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Keys factors influencing multidrug-resistant tuberculosis: A Mixed Effects Modelling Study in Burundi

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Keys factors influencing multidrug-resistant tuberculosis: A Mixt Effects Modelling Study in Burundi

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Abstract

Background: Tuberculosis is a serious global public health problem, and it is in the top 10 causes of mortality in low and middle income countries. MDR-TB and XDR-TB still being a challenge for clinicians and staff operating in national TB programs .Particularly in sub-Saharan African countries, it particularly coexists with high burden of other infectious and no communicable diseases , creating a complex public health situation which is difficult to address. Tackling this will require targeted public health intervention based on evidence well defines the at risk population. In this study, using data from two referral anti tuberculosis in Burundi, we model the determinants factors associated with MDR-TB in Burundi.

Methods: Prospective data of a sample of 180 tuberculosis randomly selected from a population of patients admitted in 2019 in two referral anti tuberculosis centres in Burundi: Kibumbu Sanatorium Centre and Bujumbura anti-tuberculosis Center. The associated factors were carried out by fixed and random effect logistic regression. Model performance was assessed by Area under Curve (AUC). Model was internally validated via bootstrapping with 1000 replications. All analysis were conducted in R 3.5.0.

Results: Over 180 participants of the study, 60 patients of them were MDR-TB and 120 were Drug Susceptible. High MDR-TB is observed in patients who lives in rural zone (51,3%),in collective residence (69,2%) ,in house with more than six people (59,5%) , many people who live in the same room(70,0%) ,in patients with TB treatment history(86.4%) and in diabetics people(66.6 %).HIV was 32.3 % and 67.7 % positive respectively in MDR-TB patients and Drug susceptible patients. More than half of cases (75%) and controls (73.3%) belonged to the age group of≤45 years.The Pearson's Chi-squared test with Yates' continuity correction showed the house's rooms (p=0,010), People by house (p<0,001), currently workers (p=0,019), MDR-TB close contact (p<<0.001), Collective residence (p=0,004), Residence area (p=0,007) and tobacco consumption (<0.001) were not independent with MDR-TB.After modelling using fixed and random effects, Residence (AOR: 1.31, 95%CI: 1.12-1.80), People by house (AOR: 4.15, 95% CI: 3.06-5.39), MDR-TB close contact (AOR: 6.03, 95% CI: 4.01-8.12), History TB treatment (AOR: 2.16, 95% CI: 1.06-3.42), Tobacco consumption (AOR : 3.17 ,95% CI: 2.06-5.45) and Diabetes(AOR: 4.09,95% CI : 2.01-16.79) were statistically associated with MDR-TBs. With 2000 stratified bootstrap replicates, the model had an excellent predictive performance (AUC), accurately predicting 88.15%(95% CI: 82.06%-92.8%) of all observations. Drug susceptible patients with no close contact had the low probability around 10 % to develop MDR-TB.

Conclusion : The relatively high prevalence of tuberculosis and associated factors of MDR-TB in Burundi raises a call for concern especially in this context where there exist an equally high burden of chronic diseases, chronic malnutrition, HIV/SIDA and others infectious diseases. Targeting interventions based on these identified factors will allow judicious channel of resources and effective public health planning.

Keys words: Tuberculosis, Multidrug-resistance, random effects, BIC, bootstrap , Burundi

Background

Tuberculosis (TB) is an infectious disease caused by an intracellular pathogen called Mycobacterium tuberculosis (Mbt) [1]. TB still being a serious global public health problem, and it is in the top 10 causes of mortality in low and middle income country .Also ,TB is the leading cause of death from a single infectious agent (ranking above HIV/AIDS)[2].It is known in the world for its magnitude, vulnerability and morbidity factors [1]. Globally, an estimated 10.0 million people felt ill with TB in 2018[3] .The burden of the disease varies enormously among countries, from fewer than five to more than 500 new cases per 100 000 population per year, and nearly 2 million among HIV- negative people die from the disease [3, 4] .In addition, 251 000 deaths among HIV-positive people [5].

The current antibiotic treatment of active drug-susceptible TB, requires administration of a combination therapy for 6 months, including the first-line drugs rifampin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) for 2 months, followed by RIF and INH for 4 months [6].According to the poor response to the conventional treatment with first line drugs, Tuberculosis's treatment is difficult and the cure rates for multidrug-resistant tuberculosis are low [4, 7]. Furthermore, about 1.7 billion people are known to be latently infected by mycobacterium tuberculosis with about 10% of them reactivating to active TB in their lifetime [6]The prevention of latent TB reactivation is also used a long treatment. It consists at least 6 months of INH, or 3 to 4 months of RIF plus INH [1, 8].
In 2018, WHO reported that there were an estimated 484,000 incident cases of MDR/rifampin-resistant (RR) TB cases, including about 78.09 % (378,000 MDR-TB cases) and 44.21 (214,000 deaths)[**6**]. The average proportion of MDR-TB cases with XDR-TB was 6.2%. Poor regimen selection, inadequate drug supply and poor adherence of patients to the 6-months therapy may lead to development of drug-resistant Mtb strains, including multidrug-resistant (MDR-TB: resistant at least to INH and RIF) and extensively-drug-resistant (XDR-TB) strains [9].MDR-TB and XDR-TB still being a challenge for clinicians and staff operating in national TB programs [10]Considering the high worldwide prevalence of TB and current increasing burden of COVID-19, recent study showed a mortality much higher than isolated COVID-19 in the patients with dual infection[11,12]

