sectional and analytical study was conducted among 418 contacts of the displaced persons, including 285 in the Walia site and 133 in the Toukra site. Data were collected using a pre-tested, semi-structured questionnaire administered by an interviewer. The identification of active cases of tuberculosis among the displaced persons was carried out by an interview to verify the presence or absence of TB symptoms. The TB-LAMP molecular technique was used to detect active tuberculosis among symptomatic and asymptomatic contacts. Instead, a GeneXpert analysis was carried out to detect cases of tuberculosis sensitive and resistant to rifampicin.

TB-LAMP detected 76 (5.5%) cases of active TB among 418 displaced persons, including 11 lost to follow-up and 65 new cases. Female patients were more dominant (59.21%) than males (40.78%), and the age of patients ranged from 12 to 65 years, with a mean age of 38.5 years with a sex ratio of 1.45 in favor of females. Loss of appetite (31%), asthenia (20.0%) and cough (16%) were the most common symptoms.

GeneXpert confirmed the 76 positive cases of *Mycobacterium tuberculosis*, of which 8 (10.52%) were resistant and 69 (90.78%) were sensitive to rifampicin.

HIV1/2 immunochromatographic tests detected 12 (15.78%) cases of HIV/tuberculosis coinfection among the positive cases.

This study highlighted the emergence of strains of the *Mycobacterium tuberculosis* complex resistant and sensitive to rifampicin.

Regular and effective screening of RR-TB contacts is necessary to stop transmission in displaced persons sites in Chad, Africa and even worldwide.

Keywords: Flood, displaced person, *Mycobacterium tuberculosis*, resistance, rifampicin, molecular technique, Chad.

INTRODUCTION

Tuberculosis (TB) remains a global health threat, exacerbated by factors such as drug resistance, co-infections, and social determinants of health[1].

The bacterium *Mycobacterium tuberculosis* causes tuberculosis and primarily affects the lungs, although it can also affect other organs[2]. Risk factors for tuberculosis include poverty, malnutrition, crowded living conditions, and immunocompromised conditions such as HIV/AIDS[3].

Symptoms of tuberculosis include cough, fever, weight loss, and night sweats, but can vary depending on the site of infection[4]. Diagnosis typically involves clinical assessment, imaging studies, and microbiological testing, with rapid molecular tests such as the Gene Xpert MTB/RIF test revolutionizing tuberculosis diagnosis. Treatment consists of a six- to nine-month course of multidrug therapy[5], with drug-resistant tuberculosis requiring longer and more complex treatment regimens[6].

Prevention and control efforts focus on early case detection, treatment adherence, infection control measures, and vaccination with Bacille Calmette-Guérin (BCG) vaccine[7]. TB research and innovation aims to develop new diagnostics, drugs, and vaccines to improve TB control and treatment outcomes[8]. Challenges in TB control include stigma, barriers to accessing health care, and the rise of drug-resistant TB strains[9]. Collaborative and advocacy efforts are essential to address TB in special populations, high-risk settings, and TB/HIV co-infection scenarios[10].

According to WHO, tuberculosis is widespread, the incidence rate is 1.41% or 144/100,000 people in Chad. The high incidence of tuberculosis and drug-resistant tuberculosis in vulnerable populations (displaced people due to floods, war refugees, etc.) highlights the problem and the factors associated with tuberculosis[11].

In Chad, in 2022, more than 155,000 inhabitants of the 7th Arrondissement of N'Djamena were forced to leave their homes due to floods and torrential rains. The 2024 floods left 502 dead and 1.7 million displaced[12]. Displaced persons are often victims of water- and air-borne diseases with direct and indirect transmission (typhoid fever, cholera, malaria, etc.) as well as tuberculosis[13,14]. In order to respond to one of the concerns of displaced persons, we decided to undertake research into active tuberculosis in confined environments of displaced persons in the 9th Arrondissement of N'Djamena, the objective of which was to describe the socio-demographic and clinical characteristics and risk factors associated with the transmission of tuberculosis and secondarily, to determine the rate of resistance and sensitivity to rifampicin of *Mycobacterium tuberculosis* species detected in two sites of displaced persons (Walia and Toukra) of N'Djamena in Chad using molecular techniques (TB-Lamp, GeneXpert) in order to better manage displaced persons suffering from pulmonary tuberculosis in Chad.

MATERIAL AND METHODS

Site, period, study population and research work progress.

This was an observational, cross-sectional and analytical study, conducted in two sites (Walia and Toukra) of displaced persons due to flooding by rainwater in the 9th District of N'Djamena in Chad for the recruitment of persons affected by tuberculosis for the detection of genes (rpoB) of resistance to rifampicin.

A pre-established form containing information (sociodemographic, symptoms, causes, risk factors, dietary lifestyle, HIV status (for participants whose tuberculosis test was positive) etc.) was administered to consenting displaced persons to collect data.

