Scientific Research Publishing

Journal of Tuberculosis Research, 2023, 11, 162-172
https://www.scirp.org/journal/jtr
ISSN Online: 2329-8448
ISSN Print: 2329-843X

Contribution to the Study of Resistance to Anti-Tuberculosis Drugs in the *Mycobacterium tuberculosis* Complex Isolated at the National Laboratory of Clinical Biology and Public Health in Bangui in the Central African Republic in 2022: Case of Rifampicin

Clotaire Donatien Rafaï[1,2*], Max Namzeka[1], Ernest Lango-Yaya[1,2], Romaric Oscar Tibet Kada[1,2], Oscar Senzongo Ndimakamoko[1], Serge Henri Gbazi[1], Le Bon Bondom[1], Christian Maucler Pamatika[3], Boniface Koffi[1,2], Alain Le Faou[2]

[1]Laboratoire National de Biologie Clinique et de Sante Publique, Bangui, Central African Republic
[2]Faculty of Science, University of Bangui, Bangui, Central African Republic
[3]Ministry of Health and Population, Bangui, Central African Republic
Email: *clotairerafai@yahoo.fr

How to cite this paper: Rafaï, C.D., Namzeka, M., Lango-Yaya, E., Kada, R.O.T., Ndimakamoko, O.S., Gbazi, S.H., Bondom, L.B., Pamatika, C.M., Koffi, B. and Faou, A.L. (2023) Contribution to the Study of Resistance to Anti-Tuberculosis Drugs in the *Mycobacterium tuberculosis* Complex Isolated at the National Laboratory of Clinical Biology and Public Health in Bangui in the Central African Republic in 2022: Case of Rifampicin. *Journal of Tuberculosis Research*, **11**, 162-172.
https://doi.org/10.4236/jtr.2023.114016

Received: November 21, 2023
Accepted: December 23, 2023
Published: December 26, 2023

Abstract

Microscopy-positive and drug-resistant pulmonary tuberculosis (MPT+) is one of the most feared diseases due to the cost of its management and the associated mortality. The GeneXpert, a new molecular test, is in greater demand for the diagnosis of MPT+ resistance cases. The application of GeneXpert to new cases of MPT+ is not effective in the country's TB screening centres. The objective of this study is to assess the contribution of GeneXpert to the determination of MPT+ resistance cases in Bangui. The study was cross-sectional and covered the period from February to July 2022. The diagnosis of tuberculosis was first performed by microscopy with Ziehl Neelsen hot stain. The GeneXpert was then used to test for resistance in the sputum of all patients with positive microscopy. The collected data was entered into Excel 2013 and analysed with Epi Info 3.3.7. We analysed data from 755 patients, 80 of whom had resistance. The 80 patients ranged in age from 6 to 68 years (mean age = 35 years). The prevalence of resistant TB was 10.60% (80/755). Primary resistance accounted for 73.75% and secondary resistance for 26.25%. The age group 20 - 39 years (57.50%), male (72.50%), 8th district (17.50%), people living in couples (53.75%), farmers (13.75%) were the socio-demo-

graphic characteristics most affected by resistance. Treatment failure (13.75%), relapses (13.75%), the notion of contagion (28.75%), a history of smoking (40%) and alcohol (61.25%) were the clinical antecedents reported by the patients. Treatment failure and relapse were the variables associated with the occurrence of resistant PMT+ ($p < 0.05$). A considerable proportion of the overall *Mycobacterium tuberculosis* resistance to anti-tuberculosis drugs (10.60%) was identified by GeneXpert. Treatment failure and relapse were the factors associated with the risk of resistance.