In the African Region, where the burden of HIV-associated TB is highest, 87% of TB patients had a documented HIV test result. A total of 477 461 TB cases among HIV-positive people were reported, of which 86% were on antiretroviral therapy [1]. According to the SDG of United Nations, the consolidated goal for health is defined as "Promote wellbeing and ensure healthy lives and for all at all ages". Target3.3, explicitly mentions TB: "By 2030, to end the epidemics of AIDS, **tuberculosis**, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases". According to the recent study conducted in six sub-Saharan Countries (Central African Republic, Cameroon, Burundi, Democratic Republic of the Congo and Rwanda), 53% presented a mutation in pncA. The frequency of resistance per country ranged Burundi in the third position in with 66% after Rwanda (87%), Democratic Republic of the Congo (68%) [44].The aim of the present study was to identify key factors influencing MDR among tuberculosis patients and probabilities prediction in order to provide evidence for planning of the targeted programmatic interventions to reduce burden of multidrug-resistant tuberculosis in Burundi.

Patients and Methods

Study Area, Study Design and Data sources

Case-control study was conducted with a convenience sample (n=180) participants in Burundi from 1th August 2019 to 15th January 2020. Data used in this study were collected in two referrals anti tuberculosis centres. The sample consisted of all confirmed cases of TB, considering the International Classification of Diseases 10th revision (ICD-10) [1].Cases were MDR-TB patients who were on treatment at Kibumbu Sanatorium centre and they have been collected from 1st August 2019 to 15th January 2020.Controls smear-positive cases who were on the first line anti-TB and have been collected during study period in Anti-Tuberculosis Centre of Bujumbura.

Population and Sampling methods

Control is defined by a confirmed pulmonary tuberculosis with a positive bacteriologic and negative gen-Xpert MTB/RIF. Our population were stratified in 2 groups in both centres. In each group. Random sampling were done. The minimal size of sample was calculated as below:

$$n = \frac{Z^2_{1-\frac{\alpha}{2}} \times p(1-p) \times \kappa}{d^2} \quad (1)$$

$Z_{1-\frac{\alpha}{2}}$ The normal distribution quintile with 95% of confidence (1.96), n minimal size sample, p prevalence of MDR-TB, κ: No response rate (10%) and d acceptable margin (5%). As the prevalence of MDR-TB is unknown, a WHO's estimated value of $p = 0.03$ was used. According to these parameters, the cases minimal size of the sample is 50 patients. One case out of two (at least) control strategy have been used.

Outcome and Independent Variables

Outcome variable was MDR-TB (Yes/No) and was defined by a confirmed pulmonary tuberculosis with a positive bacteriologic and gen-Xpert MTB/ RIF tests. Independent variables are Sex (Men /Women), Age (years), Marital status (Unmarried/Married/Separated), Education level (None/Primary/Secondary/University), Patients residence (Urban/Rural), Collective residence(Yes/No),Work(Yes/No),People by house (6</≥6), Rooms by house (One/Two/Three/Four/Five),People by room(One/Two/Three/Four/Five).TB treatment history(Yes /No), MDR-TB Previous close contact(Yes/No) Tobacco consumption (Yes/No),Alcohol consumption (Yes/No), HIV status(Positive/Negative),Diabetes(yes/No) and , ID and patient's province as random effects.

Data Management and Analysis

Data analysis were undertaken in different steps: descriptive statistic, binary logistic modelling with fixed and random effects, power predictive of final model and probabilities prediction. MDR-TB associated risk factors were done by logistic regressions .Odds ratios (ORs) at 95% confidence level for each covariate were calculated to identify predictors of MDR-TB. The risk estimate equation for multiple logistic regression is as follows:

$$p = \frac{e^{\beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k + \varepsilon}}{1 + e^{\beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k + \varepsilon}} \quad (2)$$

$$\text{logit}(p) = \log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k + \varepsilon \quad (3)$$

Where p is outcome realization probability, β_0 intercept, β_i coefficients, X_i independents variables and ε error significant variables on 15% threshold were introduced in multivariate logistic modelling to determine a combined effect on the outcome. Finally, the predictsor variables of the model were manually selected step by step using decreasing method on a 5% threshold. The likelihood ration test, the score test and the Wald test were used to determine significance of independent variables on the outcome[13].To select the best model for this study, the Bayesian Information Criterion (BIC) based on adjustment [14-16]were used in a given equation as:

$$BIC = p \times \ln(n) - 2\ln(L) \quad (5)$$

Where p model parameters number, n observations number, and L refers to the maximum value of the likelihood function of the model. The best model is one with lowest BIC's value. The relevance of the final model to make prediction was assessed by Pearson residuals test. Receiving Operating characteristics (ROC) and Area under Curve (AUC) were respectively used to compare and evaluate performance and predictive power of the model. Furthermore, the ROC was used to determine the discriminatory performance of the model, determining the false positive and false negative rates. The Mann Whitney statistics method showed that the two distributions were offset: Drug susceptible patients had an average higher scores than MDR-TB people. Each individual's score was ranked in ascending order. Thus, the AUC which determined the number of observations accurately predicted was calculated. The R software (3.5.0) was used in processing and data analysis, lme4, and forest model packages were also used to carry out results in this study [17]. In validating internal performance of the model, a bootstrapping procedure with 2000 replications was conducted.