Eligibility criteria

Inclusion criteria

Included in this study were:

- ✓ Displaced persons living in one of the two sites (Walia and Toukra) in the 9th Arrondissement of N'Djamena;
- ✓ Signed informed consent from participants or the child's guardian is obtained.

Non-inclusion criteria

Not included in this study were:

- ✓ People visiting the migrants' families and street vendors of goods in the displaced persons' sites;
- ✓ Absence from the site during the survey hours or refusal to participate in the study.

Laboratory analysis procedures: sample collection, sputum analysis and HIV testing

Sputum samples were collected from October 1, 2022 to February 31, 2023 in the Walia site and concerned 285 displaced persons, including 148 women and 137 men. The second round of sputum sampling took place from October 1, 2023 to February 31, 2024 in the Toukra site and concerned 133 people displaced due to rainwater flooding (91 women and 42 men) with signs suggestive of tuberculosis for the search for *Mycobacterium tuberculosis*.

The sampling list/frame for symptomatic and asymptomatic contacts of the displaced was created and their geographical location was plotted on a map (Figure 1) to visualize the concentration and movement of participants for data collection. Contacts were considered symptomatic for TB if they reported any of the symptoms mentioned. A sputum sample was collected in a sealed container from symptomatic and/or asymptomatic contacts on the same day of the interview. The participant was asked to gurgle and rinse their mouth with water, then asked to stand and take deep breaths followed by forced exhalation, and then spit the sputum up to the marked value of 10 mL. The samples were transported to the Mycobacteria laboratory of the National Reference University Hospital of N'Djamena for tuberculosis screening with the TB LAMP machine followed by GeneXpert analysis to detect cases of active rifampicin-resistant (RR-TB) and rifampicin-sensitive (SR-TB) tuberculosis, maintaining a temperature of 2 to 8 °C.

A total of 447 displaced persons were surveyed in the two sites, of whom 418 consented and 29 refused. Of the 418 displaced persons included in the study, 239 were women and 179 were men.

A total of 76 non-duplicate *Mycobacterium tuberculosis* isolates were detected in 418 samples screened for *Mycobacterium tuberculosis* rifampicin resistance genes (rpoB). Bacterial DNA was extracted from sputum using the GenoLyse kit (Hain Life science) according to the manufacturer's protocol. The extracted DNA was stored at -20 °C until processing.

Detection of tuberculosis by two molecular techniques[15, 16]

Detection of tuberculosis by the TB-LAMP machine

TB-LAMP is a molecular diagnostic technique that has enabled sensitive and accurate detection of tuberculosis. It is easy to use and gives reliable results within one hour of time. The process is carried out in four 4 steps namely:

- Sputum preparation: 60 µL of sputum was transferred to the heating tube, shaken to mix well and incubated in the heating unit of HumaLoop T at 90 ° C for 5 minutes;

- DNA extraction: The sample pretreated in the heating tube (lysed) was transferred to the absorbent tube with absorbent powder which removes all possible inhibitors of the LAMP reaction. The purified DNA was extracted and directly transferred to the LAMP reaction tube;

- Amplification: DNA transferred to the LAMP reaction tube was incubated for 2 minutes at room temperature to reconstitute the reagents in the cap, then homogenized several times and tapped until the reaction mixture accumulated at the bottom of the tube. The reaction tube was then transferred to the HumaLoop T reaction unit at 67 °C for 45 minutes.

Reading the results

The reaction tube was finally inserted into the UV lamp detection unit and the lamp was turned on:

- A positive result gives a green light;

- A negative result does not give fluorescence.

Reading the turbidity in real time and automatic reporting of the results.

Detection of sensitivity and resistance to rifampicin with the GeneXpert machine

Principle: it is based on amplification of a fragment of the rpoB gene containing the central region of 81 base pairs and fragments of the target sequences of the IS1081 and IS6110 insertion elements with multiple copies by primers.

Using a Pasteur pipette, 2 mL of sputum and 4 mL of the reagent were collected and mixed in another sterile jar. The mixture was vortexed and incubated at room temperature for 10 minutes. The jar was vortexed again and incubated at room temperature for 5 minutes. Then, 2 mL of the liquefied mixture was aspirated and transferred to the Xpert® MTB/RIF ULTRA cartridge and the test was launched for a duration of 1 hour 30 minutes.

HIV detection

Immunochromatographic tests (Determine HIV1/2 and One step SD Bioline HIV1/2) were used for rapid detection of HIV following the manufacturers' instructions.

Data analysis

The results including paraclinical data and data from the information forms were entered with Microsoft Office Word and saved from a table in MS-EXCEL. The descriptive analysis consisted of describing the data collected in the form of numbers, percentages and means. Statistical tests were performed with SPSS software. For this purpose, the chi-square test (x^2) was used to assess the link between the occurrence of tuberculosis and/or HIV and exposure factors (age, family contacts, socio-economic conditions). The probability value (p) was used to show the degree of significance of the links at the 0.05 threshold.