Keywords

GeneXpert, Resistance, *Mycobacterium tuberculosis*, Bangui

1. Introduction

Multidrug-resistant tuberculosis is defined as an infection caused by a mycobacterium of the *Mycobacterium tuberculosis* complex, resistant to at least isoniazid and rifampicin, the two standard anti-tuberculosis drugs. Resistance to anti-tuberculosis drugs is a public health problem worldwide [1]. The infection is mainly transmitted through the air from a patient suffering from pulmonary tuberculosis. *Mycobacterium tuberculosis* is transmitted between humans. The bacilli are excreted by coughing and sneezing. The often small particles (<5 μM) can remain in suspension for several hours and can be carried over long distances by air flow [2]. These are small droplets of bronchial secretion which can remain suspended in the air and which are likely to be inhaled by contact subjects. The symptoms of tuberculosis are observed by cough, hemoptysis, weight loss and fever [3]. The unreasoned use of anti-tuberculosis drugs leads to the emergence of resistant strains of *Mycobacterium tuberculosis* [2]. The Central African Republic is one of the countries in the world most affected by tuberculosis with an incidence of 423 cases per 100,000 inhabitants. However, a recent hospital study by Tekpa *et al.* reports a hospital prevalence of 10.99% in 2019 [4]. In 2015, the Pasteur Institute in Bangui (C.A.R) carried out a study on the monitoring of rifampicin resistance in strains of *Mycobacterium tuberculosis* using the GeneXpert MTB/RIF technique and published a first result after three years of activities [5]. Despite the efforts of the National Tuberculosis Control Program (PNLT), the fight against this pandemic remains insufficient in the country. The successive military-political crises have brought the health system in CAR into decline; it is not able to provide an adequate diagnosis and sufficient care for the population; which has the corollary of late detection and insufficient monitoring of patients delaying their initiation of treatment.

Thus, faced with the problem of resistance to anti-tuberculosis drugs in strains of *Mycobacterium tuberculosis* in the world and in particular the Central African Republic, it was very important to also carry out this study at the National Laboratory which now has this platform (GeneXpert).

1.1. Main Objective

Contribute to the study of resistance to anti-tuberculosis drugs in strains of *Mycobacterium tuberculosis* isolated at the National Laboratory of Clinical Biology and Public Health in Bangui in the Central African Republic: Case of Rifampicin.

1.2. Specific Objectives

- Identify *Mycobacterium tuberculosis*;
- Determine the resistance profile to Rifampicin;
- Identify the variables associated with resistance to Rifampicin.

2. Patients and Methods

This study was carried out at the National Laboratory of Clinical Biology and Public Health in Bangui in the Central African Republic. This is a six (6) month cross-sectional study running from February to July 2022. The study sample consisted of 755 patients with microscopy-positive pulmonary tuberculosis (TPM+) with 80 cases of resistance. The microscopic examination (Bacilloscopy) is based on the analysis of sputum in one day using Ziehl Neelsen staining. The coloring is done in three stages: Coloring with Carbol Fushine, decolorization with a sulfuric acid-alcohol mixture and counter-coloring with Methylene Blue. The stained slides are then dried. The colored slides are read under a microscope with a 100× objective. The bacilli are colored red by Fushine on a blue background. The test is negative if there is no AFB on 300 fields. The test is rare positive AFB if there are 1 to 10 per 100 fields, positive 1+ if there are 10 to 99 AFB per 100 fields, positive 2+ if there are 1 to 10 AFB per field and positive 3+ if there are more than 10 AFB per field. Sputum microscopic examination techniques have variable specificity depending on the quality of the microscopist and the quantity (> or = 10 mL) of sputum to be analyzed.

The GeneXpert molecular method was applied to detect *Mycobacterium tuberculosis* and also rifampicin resistance. 2 ml of sputum for 4 ml of Reagent sample were homogenized and left for 2 to 5 minutes then homogenized again and left for 30 minutes. 4 ml of the solution was introduced into the MTB/RIF cartridge and the result comes out in less than two hours.

Quality Checks Were Carried out as Follows

For the microscopic examination after Ziehl Nielsen staining, microscopists regularly trained in the recognition of AFB were subjected daily to the test of a colored slide and an unstained slide which served as an internal control.

For analysis by GeneXpert, 5 positive fluorescences (taking into account the set Cycle Threshold value) should be obtained to validate a positive sample while a positive sample should when the positive external controls were amplified.

The results recorded in a register should corroborate those returned to patients via the computerized system protected by an access code.

Study participants gave their consent and their anonymity was guaranteed by signing the consent form. Sociodemographic data were thus collected and collected while respecting patient confidentiality.

3. Results

3.1. Sociodemographic Characteristics of Patients

3.1.1. Distribution of Patients by Age

In total, we analyzed data from 755 patients with microscopy-positive pulmonary tuberculosis with 80 cases of resistance. The patients were aged 4 to 72 years with a mean age of 32 ± 7. The age group from 20 to 39 was predominant (45.82%). Figure 1 shows the distribution of patients by age.

3.1.2. Distribution of Patients by Sex

Among the 755 patients screened for positive TPM, the male gender was more represented (65.16%) as shown in Figure 2.