Results

Socio-Demographic Characteristics of the Patients

A total 180 respondents, 60 cases and 120 controls in the study (**Table 1**).The mean age of study's participant is 36.25± 14.17, the youngest was 15 year old and the oldest was 85 years old. Mean age in women and men are respectively 35.78±17.14 and 36.47±12.63.That difference is insignificant (p= 0.784).The median age is 33 years. This study shows that overall prevalence of MDR-TB was 33.3% (95% CI [30.74-59.26]). The table below shows characteristics participants according to the MDR and Drug susceptible profile.

Table 1: Socio-demographics characteristics of participants

Characteristics	Modalities	N	C^a	C^o	P^+	95% CI	p
Sex	Women	57	19	38	33.3	[21.40-47.06]	0.999
	Men	123	41	82	33.3	[25.09-42.40]	
Age (Years)	<45 Years	133	45	88	33.8	[25.86-42.54]	0.910
	≥45 Years	47	15	32	31.9	[19.09-47.12]	
Education level	None	34	5	29	14.7	[4.95 - 31.06]	
	Primary	89	34	55	38.2	[28.10-49.11]	0.057
	Secondary	45	18	27	40.0	[25.70 55.67]	
	University	12	3	9	25.0	[5.49 - 57.19]	
Marital status	Single	63	17	46	26.9	[16.57-39.65]	0.282
	Married	96	37	59	38.5	[28.78-49.03]	
	Separated	21	6	14	28.6	[11.28-52.18]	
Residence	Rural	39	20	19	51.3	[34.78-67.58]	0.007
	Urban	141	40	101	28.4	[21.10-36.57]	
Collective résidence	No	167	51	116	30.5	[23.67-38.13]	0.004
	Yes	13	9	4	69.2	[38.57-90.91]	
With jobs	Yes	148	55	93	37.2	[29.37 45.48]	0.019
	No	32	5	27	15.6	[5.28- 32.79]	
People by house	≤6	143	38	105	26.6	[19.54-34.60]	<0.001
	>6	37	22	15	59.5	[42.10-75.25]	
Room by house	One	32	10	22	31.3	[16.12-50.01]	
	Two	88	21	67	23.9	[15.42-34.14]	
	Three	51	25	26	49.0	[34.75-63.40]	0.010
	Four	7	2	5	28.6	[3.67 - 70.96]	
	Five	2	2	0	100	[15.81-100.0]	
People by Room	One	10	7	3	70.0	[34.75-93.33]	
	Two	87	23	64	26.4	[17.55-36.98]	
	Three	67	24	43	35.8	[24.47-48.47]	0.083
	Four	13	5	8	38.5	[13.86-68.42]	
	Five	3	1	2	33.3	[0.84 - 90.57]	
HIV	No	149	50	99	33.5	[26.04-41.74]	0.999
	Yes	31	10	21	32.3	[16.68-51.37]	

Diabetes	No	174	56	118	32.2	[25.31-39.67]	0.186
	Yes	6	4	2	66.6	[22.28-95.67]	
TB treatment history	No	158	41	107	25.9	[19.31 33.51]	<0.001
	Yes	22	19	13	86.4	[65.09-97.09]	
MDR-TB close contact	No	160	43	117	26,9	[20.18-34.45]	<0.001
	Yes	20	17	3	85,0	[62.17-96.79]	
Tabacco	No	143	38	105	26.6	[19.54-34.60]	<0.001
	Yes	37	22	15	55.5	[42.10 75.25]	
Alcohol	No	54	12	42	22.2	[12.04-35.60]	0.038
	Yes	126	48	78	38.1	[29.59-47.17]	
Total		**180**	**120**	**60**	**33.3**	[30.74 59.26]	

N: Effectives, C^a: Cases, C^o: Control+: Multidrug –resistance proportions

More than half of cases (75%) and controls (73.3%) belonged to the age group of ≤45 years. Men constituted 68.3 % of cases and 68.3% of controls. Less than the overall prevalence is observed in young people over 45 years (31.9%), people with no any education level (14,7%) or University(38,2%), single(26,9%) or separated people (28,6%), urban people (28,4%) ,no workers(15,6%), Less than six (26,6%) by house , people who lives in the house with one (31,3%) ,two(23,9%) or four (28,6%)rooms ,two people by room(26,4%) ,in no diabetics people(32.2%) and HIV patients(32.3%). High prevalence are observed in people who lives in rural zone (51,3%),in collective residence (69,2%) , in **household with** more than six people by house (59,5%) , one people by room(70,0%) ,people with TB treatment history(86.4%) and in diabetics people(66.6 %).

Inferential analysis

According to the Pearson's Chi-squared test with Yates' continuity correction, MDR-TB is significantly associated with the room's number by house (p=0,010), People by house (p<0,001), currently workers (p=0,019), MDR-TB close contact (p<0.001), Collective residence (p=0,004), Residence area (p=0,007) and tobacco consumption (<0.001) .In contrary, Sex, Age (Years), Diabetes, Education level and People by room were not associated with MDR-TB. Therefore, the table below shows determinants of MDR-TB founded by using logistic regressions with fix and random effects (Table 2).