RESULTS

Mapping of flood-displaced persons sites in N'Djamena, Chad

Figure 1 illustrates the two sites of displaced persons (Walia and Toukra) in the 9th Arrondissement of N'Djamena. Chad is located between the 7th and 24th degrees of latitude North and the 13th and 24th degrees of longitude East. It covers an area of 1284000 km^2; it is the fifth largest country in Africa after Sudan, Algeria, Zaire and Libya. From north to south, it extends over 1700 km and, from east to west, over 1000 km. It shares its borders with Libya to the north, Sudan to the east, the Central African Republic to the south and Cameroon, Nigeria and Niger to the west. Mayo Kebbi province is located southwest of N'Djamena and shares its borders with Cameroon. The country belongs politically and economically to Central Africa, but due to the similarities in climatic conditions, it is also attached to the Sahelian countries. The 9th Arrondissement housing the displaced persons sites is a basin located between two rivers (Chari and Logone) and during each flood period after the rainwater there are always floods. The geolocation of the two displaced persons sites would certainly have contributed to the transmission of new cases of tuberculosis.

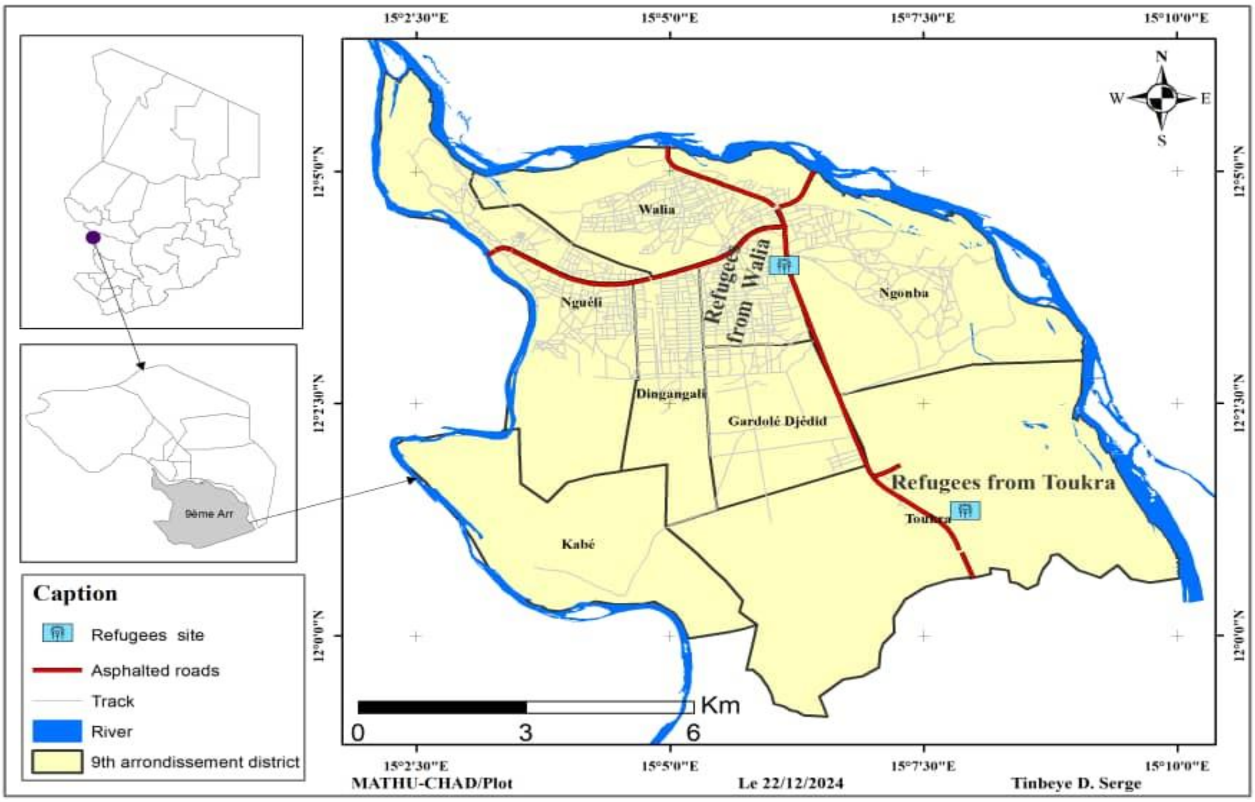


Figure 1: Mapping of displaced persons sites

Detection of tuberculosis among contacts of displaced persons with rifampicin-resistant tuberculosis

A systematic screening was carried out among 418 sputum samples by the TB-LAMP technique which revealed 76 positive cases (5.5%). Of the 418 samples analyzed, 304 asymptomatic cases including 5 (1.64%) were positive for pulmonary tuberculosis and 114 symptomatic cases including 71 (62.28%) positive cases for pulmonary tuberculosis. A second screening of 76 positive cases with GeneXpert detected 8 (10.52%) cases of rifampicin resistance (RR-TB) including 1 (1.31%) case from asymptomatic and 7 (9.21%) cases from symptomatic diagnosed (Figure 2).

