Epidemiological profile of multidrug-resistant and extensively drug-resistant Mycobacterium Tubrculosis among Congolese patients

Darrel ELION ASSIANA
Fondation Congolaise pour la Recherche Médicale
Pacôme ACHIMI ABDUL
CERMEL
Laure Stella GHOMA LINGUISSI
IRSSA
Micheska EPOLA
CERMEL
Jeannhey VOUVOUNGU
FCRM
Albert MABIALA
Hospital de Base
Christopher Biyogho
CERMEL
Jean Ronald EDOA
CERMEL
Bayodé ADEGBITE
CERMEL
Akim ADEGNIKA
CERMEL
Linzy Elton
University College London
Julio Ortiz Canseco
University College of London
Timothy D McHugh
University College of London
Gabriel AHOMBO
University Marien Ngouabi
Francine Ntoumi (ffntoumi@hotmail.com)
Fondation Congolaise pour la Recherche Médicale

Research

Keywords: Epidemiological profile, multidrug-resistant TB, extensively drug-resistant TB, Xpert MTB / RIF, Line Probe Assay SL, Republic of Congo

DOI: https://doi.org/10.21203/rs.3.rs-143388/v1

Abstract

Background

Tuberculosis (TB) remains a public health problem and early detection of drug resistance is crucial to prevent transmission of drug-resistant TB and avoid mortality. There is paucity of data on the prevalence and distribution of MDR-TB at the Republic of Congo. However, the challenges of establishing a robust testing program are significant. In resource limited settings there is a need to gather data to enable prioritization of actions. The objective of this study was to characterize the epidemiological profile of MDR and XDR-TB among presumptive tuberculosis patients referred to Makélékélé hospital in Brazzaville, Republic of the Congo.

Methods

We have conducted a cross-sectional study, including a total of 92 patients recruited at the Makélékélé hospital from October 2018 to October 2019. The socio-demographic and clinical data were collected as well as sputum samples. Rifampicin resistance was investigated using Xpert (Cepheid) and second-line TB drugs Susceptibility testing were performed by the Brucker HAIN Line Probe Assay (GenoType MTBDRsl VER 2.0 assay) method.

Results

From the 92 recruited patients, 57 (62%) were found positive for the Mycobacterium tuberculosis complex. The prevalence of rifampicin-resistant tuberculosis (RR-TB) was 9.8% (9/92) and importantly 2.2% were pre-XDR/XDR.

Conclusion

This study showed a high rate of rifampicin resistance and the presence of extensively drug-resistant tuberculosis in the study area in new patients. This study suggests early diagnosis of resistant tuberculosis should be considered using more sensitive diagnostic tools. Rapid molecular diagnostic tools such as GeneXpert need to be installed in health centers for better management of resistant tuberculosis.

Introduction

Tuberculosis (TB) is a major public health problem worldwide. The World Health Organization (WHO) estimated that there were 10 million new people of tuberculosis in 2019, of which 860,000 occurred among PLHIV and 484,000 people were found to have rifampicin resistant tuberculosis (RR-TB) (WHO, 2019). (WHO, 2019)

For several decades, the emergence Of MDR-TB as well as XDR-TB has been an obstacle to the control of the disease (Ntoumi et al., 2016; Zumla et al., 2012). Early detection of drug resistance is crucial to prevent transmission of drug-resistant TB and avoid mortality (Gardee et al., 2017). However, the challenges of establishing a robust testing program are significant. In resource limited settings there is a need to gather data to enable prioritization of actions. In the present study we demonstrate this process for the Republic of Congo. In the Republic of Congo, the annual incidence of tuberculosis is estimated at 375 cases per 100,000 population. The proportion of people with tuberculosis who are also co-infected with HIV was 108 cases per 100,000 population. (WHO Report Country profiles TB, 2019). It is reported that MDR-TB accounts for 2.4% of new cases (WHO, 2019). However, no national survey on MTB drug resistance has been carried out (PNLT, 2014–2018) and there is paucity of data on the prevalence and distribution of MDR-TB in the country. Such information is essential to facilitate effective control measures and the results of these tests are essential for clinicians in the design of the treatment regimen in the management of MDR-TB patients (Zumla et al., 2012). Failure to diagnose and treat MDR-TB patients have a negative impact on resistance level, transmission and mortality (Boehme et al., 2010; Zumla et al., 2012).