Table 2: Logistic regressions

Variables	**Modalities**	**N**	**AOR**	**95% CI**	**p** Multilevel
Residence	Urban	141	Reference		
	Rural	39	1.31	[1.12-1.80]	0.020
People per house	≤6	143	Reference		
	>6	37	4.15	[3.06-5.39]	<0.001
MDR-TB close contact	No	160	Reference		
	Yes	20	6.03	[4.01-8.12]	<0.001
History TB treatment	No	148	Reference		
	Yes	32	2.16	[1.06-3.42]	<0.001
Tobacco	No	143	Reference		
	Yes	37	3.17	[2.06-5.45]	<0.001

Diabetes	No	174	Reference		
	Yes	6	4.09	[2.01-6.79]	0.030

N : Effectif, AOR : Adjusted Odds ratio, CI : Confident interval, p : p value

A saturated equation model was derived from the above multivariate model . After controlling the cofounding variables using fix and random effects, an adjusted odds ratio, their lower and upper bound along with a corresponding p-value were derived.In the adjusted model, the significant associations are showed. Six factors are significantly associated with tuberculosis MDR: Patient residence (OR=1,31; 95% CI=1.12-1.80;p=0.020), people per house(OR=4,15;95% CI=3,06-5,39;p<0,001), MDR-TB close contact(OR=6,03;95% CI=4,01-8,12;p<0,001), TB treatment history(OR=2,16; 95% CI=1,06-3,42;p<<0,001),Tobacco(OR=3,17 ;95% CI : 2,06-5,45; p<0,001) and Diabetes(OR=4,09; 95% CI=2,01-6,79;p=0,030).In contrary, some socio-demographics factors as Sex, marital status and Age of participant were not significantly associated. Furthermore, Room by house, collective residence and having work are not significantly associated with MDR-TB. The figures below shows the Area Under Curve and Outliers of our final model.

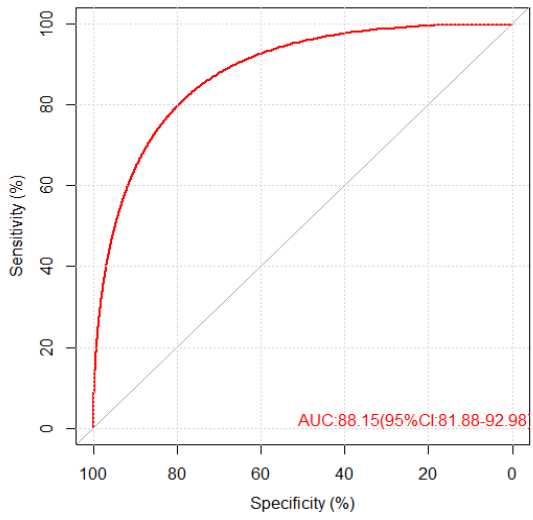


Figure 1: Area under curve

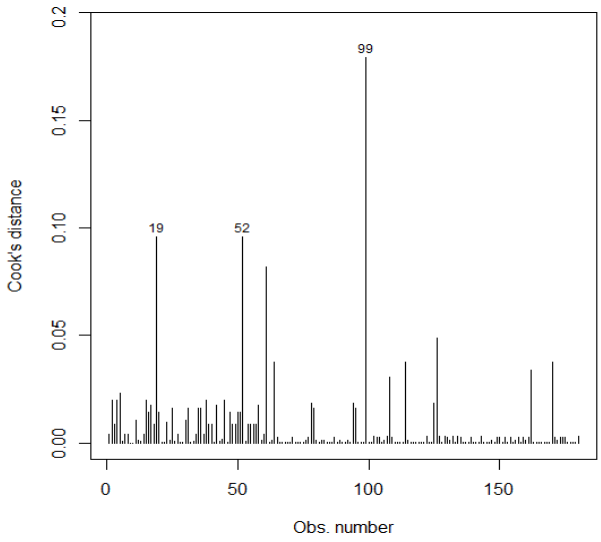


Figure 2: Cook's distance

The model predictive power evaluation based 2000 stratified bootstrap replicates and binormal Smoothing showed that the AUC : 88.15%(95% CI: 82.06%-92.8%) which consequently suggest an excellent discrimination (**Figure 1)** .Cook's distance shows that 3 points (19, 52 and 99) are outliers, it means the influential points are not numerous(**Figure 2)**. Pearson residuals test of (X^2= 183.86, df =173) was determined with a p-value of 0.272 which shows the model was well adjusted on the observations. A McFadden's statistic (R^2: 0.346) also indicates that this model has a good fit.

Cross validation and decision tree

In supervised learning, the resubstition error rate is supposed to indicate the performance of the model when it is employed in the population. However, we know, being estimated on learning data, it is biased. By using K folds method, the cross-validation error rate each group were **0.33,**

0.333, 0.133, **0.200, 0.2333 and 0.333** respectively. The mean error which is the best quality estimator than the substitution error rate is 0.2611.The **figure 3** below show the pruned classification tree.