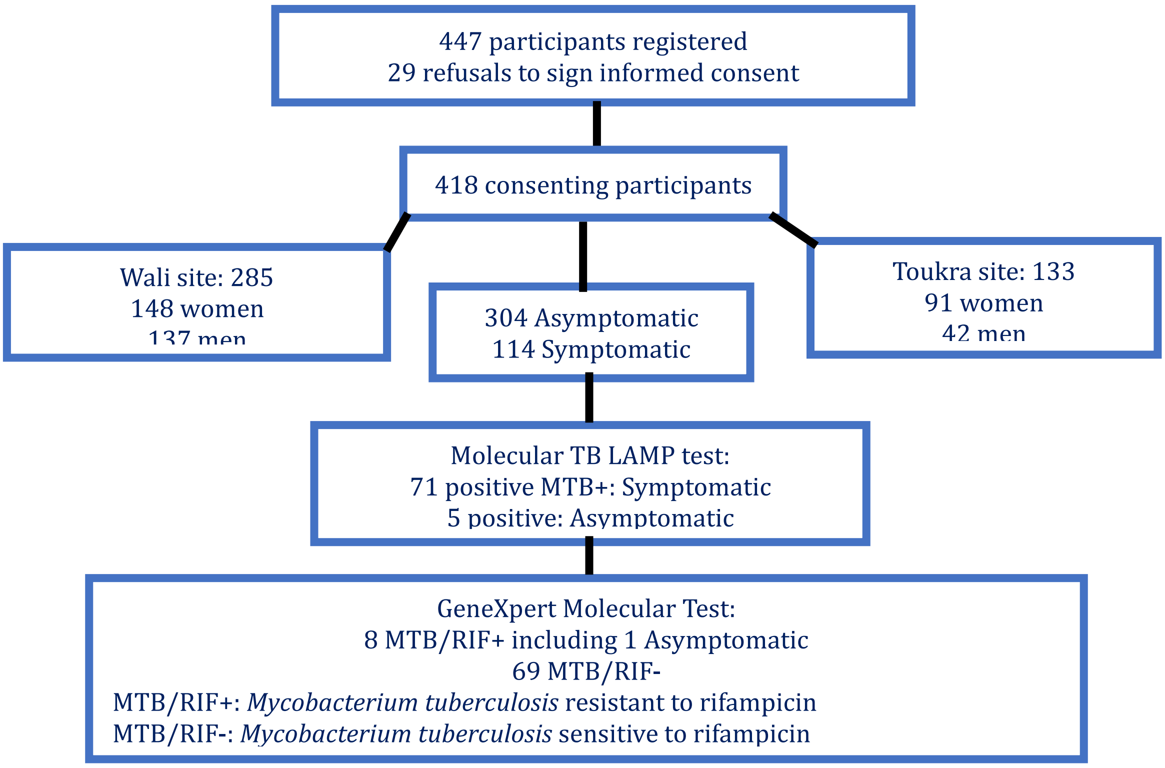


Figure 2: Detection of tuberculosis among contacts of displaced persons with rifampicin-resistant and -sensitive tuberculosis

Distribution of symptoms among 71 symptomatic tuberculosis patients

Figure 3 reveals that among household and person-to-person contacts of participants, the most common symptom was loss of appetite (31%), followed by asthenia (20.0%) and cough (16%).