The gold standard methods for the detection of MDR-TB are *in vitro* culture and drug susceptibility testing (DST). These methods are time consuming, expensive (Nguyen et al., 2019) and also require a high-level biosafety facilities (BSL3 / P3) with qualified personnel (Nguyen et al., 2019). In the absence of culture facilities rapid molecular diagnostic tests have been developed to overcome this diagnostic obstacle like such as the Xpert MTB / RIF (Cepheid, Sunnyvale, CA, USA) system and Line probe Assays (LPA)with a focus on the rapid detection of TB drug resistance (Pai et al., 2016; Gilpin et al., 2016). Indeed, since 2010, WHO approved the Xpert MTB / Rifampicin test (Cepheid, Sunnyvale, CA, United States) as a routine tool to be used for screening suspected MDR-TB patients or TB-HIV co-infected individuals (Sachdeva et al., 2015). Furthermore, in 2016, WHO approved the use of version 2 of the HAIN GenoType MTBDRsl as the genotypic test for drug susceptibility testing to detect resistance to fluoroquinolones and injectable second-line drug (SLI) (WHO, 2016).

However, in many countries the roll out of Xpert based systems has not been straightforward. Indeed, the introduction of the first GeneXpert in the Republic of Congo in 2013 (Okemba-Okombi et al., 2015a) did not help to meet the expectations because of limited financial resources that did not allowed to purchase cartridges. Under the support of the Central Africa clinical Research Network (CANTAM, www.cantam.org), our institution acquired a new GeneXpert and necessary reagents to conduct the present study with the main objective of determining the epidemiological profile of MDR- and XDR-TB among presumptive tuberculosis patients referred to the Makélékélé hospital in Brazzaville, Republic of the Congo.

Materials And Methods

Ethical approval and consent

The protocol of this study was submitted to the institutional ethics committee of the Fondation Congolaise pour la Recherche Médicale and got the ethical approval referencenced under the number 015/CIE/FCRM/May 30, 2018. All adult participants gave their written informed consent and minor participants gave their assent, we also obtained the consent of their parent or guardian. Confidentiality of data was ensured, prior inclusion into the study.

Study location

The study was conducted in Brazzaville which is the political and administrative capital of the Republic of Congo. Study participants were enrolled at the Makélékélé Hospital, which is the second largest hospital of reference located in the south of Brazzaville, and covers the first sanitary district of the city covering an estimated population size of 74,815 inhabitants and an area of 15.53 km².

At Makélékélé hospital, the study was conducted in the infectious diseases department. All Presumptive tuberculosis individuals coming for consultation at Makélékélé Hospital are received in the department of infectious diseases. This department makes the diagnosis, treatment and hospitalization of patients. It has a mycobacteria laboratory. At the department level, Directly Observed Treatment Short-course (DOTS) is given free of charge to tuberculosis patients (Okemba-Okombi et al. 2020). Antiretroviral therapy (ART) is also provided free of charge to TB/HIV co-infected patients. The prevalence of TB patients confirmed by bacteriological tests was estimated at 17%, according to the department's registry.

Type and population of study

This is a cross-sectional study conducted at from October 2018 to October 2019 and targeted presumptive pulmonary tuberculosis participants (only new patients). Eligible participants were between 8 and 70 years of age, suspected to suffer from TB, without prior anti-TB treatment, voluntarily consented and assented to HIV testing, and resided in Brazzaville during the study period. Participants with diseases such as cancer, advanced HIV-AIDS, severe malaria and hepatitis were excluded. The study was based only on pulmonary TB and all participants with extra-pulmonary TB were not eligible.

Operational definitions

Presumptive tuberculosis participants: individuals with evocative symptoms of TB (coughing for 3 weeks or more, persistent and productive, sputum sometimes streaked with blood, chest pain, weight loss, tiredness, anorexia, fever and night sweats).

New Patients: patients who have never received anti-TB drugs or who have received treatment for less than a month.

Sample collection and study design

The study design is summarized on Fig **1**. Briefly, after signing the informed consent, the socio-demographic data were collected by the study physician during the clinical examination. A total volume

of 5 mL of the blood was collected from all participants for hepatitis and HIV testing (Pre-counseling was done before the HIV test). Participants found to be positive for hepatitis B and/or C were excluded from the study.