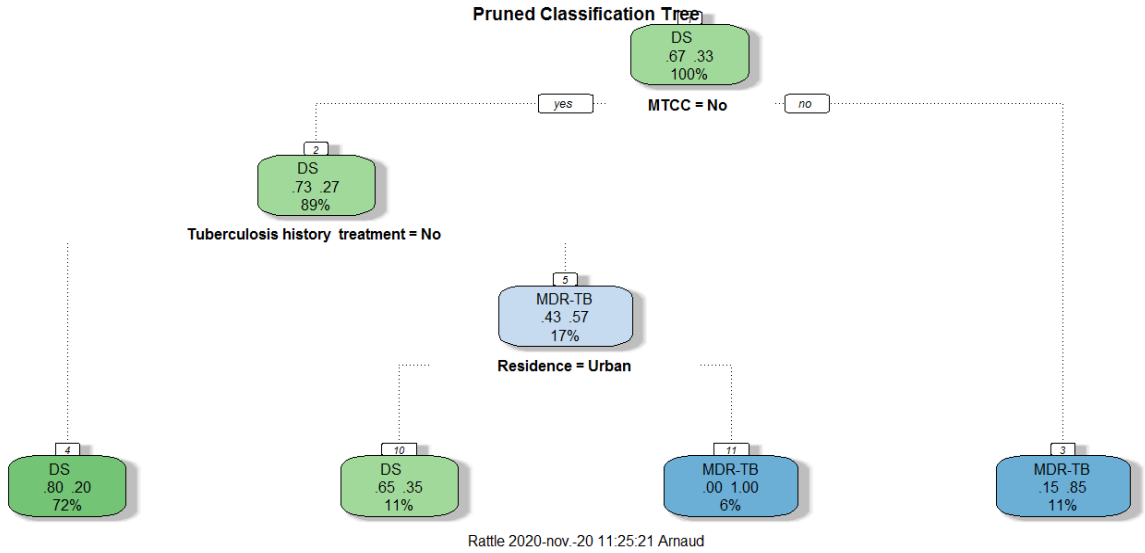


Figure 3. Decision tree

In Validation of decision tree using the "Complexity Parameter" and cross validated error, printcp and pltcp functions were used to validate the model. The tree were pruned to avoid any overfitting of the data and the convention is to have a small tree and the one with least cross.Drug susceptible(DS) patients with no close contact had the probability around 10 % to develop MDR-TB. That probability is 6% in Urban patients .DS patients with no tuberculosis history treatment had 72% to stay drug susceptible

Discussion

In this study, we determined the proportions of MDR-TB in different categories of patients and identified **main** factors associated with MDR-TB.The growing prevalence of MDR-TB strains is a major public health problem globally and in Burundi.

In this study, six **main** risk factors of MDR-TB are identified. Besides the major biological factors leading the MDR-TB, as the mutation ability, virulence variation and the fitness of drug-resistant mycobacterium TB strains [18];multivariable logistic regression analysis showed that significant independent factors for the occurrence of MDR-TB variables were: Patients residence, high number of people by house, MDR-TB close contact, TB history treatment , Tobacco consumption and Diabetes was identified as strongest association with MDR-TB ,which are consistent with previous study[18,19].

This study showed that patients who had contact with known MDR-TB patients were about 6.03 times more likely to develop MDR-TB than control patients. Similar findings have been reported in previously studies conducted in Africa (Ethiopia) and South America (Peru) [20, 21]. In low-income countries , it can be explained by delays in diagnosis and treatment of MDR-

TB patients than Control patients, especially due to sub-optimal availability of diagnostic and treatment coupled with poor infection prevention measures at health care facility level and at home.

Patients with history of TB treatment had about 2 times the risk to become MDR-TB (AOR: 2.16).This finding was consistent with studies conducted in Central Nepal and South Africa [22, 23]. Around 85% of retreatment TB patients were MDR-TB in our study. Those results are comparable to those founded in the previous study conducted in China which show that more than 30% of retreated patients were MDR-TB [18].

In addition, many research showed that MDR-TB was frequently identified in patients with a history of TB treatment, which is also evidenced in this study trough a significant statistical association [24-30].Contrary to this study, findings of other studies reported that HIV was as principal risk factor, with creation of fertile ground to the TB disease. The TB-HIV co-infection rate was 11.67%.This finding is comparable with the estimated prevalence in studies conducted **in** Ethiopia in 2012 and 2017 [21, 31]. Probably due to the high mortality rate among MDR-TB patients, HIV-positive patients are less among MDR-TB than drug susceptible TB patients .Our findings are contrary to those showed by a study conducted in Europe in which HIV was found to be and independent determinant for MDR-TB [32].Also, majority of Cases (31.6%) than controls (10.8%) had previous history of TB treatment. Developing MDR-TB depends on type of TB patients during their previous treatment. Similar findings are observed in recent study conducted in Ethiopia in 2020 which showed that MDR-TB is less observed in controls patients (14.4%) than cases patients (91.7%) [33].

Accord to the poverty in Burundian population with low income and very low index of wellbeing, the current study showed that socio-demographic factors are associated **with** MDR-TB. Collective residence was significantly associated **with** the MDR-TB. This is correlated to the findings of multilevel logistic regression which showed that 20 patients with close contact with MDR-TB patients had high risk (6.03 times) to become MDR-TB .Recent study conducted in Ethiopia (2020) , Sudan (2012) and Namibia (2019) respectively showed that close contact with known MDR-TB patients was among the determinants factors of MDR-TB[33-35]. As close contact with MDR-TB patients increases in living in the same house hold, the transmission risk of MDR-TB also increases the same house and the many people in the same room. Therefore, health education for TB patients and their family members on TB infection is necessary to control the MDR-TB spread in among household members. Also, in this study education level of patients were not significant associated to MDR-TB (p=0.057) but residence was significantly associated (p=0.007).According **to** multilevel analysis, patients from rural region, had 1.31 times the risk to develop MDR-TB than urban patients. Those findings are constant with a study conducted in Pakistan which showed the significant association [36]. This risk can be due to high illiteracy in rural's patients .The last one my cause TB patients to have low skills on TB. It can also delayed health-seeking behavior during the disease occurrence, lead to misuse of treatment and no adherence to the treatments.