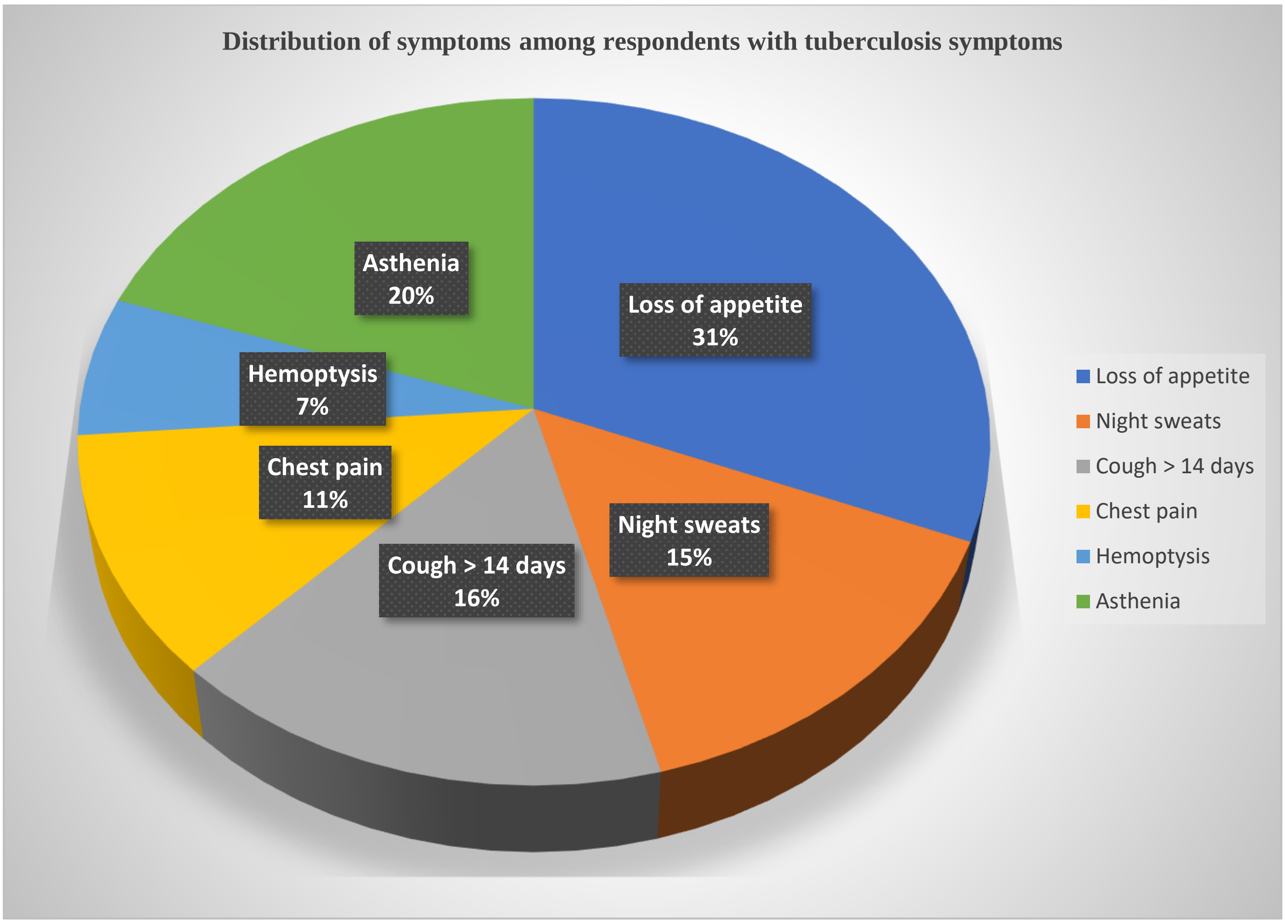


Figure 3: Distribution of symptoms among respondents with tuberculosis symptoms

Distribution of the 76 patients according to sociodemographic characteristics, sites, HIV status and biological parameters

Table 1 reveals that out of a total of 76 (5.5%) positive sputum samples, females were more dominant 45 (59.21%) than males 31 (40.78%) and the age of the patients ranged from 12 to 65 years, with a mean age of 38.5 years with a sex ratio of 1.45 in favor of females. The displaced persons from the Walia site were the most infected (61.84%). The proportion of rifampicin-resistant MTB compared to the total confirmed MTB was 8/76 (10.52%) against 69/76 (90.78%) (Table 1).

Similarly, displaced persons aged 32–41 and 22–31 years (p = 0.20; non-significant difference) were more likely to have TB than those in the 12–21 and > 52 years age group.

Recruited loss-to-follow-up (p = 0.02; significant difference) were more likely to be TB positive than new cases (Table 1). Of a total of 76 TB-positive patients detected by the GeneXpert, the proportion of RR-TB-positive patients was 8 (10.52%) (Table 1).

Table 1: Distribution of patients according to sociodemographic characteristics, sites, HIV status and biological parameters

Variables	**Frequency**	**Percentage**	**Khi2**
Site			
Walia	47	61.84	
Toukra	29	38.15	0.30
TB Treatment History			
New case	65	85.52	
Lost/failure	11	14.47	0.02
Sex			
Man	31	40.78	
Woman	45	59.21	0.20
Age (year)			
12-21	11	14.47	
22-31	16	21.05	
32-41	32	42.10	0.20
42-51	11	14.47	
> 52	6	7.89	
HIV statute			
Positive HIV	12	15.78	
Negative HIV	64	84.21	
GeneXpert result			
MTB+/RIF+	8	10.52	
MTB+/RIF-	69	90.78	

Distribution of patients according to the profile of sensitivity and resistance to rifampicin according to sex

Figure 4 illustrates the distribution of patients with the MTB+ profile sensitive and resistant to rifampicin. Among the 76 positive cases, there were 69 MTB+RIF- of which 37% of males (n = 28) and 53% (n = 40) of females had the MTB+ profile sensitive to rifampicin. Among the 8 MTB+RIF+ cases, 4% (n = 3) of males and 7% (n = 5) of females harbored the *Mycobacterium tuberculosis* complex resistance gene (rpoB) and were resistant to rifampicin.