Two sputum specimens of 3mL each were collected from enrolled study participants in accordance with the guidelines of the national tuberculosis control program (PNLT, 2016). The first (spot) sputum specimen was collected at Makélékélé Hospital on the first day. The second (morning specimen) was collected at home on the second day and delivered the same day to the mycobacteria laboratory at Makélékélé Hospital.

The sputum and blood samples were transported at 4-8 ° C at the Mycobacterium TB laboratory (MTBL) of the Centre de Recherches des Maladies Infectieuses - Christophe Mérieux (CeRMI-CM), Republic of Congo. On receipt of the samples at the MTBL Blood samples were tested for hepatitis with the Hepatitis B rapid test and the Promed Gold Hepatitis C test, as well as for HIV with the Determine HIV 1/2 rapid test (Alere GmbH, Cologne, Germany) and the enzyme-linked immunosorbent assay (ELISA, Vironostika®HIV-1 Plus O Microelisa System, United Kingdom). Sputum samples were decontaminated using the BD BBL® MycoPrep™ Specimen Digestion / Decontamination Kit (Becton Dickinson) following the manufacturer's instructions. The decontaminated samples were stored at -80 ° C until further analyses.

Detection of *Mycobacterium tuberculosis* complex and rifampicin resistance in the sputum was using the Xpert® MTB/RIF test (Cepheid, Sunnyvale, CA, USA). All rifampicin-resistant samples were subjected to Line probe Assay test (LPA: Geno Type® MTB DR sl assay; Hain Life Science, Gmbh, Germany) to detect resistance to fluoroquinolones and second-line injectable drugs (Amikacin, Kanamycin and Capreomycin).

GenoType MTBDR sl

From the decontaminated sputum samples, we extracted the DNA by thermal lysis and sonication as described below. Briefly, 500 µL of decontaminated sputum was centrifuged at 10,000xg at 4 ° C for 15 minutes. The supernatant was discarded, the pellet was resuspended in 100 µl of sterile distilled water and the mycobacteria were lysed by incubation at 95 °C for 20 minutes and the sonication for 15 minutes, then centrifuged at 13000×g for 5 minutes. The supernatant was collected and stored at -20 °C (HAIN LifeScience, 2015).

With the extracted DNA, amplification and hybridization were performed with the reagent GenoType MTBDRsl VER2.0 (Hain Lifescience, Nehren, Germany) following the manufacturer's instructions.

Statistical analysis

The data were analyzed using SPSS Statistical Software version 24(IBM Corp, Armonk, NY). Socio-demographic data, TB risk Behaviours and clinical information were associated to the positivity of GeneXpert method by logistic regression model and their Odd Ratio with the confidence interval at 95% was determinate. The Mann-Whitney test and Kruskal-Wallis test were used to see the dependence of the

Rifampicin Susceptibility and the factors. Differences were considered statistically significant when the p-value was < 0.05.

Results

Socio-demographic characteristics of the participants

From October 2018 to October 2019, 110 suspected MTB patients were screened at Makélékélé hospital in Brazzaville for TB. Based on clinical examination and inclusion criteria, 92 patients were included in the study, 18 were excluded from the study because of hepatitis B and C positivity (Fig **1**) or manifestation of extrapulmonary tuberculosis.

This total of 92 patients consisted of 47 (51.1%) females and 45 (48.9%) males. The average age was 38.2 (± 15.1) years. However, most were 18 to 44 51(55.4%), followed by ≥ 45 years 33(35.9%) and ≤17 years 8(8.7%) (Table **1**).

Clinical signs, co-infection and associated risk factors of the participants

Of the 92 participants in the study, 66(71.7%) had a chronic cough, 28(30.4%) had an acute cough, 72(78.3%) had a fever, 82(89.1%) had a weight loss, 27(29.3%) had a physical asthenia and 19(20.7%) had an anorexia. The HIV positivity rate was 22(23.9%). Of all participants, 43(46.7%) accepted to be alcoholic consumer, 20(21.7%) recognized to be smoker and 5(5.4%) recognized to be cannabis consumer (Table **1**).