The current study showed that living in less roomed house ,in partucular more than six patients by house had high risk to become MDR-TB. Simillar findings are observed in two recents studies conducted in Addis in 2013 and 2019 respectively[37,38]. Knowing the diabetes as public health burden ,our study showed that more than half (66.7%) of diabetics patients was MDR-TB and had 4.09 times the risk to develop MDR-TB. No similar findings are observed in a previous study conducted in 2018 in Serbia which didn't showed no significant association with MDR-TB[39]. However , this study didn't indicate that Age, sex,eduction level ,marital status ,current work, people by room and HIV infection were significantly associated with development of MDR-TB ,as serveral other previous study[40-43]. DS patients with no close contact had the probability around 10 % to develop MDR-TB. That probability decrease from

10 % to 6% in Urban patients .DS patients with no tuberculosis history treatment had 72% to stay drug susceptible

The major strength of this study was inclusion of patients from two national areas, and selecting Cases and Controls based on the result of biological test. Some increasing of the case control study was achieved by increasing the number of controls (two controls were used).Another strength is combining descriptive and inferential statistics , logistic regressions with fix and random effects, Wald test and Pearson's Chi-squared test with Yates' continuity correction Cross validation and decision tree.Limitations of his study should be noted during interpretation, conclusion, generalisation and policy formulation because it concerned few people for no longer time in two areas in in the country. In addition, some information on uses of different substances were not sufficient.

Conclusion

This study showed that MDR-TB was founded 33.3% of participants. Around three quarters of cases (75%) and controls (73.3%) belonged to the age group of ≤45 years. Men constituted more than 60 % of cases and controls .High MDR-TB over 50% is observed in people who lives in rural zone, in collective residence,in more than six people **per** house , one people by room ,people with TB treatment history and in diabetics people .According to the Pearson's Chi-squared test with Yates' continuity correction, MDR-TB was significantly associated with the room's number by house , People **per** house , currently workers , Collective residence, Residence area and tobacco consumption . Besides the major biological factors leading the MDR-TB, multivariable logistic regression analysis showed that six variables were significantly independent factors for the occurrence of MDR-TB: Patients residence, high number of people by house, MDR-TB close contact, TB history treatment, Tobacco consumption and Diabetes was identified as strongest association with MDR-TB , which are consistent with previous study.Resources in Burundi are scarce, therefore, the tackling the high burden of tuberculosis diseases and its MDR should be based on instituting systems for early detection and prompt treatment especially those identified as high risks.

To our knowledge, no recent study on MDR-TB factors have been carried in Burundi. At the community level, efforts should be channelled towards intensifying innovative and inclusive health promotion aimed at behavioural change in people lifestyle. At the health system, identification of factors could allow those at high risks to be identified early and well-targeted with the needed treatment with good health care services. Finally, provision of term care for those identified with risk factors will depend on not just consistent treatment but also on the overall health systems' strengthening. This will ensure sustainability and effectiveness of public health interventions aimed at tackling MDR-TB along with other high burden infectious and chronic diseases.

List of Abbreviations

Abbreviations	Full meanings
AIDS	
AOR	Adjusted Odds Ratio
AUC	Area Under Curve
BIC	Bayesian Information Criterion
Mbt	Mycobacterium tuberculosis
HIV	
TB	Tuberculosis
INH	Izoniasid
PZA	Pyrazinamid
EMB	Etambtol
RIF	Rifampicin
MDR	Multidrug resistance
XDR	Extra drug resistance
WHO	World Health Organisation
OR	Odds Ratio
ROC	Receiving Operating Characteristics
Rce	Residence
MTCC	Multidrug resistance close contact
THT	Tuberculosis history treatment

Data Sharing and Statement

The dataset used in this study are available from the corresponding author on reasonable request

Ethics approval and consent to participate

We first submitted the research proposal to the Kamenge Teaching Hospital University and received ethical clearance .Written permission was acquired from ethical committees of the two anti-tuberculosis centres to use theirs dataset for this study. All participants' responses were promised and have been confidential and will not be shared with anyone other than our investigative team members. Patient data were anonymised and replaced with unique codes in effort to secure patient identity.Participants were not required to take the survey. Informed consent was waived by the ethics committee which approved the study. All methods were carried out in accordance with relevant guidelines and regulations.

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Disclosure

The authors reports no conflicts of interest in this study.

Consent for Publication
Not Applicable

Author's declarations
All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable all the aspect of the work. Specifically, AI and IS conceptualised and designed the study and wrote the first draft. IS lead and represented the team in study permissions. CI and ENO provided technical support, reviewed the first draft and wrote some sections of the manuscript .NN, GPN and SD lead the data collection and assisted in writing first draft and also provided reviews for subsequent versions of this manuscript. All authors read and approved the final version of this manuscript to submission.