3.2. Prevalence of Resistance to Anti-Tuberculosis Drugs

3.2.1. Overall Prevalence of Resistance

Among the 755 patients registered, 80 tested positive by GeneXpert ® for resistance to first-line anti-tuberculosis drugs. The overall prevalence of resistance was 10.60% (Figure 3).

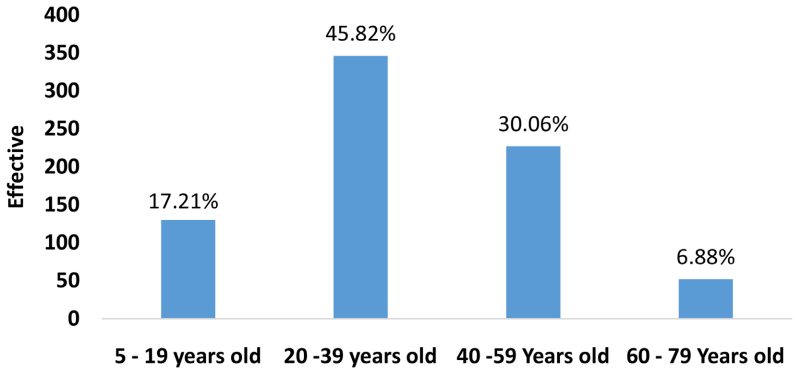

Figure 1. Distribution of patients according to age group.

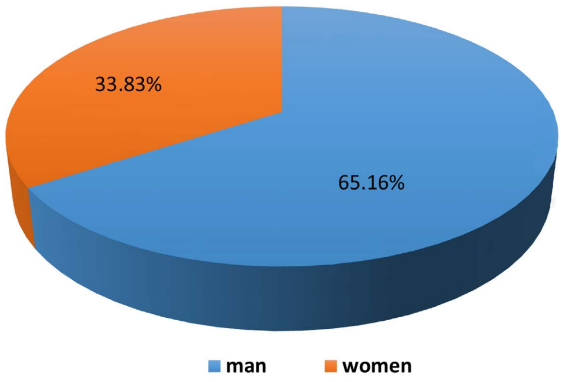

Figure 2. Distribution of patients by sex.

3.2.2. Type of Resistance to Anti-Tuberculosis Drugs

Primary resistance to rifampicin accounted for 73.75% and secondary resistance was 26.25%. Figure 4 shows the distribution of TPM+ resistance according to the type of resistance.

3.2.3. Distribution of Resistance Cases According to Patient Characteristics

1) Distribution of cases of resistance according to type and age

According to the multivariate analysis, age was not associated with the type of resistance (p-value > 0.05). Table 1 presents the distribution of patients who developed resistance according to age group.

2) Distribution of resistance cases according to type and sex

The male gender was predominant among patients with TPM+ resistance 72.50%. The occurrence of resistance was not associated with sex (p = 0.89) as shown in Table 2.

3) Distribution of cases of resistance according to type and marital status

Primary resistance and secondary resistance predominate in these patients who live as a couple as shown in Table 3.

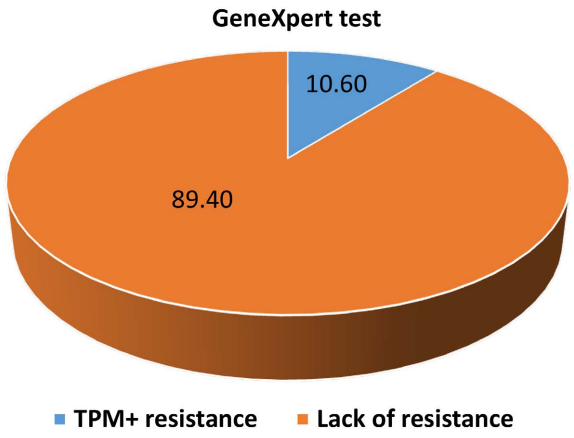

Figure 3. Prevalence of resistance to anti-tuberculosis drugs.