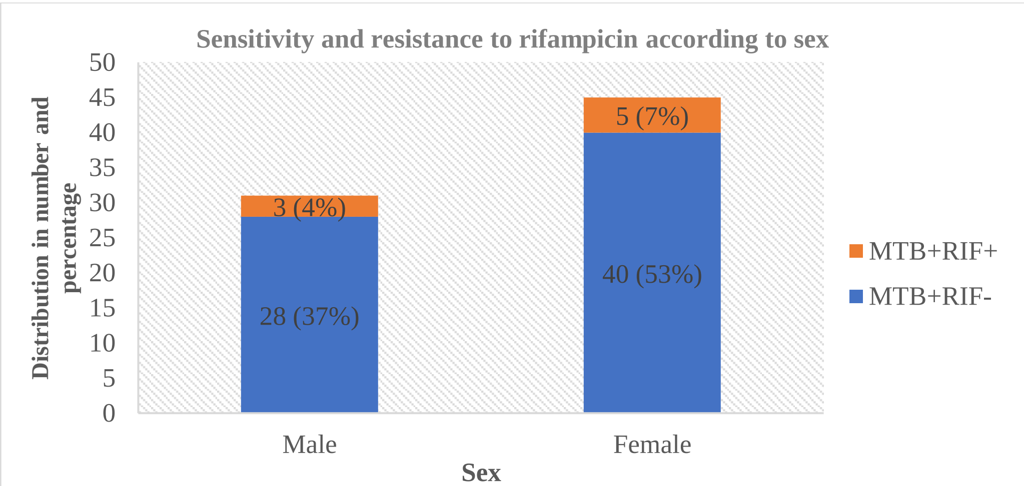


Figure 4: distribution of patients according to the profile of sensitivity and resistance to rifampicin according to sex

Distribution of patients according to level of education and promiscuity

Figure 5 illustrates the distribution of patients according to level of education. The uneducated come first and followed by primary, secondary and higher levels with the proportions of 37 (49%), 12 (24%), 18 (16%) and 9 (12%) respectively. In addition, the survey revealed that promiscuity and family and interhuman contacts in the sites (Walia and Toukra) of displaced persons due to flooding by rainwater from 2022 to 2024 were indexed as a source of contagiousness and transmission of diseases such as tuberculosis, HIV, etc. (photo o and p: table 2).

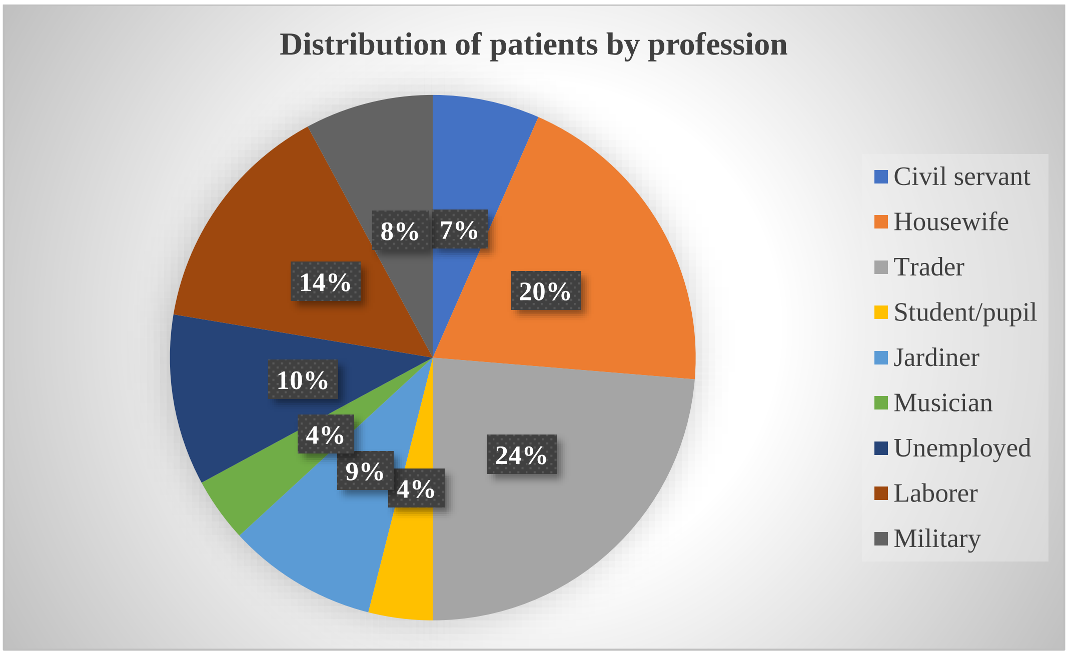


Figure 5: Distribution of patients according to level of education

Distribution of patients by occupation

Figure 6 illustrates the distribution of patients by occupation. Traders (24%) and housewives (20%) were in the lead followed by the resourceful (14%) and unemployed (10%).