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Figures

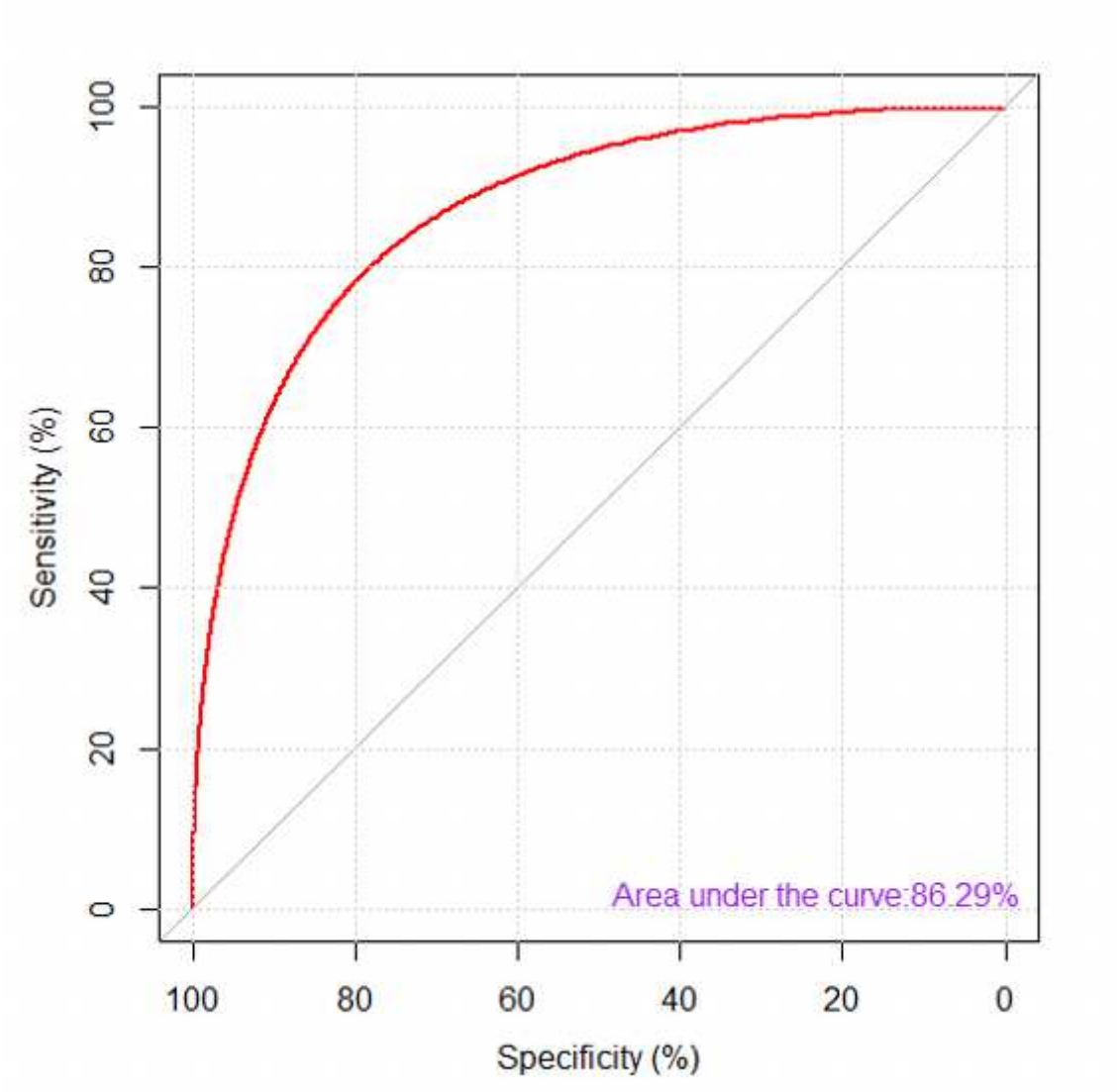


Figure 1

Area under curve