Proportion of *Mycobacterium tuberculosis* complex (MTBC) positivity and associated characteristics

Of the 92 participants enrolled in the present study, 57 (62%) were found to be positive for MTBC by the Xpert MTB/RIF test. The association between potential exposure variables and the participants' MTBC positivity was analyzed and presented in Table **1**. There was a significant association between the participants' positivity to the MTB complex and seropositivity (95% CI = 0.07-0.53, P = 0.002), as well as an association with acute cough (95% CI = 0.15-0.98, P = 0. 042). However, there was no significant association between the other variables and positivity to the MTB complex.

Rifampicin sensitivity profile

Of the 57/92 CMTB-positive participants, 2/92 (2%) were indeterminate and so removed from the analysis, 9/55 (16.4%) were resistant to rifampicin, and 46 were rifampicin-sensitive (Table **2**).

The association between the potential exposure variables and the participants' rifampicin-resistant tuberculosis (RR-TB) was analyzed and presented in Table **2**. Rifampicin-resistant tuberculosis was statistically significant in HIV-positive participants (P = 0.006), there was a significant association between rifampicin-resistant tuberculosis and chronic cough (P = 0.019), also a significant association with acute cough (P = 0.019), and a significant association with anaemia (P = 006) and physical

asthemia (P = 0.098). However, there was no significant association between the other variables and RR-TB.

Sensitivity profile for second-line drugs

For the 9 participants resistant to rifampicin, the results of the second-line drug sensitivity tests were reported in Table **3**. We found that 1/9 (11.1%) was resistant to fluoroquinolones and 1/9 (11.1%) was resistant to both fluoroquinolones and injectable second line drugs. The remaining 7 rifampicin-resistant participants were sensitive to second line drugs.

Discussion

The present study showed that the prevalence of rifampicin-resistant tuberculosis (RR-TB) among the 92 participants suspected of having tuberculosis and who had never received treatment was 9.8% (9/92) and importantly 2.2% were pre-XDR/XDR. Currently, the data available in the study area do not allow a more precise analysis of the exact causes of this increase (type of exposure, contact persons). However, the detection of the relatively high rate of RR-TB resistance in the study population could be due to the late diagnosis (patients with resistant strains are diagnosed late and often at the advanced stage of the disease) which would be responsible for the spread of resistant strains in the community. The lack of access to culture facilities and limited availability of rapid molecular diagnostic tools in some hospitals means that the delay in diagnosing resistance is often long (Amona et al., 2017). The eligibility criteria for GeneXpert set up by the national tuberculosis control program is such that only patients in therapeutic failure are diagnosed with this molecular tool, for reasons of limited financial resources causing breaks in the purchase of cartridges (Okemba-Okombi et al., 2015a). According to the WHO, the estimate of MDR-TB/MDR-TB at the national level was 2.4% in new patients (WHO, 2019).

The prevalence of RR-TB found in the present work is lower than that reported in the study conducted in Gabon, in a sample of 124 patients (new and failed treatment), a prevalence of RDR-TB of 17% was noted (Alame-Emane et al., 2017). Indeed, an earlier study conducted in the Republic of Congo at the Tuberculosis Center reported a prevalence of 18% in a sample of 111 patients in treatment failure (Okemba-Okombi et al., 2015a). Importantly, our study was conducted only in new patients, in contrast to this study, and this is a cause for concern as it indicates increased transmission of drug resistant forms of *Mycobacterium tuberculosis*.

It should be noted that, in most cases, it is possible to cure rifampicin-resistant tuberculosis, although second-line treatment is long and requires strict adherence to a treatment regimen with support and supervision of the patient during treatment (Nunn et al., 2019). First- and second-line treatment of tuberculosis is provided free of charge by the National Tuberculosis Control Program in the Republic of Congo (Okemba-Okombi et al.2020).

Our study also showed that HIV status (p = 0.006) was the only significant factor (p = 0.005) associated with rifampicin-resistant tuberculosis; other factors such as alcohol, tobacco, and cannabis use were not

significant. Thus, there is a relationship between rifampicin-resistant tuberculosis and HIV status. This could be explained by the fact that tuberculosis is the most common opportunistic disease in HIV-infected patients. This finding has also been made by several authors (Harries et al., 2019; Najjingo et al., 2019; Phyo et al., 2019).