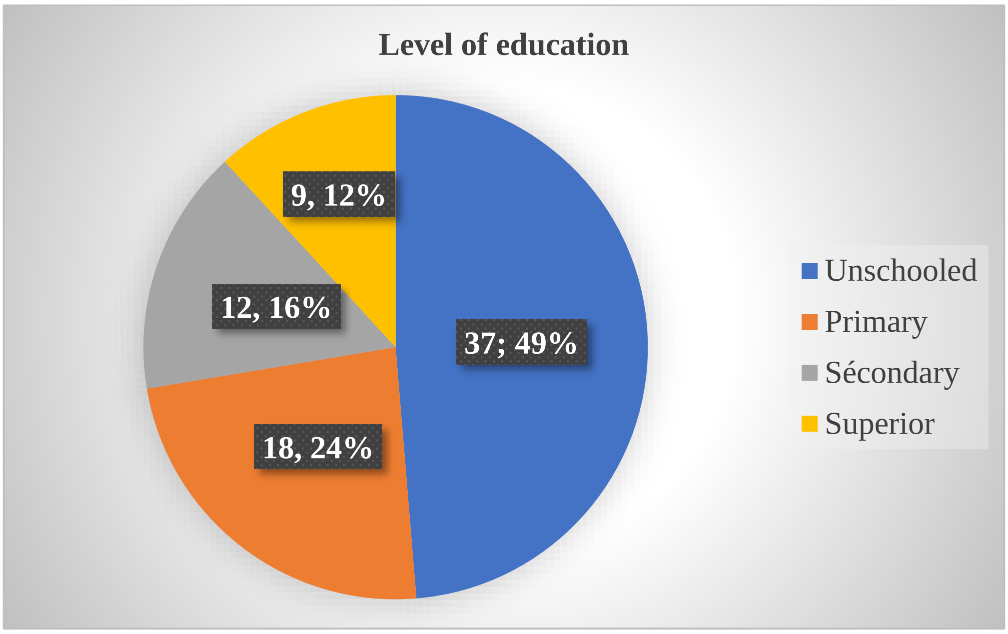
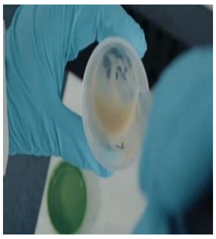
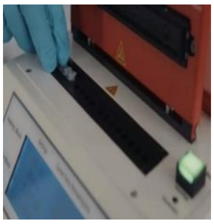
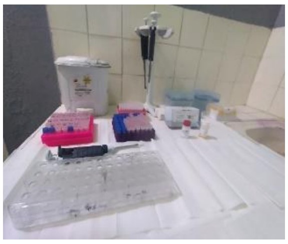
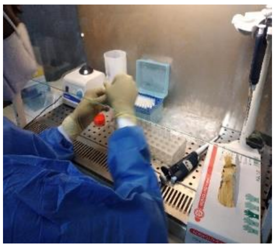


Figure 6: Distribution of patients by profession

Table 2: Biotechnological steps in the detection of *Mycobacterium tuberculosis* and rpoB genes by TB-LAMP and GeneXpert techniques

1	**a** : TB-LAMP: HumaLoop T automaton **b** : sputum sample **c** : transfer and lysis of the sputum sample			
2	**d** : : DNA extraction **e** : amplification **f** : reading TB-LAMP results (appearance: milky (positive), clear (negative)			
3	**g** : automaton :Gene Xpert **h** : spit preparation under the safety hood **i** : transfer prepared sputum into GeneXpert cartridge			
4	**j** : introduction of the cartridge into the GeneXpert machine **k** : reading the results on the GeneXpert machine screen			
5	**l** : sample preparation **m** : DNA extraction **n** :amplification			
6	**o** : evacuation of the population by pirogues to the sites of Walia and Toukra **p** : houses submerged by rainwater causing the displacement of populations by canoe.			

Source : (Djimenan et al, 2023)

DISCUSSION

Data on tuberculosis in flood-displaced people sites provide insight into current transmission and help assess the effectiveness of *Mycobacterium tuberculosis* complex (MTB) control programs or predict future trends in MTB transmission in confined settings. Local data on MTB among displaced people will help regions, countries, and stakeholders design TB prevention and control strategies in these vulnerable groups.