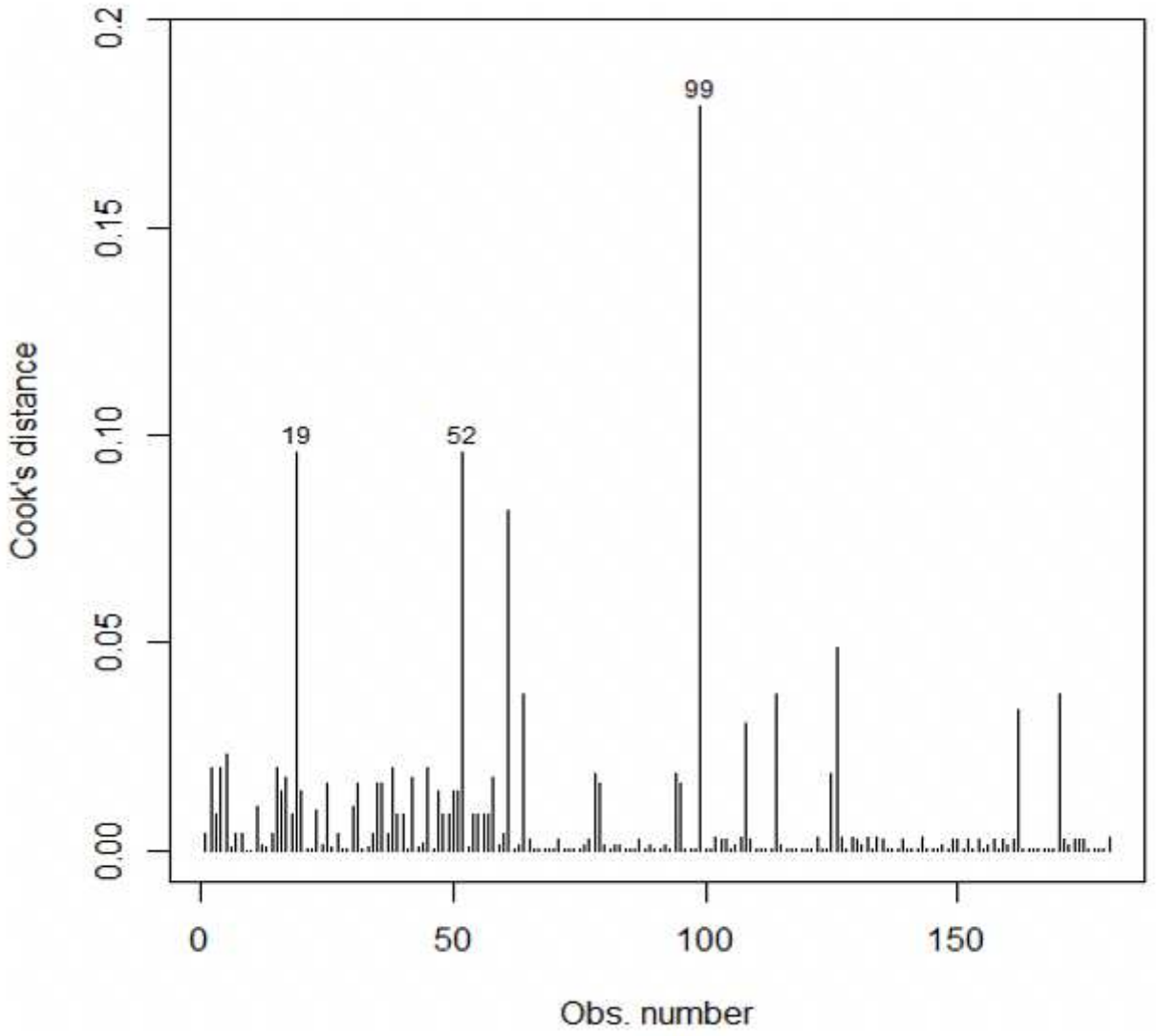


Figure 2

Cook’s distance

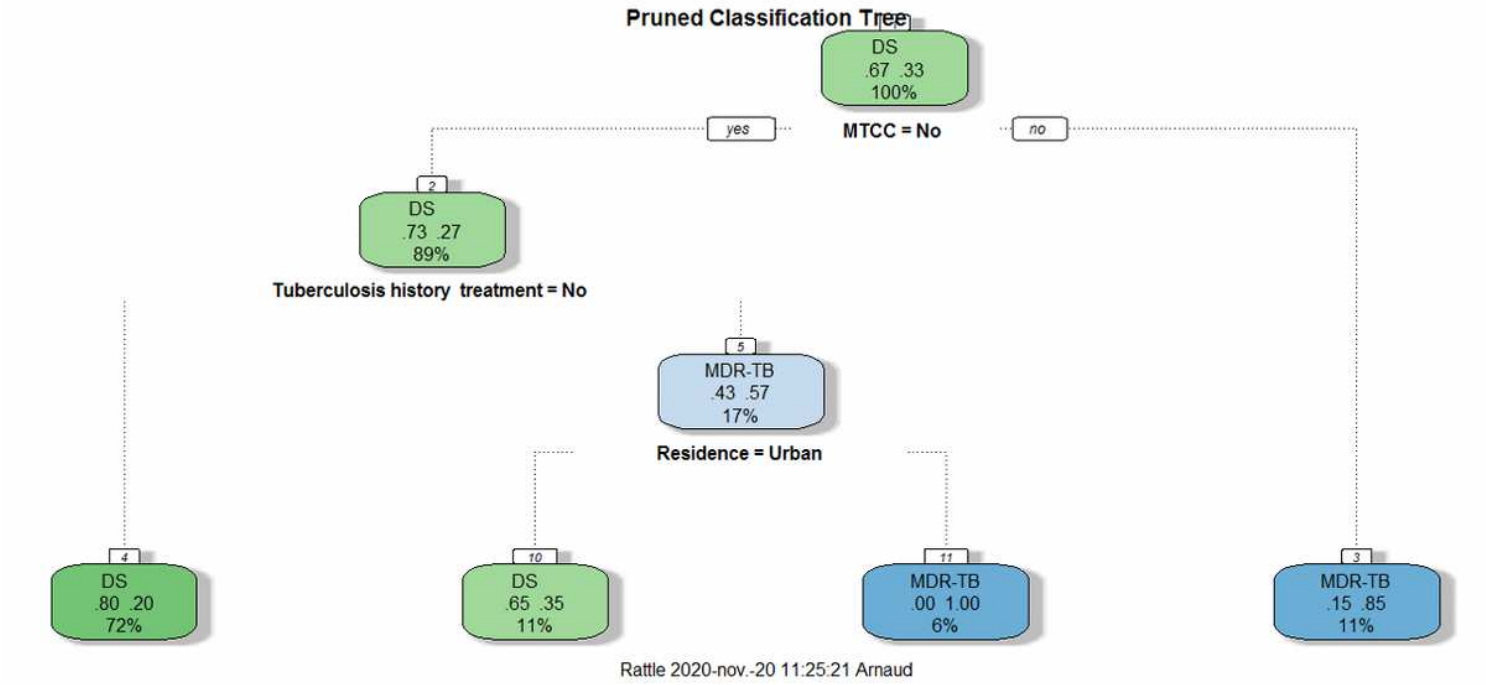


Figure 3

Decision tree