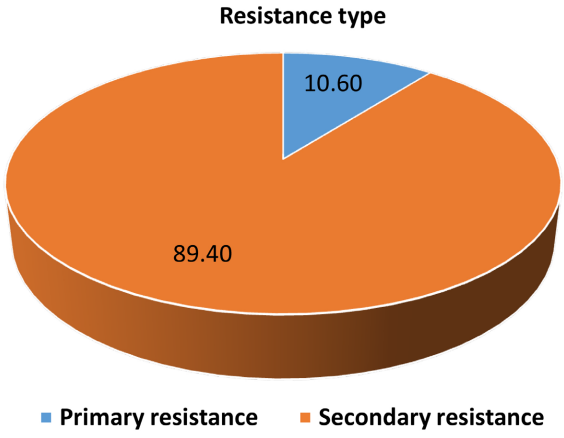

Figure 4. Distribution of rifampicin resistance by type.

Table 1. Distribution of cases of resistance according to type and age group.

Age class	TPM+ Resistant	Resistance type		p-value
	N (%)	Primary	Secondary	
5 - 19 years old	5 (6.25)	4	1	0.80
20 - 39 years old	**46 (57.50)**	**35**	**11**	
40 - 59 years old	27 (33.75)	19	8	
60 - 79 years old	2 (2.50)	1	1	
Total	80 (100)	1	21	

Table 2. Distribution of resistance cases according to type and sex.

Sex	TPM+ Resistant	Resistance type		p-value
	N (%)	Primary	Secondary	
Women	22 (27.50)	16	6	0.89
Man	**58 (72.50)**	**43**	**15**	
Total	**80 (100)**	**59**	**21**	

Table 3. Distribution of resistant cases according to type and marital status.

Marital status	TPM+ Resistant	Resistance type		p-value
	N (%)	Primary	Secondary	
Bachelor	19 (21.25)	13	6	0.31
Married	14 (17.50)	8	6	
Life as a couple	**43 (53.75)**	**35**	**8**	
Not applicable	4 (5.00)	3	1	
Total	**80 (100)**	**59**	**21**	

4) Medical and clinical history of patients

Among the cases of resistance to anti-tuberculosis drugs, 11 patients had experienced treatment failure due to anti-tuberculosis drugs (13.75%) and 11 cases of treatment relapse (13.75%). The notion of contagion was found among patients (28.75%). A history of tobacco and alcohol was found respectively in 40% and 61.25% of cases in patients with resistant TPM+. Primary resistance was more common in patients who did not experience treatment failure and in those who did not experience a relapse. Treatment failure and relapse were the variables associated with the occurrence of resistant TPM+ ($p < 0.05$). The risk of developing resistant TB was 21.37 times higher in patients who experienced a relapse (OR = 21.37 [4.07 - 31.71]). Table 4 presents the distribution of patients' medical and clinical histories.

Table 4. Distribution of history of patients with resistant TPM+.

Variables	TPM+ Resistant	Ty Resistance type		p-value	Raw GOLD [CI, 95%]	p-value	ajusted OR [CI, 95%]
	N (%)	Primary	Secondary				
Treatment failure							
Yes	11	**0**	**11**	0.001	1.20 [1.01 - 5.45]	<0.0001	1.21 [1.02 - 5.44]
No	69	**59**	10				
Relapse							
Yes	11 (13.75)	2	9	0.0005	21.35 [4.04 - 31.69]	0.0006	21.37 [4.07 - 31.71]
No	69 (86.25)	**57**	**12**				
Concept of storytelling							
Yes	23 (28.75)	**15**	8	0.27	0.20 [0.21 - 2.40]	NA	NA
No	57 (71.25)	44	13				
Tobacco							
Yes	32 (40)	**24**	8	0.83	0.54 [0.21 - 4.15]	NA	NA
No	48 (60)	35	13				
Alcohol							
Yes	31 (38.75)	**38**	11	0.33	1.78 [0.13 - 5.21]	NA	NA
No	49 (61.25)	21	10				
Total	**80 (100)**	**59**	**21**				

NA = not applicable (p-value > 5%).

4. Discussion

The study carried out at the National Laboratory of Clinical Biology and Public Health of Bangui aimed to evaluate the resistance to anti-tuberculosis drugs of the *Mycobacterium tuberculosis* complex in patients with microscopy-positive pulmonary tuberculosis from February to July 2022. The reliability of these results was based on the quality of the set of methodologies used. This exclusivity made it possible to have as a target population both male and female patients coming for the diagnosis of tuberculosis at the LNBCSP in Bangui. This cross-sectional study made it possible to analyze fairly recent data in order to have an idea of the epidemiological situation of multidrug-resistant tuberculosis in the Central African Republic. During this study, 755 patients with microscopy-positive pulmonary tuberculosis with 80 cases of resistance. The 80 patients were aged 6 to 68 years. Their average was 35 years. The age group of 20 to 39 was predominant with 57.50%. The minimum age of patients in our study was lower than the minimum age of patients in a study carried out in England, Norway, Ireland, Burkina Faso, Djibouti, Ethiopia and South Africa including Minimum age was 18 years [6] [7]. The maximum age is higher than that of studies carried out in Europe [6], in Tunisia [8] [9], and lower than that of the study carried out