Clinical signs such as chronic cough (p = 0.019), acute cough (p = 0.019), anemia (p = 0.06) and physical asthenia (p = 0.098) were statistically significant (p = 0.005). The clinical signs of susceptible tuberculosis are the same as those of resistant tuberculosis according to the WHO. Other authors have also pointed out the presence of these clinical signs in relation to rifampicin-resistant tuberculosis (Okemba-Okombi et al,2020.; Ossibi Ibara et al., 2016).

In this study, genotypic testing for second-line drug susceptibility was performed on the 9 participants detected with rifampicin-resistant tuberculosis using the GenoType MTBDR sl test. This test recorded 1 participant who was resistant to fluoroquinolones and also 1 participant who was resistant to both fluoroquinolones and second line injectable drugs. The proportion of this form of extensively drug-resistant tuberculosis in our study population is of concern, requiring significant community action to prevent the spread of resistant strains. These data suggest that efforts should be made to ensure that all patients diagnosed with XDR-TB undergo sensitivity testing with fluoroquinolones and second-line injectables in order to initiate early and effective treatment. A study conducted in the Republic of Congo reported that in a sample of 13 previously treated patients, a proportion of 3 patients were resistant to fluoroquinolones and 1 patient was resistant to fluoroquinolones and second-line injectable drugs (Okemba Okombi et al., 2018). The particularity of our study is that we detected this form of resistance in untreated patients, whereas in the Okemba-Okambi et al study, this form of resistance was detected in previously treated patients.

It is important to make the right diagnosis at an early stage in order to initiate effective treatment as early as possible. It is possible to cure XDR-TB, but with the drugs currently available, the probability of cure remains low. Cure depends on the extent of drug resistance, the severity of the disease and the state of the immune system (WHO, 2019).

Our study is the first to show a high prevalence of RR-TB and the presence of XDR-TB in new patients. These results provide some useful information that should attract the attention of our health authorities regarding the practical management of patients with drug-resistant TB. These data will further strengthen the advocacy at the level of the national tuberculosis control program on the need to install rapid molecular diagnostic tools for the detection of resistance in health centers. This will allow early detection and better management of patients.

It would be necessary to extend this study to other hospitals in Brazzaville in order to have a better understanding of the current status of the epidemiological profile of resistance at the national level. It would also be important to establish surveillance systems for resistance to first- and second-line anti-tuberculosis drugs, which can serve as key tools for data collection to provide indicators on the

epidemiological characteristics of resistant tuberculosis on which the national tuberculosis control program can be based.

However, this study is not without limitations. We were not able to conduct timely drug susceptibility testing (DST) with other first-line anti-tuberculosis drugs to determine whether polyresistant TB was present in our study. In addition, our sample size did not allow us to make comparisons with other studies.

Conclusion

This study showed a high rate of rifampicin resistance and the presence of extensively drug-resistant tuberculosis in the study area in new patients. This study suggests early diagnosis of resistant tuberculosis should be considered using more sensitive diagnostic tools. Rapid molecular diagnostic tools such as GeneXpert need to be installed in health centers for better management of resistant tuberculosis.

Declarations

Funding

This study received financial support from CANTAM (EDCTP-RegNet2015-1045).

Ethical considerations

This study was approved by the Institutional Ethics Committee of the Fondation Congolaise pour la Recherche Médicale (Number 015/CIE/FCRM/2018). Written informed consent was obtained from adults and the parents of children prior to the start of patients enrolment at study.

Availability of data and material

The raw data presented here are available upon request to the corresponding author.

Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

FN, PAA and **LSGL** designed the study. **DOEA**, **AAA** participated in the study design**, DOEA** and **CMB** performed the experiments. **GA, ME, AAA** and **LSGL** supervised the study procedures. **CV** analyzed the data. **FN** was responsible for overall study. All authors participated in drafting the manuscript, read and approved the final version.

Acknowledgments

We are grateful to the children and adults who consented to participate in this study. We thank the staff of the Makélékélé Hospital for their participation. We also thank the staff of TB Lab CERMEL This work has been supported through the Central Africa Clinical Research Network, which is a network of excellence supported by The European & Developing Countries Clinical Trials Partnership (EDCTP). **FN, LGL, EL, TMH and AAA** are members of CANTAM (EDCTP RegNet2015-1045).