This current study revealed positive cases of active TB among household contacts and among IDPs who had one or more symptoms (Table 1). Much higher rates of TB-like symptoms among contacts of refugees and migrants with active multidrug-resistant TB (MDR-TB) were observed[17]. The lower occurrence of symptoms in the current study could be explained by the difference in study population, as this study considered only IDPs with rifampicin-resistant (RR-TB) and rifampicin-susceptible (SR-TB) TB while other studies included migrants and refugees with MDR-TB. In addition, the list of TB symptoms explored in this study and others were different.

Overall, the rate of MTB detected by the molecular technique TB-LAMP and confirmed positive by GeneXpert who also had detected RR-TB was 5.5%.

Much higher rates of TB type among household contacts of MDR-TB patients were observed in the Indian states of Andhra Pradesh and Telangana (16.6%), (39.0%) Myanmar[18], three cities (Karachi, Lahore, Murree) of Pakistan[19] (12.0%), and in a study of eight countries (Botswana, Brazil, Haiti, India, Kenya, Peru, South Africa, and Thailand) 23.0% was found[20, 21,22]. Moreover, the list of TB symptoms explored in the present study and the others were different. This study used the guidelines of the National Tuberculosis Control Program of Chad[23] while other studies used guidelines according to their regions, which are different from the guidelines used in the current study. Another fact could be that all studies, other than the current one, were conducted between the years 2011-2017, which were pre-COVID. But the current study was conducted in the post COVID-19 pandemic period. It is evident that infection control with personal safety precautions can reduce the risk of developing TB and due to the improvement in personal hygiene, and the habit of using masks and social distancing after the COVID-19 pandemic period, this could have reduced the risk of transmission of TB bacilli. This statement is supported by the global TB report in 2022, where it is mentioned that compared to 2019, there was a significant decrease (18%) in the number of new TB cases recorded in 2020[24].

Variations in prevalence could also be explained by differences in methods (culture or Xpert), sample size, study period, geography, and MTB control and prevention policies. In addition, the Gene Xpert test was indicated for patients coinfected with TB and HIV and patients with suspected multidrug-resistant TB.

Similarly, displaced persons aged 32–41 and 22–31 years (p = 0.20; non-significant difference) were more likely to have TB than those in the 12–21 and >52 years age group (Table 1). This is an important finding that may explain the mode of transmission of recent active TB by people in confined settings and may hamper future MTB control strategies in the future.

Female patients were more likely to be TB positive than males. This was in contrast to the study in Sudan, where males were more likely to be TB positive.

Positive tests for MTB infections were significantly higher among new cases compared to previously treated lost displaced persons ($p = 0.02$). This result was consistent with the study conducted in Sudan[25]. The high prevalence of MTB in new cases reported by this study could indicate the presence of MTB transmission in the community, which requires coordinated work to prevent and control TB in the two study sites (Walia and Toukra: Figure 1) and elsewhere.

Given the proportion of RR-TB (10.52%) detected, was higher than similar reports from Addis Ababa, Ethiopia, 7.9%, Oromia region, Ethiopia, 0%, and Uganda, 5.7%[26,27,28,29]. We report higher RR-TB positivity (5.55%) in cases lost/failed to anti-TB treatment (p = 0.02) compared to treatment naïve patients. While high MDR infection in new cases suggests the important role of ongoing transmission in the development of MDR-TB, increased infection among lost-to-follow-up cases implies poor treatment outcomes among displaced persons. This implies that it is an urgent public health problem in MTB in community settings (displaced persons, prisons, migrants, military in concentration camps etc.[30,31,32,33,34,35]

The strength of this study was its multicenter nature based on two sites of displaced persons. This can provide up-to-date information on MTB and RR-TB among migrants for regional and national governments and interested stakeholders. However, this study has limitations. Its results cannot be generalized to all migrants nationwide since it was conducted in two IDP sites in the 9th District of N'Djamena in Chad.

Apart from resistance of tuberculosis to rifampicin (RR-TB), we could not assess resistance to other first-line anti-tuberculosis drugs (ethambutol, isoniazid etc.) and second-line anti-tuberculosis drugs (Levofloxacin Amikacin, Kanamycin and Capreomycin etc.).

We did not collect information on history of contact with multidrug-resistant tuberculosis, MTB, education, place of residence of the displaced. Thus, we could not establish an association between these factors and the outcome variables.

CONCLUSION

This study, although localized, made it possible to identify and detect cases of pulmonary tuberculosis within the community of displaced persons (asymptomatic and symptomatic) by the molecular technique TB LAMP. Then, the Gene Xpert test was used to confirm and detect the rifampicin-resistant rpoB gene. The results of this study highlight the need for special attention in the study area to save the lives of these populations and control the future burden of tuberculosis in confined environments.

Conflict of interest statement: The authors declare no conflict of interest.

Author Contributions: All authors contributed significantly to the writing and editing of this manuscript. It has been viewed and approved by all authors. This manuscript has not been submitted for publication elsewhere.

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