in South Africa [10]. Our study did not demonstrate an association between age and the occurrence of TPM+ resistant to anti-tuberculosis drugs (p > 5%). In contrast, a study carried out in Tunisia showed that the age of patients (elderly or not) is a risk factor associated with resistance [8]. The male gender was predominant among patients with TPM+ resistance. A study carried out in Niger in 2016 showed that the male sex was dominant. Primary resistance and secondary resistance were predominant in males. The predominance of the male sex among tuberculosis cases had been the subject of several studies carried out in CAR [3] [11]. The predominance of resistant TPM+ in men in CAR has also been observed in other studies carried out in other countries [9] [12]. Unlike our data which did not highlight a link between sex and resistant tuberculosis, male sex was identified as a risk factor associated with resistance to anti-tuberculosis drugs in Tunisia [8]. In this study, marital status is not a risk factor for contracting tuberculosis (p-value = 0.31). In a study carried out by Laoulet and colleagues in Bangui, the p-value is greater than 0.05 [13]. This p-value is in line with the p-value obtained in this study.

TPM+ is a disease essentially transmitted between humans, it is a cosmopolitan infectious disease caused by mycobacteria of the Tuberculosis complex. But at the end of the 1980s the HIV pandemic led to a resurgence of tuberculosis in many countries and the hope of rapid eradication was definitively abandoned. This disease constitutes a historical evil and still remains a growing global scourge, especially in developing countries, despite the control actions implemented for several years. Resistant tuberculosis is the most worrying due to the cost of its treatment. This study initially included 755 patients screened for TPM+ at the LNBCSP in Bangui. This number includes both patients under treatment and control and new screening cases. Of the 755 patients, 80 developed resistance to anti-tuberculosis drugs; which represents a prevalence of 10.60%. A lower prevalence of resistant tuberculosis was found in England with a rate of 7.86%, in Norway 4.12%, in Northern Ireland 4.40% [5] and in Schwaziland a percentage of 6.3% [14]. In Africa, a prevalence more or less high than that of our study was found in Burkina Faso (15.25%), Djibouti (11%), Ethiopia (5%) and South Africa (17.80%) [6] [7]. This is not surprising since upstream in the 1990s in the United States, the problem posed by multi-resistant strains (MDR or Multi Drug Resistant tuberculosis) of tuberculosis appeared inevitable. Due to the severity of the epidemic in South Africa, the threat has escalated with ultra-resistant forms or XDR (Extreme drug resistant tuberculosis). The ultra-resistant form is characterized by its rapid spread, co-infection with HIV, and multi-resistance [7]. It is known from the literature that the prevalence of tuberculosis in Sub-Saharan Africa is higher than that in Europe [15]. This justifies the high frequency of this resistance in Africa. The prevalence of resistant tuberculosis is high in South Africa compared to other African countries. In many countries, tuberculosis appears to be a specific problem of the disadvantaged classes.

The bacillus already in contact with anti-tuberculosis drugs can mutate and therefore become resistant. Compliance with treatment and HIV status were not addressed in our study.

When anti-tuberculosis treatment is incorrectly prescribed or poorly followed by the patient, it can lead to the selection of resistant mutants (secondary resistance). This is the major cause of therapeutic failure. Strains that have acquired resistance to the most effective first-line anti-tuberculosis drugs are called multi-resistant. Multi-resistant strains which have also acquired mutations leading to resistance to the most effective 2nd line anti-tuberculosis drugs are called ultra-resistant [15] [16] [17] [18] [19]. Among the cases of resistance to anti-tuberculosis drugs, 13.75% of patients had experienced treatment failure with anti-tuberculosis drugs. Primary resistance was more common in patients who did not experience treatment failure (100%). In Ivory Coast the proportion of failure cases revealed by a study was 30.6% [15]. Of the 80 patients in the study, 13.75% were cases of treatment relapses.