References

Alame-Emane, A.K., Pierre-Audigier, C., Aboumegone-Biyogo, O.C., Nzoghe-Mveang, A., Cadet-Daniel, V., Sola, C., Djoba-Siawaya, J.F., Gicquel, B., and Takiff, H.E. (2017). Use of GeneXpert Remnants for Drug Resistance Profiling and Molecular Epidemiology of Tuberculosis in Libreville, Gabon. J. Clin. Microbiol. *55*, 2105–2115.

Amona, M., Aloumba, A.J., Moukassa, D., Mouroumouyoka, A., Kokolo, B., Loumouamou, M.L., Amona, R.F., Mbita, A.M., Moubie, S., Ngankeni, G., et al. (2017). Tuberculose multirésistante. Evaluation situationnelle à l'Hôpital Central des Armées de Brazzaville au Congo. 5.

Boehme, C.C., Nabeta, P., Hillemann, D., Nicol, M.P., Shenai, S., Krapp, F., Allen, J., Tahirli, R., Blakemore, R., Rustomjee, R., et al. (2010). Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. N Engl J Med *363*, 1005–1015.

Brossier, F., Guindo, D., Pham, A., Reibel, F., Sougakoff, W., Veziris, N., and Aubry, A. (2016). Performance of the New Version (v2.0) of the GenoType MTBDRsl Test for Detection of Resistance to Second-Line Drugs in Multidrug-Resistant Mycobacterium tuberculosis Complex Strains. J Clin Microbiol *54*, 1573–1580.

Farra, A., Manirakiza, A., Yambiyo, B.M., Zandanga, G., Lokoti, B., Berlioz-Arthaud, A., Ngaya, G., Hermana, G., Ourandji, L.M., Ignaleamoko, A., et al. (2019). Surveillance of Rifampicin Resistance With GeneXpert MTB/RIF in the National Reference Laboratory for Tuberculosis at the Institut Pasteur in Bangui, 2015–2017. Open Forum Infect Dis *6*.

Gardee, Y., Dreyer, A.W., Koornhof, H.J., Omar, S.V., da Silva, P., Bhyat, Z., and Ismail, N.A. (2017). Evaluation of the GenoType MTBDRsl Version 2.0 Assay for Second-Line Drug Resistance Detection of Mycobacterium tuberculosis Isolates in South Africa. J Clin Microbiol *55*, 791–800.

Gilpin, C., Korobitsyn, A., and Weyer, K. (2016). Current tools available for the diagnosis of drug-resistant tuberculosis. Ther Adv Infect Dis *3*, 145–151.

Harries, A.D., Schwoebel, V., Monedero-Recuero, I., Aung, T.K., Chadha, S., Chiang, C.-Y., Conradie, F., Dongo, J.-P., Heldal, E., Jensen, P., et al. (2019). Challenges and opportunities to prevent tuberculosis in people living with HIV in low-income countries. Int J Tuberc Lung Dis *23*, 241–251.

Horne, D.J., Kohli, M., Zifodya, J.S., Schiller, I., Dendukuri, N., Tollefson, D., Schumacher, S.G., Ochodo, E.A., Pai, M., and Steingart, K.R. (2019). Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis

and rifampicin resistance in adults. Cochrane Database Syst Rev *2019*.

Liu, Z., Zhang, M., Wang, J., Chen, S., Wu, B., Zhou, L., Pan, A., Wang, W., and Wang, X. (2020). Longitudinal Analysis of Prevalence and Risk Factors of Rifampicin-Resistant Tuberculosis in Zhejiang, China. BioMed Research International *2020*, 1–8.

Najjingo, I., Muttamba, W., Kirenga, B.J., Nalunjogi, J., Bakesiima, R., Olweny, F., Lusiba, P., Katamba, A., Joloba, M., and Ssengooba, W. (2019). Comparison of GeneXpert cycle threshold values with smear microscopy and culture as a measure of mycobacterial burden in five regional referral hospitals of Uganda- A cross-sectional study. PLoS One *14*.

Nguyen, T.N.A., Anton-Le Berre, V., Bañuls, A.-L., and Nguyen, T.V.A. (2019). Molecular Diagnosis of Drug-Resistant Tuberculosis; A Literature Review. Front Microbiol *10*.

Ntoumi, F., Kaleebu, P., Macete, E., Mfinanga, S., Chakaya, J., Yeboah-Manu, D., Bates, M., Mwaba, P., Maeurer, M., Petersen, E., et al. (2016). Taking forward the World TB Day 2016 theme 'Unite to End Tuberculosis' for the WHO Africa Region. Int J Infect Dis *46*, 34–37.

Nunn, A.J., Phillips, P.P.J., Meredith, S.K., Chiang, C.-Y., Conradie, F., Dalai, D., van Deun, A., Dat, P.-T., Lan, N., Master, I., et al. (2019). A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med *380*, 1201–1213.

Okemba Okombi, F.H., Bemba, E., Bopaka, R.G., Oosale Abacka, K.B., and Kaswa, M. (2018). Extensively resistant tuberculosis: Four cases in the Republic of Congo. Med Sante Trop *28*, 289–291.

Okemba-Okombi, F., Essango, E.N., Kayomo, M.K., Abacka, B.O., Bopaka, R., and Ibara, B.A. (2020). Multi-resistant tuberculosis in Brazzaville: Epidemiologi- cal, clinical, radiographic and progressive aspects. *11*, 6.

Okemba-Okombi, F.H., Itoua, A., Biniakounou, J.B., Illoye-Ayet, M., Bemba, E.L.P., Ossalé Abacka, K.B., and Bopaka, R.G. (2015a). Apport du GeneXpert dans le diagnostic de la tuberculose pulmonaire : étude préliminaire et perspectives en République du Congo. Revue des Maladies Respiratoires *32*, A211.

Okemba-Okombi, F.H., Itoua, A., Biniakounou, J.B., and Madzou, L. (2015b). Évaluation de la prise en charge des patients admis au régime de retraitement au Centre anti-tuberculeux de Brazzaville. Revue des Maladies Respiratoires *32*, A213.

Ossibi Ibara, B., OKemba Okombi, F., Obengui, Mbemba Esther, LP., Boumandouki, J., Obame Ontsi, F., and Puruehnce, M. (2016). Associated pulmonary tuberculosis in HIV patients in Department of Infectious Diseases of the University Hospital of Brazzaville: Prevalence and Associated factors. JFVP *7*, 24–28.

Pai, M., Behr, M.A., Dowdy, D., Dheda, K., Divangahi, M., Boehme, C.C., Ginsberg, A., Swaminathan, S., Spigelman, M., Getahun, H., et al. (2016). Tuberculosis. Nat Rev Dis Primers *2*, 16076.

Phyo, K.H., Oo, M.M., Harries, A.D., Saw, S., Aung, T.K., Moe, J., Thuya, S.S., Mon, Y.Y., Min, A.C., Naing, N.N., et al. (2019). High prevalence and incidence of tuberculosis in people living with the HIV in Mandalay, Myanmar, 2011-2017. Int J Tuberc Lung Dis *23*, 349–357.

Sachdeva, K.S., Raizada, N., Sreenivas, A., van't Hoog, A.H., van den Hof, S., Dewan, P.K., Thakur, R., Gupta, R.S., Kulsange, S., Vadera, B., et al. (2015). Use of Xpert MTB/RIF in Decentralized Public Health Settings and Its Effect on Pulmonary TB and DR-TB Case Finding in India. PLoS One *10*.

World Health Organization (2019). Global tuberculosis report 2019.

Zumla, A., Abubakar, I., Raviglione, M., Hoelscher, M., Ditiu, L., Mchugh, T.D., Squire, S.B., Cox, H., Ford, N., McNerney, R., et al. (2012). Drug-Resistant Tuberculosis—Current Dilemmas, Unanswered Questions, Challenges, and Priority Needs. The Journal of Infectious Diseases *205*, S228–S240.

Tables

Table 1 : Positivity of *Mycombacterium tuberculosis* Complex of GeneXpert method according the sociodemographic, risk Behaviours, co-morbidity and clinical characteristic.