Higher proportions of relapse cases were reported in Senegal (21.46%) and Côte d'Ivoire (69.4%) [17] [19]. Treatment failure and relapse were associated with the risk of developing resistant TPM+. This risk was 21.37 times higher in patients who experienced a relapse. Treatment failure as associated with the risk of multidrug-resistant tuberculosis was the subject of analyses in a study carried out in Democratic Congo [20]. The notion of contagion found in 23 patients (28.75%) of our study has already been described in Senegal (31.94%) by Niang and collaborators [17]. History of tobacco and alcohol was found in 40% and 61.25% of cases, respectively, in patients with resistant TPM+ in this study. According to some authors, alcohol consumption and tobacco use are risk factors for drug-resistant tuberculosis [9]. Alcohol consumption is a problem for the metabolism of anti-TB drugs. The negative impact of smoking on the outcome of treatment is not to be questioned.

5. Conclusions

The GeneXpert molecular test was initially developed for the diagnosis of tuberculosis with tuberculosis-resistant bacilli. This test has shown its usefulness in the diagnosis of pulmonary tuberculosis, especially in subjects infected with HIV. It made it possible to reduce the diagnosis time and improve it in subjects infected with HIV. In the Central African Republic, screening for new cases of microscopy-positive pulmonary tuberculosis is based on chest x-rays and microscopic examination of sputum or, failing that, gastric contents by tubing. The aim of the present study was to study the contribution of the molecular test using GeneXpert to the diagnosis of pulmonary tuberculosis resistant to anti-tuberculosis drugs in Bangui. A considerable proportion of the overall resistance of *Mycobacterium tuberculosis* to anti-tuberculosis drugs has been determined.

GeneXpert not only made it possible to highlight cases of primary resistance; but also to detect primary resistance in a significant proportion. The data from this study also allowed us to understand that some patients with primary resis-

tance would be ignorantly placed on inadequate treatment with the first-line anti-tuberculosis drug, Rifampicin. That said, reform actions regarding TPM+ screening in accordance with WHO recommendations must be implemented. This will not only improve laboratory diagnosis; but also the medical treatment of cases of resistance.

Acknowledgements

We thank Mr. Javan Allan Bengba for help with the translation and Mr. Maurel Annicet Adonis Ouoko Fa-Tigbia for design's work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Ethics

This study benefited from ethical clearance from the scientific committee of the Faculty of Health Sciences of the University of Bangui which approved the research protocol before starting. In addition, it is a public utility activity supported by the highest authority in matters of public health.

References

[1] Briand, M. (2018) Tuberculose multirésistante: Stratégies thérapeutiques actuelles et place de la bédaquiline (Sirturo).

[2] Veziris, N. and Robert, J. (2010) Anti-Tuberculosis Drug Resistance and Therapeutic Dead End. *Medecine/Sciences*, **26**, 976-980. https://doi.org/10.1051/medsci/20102611976

[3] Diande, S. (2010) Evaluation de la Resistance de *Mycobacterium tuberculosis* Aux Antibiotiques et Exploration des Facteurs de Risque Associes a La Multiresistance Au Burkina Faso, 113.

[4] Tékpa, G., Fikouma, V., Téngothi, R.M.M., Longo, J.D., Woyengba, A.P.A. and Koffi, B. (2019) Epidemiological and Clinical Features of Tuberculosis at the Hopital de l'Amitié in Bangui. *The Pan African Medical Journal*, **33**, Article No. 31. https://doi.org/10.11604/pamj.2019.33.31.13442

[5] He, H., Yb, K., Fn, E., Ihbibane, F., Soraa, N., Tassi, N., *et al.* (2020) Apport du Test Xpert MTB/RIF dans le diagnostic et le traitement de la tuberculose. The Contribution of the Xpert MTB/RIF Test in the Diagnosis and Treatment of Tuberculosis. *Revue Malienne d' Infectiologie et de Microbiologie*, **16**, 36-40. https://doi.org/10.53597/remim.v16i2.1868

[6] Irish, C., Herbert, H., Bennett, D., Gilham, C. and Drobniewski, F. (1999) Database Study of Antibiotic Resistant Tuberculosis in the United Kingdom. *BMJ*, **318**, 497-498. https://doi.org/10.1136/bmj.318.7182.497