Characteristic	All patient (%) N=92	Number of positive MTBC (%) N=57	Crude Odd Ratio (CI.95%)	*P.* value
Sociodemographic				
Age group (years)				
<18	8(8.7)	07(87.5)	1	
18 – 44	51(55.4)	34(66.7)	0.28(0.03-2.51)	0.259
≥45	33(35.9)	16(48.5)	0.13(0.01-1.21)	0.071
Gender				
Female	47(51.1)	30(63.8)	1	
Male	45(48.9)	27(60.0)	0.85(0.37-7.97)	0.705
Rain season	57(62.0)	31(54.4)	1	
Dry season	35(38.0)	26(74.3)	2.42(0.96-6.09)	0.056
TB risk Behaviours				
Alcoholic	43(46.7)	27(62.8)	1.07(0.45-2.48)	0.878
Smoking	20(21.7)	13(65.0)	1.18(0.42-3.32)	0.753
Cannabis	05(05.4)	04(80.0)	2.57(0.27-23.9)	0.395
Comorbidity with HIV				
No	70(76.1)	50(71.4)	1	
Yes	22(23.9)	7(31.8)	0.19(0.07-0.53)	0.002
Clinical				
Chronic cough	66(71.7)	44(66.7)	2(0.79-5.03)	0.140
Acute cough	28(30.4)	13(46.4)	0.39(0.15-0.98)	0.042
Fever	72(78.3)	45(62.5)	1.11(0.40-3.06)	0.839
Anaemia	10(10.9)	04(40.0)	0.36(0.09-1.40)	0.132
Neurological signs	04(04.3)	03(75.5)	1.89(0.19-18.9)	0.508
Night sweat	15(16.3)	10(66.7)	1.28(0.39-4.10)	0.683
Physical asthenia	27(29.3)	18(66.7)	1.33(0.52-3.42)	0.549
Anorexia	19(20.7)	12(63.2)	1.07(0.37-3.03)	0.904
Weight loss	82(89.1)	54(65.9)	4.5(1.08-18.76)	0.039

Table 2 The sociodemographic, risk behaviors, co-morbidity and clinical characteristics associated with RR-TB status among participants positive for *Mycobacterium tuberculosis* complex by GeneXpert

Characteristic	Rifampicin Susceptible (%) N=46	Rifampicin Indeterminate (%) N=2	Rifampicin Resistant (%) N=9	*P.* value
Sociodemographic				
Age group (years)				
<18	4(8.7)	1(50.0)	2(22.2)	
18 – 44	30(65.2)	1(50.0)	3(33.3)	0.323
≥45	12(26.1)	0	4(44.5)	
Gender				
Female	22(47.8)	2(100.0)	6(66.7)	
Male	24(52.2)	0	3(33.3)	0.156
Rain season	26(56.5)	2(100.0)	3(33.3)	
Dry season	20(43.5)	0	6(66.7)	0.191
TB risk Behaviours				
Alcoholic	24(52.2)	0	3(33.3)	0.236
Smoking	12(26.1)	0	1(11.1)	0.462
Cannabis	3(6.5)	0	1(11.1)	0.822
Comorbidity with HIV				
No	43(93.5)	2(100.0)	5(55.6)	
Yes	3(6.5)	0	4(44.4)	0.006
Clinical				
Chronic cough	38(82.6)	0	6(66.7)	0.019
Acute cough	8(17.4)	2(100.0)	3(33.3)	0.019
Fever	35(76.1)	2(100.0)	8(88.9)	0.529
Anaemia	1(2.2)	1(50.0)	2(22.2)	0.006
Neurological signs	3(6.5)	0	0	0.689
Night sweat	8(17.4)	1(50.0)	1(11.1)	0.431
Physical asthenia	14(30.4)	2(100.0)	2(22.2)	0.098
Anorexia	11(23.9)	1(50.0)	0	0.168
Weight loss	44(95.7)	2(100.0)	8(88.9)	0.673

Table 3: *Mycobacterium tuberculosis* resistant to second-line anti-tuberculosis drugs by LPA using GenoType MTBDRsl VER 2.0 assay for 9 rifampicin resistant samples

Drug / no. of isolates n=9	FLQ	SLI
		KAN / AMK / CAP
Resistance to FLQ		
n=1	R	S
Resistance to FLQ and SLI		
n=1	R	R
No Resistance to FLQ and SLI		
n=7	S	S

FLQ : Fluoroquinolones, **SLI** : Second Line Injectable,
KAN : Kanamycin, **AMK** : Amikacin, **CAP** : Capreomycin,
R: Resistant, **S**: Susceptible