[7] Ilboudo, D., Bisseye, C., Djigma, F., Diande, S. and Yonli, A. (2015) Diagnostic moléculaire du complexe *Mycobacterium tuberculosis* résistant à l'isoniazide et à la rifampicine au Burkina Faso. *The Pan African Medical Journal*, **21**, Article No. 73. https://doi.org/10.11604/pamj.2015.21.73.5494

[8] Labie, D. (2007) *Mycobacterium tuberculosis*. *Médecine/Sciences*, **23**, 205-209.

https://doi.org/10.1051/medsci/2007232205

[9] Smaoui, F.S., Mzid, H., Marouane, C. and Kammoun, S. (2015) Multidrug-Resistant Tuberculosis: Epidemiology and Risk Factors. *Revue de Pneumologie Clinique*, **71**, 233-241. https://doi.org/10.1016/j.pneumo.2015.03.004

[10] Mjid, M., Hedhli, A., Zakhma, M., Zribi, M., Ouahchi, Y. and Toujani, S. (2018) Clinical and Microbiological Profile of Patients Experiencing Relapses of Tuberculosis in Tunisia. *Revue de Pneumologie Clinique*, **74**, 76-80. https://doi.org/10.1016/j.pneumo.2018.01.002

[11] Chia, B.S., Lanzas, F., Rifat, D., Herrera, A., Kim, E.Y., Sailer, C., *et al.* (2012) Use of Multiplex Allele-Specific Polymerase Chain Reaction (MAS-PCR) to Detect Multidrug-Resistant Tuberculosis in Panama. *PLOS ONE*, **7**, e0040456. https://doi.org/10.1371/journal.pone.0040456

[12] Xavier, L. and Nouvel, M. (2005) Recherche de marqueurs génétiques de souches de *Mycobacterium tuberculosis* multirésistantes aux antibiotiques en République Centrafricaine.

[13] Laoulet, K.T., Mossoro-Kpindé, C.D. and Pamatika, C.M. (2021) Dépistage systématique du VIH chez les patients suspects de tuberculose pulmonaire au Centre de Santé Urbain de Malimaka à Bangui. *Médecine d'Afrique Noire*, **68**, 32-38.

[14] Helbling, P., Altpeter, E., Raeber, P.A., Pfyffer, G.E. and Zellweger, J.P. (2000) Surveillance of Antituberculosis Drug Resistance in Switzerland 1995-1997: The Central Link. *European Respiratory Journal*, **16**, 200-202. https://doi.org/10.1034/j.1399-3003.2000.16b03.x

[15] Sante, D. (2000) Cinquante-Troisieme Cinquante-Troisieme. 15-20.

[16] Caminero, J.A. (2010) Multidrug-Resistant Tuberculosis: Epidemiology, Risk Factors and Case Finding. *The International Journal of Tuberculosis and Lung Disease*, **14**, 382-390.

[17] Niang, S., Abdallahi, E.W., Thiam, K., Mbaye, F.B.R., Cissé, M.F., Ndiaye, E.M. and Badiane, N.T. (2018) Aspects épidémiologiques, diagnostiques et évolutifs de la tuberculose pulmonaire à microscopie positive au District Sanitaire de Saint-Louis. Epidemiological, Diagnostic and Evolutionary Aspects of Pulmonary Tuberculosis with Positive Microscopy in the S. *Revue Africaine de Médecine Interne*, **5**, 65-69.

[18] Sahebi, L., Ansarin, K., Seyyedi, M., Monfaredan, A., Farajnia, S., Moaddab, S.R., *et al.* (2016) Epidemiology and Patterns of Drug Resistance among Tuberculosis Patients in Northwestern Iran. *Indian Journal of Medical Microbiology*, **34**, 362-368. https://doi.org/10.4103/0255-0857.188352

[19] Man-Koumba, S., Kouamé, D.M., Constant, K.J., Harvey, A., Abdoulaye, O., Youssouf, T., *et al.* (2018) Épidémiologie de la tuberculose en Côte d'Ivoire: Une revue systématique de la littérature. *Revue Internationale des Sciences Médicales*, **20**, 140-147.

[20] Misombo-Kalabela, A., Nguefack-Tsague, G., Kalla, G.C.M., Ze, E.A., Diangs, K., Panda, T., *et al.* (2016) Facteurs de risque de la tuberculose multi-résistante dans la ville de Kinshasa en République Démocratique du Congo. *The Pan African Medical Journal*, **23**, Article No. 157. https://doi.org/10.11604/pamj.2016.23.157.6137